HYPERSENSITIVITY PNEUMONITIS

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INTERNAL MEDICINE GRAND ROUNDS

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Mr. Holmes to Dr. Watson: "You see, but you do not observe. The distinction is clear."

The Adventures of Sherlock Holmes: A Scandal in Bohemia, Sir Arthur Conan Doyle, 1891.

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Introduction

The structure of the mammalian lung is efficiently suited to its major function of gas exchange but also creates the opportunity for continuous and extremely varied challenge from the environment. Thus, the lung is also equipped to serve as an important defensive interface. While the scope of potential insults is almost boundless, the lung can respond through only a limited number of stereotypical pathophysiological mechanisms. This is particularly well illustrated by a group of diseases referred to collectively as hypersensitivity pneumonitis. The British characteristically use the more descriptive term extrinisic allergic alveolitis to refer to this same group of diseases. As our understanding of this syndrome grew, it was unfortunately fashionable to name each different form of exposure as a decreet disease. The literature is thus replete with a number of colorful and arcane variations on the single theme of hypersensitivity pneumonitis. A number of these have been compiled in the Appendix for the interested reader. Many of these are of little practical importance, having occurred in only a small number of individuals engaged in rare or outdated occupations. A number of drugs have also been reported to cause hypersensitivity pneumonitis and are thus included in the Appendix. This discussion will focus upon those forms of hypersensitivity pneumonitis which are caused by inhalation of antigenic materials and which may occur with significant frequency in the United States: farmer's lung, bird-breeder's lung, and ventilation hypersensitivity pneumonitis.

History

Agricultural workers who have been involved in the dusty labor of handling grains or hay have been known to suffer from respiratory ailments for centuries. Ramazzini's description of a pulmonary disorder occurring in grain handlers in 1713 is acknowledged to be the first written account of the disease which has come to be known as farmer's lung (108). Campbell provided the first modern and detailed description of this clinical entity in 1932. He described the typical clinical features and noted the association to dusts created when farmers removed hay from lofts after the hay had been put up wet and subsequently became moldy. Affected individuals complained of fever, chills, cough and dyspnea 4 to 6 hours after exposure to dusts from the moldy hay (22).

Originally it was thought that the disease represented a true mycotic infection of the lungs (152), but this view was challenged 25 years later by Fuller who suggested that the disease resulted from sensitization from mold-spore products or grass particles which led to a miliary inflammatory response (55). Pepys and others emphasized the immune nature of the disease by demonstrating the presence of precipitating antibodies in the sera of affected patients to antigens extracted from moldy hay (74, 102). The same group soon thereafter reported that the antigens responsible came specifically from a group of related bacteria with fungal morphology, the thermophilic actinomycetes (103). Williams successfully reproduced the clinical syndrome in patients with the disease by inhalational challenge (160).

A similar clinical syndrome has been described occurring in subjects exposed to a wide variety of organic dusts (see Appendix). In most instances each of these separate variations of hypersensitivity pneumonitis is caused by specific organic antigenic material and is frequently accompanied by precipitating antibodies in serum. Thus, the presence of specific causative antigens in offending dusts and corresponding antibodies in the sera of

affected individuals demonstrated the immune nature of the disease. Dickie and Rankin described the same syndrome in Wisconsin farmers and included biopsies which demonstrated the lymphoid and granulomatous nature of the pathologic response in the lung (38). These observations coupled with experimental data from animal models of hypersensitivity pneumonitis have led to current concepts of the pathogenesis of the disease which emphasize the importance of cell-mediated immunity (13,36,45,47,81,118,123,125,140).

Clinical Features

Hypersensitivity pneumonitis is a syndrome caused by a wide variety of inhaled organic dusts or chemicals which produce an immunologically mediated inflammatory response of the alveoli and terminal bronchioles which is frequently accompanied by systemic symptoms. In general there are two forms of clinical presentation of hypersensitivity pneumonitis: acute and chronic. The specific presentation of an individual patient is likely determined in part by genetic factors (149), but more importantly by the frequency and intensity of the exposure. The acute form of the disease tends to occur in patients with intermittent or massive dust exposure, whereas the chronic form predominates when the exposure is more continuous and low-intensity in nature (27,45,46).

Acute Episodes

Intermittent or massive exposure
Onset follows 4-6 hour latency
Fever
Chills
Dyspnea, exertional or at rest
Cough, usually non-productive
Malaise
Fatigability
Anorexia
Headache

The acute attack characteristically begins following a latent period of 4 to 6 hours from the time of exposure; this latency may be as long as 12 hours. In contrast to extrinsic asthma, the symptoms are thus delayed. This may lead to diagnostic difficulty as the patient may not recognize the temporal relationship unless questioned carefully. Symptoms may begin abruptly with a rapid rise in temperature. Fever is generally in the range of 100 to 101°, but may be as high as 104°. This is usually accompanied by chills; frank rigor is uncommon (22). Dyspnea is virtually universal and is often accompanied by cough (38). The cough is usually non-productive and particularly aggravating; many report paraxysms of cough precipitated by deep inspiration (41). Sputum production when present is typically mucoid; purulent sputum and hemoptysis are rare. Malaise, lassitude, easy fatigue, anorexia are also commonly present. Frontal headache and arthralgias are also reported. Chest pain, frank arthritis, myalgias and gastrointestinal complaints are not typical features of hypersensitivity pneumonitis. There have been reports of a rare association between gluten-sensitive enteropathy and hypersensitivity pneumonitis (12,77,153); the significance of this association is not clear.

In the acute attack, fever and cough usually subside in 2 to 3 days; however, exertional dyspnea, fatigue and general lassitude may persist for several weeks (89). The acuteness of these attacks will cause the patient to spontaneously avoid the offending agent and thus the attacks are self-limiting. This time course and tendency to spontaneous recovery must be considered when evaluating the results of therapy, especially in the case of corticosteroids. Many cases will be confused with pneumonia of bacterial or "atypical" (viral, mycoplasmal) etiology. The correct diagnosis may be especially difficult since many patients will appear to respond to antibiotic therapy.

If the exposure to dust is more insidious, then the chronic form of hypersensitivity pneumonitis may result. In contrast to the acute form, fever and chills are usually absent. Typically, patients complain of the gradual onset of dyspnea, especially with exertion. Weight loss is common and may be profound (42). Patients frequently have had exposure to the causative agent for many months or years before the onset of symptoms. Co-workers and other family members with similar degrees of exposure commonly are asymptomatic. This coupled with the insidious onset of symptoms and lack of acute attacks makes the association of the disease to the inhalation of dusts inapparent to the patient; diagnosis is thus extremely difficult in patients with the chronic form of hypersensitivity pneumonitis unless the physician obtains a careful occupational and exposure history. In time the disease may progress to severe disability and the development of pulmonary fibrosis and cor pulmonale (10,55,58,59).

Chronic Illness

Continuous or low-intensity exposure
Lacks identifiable onset
Exertional dyspnea
Weight loss
Cough

The physical examination is usually normal except for the presence of diffuse rales. This commonly is present shortly after or at the onset of systemic symptoms in acute attacks. Rales may persist for many weeks after an acute attack or during chronic stages of the disease (38,42). It is not uncommon to hear rales in the patient's chest at times when the patient is asymptomatic or when the chest x-ray is clear. Indeed, rales have been described in individuals with a known exposure to causative dusts and with precipitating antibodies in serum who have never noted symptoms and who have normal chest x-rays and lung function. Thus, the presence or absence of rales on exam is non-specific and correlates poorly with disease activity. These observations also suggest that a "low-grade alveolitis" may exist or persist in some individuals without causing significant disease (33,34).

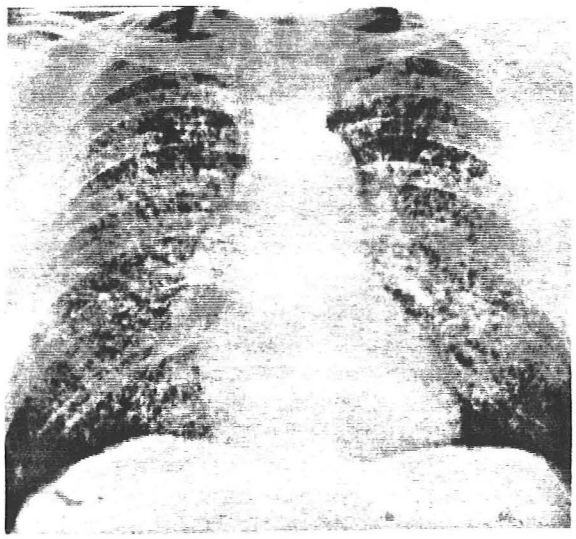
Wheezing is not a characteristic symptom or physical finding, but has been described in some patients. It has been suggested that the presence of airways obstruction has negative prognostic implications (10).

Laboratory Findings

During acute attacks of hypersensitivity pneumonitis laboratory analysis freqeuntly shows a modest leukocytosis with total white blood cell counts (WBC) of from 12,000 to 15,000 cells/mm^3; the WBC may reach as high as 20,000 to 30,000 in some cases, however (41). The differential cell counts show neutrophilic predominance with a leftward shift. Eosinophilia may occur in rare instances, but is mild when present; in general, eosinophilia is decidely not a typical feature of hypersensitivity pneumonitis (41). The erythrocyte sedimentation rate is normal in the majority of cases but may be 20-40 mm/hr in 31% of patients and greater than 40 mm/hr in 18% (89). Serum immunoglobulins may show increases in total levels of IgG and IgM classes, as well as occasional elevations of total IgA (7). Rheumatoid factor may be present as well (150). As with osinophilia, total levels of serum IgE are not increased in patients with hypersensitivity pneumonitis. The presence of precipitating antibodies specific for the causative agents of the disease is common, though as discussed below, this finding is primarily an indicator of exposure rather than disease and may be lacking in terms of both clinical sensitivity and specificity. There is no single laboratory test or abnormality which is pathognomonic for hypersensitivity pneumonitis.

Radiographic Findings

In the acute form of hypersensitivity pneumonitis the chest radiograph will most commonly display a fine, soft, reticular pattern with multiple small ill-defined nodules. This appearance has also been described as that of fine alveolar "mottling" (55) or even as a "ground-glass" appearance (90). The nodular shadows are usually diffuse, having a predilection for the middle and lower zones or of the central 2/3 of the lung fields. The apex, base, and peripheral regions are generally spared (29). With progression of disease to a more chronic form, the infiltrates take a more coarse interstitial pattern and may lead to a "honey-comb" appearance in advanced cases.



Although the small nodular shadows may tend to coallesce, frank segmental or lobar consolidation is unusual, but may be seen in as many as 7% of acute cases (60). Pleural effusion(s) and hilar or mediastinal adenopathy are not seen with hypersensitivity pneumonitis.

It has frequently been observed that the patient's symptoms are likely to be far worse than would be expected from the subtle radiographic findings, quite the opposite to the experience with mycoplasmal pneumonia. In fact patients may have a completely normal chest radiograph. In acute cases 4% will have normal films and 40-45% may have minimal changes which might be easily overlooked (90). The radiographic findings tend to regress or resolve over 4 to 6 weeks if further exposure is avoided. Radiographic resolution tends to preceed resolution of pulmonary function abnormalities, especially the diffusing capacity. During quiescent intervals, 60% of chest radiographs will be normal (90). Thus, the finding of a normal chest film does not exclude the diagnosis of hypersensitivity pneumonitis. In general, radiographic changes correlate poorly with disease activity.

Pulmonary Function Testing

Spirometry performed during an acute attack of hypersensitivity pneumonitis typically presents a restrictive pattern, with reduced vital capacity and proportionally decreased FEV_1. Static lung compliance and lung volumes are decreased if measured. The most sensitive and characteristic abnormality in these patients is a reduction in the diffusing capacity (DLCO). Hypoxemia may be present at rest in severe cases. Other abnormalities of gas exchange are common, including exercise-induced oxygen desaturation. Respiratory alkalosis is common; hypercarbia is rare. Obstructive patterns are not characteristic, but there may be evidence of peripheral airway involvement as evidenced by reductions in the mid-range flow rates (FEF_{25-75}).

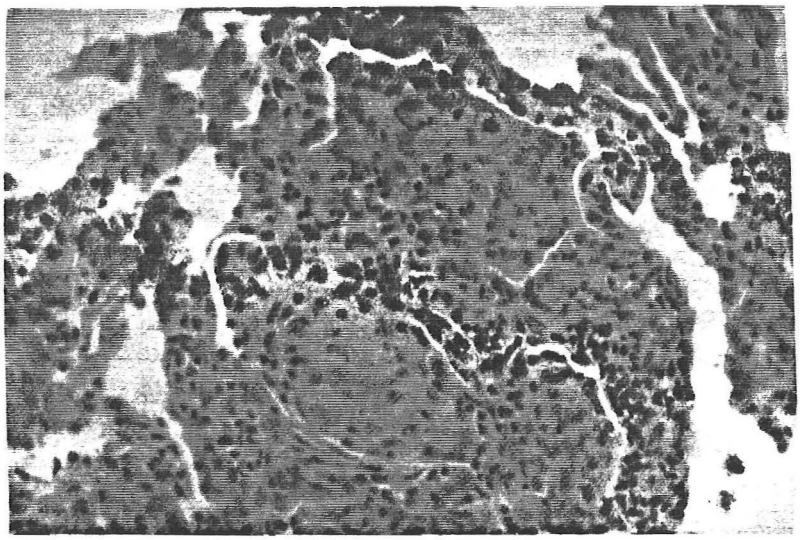
Pulmonary function abnormalities will be apparent beginning from 4 to 6 hours after an acute exposure or challenge. Once removed from exposure, improvement occurs over the next 12 to 18 hours (45). The majority of abnormalities will have resolved by the end of the first month, but 4 to 6 months may be required for complete resolution. (31,89). With repeated exposure there may be failure to resolve completely, and progression to disability occurs in some individuals. Pulmonary function abnormalities are not reversible with inhaled beta-agonist bronchodilation.

Histopathology

Specimens obtained by open lung biopsy or at autopsy from patients with hypersensitivity pneumonitis typically show evidence of a mononuclear cell inflammatory response involving primarily the alveoli, alveolar walls, and terminal bronchioles. Lymphocytes predominate, with some plasma cells as well. Large, foamy histiocytes representing activated macrophages are common within the alveoli (133,146)

Noncaseating granulomas are common and may be present in from 67 to 90% of cases. It has been reported that the granulomas of hypersensitivity pneumonitis differ from those of sarcoidosis in that they: are smaller, contain more lymphocytes, and occur more commonly in alveolar tissue rather than with bronchioles (71). These distinctions are arguably subtle, and should not be relied upon. The diagnosis of both sarcoidosis and hypersensitivity pneumonitis is made from a combination of clinical findings; diagnosis cannot be made by histology alone.

In advanced cases there may be evidence of interstitial fibrosis. Findings consistent with bronchiolitis obliterans have also been reported (111). Organic material and fungal spores may be seen, especially in cases with recent massive exposure; foreign-body type granulomas may be seen in association with such material. However, invasive mycotic changes are not seen.



In general immunohistologic techniques have been unrewarding (97). Positive fluorescent staining for antigen-immunoglobulin complexes and for complement has been reported in the intraalveolar septa. However, despite the prevalence of precipitating antibodies in serum of these patients, vasculitic changes and deposition of immunoglobulins or complement in or around vessels has only rarely been described (133). Thus, the histologic features are more compatible with a cell mediated-hyperimmune response than with immune complex mediated disease.

Skin Testing

Immediate (10 to 15 min) weal and flare as well as delayed (4 to 6 hr) Arthus-type skin reactions to hypersensitivity pneumonitis antigens have been described (91). However, the clinical utility of these tests has not been accepted. The antigenic extracts used for these tests are crude at worst and contain a multiplicity of different antigens at best. Most fail to distinguish between patients with disease and asymptomatic individuals with natural exposure. A significant fraction of presumably asymptomatic and non-exposed subjects will also give positive reactions. This may result from non-specific irritant effects or be a manifestation of generalized atopy rather than a reflection of hypersensitivity pneumonitis (160).

Skin Testing in Farmer's Lung

Subjects Tested	Response to Moldy Hay Antigens (% positive)		
	10-15 min	4-6 hr	48 hr
Farmer's Lung	83	100	44
Asymptomatic Farmers	28	68	4
Non-farmers	26	31	0

After Morell, 1985

Type IV delayed skin testing with hypersensitivity pneumonitis antigens has been particularly non-rewarding. Indeed, it has been reported that patients with hypersensitivity pneumonitis may have non-specifically impaired delayed cutaneous hypersensitivity; bird fanciers were found in one study to have a degree of cutaneous anergy which was similar to patients with sarcoidosis (100). It was suggested that this finding might suggest that the immune response remains compartmentalized within the lung; however, it might be caused by increased suppressor T-cell activity (123).

Thus, despite the immune nature of hypersensitivity pneumonitis, skin testing to relevant antigens currently has little or no role in diagnosis or management. These tests lack in both specificity and sensitivity.

Inhalation Challenge

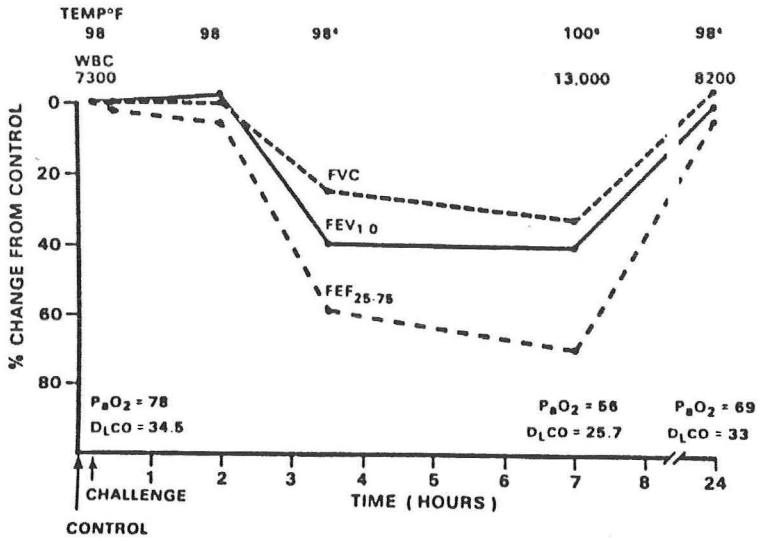
Williams' early work from the Brompton Hospital with patients suffering from farmer's lung successfully reproduced the acute symptoms and findings of hypersensitivity pneumonitis using inhalation challenge. Aerosols were prepared from crude moldy hay dust, from extracts prepared from moldy hay, and from extracts of fungi isolated from moldy hay. In each case, the disease was reproduced in farmers with prior evidence of disease. Challenge with extracts from "good hay" in farmer's lung patients or with extracts from moldy hay given to normal subjects failed to produce the disease (160).

Inhalation Challenge in Farmer's Lung

Subject	Type of Aerosol	Response
Farmer's Lung Patient	Moldy hay dust	+
	Moldy hay soluble extracts	+
	Moldy hay fungal* extracts	+
	"Good" hay extracts	-
Control	Moldy hay extracts	-

From Williams, 1963
*Later identified as thermophilic actinomycetes

Inhalation challenge tests have typically been performed by administering mixtures of antigenic material via aerosol. Unlike bronchoprovocation tests with asthmatic subjects, there is no immediate symptomatic or pulmonary function change. Four to six hours later, however, subjects with positive responses feel ill, complain of dyspnea, fatigue, and chills; temperature elevation and rales are noted on exam. Pulmonary function concommitantly displays a significant fall in vital capacity and diffusion capacity. These changes resolve over the ensuing 12 to 18 hours (45,46,51).



Typical hypersensitivity pneumonitis response to inhalation challenge. (Fink, 1984).

The materials used for these tests are generally prepared by either creating a dust from the suspected material or by extracting a mixture of antigenic substances through a variety of chemical procedures. In any case, the inhalational agents are invariably mixtures of materials and frequently contain non-specific irritants. There is no readily available commerical source of standardized, purified, specific antigen for use in inhalation challenge for any of the syndromes of hypersensitivity pneumonitis. Furthermore, there is no standardized method for administering the test or reliable dose/response data. Susceptible patients may become quite ill after the test; significant hypoxia is not uncommon (140,160). Understandably, many patients are reluctant to submit themselves to such an experience. Because of the delayed onset of findings, and the need for repeated spirometry and/or diffusion capacity testing, the test is also time consuming (140).

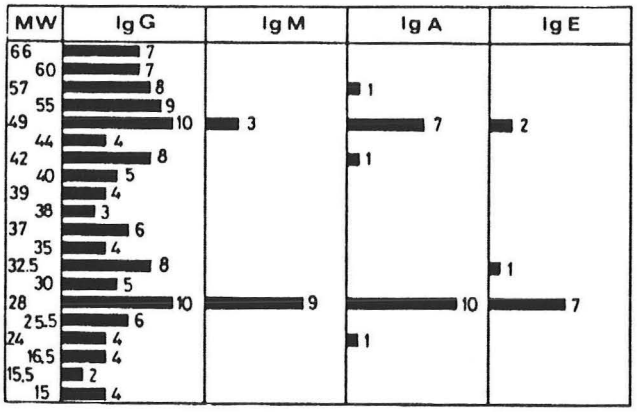
Fortunately, the diagnosis of hypersensitivity pneumonitis rarely requires such measures. In non-research settings, it would be difficult to recommend such testing for any purpose. Nonetheless the occasional circumstance may arise where the patient requires convincing evidence of the specific cause of their illness before accepting treatment advice (the economic and social consequences of leaving the farm, for example, may be devastating for some farmers). When inhalation challenge has been deemed clinically necessary, some have recommended attempting to perform the test by exposing the patient to the natural environment (e.g. working in the hay barn or pigeon loft) while noting symptoms, exam and measuring vital capacity serially. Unfortunately, however, those most likely to be skeptical of the suggested diagnosis are those with chronic forms of the illness; these patients may not demonstrate an acute response in the natural setting unless they are exposed to an exceptionally large challenge. Thus, the clinical utility of inhalation challenge in these patients is marginal at best.

Hypersensitivity pneumonitis is one of several conditions other than asthma which has been associated with non-specific airway reactivity to bronchoprovocation. Monkare reported that 22% of patients with

hypersensitivity pneumonitis displayed bronchial hyper-reactivity to histamine challenge (88,89). However, this was seen almost exclusively in those studied during or shortly after an acute attack; only 4% of the total group had bronchial hyper-responsiveness at follow-up.

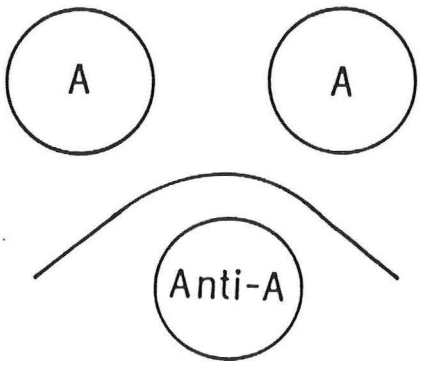
Serum Precipitins

Pepys was one of the earliest investigators to report the presence of antibodies in the serum of patients with farmer's lung disease which would form visible precipitation reactions in agar diffusion with antigens obtained from moldy hay or thermophilic actinomycetes (102,103). Subsequently precipitating antibodies have been described in a variety of other forms of hypersensitivity pneumonitis using antigen extractions from relevant organic material (see Appendix).



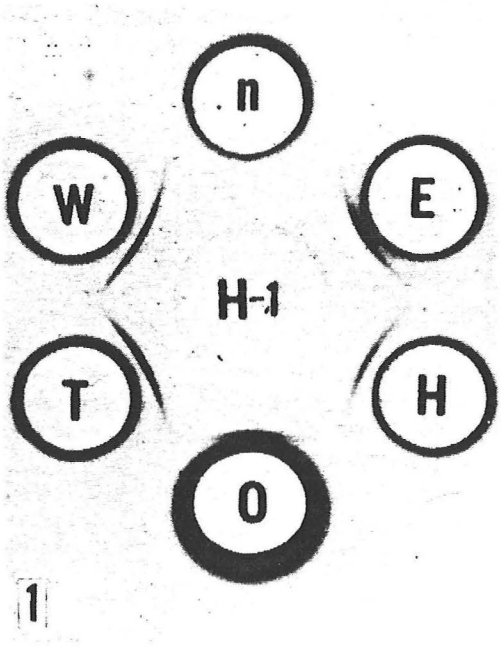
Distribution of immunoglobulins by class and molecular weight in ten patients reacting with M. faeni. (Aznar, 1988).

Patients with hypersensitivity pneumonitis frequently have increased total serum globulin proteins, as well as quantitative elevations in specific classes of immunoglobulins: especially IgG, and to a lesser extent IgM and IgA (7). When these antibodies are mixed in solution with specific antigen in optimal proportions, the antigen-antibody complexes will precipitate. When this is done in an agar suspension, then a visible precipitin band is formed in the zone of equivalence.



Line of precipitation in agar diffusion between wells containing antigen (A) and serum with specific antibodies (Anti-A).

The agar double diffusion technique of Ouchterlony has been used extensively in detection of such serum precipitins in patients with hypersensitivity pneumonitis and has aided in the determination of which organic agents are responsible for the various hypersensitivity pneumonitis syndromes (8,65,74,102,103,148,158). Precipitating antibodies can be detected by a variety of other techniques (4,7,52,85,104) including the micro-Ouchterlony method, immunoelectrophoresis, and immunoenzyme techniques (ELISA and ELIEDA). In general these techniques are more sensitive than standard immunodiffusion, but all tend to be non-specific with respect to identifying patients with disease. The principle shortcomings of these tests rests with: 1) the antigens employed, 2) the prevalence of non-relevant preciptins in the general population, and 3) the prevalence of relevant precipitins in asymptomatic, but exposed individuals. Furthermore, recent work has also called into question the pathogenetic importance of these antibodies.



Agar diffusion precipitation with moldy hay antigens (H-1) and serum from normals (n) and farmer's lung patients (E,H,O,T,W). (Kobayashi, 1963).

Antigens are considered relevant to the pathogenesis of specific syndromes if the antigen can be extracted from the dust source and if challenge with the antigen reproduces disease; precipitating antibodies to the antigen are usually present in the serum of affected patients. Early work employed antigens which were extracted in a variety of ways from such material as moldy hay, broth cultures of fungi or bacteria from suspected material (74,102,160), or animal products including droppings, urine, serum, feathers, and fur (109). Extracts have even been prepared from whole organisms such as wheat weevils (54) or amebae (40). Claims for greater sensitivity and

specificity for the presence of disease have been made when modifications of the extraction process are made, e.g. using trichloroacetic acid (TCA) rather than carbol extraction (119). However, although the methods available for separation of these antigens have become more sophisticated, all of the currently available antigen preparations are in fact mixtures of antigens. To date, in no instance has a single, specific antigen been described which is responsible for a particular hypersensitivity pneumonitis syndrome.

Despite these technical problems, precipitins have been identified in a substantial proportion of patients with a clinical diagnosis of hypersensitivity pneumonitis. The majority of patients with acute forms of disease such as farmer's lung or pigeon breeder's lung have precipitating antibodies in their serum to relevant antigens. Antibodies persist for at least one year in the majority and for as long as three years in many even when exposure to antigen ceases (30,32). In such cases, it is not uncommon to find persistent antibody reactions despite the total absence of clinical features of disease (79).

False negative cases clearly occur (39). This is due in part to methodological differences or to the inability to define the relevant antigen(s). The exact incidence of false-negative reactions is difficult, if not impossible to determine due to differences from one syndrome to another and as some authors have tended to define disease in terms of precipitin reactions.

Of greater importance than the clinical sensitivity of these tests is the lack of specificity. Amongst asymptomatic farmers the incidence of positive serum precipitins to thermophilic actinomycetes varies: 8% in Quebec (32), 9% in Wisconsin (119), and 22% in Finland (148). For asymptomatic pigeon breeders, antibodies to pigeon serum may be detected in as many as 51% (85). In an industrial outbreak of ventilation hypersensitivity pneumonitis, 12% of employees in the involved building who had no evidence of chest disease had positive precipitin reactions (161). Wisconsin state employees had an incidence of 5.3% positive reactions to a battery of "hypersensitivity pneumonitis antigens" and 10% of unselected patients in one hospital had precipitins (26).

The prevalence of positive tests in asymptomatic individuals also fluctuates over time, with subjects testing either positive or negative at different times (30). In patients with clinical disease, furthermore, the quantitative level of antibody correlates poorly, if at all, with disease activity. In part this variability may be dependent upon the nature and intensity of exposure. Individual host variables also appear to have some influence; cigarette smoking decreases the presence of precipitins (4,8).

Thus, the presence of precipitating antibodies is not diagnostic of hypersensitivity pneumonitis, and the absence of antibodies does not exclude the diagnosis. Serum precipitins should best be viewed as correlating with antigen exposure, rather than with disease. Nonetheless, testing for antibody may be useful for confirmatory purposes or when hypersensitivity pneumonitis is suspected based on clinical data but the exposure history is not strong. Commercial kits using the micro-Ouchterlony immunodiffusion technique are available (see Appendix) with antigen mixtures relevant to hypersensitivity pneumonitis syndromes such as farmer's lung, pigeon breeder's lung (but not other bird species), ventilation hypersensitivity pneumonitis, and bagassosis (Greer Laboratories, Lenoir, NC). Testing for precipitating antibodies using a "hypersensitivity pneumonitis battery" for screening purposes or in the absence of clinical evidence of disease is clearly not justifiable.

Diagnosis

The diagnosis of hypersensitivity pneumonitis is based predominantly upon clinical information; laboratory and pathologic material serve primarily to add support to the diagnosis and/or exclude other diseases. Diagnosis requires: 1) characteristic symptoms, signs, radiographic findings and pulmonary function data, 2) evidence of exposure to a relevant antigen with plausible temporal relationship to the clinical findings, and 3) exclusion of other related illnesses.

The clinical findings typical of hypersensitivity pneumonitis have been described; however, these features are not sufficiently specific to render a firm diagnosis. Thus, the most important aspect of diagnosis is the establishment of antigen exposure. A high index of suspicion is crucial and the diagnosis should be considered in any patient who presents with interstitial lung disease or recurrent respiratory problems, especially with a history of recurrent "pneumonia".

The exposure is best established through a careful history; it is on this point where the majority of cases are either missed or made inappropriately. Just as Sherlock Holmes chided his friend Dr. Watson, physicians and patients are both apt to overlook the significant exposure and its relationship to disease because all too often we "see, but do not observe" (Sir Arthur Conan Doyle). The physician must take care to explore the patient's occupational history in a systematic fashion, e.g. inquiring about each and every job from earliest employment to the present. It is clearly not sufficient to inquire about current occupation and whether the patient is aware of exposure to any "toxins or dusts".

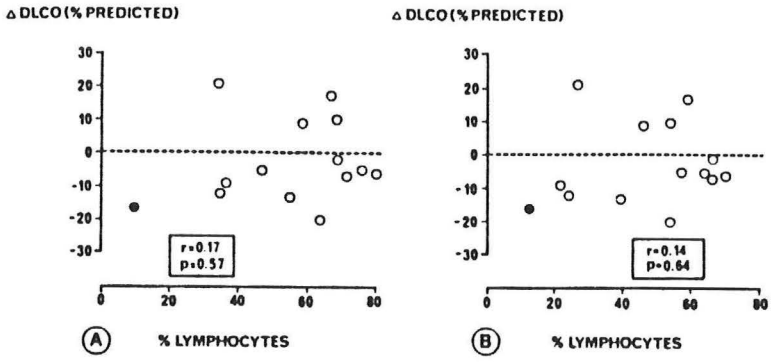
Indeed, one of the commonest pitfalls stems from the inability of patients to accept the exposure as being relevant to the disease, even after it has been pointed out. This is not surprising since in many cases exposure had been present for many years prior to onset of symptoms. The latency between exposure and symptoms in acute cases and the fact that most co-workers and family members remain well despite similar exposures will also entice the patient into neglecting or minimizing the significance of the exposure.

The environmental history must also explore exposures to pets and other domestic animals which may not be directly used in the patient's primary vocation. It is not uncommon for individuals with non-agrarian jobs to live in rural areas and keep a small number of animals or fowl. Hobbies and recreational activities are important as well. Furthermore, certain tasks may entail significant exposure but not be considered either a "job" or a "hobby"; gardening and lawn care for example are likely to be viewed as a routine "chore".

Thus, a careful environmental history is the cornerstone of diagnosis for hypersensitivity pneumonitis. Serum precipitin determination to relevant antigens may serve to confirm the history. Because of the numerous limitations of the measurement and interpretation of precipitating antibodies as detailed earlier, these tests should not be relied upon to supplant the history.

Pathologic diagnosis is rarely required to make the diagnosis. Indeed, the findings are not pathognomonic, but are at best consistent with the diagnosis. The importance of histologic sampling is primarily to exclude other potential diagnoses. In this regard, bronchoscopy will usually be sufficient (154) when tissue sampling is felt to be indicated; however, it is not required in most cases. Where sufficient diagnostic uncertainty exists, open lung biopsy is preferable given the propensity of hypersensitivity pneumonitis to affect primarily the alveoli and terminal bronchioles.

As with other interstitial lung diseases such as sarcoidosis and idiopathic pulmonary fibrosis, bronchoalveolar lavage (BAL) has been employed in the evaluation of patients with hypersensitivity pneumonitis. When it is performed, BAL will show an increase in the percentage of lymphocytes (112). These lymphocytes are usually T-cells (78). Although these studies have been very helpful in furthering our understanding of the pathogenesis of this disease, the use of bronchoalveolar lavage for clinical purposes has not proven to be beneficial despite early claims. BAL lymphocytosis is not specific or pathgnomonic for hypersensitivity pneumonitis. Testing for T-cell subsets is somewhat more discriminating (72,73,136,137,138), but seems excessive in comparison to standard diagnostic measures. Most importantly, BAL findings in hypersensitivity pneumonitis do not distinguish disease from exposure (33,34) and do not correlate with disease activity or serve as prognostic indicators (34). Gallium scanning has also been touted for use in this disease (155), but would appear to be no better than standard measures such as the history, exam, radiographs, and pulmonary function.



Lack of correlation between % lymphocytes in BAL and DLCO two years apart.
(Cormier, 1987).

Differential Diagnosis

Granulomatous Infections

An important group of diseases which resemble hypersensitivity pneumonitis must be excluded before the diagnosis is established. Infectious agents causing granulomatous disease are important in this regard. Thus, skin testing and exam of sputum or histology for mycobacterial or invasive fungal agents is important.

Atypical Pneumonia

The symptoms and findings of acute hypersensitivity pneumonitis are very similar to those of the so-called "atypical" pneumonias, such as those due to viral or mycoplasmal agents (27). With a single episode, an infectious etiology would likely be considered; the apparent response to antibiotics would tend to reinforce this conclusion. However, a history of having had recurrent "pneumonia" should be a stimulus to explore the environmental history carefully.

Asthma

Episodes of asthma are frequently precipitated by exposure to organic dusts, especially in those with so-called "extrinsic asthma". Asthmatic exacerbations typically begin immediately or shortly after the exposure. The presence of wheezing, absence of rales, laboratory findings, radiographic changes, and obstructive pulmonary function pattern with normal diffusing capacity should easily distinguish asthma from hypersensitivity pneumonitis. Elevated serum IgE, eosinophilia, and a history of atopy are commonly present with asthma, but not with hypersensitivity pneumonitis.

Many of the dusts or antigens which have been reported to cause hypersensitivity pneumonitis may also cause or trigger asthma. Organic dusts and chemicals are clearly an important cause of occupational asthma. Examples of these include: isocyanates (24,162), animal dander and excreeta (23,105), grain handlers, woodworkers (61,99), and washing powder disease (96).

Sarcoidosis

In the chronic form of hypersensitivity pneumonitis the presence of interstitial lung changes, restrictive pulmonary function, decreased diffusing capacity, and findings of non-caseating granulomas would clearly also be compatible with sarcoidosis. Episodic worsening or the establishment of a clear exposure would tend to favor hypersensitivity pneumonitis. The presence of hilar or mediastinal adenopathy would suggest sarcoid; but its absence does not exclude the diagnosis. The most important clues to the diagnosis of sarcoidosis are those which suggest extrapulmonary disease. The serum angiotension converting enzyme (ACE) may be elevated in a number of granulomatous diseases, including both sarcoidosis and hypersensitivity pneumonitis (139).

Other Interstitial Diseases

In its fibrotic late stages, hypersensitivity pneumonitis may be indistinguishable from a variety of other diseases. Idiopathic pulmonary fibrosis is by definition a diagnosis of exclusion and would not be associated with granulomatous pathology. The diagnosis of most pneumoconiosis syndromes due to inhalation of inorganic dusts are established by the environmental history. Collagen vascular diseases are established based upon the non-pulmonary manifestations of the individual syndromes. Rheumatoid factor can be found in patients with hypersensitivity pneumonitis (150); anti-nuclear antibodies are not.

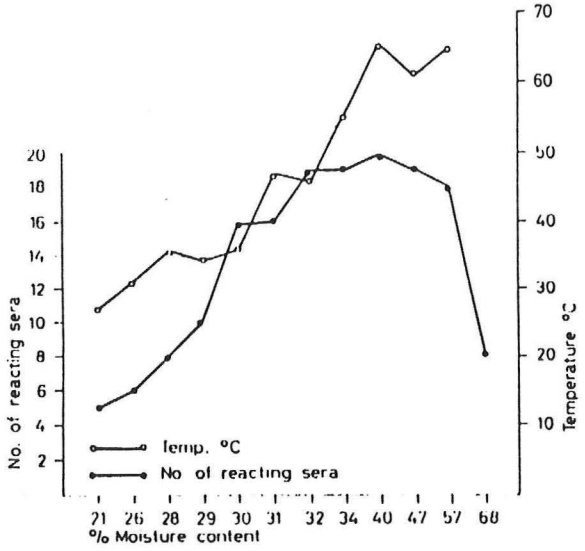
Syndromes of Hypersensitivity Pneumonitis

Farmer's Lung

Farmer's lung disease was the first hypersensitivity pneumonitis syndrome to be described (22); it is also the best understood and commonest of these disorders. The exact incidence and prevalence of this disease varies over time and geography; the most comprehensive estimates come from Finland where it is estimated that 2% of farmers engaged in raising livestock are afflicted with the disease (147,148).

The disease is caused by the inhalation of spores from thermophilic actinomycetes which proliferate in moldy hay. If hay is put up or stored while it is wet from rain occurring at the time of mowing, it will warm through spontaneous fermentation. The combination of high temperature and moisture a well as the concommitant changes in acidity favor the growth of these thermophilic organisms. Minimal numbers of organisms are found in the

outside air of the farm and modest numbers are present in the air of undisturbed barns where hay is stored. However, when the hay is subsequently broken up for use in feeding livestock, large numbers of spores and antigenic particles are contained in the ensuing dust (55). These spores have an average diameter of 0.5 to 1.0 m; this is ideal for deposition of particles to the lower airways of the lung where the hypersensitivity reaction occurs.



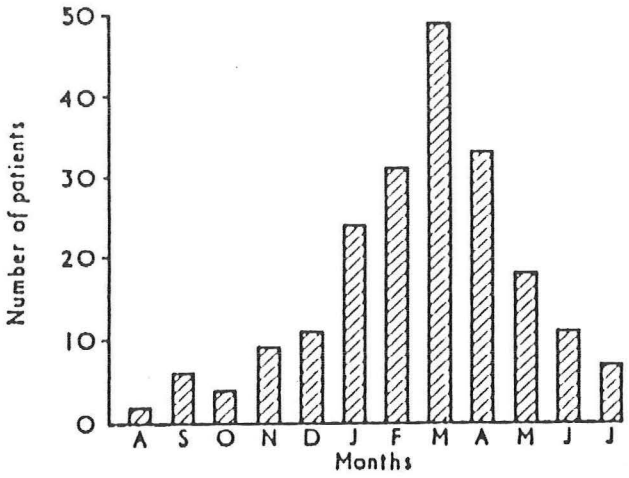
Relationship between moisture content, number of reacting sera, and temperature achieved in hay allowed to self-heat. (Pepys, 1969).

Thus, mowing or baling hay is not likely to produce disease. Disease is also not likely to occur unless the hay was put up wet and stored for a period of time prior to use. Activities which produce large quantities of dust, such as mechanical conveyances in dairy barns, produce favorable conditions for exposure if the farmer is present during distribution of hay in an enclosed area. Important preventative measures begin with alterations in farming techniques to minimize the development of mold, dust, or both (63).

Ambient Mold Density in Cowbarns

Outside Air	Inside, Undisturbed	After Bringing in Hay
13	133	926

Mean values for number of colonies/sample. (Fuller, 1953).



Monthly incidence of farmer's lung in Wales. (Hapke, 1968).

Not surprisingly, farmer's lung shows both seasonal and geographic variation in incidence. The disease is most common in late winter when stored hay is used to feed cattle (55). It is especially common in years with excessive rainfall in late spring or summer when the hay is mowed and baled. Farmer's lung occurs most commonly in regions with both heavy rainfall and harsh winter conditions. Thus, the disease has been observed with some regularity in Great Britain (22,55), northern Europe (148), Canada (32), and in the northern regions of the midwestern United States (36,41).

The antigenic material responsible for farmer's lung disease comes from a group of organisms which are true bacteria, but which have fungal morphology; they grow best in the conditions provided by molding hay but can be isolated from numerous other sources in nature. These organisms are collectively referred to as thermophilic actinomycetes. Commonly implicated species include: Micropolyspora faeni, Thermoactinomyces vulgaris, Thermomonospora viridis, and Thermoactinomyces candidus. Several species of aspergillus have also been implicated, including a variety of strains of A. fumigatus and A. umbrosus.

Bird-Breeder's Lung

Plessner first described hypersensitivity pneumonitis in the French literature in 1960; disease occurred in workers engaged in breeding ducks and geese for their feathers (107). Since then, the same disease has been most commonly found in those who raise pigeons for sport and racing (110). The disease has also been recognized with exposure to turkeys (turkey handler's lung), chickens, parakeets (budgerigar breeder's) (101), doves (126), and other species. The group of diseases is frequently referred to collectively as bird-breeder's (USA) or bird-fancier's (Britain) lung disease.

Because the exposure in bird breeders tends to occur more continuously than with the seasonal variations of farmer's lung, it is more common to encounter the chronic form of disease without acute episodes (50). Also, this is thought to explain the higher incidence of serum precipitins in bird-breeder's (30%) than in farmers (8-10%) who are asymptomatic (32,85,119,148).

Unlike the responsible agents with farmer's lung, the antigens with this group of diseases are avian proteins rather than microbiologic products of decomposing material. Relevant antigens have been found in feathers and down (19), but the commonest are relatively non-degradable serum proteins which are excreeted in urine and feces. Bird serum and egg white proteins have served as good sources of antigen. Currently the only readily available commercial antigens are from pigeon serum (see Appendix).

As with other forms of hypersensitivity pneumonitis, the usual therapeutic recommendation is avoidance of antigens. Interestingly, although most individuals with disease raise birds as pets or for hobby, bird-breeders are frequently extremely reluctant to give up their birds; Fink reported that not one of 12 patients described in a series reported in 1968 gave up exposure to their pigeons despite frequent symptoms (51).

Ventilation Hypersensitivity Pneumonitis

More recently hypersensitivity pneumonitis has been described in a variety of settings which result from antigenic exposure to organic material in contaminated ventilation systems (3,9,40,44,48,49,62,66,120,161). The syndrome has occurred in homes (40) and in industrial settings (161). Air conditioners (91), forced air systems (48,49), water-tower humidifiers (161), and cool-mist vaporizers (62) have all been implicated.

The disease should be suspected when it occurs in clusters of co-workers or multiple family members. Subsidence of symptoms on weekends and during vacations are useful clues as are exacerbations occurring at the end or shortly after the work day. In most cases the problem can be eliminated through disinfection, cleaning, and/or modification of the ventilation system.

The antigens responsible for these disorders are extremely varied. Causative agents include: thermophilic actinomycetes such as T. vulgaris, T. candidus, and strains resembling M. faeni; fungi such as Aspergillus fumigatus, Aurobasidium pullulans, and Penicillium sp.; and protozoa such as the amoeba Naegleria gruberi.

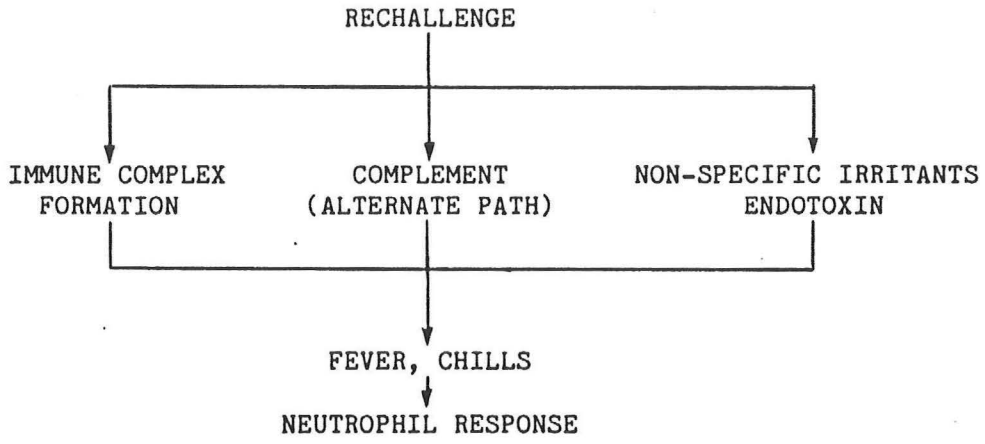
Pathogenesis

It is quite clear that hypersensitivity pneumonitis is not a manifestation of immediate-type hypersensitivity for the symptoms, clinical findings, and time course are not compatible. Furthermore, serum levels of IgE are not elevated, eosinophilia is not common, and other atopic findings are not characteristic (45,118,125,140).

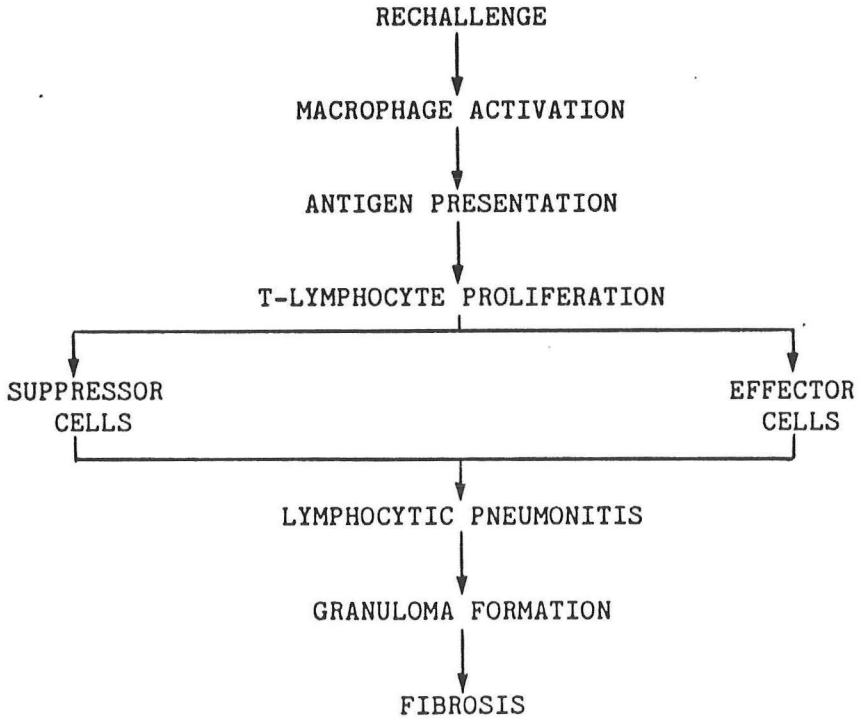
Early speculation that hypersensitivity pneumonitis was caused by mycotic infection of the lung (142) or by irritant factors in the inhaled dusts (14) gave way to the recognition of the immune nature of the disease. This was sparked by the observations of serum precipitating antibodies to inhaled antigens in affected patients. This when coupled with the usual onset of symptoms at 4 to 6 hours after exposure suggested that the disease was the direct result of antigen-antibody immune-complex disease ("serum sickness of the lung").

Although this theory was accepted for many years, several important observations tend to minimize the significance of precipitating antibody in the pathogenesis of hypersensitivity pneumonitis. As discussed earlier, antibody levels are present in many exposed individuals with no evidence of disease and quantitative levels of these antibodies correlate poorly, if at all, with disease activity. The pathologic findings rarely, if ever, show the typical vasulitic findings of immune-complex disease (118). Animal models which would favor immune-complex disease have resulted in pathophysiologic

EARLY RESPONSES



LATER RESPONSES



changes which do not resemble natural hypersensitivity pneumonitis; the lesions produced are those of acute edema and hemorrhagic pneumonitis (81).

Compliment activation via the classical pathway also does not appear to play an important role. Compliment levels in serum do not fall during the course of acute stages of the disease or in response to inhalational challenge (123). However, there is evidence that complement activation may occur through the alternate pathway (39,143). This could be produced by non-specific effects of antigen or other irritants in inhaled dusts. The earliest alveolar changes as assessed by bronchoalveolar lavage are those of a transient influx of neutrophils (53,124). It has therefore been suggested that the early symptoms and findings may in fact result from antigen-antibody formation (36), activation of the alternate complement pathway, and/or non-specific irritation or endotoxin effects (123).

The more typical pathologic findings of lymphoid pneumonitis and granuloma formation of course suggest an important role for cellular immunity in the development of hypersensitivity pneumonitis. Lymphocytosis from bronchoalveolar lavage of hypersensitivity pneumonitis patients (112) and the presence of lymphokines such as migration inhibition factor and blastogenic factor in the lavage fluid (125) are further evidence favoring cellular immune responses. Activated alveolar macrophages are also found in histologic or lavage specimens; it has been suggested that macrophage activation and antigen presentation may in fact be the sentinel steps in the progression of subsequent lymphocyte responses (123). Phenotypic and functional analysis of lymphocytes recovered in lavage has shown the predominant cells to be T-cells, especially suppressor and cytotoxic lymphocytes (78, 135-138).

The most convincing data supporting the cellular nature of the immune response has come from animal models of hypersensitivity pneumonitis. Lymphoid cells passively transferred from sensitized rabbits to non-exposed, non-sensitized animals produces disease which closely resembles human hypersensitivity pneumonitis when the animals are subsequently given inhalation challenge (13). Passive transfer of serum containing antibody alone from sensitized animals on the other hand does not lead to disease following challenge (13). Similar findings have been reported using passive transfer of T-cells which have been activated in vitro with either mitogen or specific antigen (132).

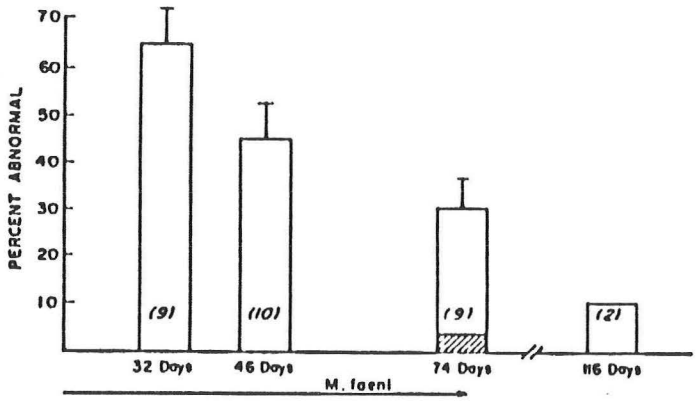
Passive Transfer from Sensitized to Naive Animals Followed by Respiratory Challenge

Transfer Experiment	Response
Lymphocytes + Challenge	Pneumonitis
Serum + Challenge	None
Lymphocytes Only	None
Challenge Only	None

After Bice, 1976

Hypersensitivity pneumonitis can progress to pulmonary fibrosis and severe impairment, but typically progression is only mild to moderate in severity (see below). Indeed, many patients continue to raise their birds or live and work on their farms despite warnings to the contrary and apparently do not suffer severe consequences. Bronchoalveolar lavage in patients with hypersensitivity pneumonitis may continue to show lymphocytosis in the later stages of recovery or during continued exposure in the absence of clinical findings or symptoms of disease (33-35). These observations suggest that repeated or continued exposure may lead to a modulation of disease activity.

Animal models can consistently produce granulomatous disease characteristic of hypersensitivity pneumonitis, but during chronic antigenic exposure the pathophysiological response becomes blunted and fails to produce chronic interstitial disease (115,129,130). Chronic disease may be prevented by specific desensitization in some circumstances (14). Nonetheless, this demodulation of the immune response is not due to the development of immune tolerance as effector lymphocytes retain their responsiveness (131).

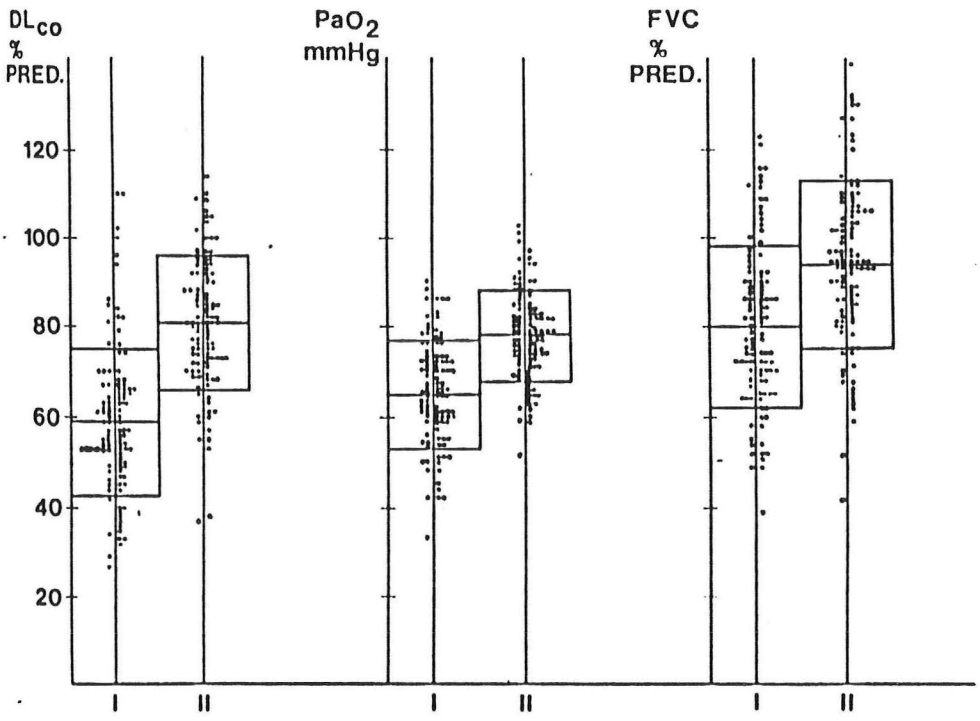


Extent of histologic abnormalities after repeated exposure to M. faeni antigen. (Schuyler, 1983).

Observations from the bronchoalveolar lavage of pigeon-breeders have shown important differences in the functional and phenotypic characteristics of the cell subpopulations; asymptomatic breeders appear to have enhanced cellular suppressor activity for T-cells and macrophages relative to pigeon-breeders with disease (72,73). The factors which influence this balance between suppressor and effector activity are not known, but would clearly be important to elucidate both for our understanding and potential management of this disease as well as perhaps for other immunologically regulated conditions.

Course and Prognosis

As noted earlier in this discussion, the acute symptoms of fever and cough have generally abated within 2 to 3 days. Fatigue, general lassitude, and especially exertional dyspnea may persist for several weeks. Pulmonary function abnormalities including diffusing capacity and vital capacity improve rapidly from days 2 through 10. Beyond the tenth day the remaining deficits are mild, if present at all, in the majority of patients. Thus, single acute episodes are self-limiting. This is probably because the acute nature of the attack causes the patient to spontaneously avoid the antigen or because hospitalization removes the patient from the usual environment.



Pulmonary function at initial (I) and 18 month (II) evaluations in 107 farmer's lung patients (Monkare, 1984).

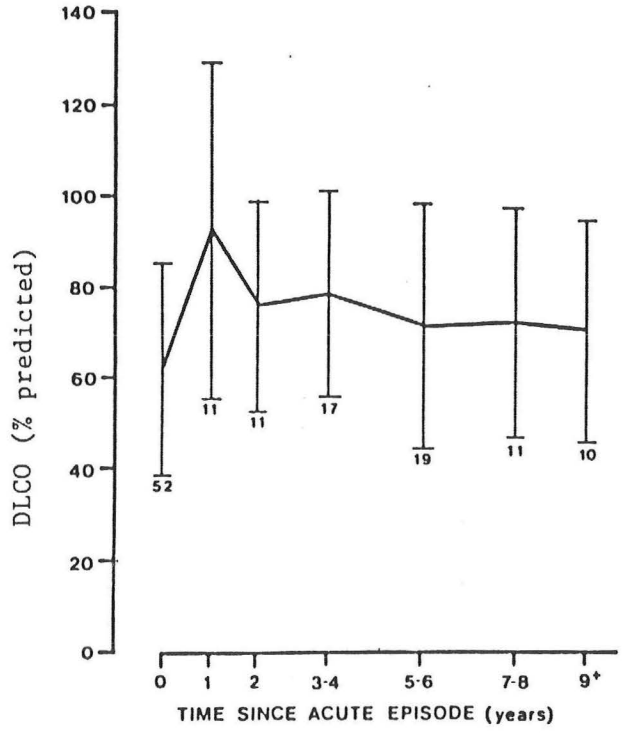
The overall prognosis for hypersensitivity pneumonitis is excellent. At the time of initial presentation with acute symptoms the mean vital capacity has been reported to be 80±18% predicted in one large series (89). The diffusion capacity is more sensitive, but mean values are 58±17% predicted (89) to 62±29% predicted (31) even in the acute stage. Indeed, less than 10 percent of patients have initial vital capacities of below 50% predicted and less than 30 percent have initial DLCO values which would be considered severe (59,89). Death or respiratory failure from acute episodes is exceedingly rare, though case reports exist (25,57,58,117,142).

Despite the generally excellent prognosis of single episodes of hypersensitivity pneumonitis, patients with repeated episodes may be at risk for progressive impairment or continued symptoms. Early reports had suggested

that the long-term mortality for patients with chronic disease was 17% (41), though more recent studies suggest the mortality is more in the range of 3 to 9% (17). A recent study in which pigeon breeders were followed for 18 years showed that the pulmonary function of those who remained symptomatic declined at an average rate four times greater than expected (128). Factors which seem to adversely affect prognosis include repeated episodes (17,59) and the presence of obstructive spirometry (10). Nonetheless, no single clinical parameter or combination of findings has sufficient predictive value to be useful in individual patients.

In several series reporting long-term followup, persistence of symptoms is common; the incidence varies from 30% (10) to 100% (17): this is likely due in part to selection bias as asymptomatic subjects would be unlikely to seek medical attention or continue long-term studies. Importantly, of those who report symptoms, they are generally mild in severity; only 11% of patients followed for 15 years reported severe, limiting symptoms (17). The incidence also varies with time, being less common over extended periods (10,88,89).

Pulmonary function abnormalities tend to be mild in the majority of patients, even those with symptoms. At six years only 16% have diffusion capacities of less than 50% predicted (10), while by 15 years only about 5% have values less than 50% of predicted (17). Indeed, while Schmidt et al demonstrated a four-fold rate of decline in pulmonary function for symptomatic individuals, at the end of 18 years all had values which were considered to be in the normal range (128); this is particularly striking since the predicted equations used are those most likely to detect abnormality in a patient population (Crapo et al, from Salt Lake City population).



Diffusion capacity over time.
(Cormier, 1985).

An important observation which likely attests to the benign nature of this illness is the frequent observation that most subjects do not give up continued exposure to antigen despite warnings to do so whether the exposure occurs in an occupational (farmers) or recreational (bird-breeders) setting. This is further supported by experimental data and longitudinal research observations suggesting down-regulation of the immune response despite continued antigen exposure (see above).

In summary, recovery following a single episode of hypersensitivity pneumonitis should be expected to be spontaneous, prompt, and total. Death is rare and severe disability is unusual. When symptoms and/or pulmonary function abnormalities persist, they are relatively mild in severity. Nonetheless, a small sub-group of patients may progress to severe, disabling disease; this group is best identified by continued deterioration in objective findings during follow-up.

Treatment

Antigen Avoidance

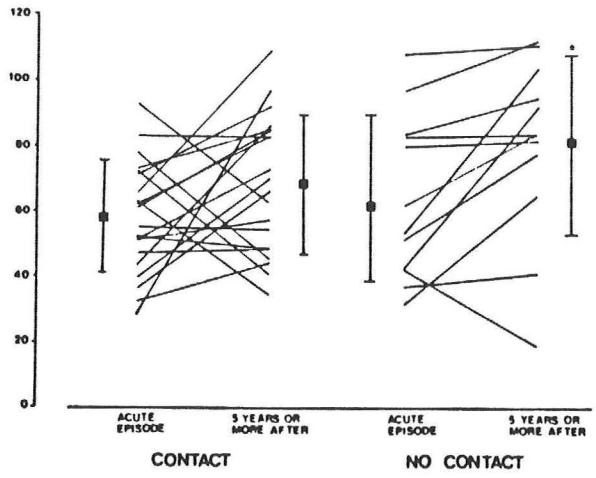
Given our understanding of the immune nature of the pathogenesis of hypersensitivity pneumonitis, the most obvious treatment would be complete avoidance of further antigen exposure. In some instances this is a simple and straight-forward matter, and is all that is required. However, the physician's advice to completely abstain from further exposure to the offending agents is frequently not followed. Within a short period of time many farmers return to their farms and usual activities (41). During long-term followup it has been reported that 50 to 60% of farmers who had episodes of hypersensitivity pneumonitis remained on the farm at 5 to 6 years (10,31); by 15 years as many at 70% remain or have returned to the farm (17). Pigeon-breeders appear to be particularly reluctant to give up their birds; Fink reported that not one of 12 symptomatic breeders gave up the sport spontaneously (50) and Bourke that 75% continued to raise pigeons at 10 years of followup (16).

Patient Acceptance of Antigen Avoidance Advice

Patient Population	Continued Exposure following Acute Episode
Farmer's Lung	50-70%
Pigeon-breeders Lung	75-100%

There are a number of reasons that the complete avoidance recommendation is so seldom heeded. The economic disruption and social consequences to the middle-aged farmer with limited or no occupational alternatives can be devastating; opting to give up work altogether is frequently either unacceptable or not possible as most farmers, being self-employed, are not eligble for unemployment or disability compensation. The tendency for the disease process to remit spontaneously and the relatively mild nature of the symptoms and pulmonary function abnormalities are likely important reasons many choose to continue exposure, especially when the syndrome is chronic. The long duration of exposure prior to symptoms in many, the 4 to 6 hour latency between acute exposure and symptoms, and the fact that many co-workers or family members have identical exposures but remain asymptomatic will all contribute to the patient's tendency to be skeptical of the physician's advice.

With these considerations in mind, it would seem that a prudent approach with respect to complete avoidance would be as follows: Carefully explain the relationship between antigenic dust exposure and disease to the patient. Complete avoidance should be advised immediately following acute episodes and in most cases where removal of the offending antigen poses no major life-style adjustments by the patient. In other cases such advice should likely be preserved for the minority of patients who truly demonstrate progressive disease; this is best accomplished through a period of continued objective followup as suggested by Barbee (10).

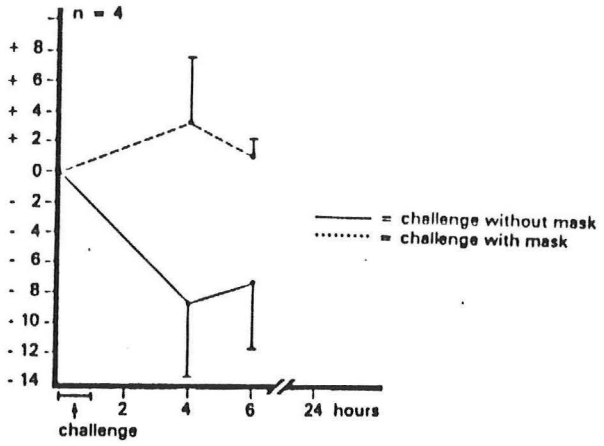


Diffusing capacity (% predicted) after 5 or more years in subjects with and without continued antigen contact. (Cormier, 1985).

When complete avoidance is not possible, a variety of environmental modifications designed to minimize exposure while allowing the patient to remain in the workplace have been suggested. With farmer's lung, for example, the simple expedient of not baling or storing hay when it is wet may be sufficient (55). Hay driers and mechanized devices for hay distribution from storage bins have been recommended (63), but are very expensive. Spraying hay with agents such as propionic acid to inhibit microbial growth has not been practical. In cases of ventilation hypersensitivity pneumonitis, the disease may be completely controlled by cleaning and disinfecting the system (9), but often requires replacing the contaminated portion of the ventilation system altogether (48,49,161). Installation of electrostatic dust filters may suffice in some home systems (66). Additional ventilation systems and electrostatic filters will not work in particularly dusty environments such as most barns (76,147).

The use of filtering masks has been shown to be effective in preventing single episodes of hypersensitivity pneumonitis (61,93,98). However, since the ideal particle size for alveolar deposition is from 1 to 5 μm and as most of the offending dusts have particle sizes less than 10 μm, these devices will work only when they are designed to effeciently remove 98% of particles 0.2 to 10.0 μm in size (61). To achieve this degree of efficiency most masks are either very bulky or have very high inspiratory resistance which make them unsuitable for work conditions requiring exertion. This resistance can be overcome by use of a powered air-flow type of mask, but this helmet-styled

device is cumbersome and expensive. Further, any of the effective masks tend to be hot and claustrophobic. Most individuals will not consistently use such masks. The long-term efficacy of filtering masks has not been tested.

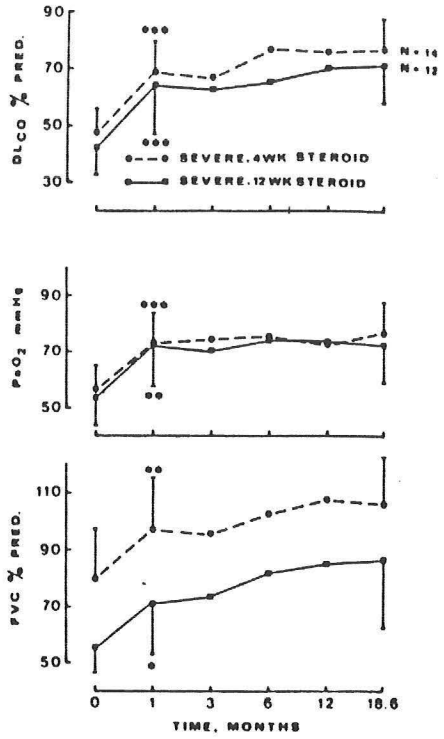


Protective effect of breathing mask as assessed by DLCO response to inhalation challenge. (Müller-Wening, 1989).

Corticosteroids

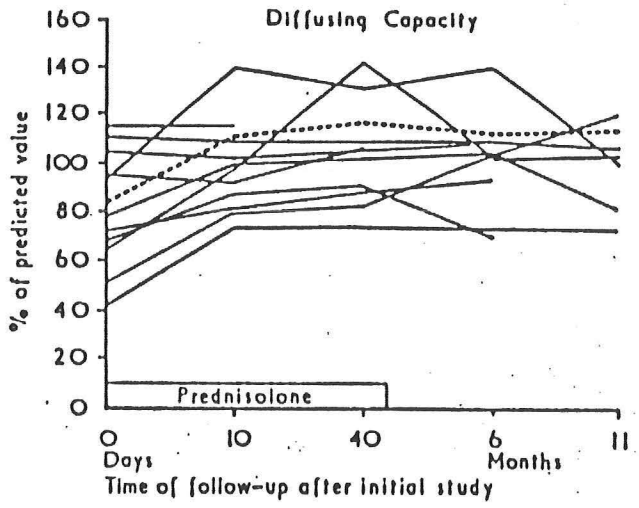
The early observation by Williams that pre-treatment of a farmer's lung patient with 40 mg of prednisone prevented symptoms ater inhalational challenge provided a basis for subsequent use of steroids in this disease (160). There are many anecdotal reports of benefit from steroids in acute attacks of hypersensitivity pneumonitis, but controlled studies are lacking. It is clear that the duration of beneficial effect, if any, is brief. Monkare showed that 4 weeks of therapy was no different from 12 weeks (88,89), and Hapke demonstrated no additional benefit beyond 10 days using 40 mg/day of prednisone (59). Indeed, given the relatively minor pulmonary function abnormalities and the usual prompt and spontaneous recovery experienced by the majority of patients, it is highly unlikely that a beneficial effect could be demonstrated in a controlled trial of acute steroid therapy. Thus, the routine use of steroids should be avoided. When the rare patient with severe disease, hypoxemia, or respiratory failure is encountered, then treatment with 40 mg/day of prednisone for a brief interval (2 to 10 days) followed by abrupt discontinuance may be of some benefit.

The only controlled trial of long-term steroid use in chronic disease failed to show any therapeutic benefit for the group as a whole, but the number of patients studied was small and the degree of impairment was minor (5). This in conjunction with the previous discussion of the natural course and prognosis of this disease suggests that steroids have a very limited role in hypersensitivity pneumonitis. In patients with chronic disease, steroids should be withheld from the majority; however, it would be difficult to adhere to this advice in all, as a small number may respond to a careful empiric trial. As in all cases of empiric use of steroids, it should only be done after clearly documenting progression of disease despite other measures, must



Effect of steroids given for 4 or 12 weeks on recovery of farmer's lung. (Monkare, 1984).

utilize therapeutic doses (40 to 60 mg/day prednisone), and requires careful objective followup for a sufficient period to determine the presence or lack of effect (4 to 8 weeks). If objective improvement is observed, then gradual tapering to minimum sustaining doses should follow; otherwise, the drug is rapidly tapered and stopped. Inhaled steroids have no effect (88,89).



Time course of DLCO for farmer's lung patients treated with corticosteroids. (Hapke, 1968).

Other Agents

Since hypersensitivity pneumonitis is not histamine or mast cell mediated, it is not surprising that cromolyn sodium is not effective (89). In fact, cromolyn has been reported to cause hypersensitivity pneumonitis on rare occasion (20). Bronchodilating agents have little or no effect unless there is superimposed airways disease.

APPENDIX: CAUSES OF HYPERSENSITIVITY PNEUMONITIS

	Syndrome	Exposure	Antigen(s)	Reference
Microbial	Farmer's Lung	Mouldy hay	Thermophilic actinomycetes *Aspergillus sp.*	Campbell, 1932 (22)
	Thresher's Lung	Mouldy grains	Thermophilic actinomycetes	Tornell, 1946 (152)
	Bagassosis	Bagasse (sugar cane)	*Thermoactinomyces sacchari*	Hunter, 1946 (64)
	Paprika Splitter's Lung	Paprika pods	*Mucor stolonifer*	Murray, 1957 (94)
	Mushroom-Worker's Lung	Compost	Thermophilic actinomycetes	Bringhurst, 1959 (18)
	Maple Bark Stripper's	Maple tree bark	*Cryptostroma corticale*	Emanuel, 1966 (42)
	Lycoperdonosis	Puff balls	Lyciderdon	Strand, 1967 (145)
	Sequoiosis	Redwood sawdust	*Aureobasidium pullulans*	Cohen, 1967 (28)
	Maltworker's Lung	Malt	*Aspergillus clavatus*	Riddle, 1968 (116)
	Suberosis	Cork tree bark	*Penicillium frequentans*	Avila, 1968 (6)
	Cheesewasher's Lung	Cheese	*Penicillium casei*	DeWeck, 1969 (37)
	Air Conditioning Lung	A/C systems	Thermophilic actimomycetes *Aspergillus sp*	Banaszak, 1970 (9)
	Washing Powder Lung	Detergent	*B. subtilis* enzymes	Newhouse, 1970 (96)
	Dog House Disease	Mouldy straw/dog's bed	*Aspergillus versicolor*	Rhudy, 1971 (113)
	Wood Pulp Worker's Disease	Paper mill workers	*Alternaria sp*	Schlueter, 1972 (127)
	Humidifier Lung	Cool mist humidifier	*Aureobasidium pullulans* Protozoal proteins	Hodges, 1974 (62)
	Dry Rot Lung	Wall dry rot in a home	*Merulius lacrymans*	O'Brien, 1978 (99)
	B. Subtilis Alveolitis	Decaying wood	*B. subtilis* proteins	Johnson, 1980 (68)

	Syndrome	Exposure	Antigen(s)	Reference
	Cheese Worker's H/P	Cheese	Penicillum roqueforti	Campbell, 1983 (21)
	Hot Tub H/P	Hot tub mists	Cladosporium sp	Jacobs, 1986 (67)
Animal	Budgerigar Breeder's	Parakeets	Bird dander	Pearsall, 1960 (101)
	Bird Breeder's Lung	Duck, goose, chicken	Feathers	Plessner, 1960 (107)
	Wheat Weevil Disease	Grain mill workers	Sitophilus granarius	Frankland, 1965 (54)
	Pigeon-Breeder's Lung	Pigeons	Feather, droppings, sera	Reed, 1965 (110)
	Pituitary Snuff Taker's	Pituitary extracts	Ox and pork proteins	Mahon, 1967 (82)
	Furrier's Lung	Fur handlers	Animal fur proteins	Pimental, 1970 (105)
	Rat Handler's Lung	Laboratory workers	Rat urine proteins	Carroll, 1975 (23)
Chemical	Vineyard Sprayers Lung	Vineyard workers	Copper sulfate spray	Pimental, 1969 (106)
	Isocyanate Lung	Paint/Varnish sprays	TDI, MDI, HDT	Charles, 1976 (24)
	Pauli's Reagent Lung	Laboratory workers	Pauli's reagent	Evans, 1979 (43)
	Hard Metal Disease	Tungsten grinders	Cobalt	Sjogren, 1980 (141)
Drug	Nitrofurantoin H/P	Patients	Nitrofurantoin	Rosenow, 1968 (121)
	Methotrexate H/P	Patients	Methotrexate	Goldman, 1971 (57)
	Cromolyn Sodium Lung	Patients	Cromolyn sodium	Burgher, 1974 (20)
	Sulfasalazine H/P	Patients	Sulfasalazine	Thomas, 1974 (151)
	Gold Salt H/P	Patients	Gold salts	McCormick, 1980 (84)
	Amiodarone H/P	Patients	Amiodarone	Akoun, 1984 (1)
	Nadolol H/P	Patients	Nadolol	Levy, 1986 (80)

	Syndrome	Exposure	Antigen(s)	Reference
	Fansidar H/P	Patients	Sulphadoxine	McCormack, 1987 (83)
	Propranolol	Patients	Propranolol	Akoun, 1989 (2)
Unknown	Weaver's Cough	Tamarind seed powder	Unknown	Murray, 1957 (94)
	Smallpox Handler's Lung	Smallpox scabs	Unknown	Morris, 1963 (92)
	New Guinea Lung	Roof thatching	Unknown	Blackburn, 1966 (15)
	Broken Wind	Equine disease/Hay	Unknown	Watkins, 1966 (159)
	Fog Fever	Bovine disease/Hay	Unknown	Watkins, 1966 (159)
	Coffee Worker's Lung	Coffee beans	Unknown	Van Toorn, 1970 (156)
	Tobacco Grower's Disease	Tobacco plants	Unknown	Lopez, 1976 (81)
	Coptic Disease	Mummy cloth wrappings	Unknown	Lopez, 1976 (81)
	Summer-Type H/P	Seasonal in Japan	Unknown	Kawai, 1984 (70)

APPENDIX: COMMERCIALLY AVAILABLE ANTIGENS FOR IMMUNODIFFUSION TESTING IN HYPERSENSITIVITY PNEUMONITIS (H/P)

Antigen Source	Commonly Associated Syndromes
Thermophilic actinomycetes	
*Micropolyspora faeni**	Farmer's Lung
Thermoactinomyces vulgaris†*	Farmer's Lung, Venilation H/P
*Thermomonospora virdis**	Farmer's Lung
Thermoactinomyces candidus	Farmer's Lung, Ventilation H/P
Thermoactinomyces sacchari	Bagassosis
True Fungi	
Aspergillus fumigatus†*	Ventilation H/P, Farmer's Lung
*Aureobasidium pullulans**	Ventilation H/P
Cryptostroma corticale	Woodworker's H/P
Aspergillus niger	Rarely implicated
Aspergillus flavas	Rarely implicated
Animal	
Pigeon serum*	Pigeon breeder's lung

*Commonly used in "hypersensitivity pneumonitis batteries"
†Multiple strains available

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