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HYPERSENSITIVITY PNEUMONITIS

Jordan Fink

INTRODUCTION AND DEFINITION

Hypersensitivity pneumonitis comprises a group of allergic lung diseases resulting from sensitization and recurrent exposure to inhaled organic dusts. The disease is a diffuse, predominantly mononuclear inflammation of the lung parenchyma, particularly the terminal bronchioles and alveoli. The inflammation often organizes into granulomas and may progress to fibrosis. A wide variety of dusts can cause the disease. These include: moldy fodder in farmer's lung; moldy sugar cane in bagassosis; bird droppings or other avian proteins in bird handler's lung; and mold spores in maple bark stripper's disease. Most individuals who develop hypersensitivity pneumonitis are exposed through their occupation. However, recent information has indicated that sensitizing organisms can also contaminate and be dispersed through forced air heating, humidification, or air conditioning systems, causing pulmonary disease in home and office occupants.*

No single clinical feature or laboratory test is diagnostic of the disease. Rather, the diagnosis is made from a combination of characteristic symptoms, physical findings, x-ray abnormalities, pulmonary function and immunologic tests. The demonstration of precipitating antibodies to a suspected inhaled antigen is particularly helpful. Occasionally, lung biopsy or inhalation challenge is needed. The diagnosis should be suspected in patients exposed to one of the offending antigens who have either repeated bouts of influenza-like pneumonitis or active interstitial lung disease. Although clinical and laboratory abnormalities tend to disappear when the offending dust is avoided, continued exposure may result in irreversible pulmonary damage. The allergic mechanisms and pathogenesis responsible for the development of this group of diseases are incompletely understood. Most individuals exposed to an incriminated dust fail to develop disease. A number of the interstitial lung diseases of unknown etiology bear clinical and pathological similarities to hypersensitivity pneumonitis.

Certain types of hypersensitivity pneumonitis may be of particular importance. Maple bark stripper's disease, for example, is a hypersensitivity pneumonitis essentially eliminated by recognizing the conditions necessary for its development. Hypersensitivity secondary to contaminated forced air and humidification systems is potentially of great practical importance, considering the widespread use of these systems. Allergic bronchopulmonary aspergillosis is typified by the presence of bronchial asthma and eosinophilia, findings not common in hypersensitivity pneumonitis. However, the presence of precipitins to Aspergillus organisms (which colonize the airways in this disease) suggests a possible pathogenetic overlap with hypersensitivity pneumonitis and emphasizes the diverse ability of lung response to inhaled antigens.

LIST OF CAUSATIVE AGENTS

Hypersensitivity pneumonitis may occur following the inhalation and subsequent sensitization of antigens in a wide variety of organic materials. Offending agents may be bacterial (thermophilic antinomycetes), fungal (Alternaria, Aspergillus), serum proteins (avian proteins), chemical (anhydrides), or yet undefined (coffee dust). See a list of such agents on the next page.

LIST OF OCCUPATIONS AND INDUSTRIES INVOLVED

This is generally covered in the list of causative agents and is as varied as the variety of organic dusts which can cause hypersensitivity pneumonitis. The major occupations and industries associated with hypersensitivity pneumonitis are those in which moldy vegetable compost is handled—which by its very nature is contami-

*See Kay Kreiss, M.D., Building-Associated Epidemics

Agent	Disease	Exposure
Definite Causative Agents		
Thermophilic actinomycetes		
Micropolyspora faeni	Farmer's lung	Moldy compost
Thermoactinomyces vulgaris	Mushroom worker's lung	
Thermoactinomyces viridis		
Thermoactinomyces sacharii	Bagassosis	Moldy sugar cane
Thermoactinomyces candidus	Ventilation pneumonitis	Contaminated forced air system
Fungi		
Cryptostroma corticale	Maple bark stripper's disease	Moldy maple bark
Aspergillus clavatus	Malt worker's lung	Moldy malt
Penicillium frequentans	Suberosis	Moldy work dust
Penicillium caseii	Cheese worker's lung	Cheese mold
Alternaria sp.	Woodworker's lung	Moldy wood chips
Pullularia sp.	Sequoiosis	Moldy redwood dust
Mucor sp.	Paprika splitter's lung	Paprika dust
Arthropods		
Sitophilus granarius	Wheat weevil disease	Infested wheat
Animal Proteins		
Avian proteins	Bird breeder's lung	Avian droppings
Chemicals		
Phthalic anhydride	Epoxy resin worker's lung	Epoxy resin
Toluene diisocyanate	Porcelain refinisher's lung	Paint catalyst
Probable Causative Agents		
Amoeba	Ventilation pneumonitis	Contaminated systems
Various fungi		
B. subtilis	Enzyme worker's lung	Detergent enzymes
Hair dust	Furrier's lung	Animal proteins
Coffee dust	Coffee worker's lung	?
Trimellitic anhydride	TMA disease	Trimellitic anhydride
Possible Causative Agents		
Altered humidifier water	Humidifier lung	Humidifier water
Various saprophytic fungi	Hypersensitivity pneumonitis	Contaminated environments

nated with thermophilic actinomycetes. Thus farmers (11)(14), sugar cane workers (10), and mushroom compost handlers (9) are exposed, as are individuals living or working in environments with ventilation systems contaminated with these organisms (5)(26).

Industries in which raw wood products are handled are prone to the development of hypersensitivity pneumonitis. There are reported prevalences in suberosis (cork) (4), sequoiosis (redwood)(13), maple bark (20), and wood pulp (57). Individuals involved in bird handling (pigeon racers, pigeon showers, budgerigar raisers) develop disease as a result of the inhalation of proteins from droppings, dander, saliva, and urine (22)(30)(49)(51).

The disease had also been described in chemical manufacturing and processing, especially when isocyanates and anhydrides are used (28)(56). Such areas include paint spraying and epoxy manufacture.

Other minor industries in which hypersensitivity pneumonitis may occur are variable and have little in common. As new areas of exposure and subsequent diseases are described, it has become apparent that a broad variety of inhalant organic dusts is capable of inducing hypersensitivity pneumonitis.

EPIDEMIOLOGY

Statistical reports of respiratory disease incidence do not commonly categorize hypersensitivity pneumonitis because the disorder is not yet widely recognized. Patients with this disease may be categorized under inhalation diseases, interstitial diseases, or occupational airway diseases (see "Estimate of Population at Risk and Prevalence of Disease"). The scant information regarding numbers at risk and estimates of numbers with diseases are depicted in Table IV-I (48).

There is little information available regarding a relationship between antigens, exposure, and disease. In a given population, similarly exposed to a potential sensitizing inhalational agent, the number of individuals with detectable disease has ranged from 3% to 15% (12)(45). Yet up to 50% of exposed but asymptomatic individuals in similar environments have detectable humoral or cellular immune responses to the antigen without clinical evidence of disease. Thus, some other unknown factor(s) is important in the genesis of hypersensitivity pneumonitis. These may include:

1. **Genetic factors** — Recent evidence has demonstrated that pigeon breeder's disease is not associated with genetic immunologic responsiveness as determined by HLA typing of ill and well pigeon breeders (54). Other evidence has suggested that farmer's lung or pigeon breeder's disease may be under genetic control with an increased frequency of the HLA haplotype in ill individuals (1) (31). Additional studies are necessary to confirm this.
2. **Infection**—Recent evidence, using animal models of hypersensitivity pneumonitis, suggests that some inflammatory event must occur in the lung—in addition to recurrent antigen inhalation exposure—for disease to develop. Animals chronically exposed to pigeon antigens demonstrated an immune response, but no pulmonary inflammation was evident until an agent such as BCG or carageenen was given (46). Such agents, including infectious organisms, may stimulate the immune response by adjuvant action or by enhancement of antigen absorption through inflamed mucosa.
3. **Toxic factors**—The induction, progression, and severity of hypersensitivity pneumonitis may be related to a variety of toxic exposures. Possible toxicants include tobacco smoke, air pollution, and industrial exposures. A recent study has linked the occurrence of pigeon breeder's disease with the use of hexachlorobenzene as a disinfectant in pigeon lofts (1). The factors may enhance absorption of antigens as a result of pulmonary inflammation. They may also increase local immune responses or may act systemically as adjuvants.

ESTIMATE OF POPULATION AT RISK AND PREVALENCE OF DISEASE

Hypersensitivity pneumonitis is not categorized in statistical reports of respiratory disease incidence. Because of its clinical presentation and pathophysiology, this disease may be classified with inhalation diseases, or even dis-

Table IV-1

AT RISK DATA ON SOME OF THE HYPERSENSITIVITY PNEUMONITIDES

Disease	Groups at Potential Risk	Numbers Potentially at Risk	Numbers with Disease
Farmer's Lung	At least, all dairy farmers At most, all farmers who store foodstuffs, doffer, or fibre	260,000 dairy farms Approximately 3 individuals per farm Maximum estimate 2.8 million workers	Unknown
Bagassosis	Persons who inhale bagassee dust—the residue of sugar cane. Recently, residue is burned, decreasing exposure.	Less than 5,000 persons	Unknown, though handling practices may have decreased exposure
Maple Bark Stripper's Disease	Persons who strip maple bark and are exposed to mold spores beneath the bark	Unknown	No new cases since log handling processes have been changed
Mushroom Worker's Disease	Persons who clean out mushroom bed houses	575 mushroom growers with 5,000—6,000 harvesters. The clean-out crews are a small percent of workers.	Unknown
Malt Worker's Lung	Workers in malting houses	1,800 persons in malt industry	Unknown
Pigeon Breeder's Disease	Breeders of pigeons for display or racing	75,000 to 100,000 breeders in the U.S.	Estimated to be from 6% to 15% of handlers
Isocyanate Disease	Paint sprayers Foam insulators	3,000 (hexamethylene) 6,000 (toluene)	Most have asthma; hypersensitivity pneumonitis reported but rare
Phthalic Anhydride Lung Disease	Workers in epoxy resin, plasticizer manufacture	54,000	Unknown
Trimellitic Anhydride Lung Disease	Workers in plasticizer, surface coating manufacture	11,000	Unknown

Source: Mushkin, S. (48)

eases of the airways. Data are available on a few specific forms—especially farmer's lung—which have been studied in England and the United States. Even this information is sketchy because closed populations of farmers have seldom been studied; and while some prevalence data are available, little or no incidence data have been published.

Grant and associates in a study of 655 farm workers in Scotland, found the prevalence of *farmer's lung* to range from 2.3% to 8.6% in three different counties (34). Staines and co-workers, in another British study, estimated the prevalence of farmer's lung in two communities to range from 0.5% to 1% of the farm population (61). A more recent study of 93 farmers by Morgan and co-workers, in an area endemic for farmer's lung, showed that 9 (9.6%) had typical clinical histories of farmer's lung (47).

A recent U.S. study surveyed 471 persons associated with farming or dairy production (42). A history typical of farmer's lung syndrome was given by 14 (3.9%) of the population. The prevalence of farmer's lung in this community located in western Wyoming was comparable to the British and Scottish studies. There is little doubt that farmer's lung is an important occupational illness in farmers in this country, but the diagnosis may be frequently overlooked due to lack of patient and/or physician awareness. Smyth and co-workers found that less than 45% of patients with farmer's lung were diagnosed during the first year of their illness.

Recently 1,045 dairy farmers in central Wisconsin were surveyed for precipitins to a panel of antigens including thermophilic actinomycetes, aspergillus, and pigeon serum (43). Eight and one-half percent of the group had precipitating antibodies to one or more of the thermophilic actinomycetes while 0.4% had precipitins to one of the aspergilli. All of the individuals with precipitins were further evaluated. Thirty-six percent had a positive history of farmer's lung; 10% had a questionable history. Based on these findings, there exists a potential development of approximately 32 cases of farmer's lung per 1,000 in the dairy farmer population. This would result in 4,800 cases in the State of Wisconsin alone, a figure far exceeding the frequency of many other diseases. Such a high estimated prevalence is particularly alarming because these patients are at risk of developing chronic irreversible lung damage.

Estimates of the socioeconomic impact of farmer's lung are difficult to make. If the definitive treatment is to remove the farmer from his environment, the consequences are far reaching. The average dairy farmer at age 45 knows no other occupation. His farm—which is his home, as well as his place of business—often represents a considerable investment which may not be easily redeemable. Furthermore, farm wives seldom have outside employment and are generally not prepared to become part of an outside work force. Thus, the impact of such a situation on the family is apparent.

Changing farm practices could produce an environment relatively free of exposure to thermophilic actinomycetes. However, sufficient information is not currently available to determine the cost and effectiveness of the changes. There have been isolated instances where the farm environment and practices have been altered, but at a prohibitive cost of $50,000 to $100,000 (Wenzel, F., personal communication).

Of the over 600 cases of *bagassosis* referred to in the literature, approximately 500 have been detected in Louisiana. However, the disease is of worldwide distribution and occurs wherever sugar cane is processed. Cases have been reported from Louisiana, Texas, Missouri, Illinois, Puerto Rico, India, Cuba, Italy, England, and Peru (49). Several cases have been seen in nonoccupationally exposed individuals such as persons using the material as a garden mulch; housewives residing in homes several miles downwind from sugar cane fields and processing areas; and employees working in air conditioned offices at or near sugar cane processing areas.

Pigeon breeder's disease has been estimated to occur in 6% to 15% of individuals who raise pigeons for a hobby (12)(29). There are approximately 75,000 breeders in the United States; therefore, if the estimated prevalence is correct, up to 10,000 of these individuals could develop irreversible lung damage.

Studies of several office worker populations exposed to contaminated air cooling systems have demonstrated a prevalence of hypersensitivity pneumonitis, 15% in one such outbreak (5) and less than 1% in another (3).

Thus, although specific prevalence and incidence data are not available for each type of hypersensitivity pneumonitis, it is known that the disease represents a serious health problem in many occupations. It is also believed to occur

more frequently in home and office environments than has been recognized (23).

PATHOLOGY, PATHOGENESIS AND PATHOPHYSIOLOGY

The lung is a unique organ in that it is presented with an extremely large number and variety of potential antigens. Important antigenic agents present in organic dusts are derived from fungal, bacterial, or serum protein sources. Because of the small particle size of these dusts (usually less than 5 μm), large quantities of antigenic material can be deposited at the alveolar level as well as in the airways. Under certain circumstances, this antigenic challenge can result in an immunologic response producing reactions in the airways and lung parenchyma. The clinical response to this challenge depends on the person's immunologic reactivity, i.e., atopic or nonatopic, the nature of the dust, the size of the particles, and the intensity of the exposure (particularly whether it is regular or intermittent)(49). The list of causative agents lists the various hypersensitivity pneumonitides and includes the type of exposure and the specific causative agent when it is known.

Pathology

Pathologic variation depends more on the timing of the antigen exposure than on the character of the offending antigen, since pathologic events are similar during the disease course for the different clinical entities (farmer's lung, bird fancier's lung, mushroom worker's lung, etc.). The intensity of any acute inflammatory event appears to vary with the dose of the specific antigen delivered to the lung and the interval between acute exposure and past episodes.

The lung morphology during acute clinical episodes is that of an acute granulomatous interstitial pneumonitis (Figure IV-1). The alveolar spaces contain numerous macrophages and foreign body giant cells, as well as neutrophils, and a modest number of eosinophils. The macrophages frequently contain some stainable neutral fat. The alveolar walls are often thickened, edematous, and infiltrated by neutrophils, a few eosinophils, and macrophages. As the chronicity of the process develops, the inflammatory exudate within the interstitial tissue has more of a plasmacytic or lymphocytic character. The inflammatory exudate is paucicellular in the earliest stages; some fibrinous exudate may also precede the inflammatory cells. The granulomatous lesions consist of dense collections of plump epithelioid cells arranged in palisaded fashion, and often surround zones of liquefaction necrosis in which some necrotic tissue debris and a few inflammatory cells remain. Bronchioles are often involved and demonstrate a necrotizing process which destroys portions of their mural structure and occludes the bronchiolar lumen with macrophages, inflammatory cells, and tissue debris. The bronchiolar epithelium may be destroyed and replaced by flat, regenerating epithelium. The involved adjacent alveoli are lined by hypertrophied cuboidal epithelial cells (59).

As the process unfolds, its course may be influenced by several factors: the degree of sensitization to the offending, specific antigenic material; the amount of antigen presented in the current episode; and the number and timing of any repeat exposures to the same antigen. If the degree of sensitivity is minimal, or the antigen dose encountered during the inciting episode small and the encounter not repeated, the inflammatory episode may resolve with little or no residual tissue changes. If the inflammatory process persists—either due to persistence of the chronic reaction or to the periodic recurrence of acute exerbations—the lung will suffer insidious or episodically overt continued tissue destruction. Noncaseating granulomas may then be seen with greater frequency. The inflammatory exudate within alveolar spaces and bronchiolar lumenina may become invaded with fibroblastic cells and will contain distinctive Masson bodies which are evidence of organization of alveolar exudate. The chronic inflammatory exudate within the interstitial and alveolar septa will increase in amount; will be characterized by a greater number of plasma cells; and will become thickened by fibroblastic invasion and hypertrophied alveolar epithelial cells (19).

After a prolonged period of repeated acute insults and persistent chronic inflammation, diffuse interstitial fibrosis or honeycomb lung may develop. Within the fibrosis, inflammation may persist in the interstitial and alveolar septa which will have been thickened by mature collagenous connective tissue and some residual chronic inflammatory cells. Noncaseating granulomas are infrequent or absent and may be replaced by collagen or hyalinized tissue. The alveolar spaces are modestly enlarged and the walls thickened

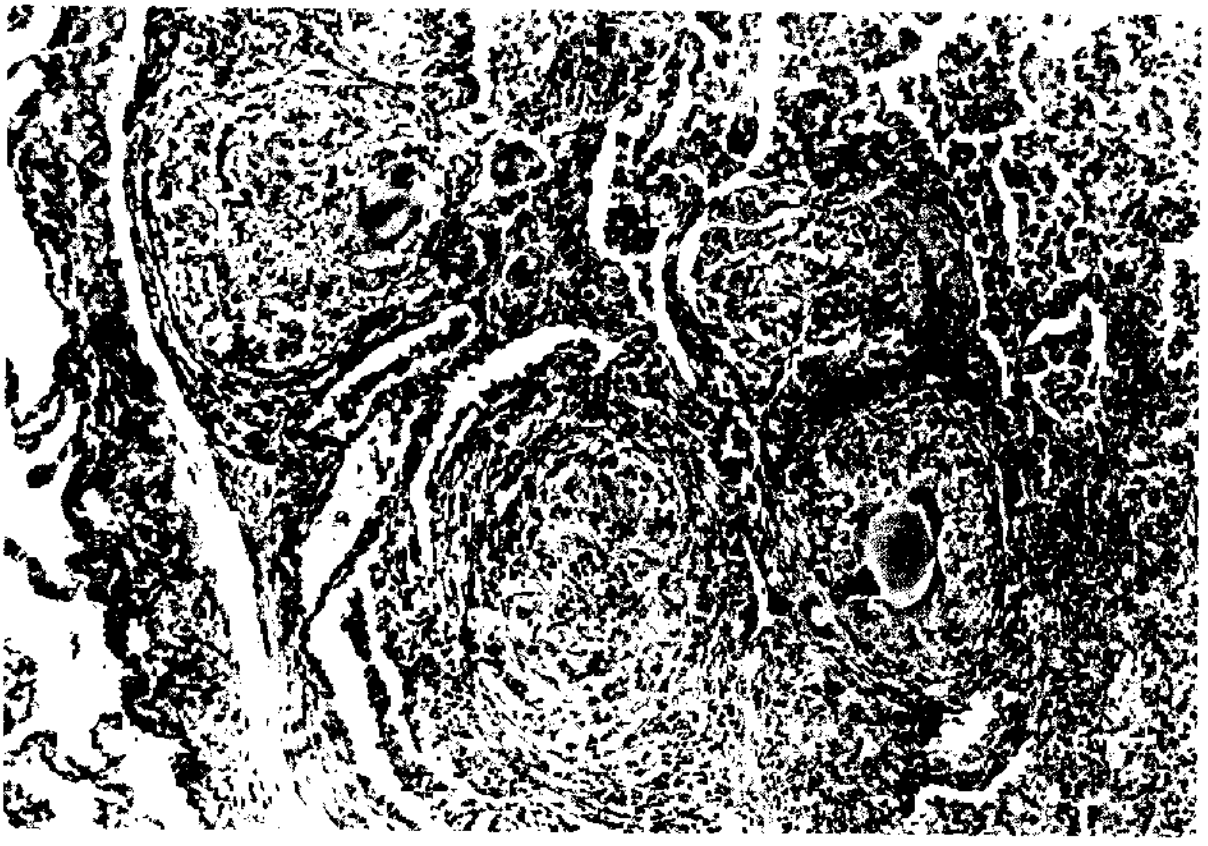

Figure IV-1. Photomicrograph of lung biopsy from 23-year-old woman with hypersensitivity pneumonitis due to contamination of the home humidification system. Sarcoid like granuloma formation and diffuse lymphocytic infiltration is evident.

by fibrosis and alveolar cell hyperplasia. Intra-alveolar organizing Masson bodies are seen. Small muscular arteries are thickened and sclerotic. In honeycomb lung, a similar residual chronic inflammatory process may be present in the interstitial and intra alveolar spaces, and the airspaces are enlarged and cyst-like—reaching a dimension of 0.5 cm to 1.0 cm. The walls of these spaces are fibrotic; contain elements of hypertrophied smooth muscle, plasmacytes, and lymphocytes; and are frequently lined by hypertrophied bronchial epithelial cells. The muscular arteries and arterioles are markedly thickened (59).

The characteristic abnormality in acute tissue reaction is acute inflammation along with granulomas composed of plump epithelioid cells with necrosis and tissue destruction. The presence of large foamy macrophages has been most frequently observed in bird fancier's lung (37) (Figure IV-2).

While bronchioles may be involved with a resulting obstructive organizing bronchiolitis, the lesion is clearly alveolar, inflammatory, and capable of tissue destruction. Since the involvement is usually focal and does not involve large amounts of lung tissue, the functional abnormalities observed may reflect alveolar wall involvement and, to a lesser degree, airways disease, which can produce a decrease in the diffusion capacity of the lung and slight compromise in tests of ventilation. In later stages, the lesions show evidence of tissue loss and some form of fibrosis or scarring.

Pathogenesis and Immunopathology

The potential antigens for hypersensitivity pneumonitis are almost infinite when one considers the number and varieties of substances inhaled into the lungs during a lifetime. A complex relationship must exist between the type and dose of inhaled antigen, the removal mechanisms, and the lung's defense systems.

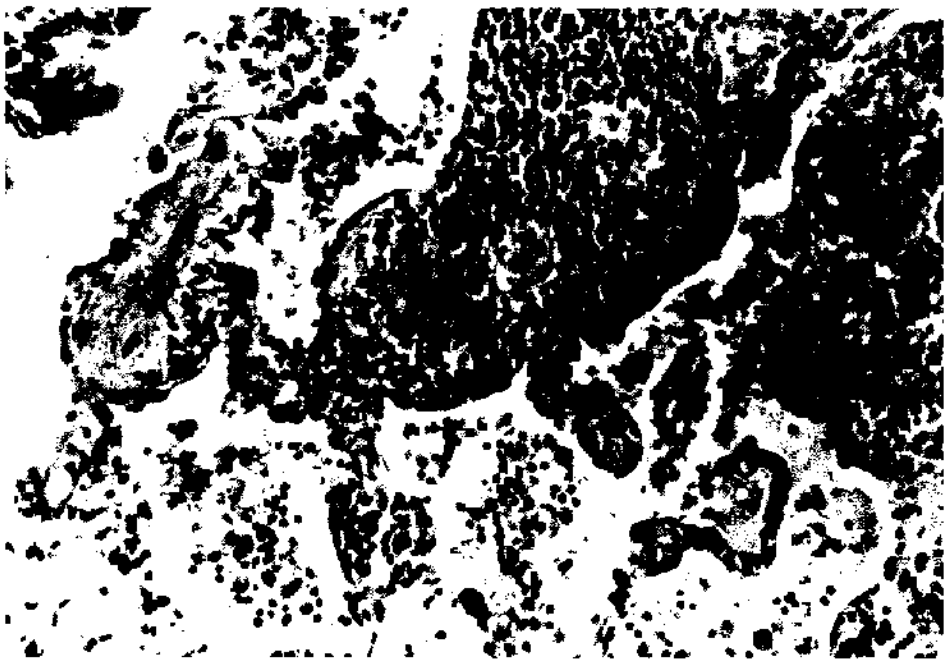

Figure IV-2. Photomicrograph of lung biopsy from 45-year-old pigeon breeder with recurrent acute episodes. Lymphocytic interstitial infiltration, foamy macrophages, and granuloma formation are evident.

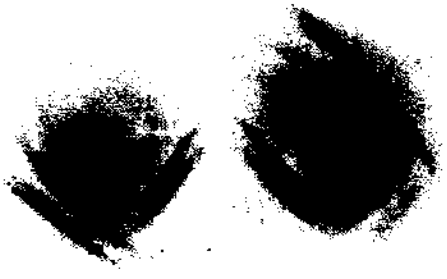

Figure IV-3. Immunodiffusion in agar of patient's serum (center wells) against pigeon antigens (peripheral wells) resulting in precipitin reaction.

The immunologic hallmark of hypersensitivity pneumonitis is the presence of serum precipitins to the inhaled antigen (49) (Figure IV-3). Precipitins are present in over 90% of patients with clinical disease and are usually of the IgG class of immunoglobulins. In comparison, as many as 50% of individuals with appropriate exposure to the antigen also have precipitins, but are asymptomatic (24). These percentages probably represent minimal estimates since the detection accuracy depends on the sensitivity of methods employed and the number and diversity of antigenic preparations available for testing. There is considerable overlap in the titers of symptomatic and asymptomatic individuals, therefore, the titer itself is neither diagnostic nor prognostic.

With the exception of patients who have an asthmatic response to an inhaled antigen, the role of serum antibodies is not clear and may represent a natural immune response to an inhaled antigen. The elevated specific IgE antibody is present only in atopic individuals who have the immediate airways obstructive reaction characteristic of asthma.

The immunologic events responsible for the physiologic and anatomic abnormalities in acute and chronic hypersensitivity pneumonitis are not well understood. There is evidence both for and against an immune complex role. The presence of IgG precipitating antibodies in the majority of patients, and the temporal relationship between antigenic exposure and the onset of acute illness (4-10) hours) are compatible with an immune complex and complement-mediated (Arthus-type) immunologic reaction. In addition, lung biopsies obtained during acute reactions show infiltration of the alveolar walls chiefly with lymphocytes and plasma cells while polymorphonuclear leukocytes and eosinophils occur only in modest numbers. Within the alveoli are foamy macrophages that contain C3 (67). In contrast to the findings in experimental Arthus-type reactions, there is no direct relationship between the antibody titer and the severity of the acute reaction in patients with hypersensitivity pneumonitis. In some patients the precipitin titers may fall below the level of detection, yet clinical sensitivity persists (49). Patients with chronic hypersensitivity pneumonitis may have low antibody levels in their sera although their broncho-alveolar lavage fluids contain increased concentrations of IgG, and in many instances, increased titers of antibody against the presumed etiologic agent (52). However, attempts to demonstrate immune complexes within alveolar lesions have been unsuccessful.

Additional evidence that IgG mediated reactions are not solely responsible for hypersensitivity pneumonitis comes from animal studies. In guinea pigs sensitized so that they produced antibodies but not cellular immunity, inhalation challenges produced a hemorrhagic alveolitis that was not morphologically compatible with farmer's lung (53). Moreover, it has not been possible to passively transfer the disease to monkeys with antibody-containing serum (36). Thus, even though skin testing of persons with pigeon breeder's disease (with pigeon serum) produces Arthus-like responses at 4-6 hours, current evidence suggests that this reaction, like the serum precipitins, is a consequence of antigenic exposure. Its relationship to the pathogenesis of the disease is unclear. Similar studies are not currently feasible in exposed farmers because there are no generally available soluble extracts of thermophilic actinomycetes suitable for skin testing for farmer's lung. Additional evidence for the participation of humoral factors in hypersensitivity pneumonitis includes demonstrations that the alternate pathway of complement fixation may be activated by spores of thermophilic actinomycetes (16). This pathway may play a direct role in the genesis of the inflammatory response within the lung or may interact with the circulating antibody and immune complexes to induce lesions.

Other evidence suggests a role for cell-mediated immune responses in the pathogenesis of hypersensitivity pneumonitis. Biopsies show lymphoid cell infiltrations and granuloma formation suggesting this type of immune response. Lymphocytes from patients with pigeon breeder's disease or farmer's lung may produce a macrophage migration inhibition factor when exposed to the appropriate antigens *in vitro*, and blood lymphocytes from symptomatic pigeon breeders may respond to pigeon serum antigens with increased thymidine incorporation (lymphocyte transformation) (35)(45). Analyses of peripheral lymphocyte subpopulations in patients with hypersensitivity pneumonitis have demonstrated reduced circulating T-cells in those with active disease (32), and analyses of lavage lymphocyte subpopulations of patients with chronic hyper-

sensitivity pneumonitis have demonstrated a significant increase in T-cells when compared with blood (52).

Animal data are also compatible with a cell-mediated reaction in hypersensitivity pneumonitis. Guinea pigs with delayed hypersensitivity to protein antigens respond to inhalation challenge with the production of interstitial infiltrations that resemble the acute disease in humans (53). Similar lesions have been induced in monkeys by passive transfer of cells from donors sensitized to pigeon serum (36). Antibodies and complement were not detectable in the pulmonary lesions of recipients. Although these observations strongly suggest cell-mediated immunity plays a role in the pathogenesis of hypersensitivity pneumonitis, it does not exclude the possibility that a combination of immune complex and complement along with cell-mediated reactions are necessary for production of clinical hypersensitivity pneumonitis in exposed individuals.

Most patients with hypersensitivity pneumonitis have demonstrable precipitating antibodies and cellular immune reactions to an offending antigen. Thus, it is likely that several types of immune reactions are important in the pathogenesis of the disease.

Pathophysiology

The nature and extent of the physiologic events occurring in hypersensitivity pneumonitis depend primarily on the clinical form of the disease.

Acute Form

The acute form of hypersensitivity pneumonitis is characterized clinically by chills, fever, cough, breathlessness without wheezing, and malaise 4-10 hours after antigen exposure (30). There is some correlation between the severity of the acute episode and magnitude of the antigenic challenge; however, immunologic responsiveness also influences the severity of an attack. In general, an acute attack subsides after 18 to 24 hours.

The classic response to antigen exposure results in maximum changes 8 to 10 hours after exposure (55). Changes are primarily restrictive with a decrease in FVC, FEV_1, and TLC. There is little change in flow rates, but small airways obstruction can be demonstrated. There is a decrease in static compliance, and dynamic compliance becomes frequency dependent. Changes in the small airways result in nonuniform ventilation distribution and, in turn, disturbance in ventilation-perfusion relationships. Hypoxemia and impaired diffusing capacity are manifestations of this mismatching (58)(65). Hypoxemia may also be caused by redistribution of blood flow with resulting ventilation-perfusion inequality or be secondary to intrapulmonary shunting of blood. The pulmonary circulatory response is unclear in the acute form of hypersensitivity pneumonitis.

Several other patterns of response are seen. The late reaction can be preceded by an immediate asthmatic reaction with decrease in FEV_1 and expiratory flow rates. These changes resolve in 1 to 2 hours.

In atopic subjects, an acute asthmatic response (with wheezing and evidence of airflow obstruction on standard testing) may occur within minutes after antigen inhalation (49)(55). This attack may subside with or without treatment, but 4-10 hours later the response will still occur. Patients with bronchopulmonary aspergillosis will also have this dual response. By contrast, however, their response is also characterized by an obstructive pattern on standard physiology testing. Less commonly, a repetitive asthmatic reaction occurs, resulting in an immediate obstructive type response with resolution and then a series of asthmatic episodes of decreasing intensity at 8 to 12 hour intervals for several days. In addition, there can be an immediate asthmatic reaction which persists for 4 to 6 hours (49).

In the majority of patients with the acute disease form—particularly with exposure avoidance—pulmonary function returns to normal within a few weeks to months. Even with repeated acute attacks, if the exposure is not intense or frequent, physiologic function may remain normal between exposures.

Subacute Form

A small number of patients show a more insidious disease form resembling a progressive chronic bronchitis with productive cough, dyspnea, easy fatigue, and weight loss (24)(30)(49). Both restrictive and obstructive defects in pulmonary function can be observed; the former, however, predominate along with a decrease in static lung compliance and diffusing capacity. Hypoxemia, although only mild at rest, may show a substantial worsening with exercise. Long-term

avoidance of exposure and administration of corticosteroids usually result in resolution of these functional abnormalities.

Chronic Form

Prolonged and intense exposure to an organic dust causing hypersensitivity pneumonitis can lead to the gradual development of disabling respiratory symptoms with irreversible physiologic changes (24)(49). Pulmonary fibrosis is the predominant finding, particularly in farmer's lung or in patients with chronic low-level exposure to antigens (6). These patients have progressive restrictive impairment, a diffusion defect, hypoxemia, and decreased lung compliance. Pulmonary fibrosis may progress, even without further exposure and despite corticosteroid therapy, eventually resulting in respiratory failure. A few patients with the chronic form of the disease have also shown signs and symptoms of obstructive disease (58). Physiologic studies show diminished flow rates, hyperinflation with markedly elevated residual volume, decreased diffusing capacity, and a loss of pulmonary elastic recoil pressure suggestive of emphysema. Biopsy specimens in these cases have revealed an obstructive bronchiolitis with distal destruction of alveoli. Avoidance of exposure (even for prolonged periods), corticosteroids, and bronchodilator therapy afford only minimal improvement; the disease tends to be progressive (30).

CLINICAL DESCRIPTION

Symptoms

The onset may be acute or insidious (24) (49). When exposure is relatively heavy but intermittent, symptoms begin abruptly 4 to 6 hours later. Chills, fever of 101 to 104 degrees (38.3° to 40 °C), malaise, dry cough, dyspnea, and easy fatigability may persist for several weeks. With repeated exposure, weight loss of 10 to 20 lbs. is usual. Involvement of the airways is exceptional, and most patients do not develop both asthma and hypersensitivity pneumonitis.

When exposure is (relatively) less intense but more continuous, chills and fever may not occur. Exertional dyspnea, cough with scanty mucopurulent sputum, easy fatigue, and weight loss are usual symptoms. An acute episode is rare, unless exposure is exceptionally intense.

In the chronic form of the disease, the symptoms are mainly respiratory and consist of progressive shortness of breath, leading to pulmonary disability. There may be associated anorexia and weight loss with mucopurulent sputum, but acute episodes do not occur (30).

Signs

Inspiratory rales, resembling crackling cellophane, can be heard throughout the lungs but are loudest at the bases. The rales may be heard only at the peak of an acute illness or may persist for weeks or months. Wheezing or prolonged expiration occur occasionally in patients allergic to birds and a few other antigens, but does not occur with exposure to thermophilic actinomycetes. Ankle edema and enlargement of the liver indicate complicating right-sided heart failure.

Other aspects of the physical examination serve mainly to exclude other diagnoses. Peripheral lymphadenopathy does not occur, and hilar adenopathy is unusual. Complicating arthritis or skin rashes are not observed.

Natural History and Prognosis

With the exception of farmer's lung, the number of patients with hypersensitivity pneumonitis seen by one group of investigators is small. This has made large-scale longitudinal studies difficult and consequently the natural history of this disease is poorly understood. In addition, only a few individuals will develop disease after antigen exposure. As a result, the problem may not be recognized in a given case. Often there will be voluntary avoidance of exposure by the affected person even though the exact cause and effect relationship is not understood.

The clinical course of this disease depends to a large extent on the intensity and duration of exposure. In general, a brief exposure, even though intense, will result in an acute reaction in the sensitive individual followed in several days to weeks by complete resolution of symptoms and return of pulmonary function to normal, or near normal, with avoidance of exposure. Recovery can be accelerated by the use of corticosteroids. However, with repeated acute exposure, to an antigen or with chronic low-level exposure, progressive disabling respiratory symptoms with irreversible physiologic changes may result. This type of exposure has frequently been found in patients with farmer's lung.

There is only limited data available on the long-term prognosis and physiologic abnor-

malities in the chronic phase of hypersensitivity pneumonitis. A study of 50 patients with farmer's lung disease over an average period of 6 years showed a mortality rate of 10% (6). In this same group, 30% had persistent respiratory symptoms and physiologic abnormalities—with pulmonary fibrosis being the major problem. In an earlier retrospective study of 24 patients, 4 died during the period of observation after a 2 to 10 year duration of illness (19). Three of five patients who had lung biopsy in the acute stage and subsequently progressed to the chronic stage have been reported (59). A recent study of farmer's lung in Devon, England included 200 patients diagnosed between 1939 and 1971 (60). There were four deaths from farmer's lung, and severe disability was present in approximately one-third. Disability was commonly associated with restriction and reduced diffusing capacity and with airways obstruction in severe cases. Both face masks and steroids were utilized by many of the farmers included in this study.

In a review published in 1958 dealing with bagassosis, it was reported that 4 of 53 patients with the disease had died, representing a mortality rate of 7.5%(10). However, this figure was felt to be falsely high since many milder cases undoubtedly escaped medical attention. Several recent studies of acute bagassosis outbreaks (the follow-up usually performed within 12 subsequent months) showed that with exposure avoidance—even without corticosteroids—the restrictive impairment and abnormal diffusing capacity returned to normal (39)(65). In contrast, another study found similar functional changes during the course of the acute illness; but while chest x-rays returned to normal, the restrictive impairment and reduction in diffusing capacity, although improved, persisted even after 12 months of follow-up (50). Ten patients with pigeon breeder's disease followed with serial pulmonary function studies for 10 years have shown a variable pattern. Individuals who had normal function at the time they were first seen have tended to remain within normal limits despite occasional acute episodes. Patients who had either a restrictive impairment or, as in 2 cases, severe airways obstruction, were found to show only slight improvement and, in some cases, a more rapid deterioration in function than normally expected even in the absence of further pigeon exposure (Schlueter and Fink, personal observations). Another study with a shorter follow-up period reported a similar finding, particularly with regard to the diffusing capacity (15). A recent study of nine afflicted breeders showed complete recovery in four patients at 8 to 30 months after they had ceased being exposed to the antigen. The other five all had evidence of interstitial damage; three had progressive increase in the degree of airways obstruction and one had loss of elastic recoil. The patients were nonsmokers, and occult antigen exposure was ruled out because the precipitating antibody studies became negative (2). Neither the nature or degree of lung function abnormality nor the form of clinical presentation was related to the development of residual damage. The period of continued exposure after symptoms developed and the patient's age appeared to be the most important factors determining recovery of lung function.

It would appear that although the spectrum of response to antigen exposure in patients with hypersensitivity pneumonitis is broad, exposure avoidance results in complete resolution of abnormalities in most cases. Continued exposure, however, can lead to progressive and irreversible disease. When a substantial volume of lung tissue is involved and alveolar hypoxia is chronic, pulmonary hypertension develops. Chronic and sustained pulmonary hypertension will lead to right ventricular enlargement and ultimately to right ventricular failure. Respiratory failure as a result of extensive destruction and fibrosis of lung tissue may be seen in the end stages of chronic, progressive lung disease.

Appropriate Laboratory Investigations

Pulmonary Function Studies

A number of pulmonary function abnormality patterns can occur depending on the clinical form of hypersensitivity pneumonitis (49)(55).

During acute episodes the most common response occurs from 4 to 6 hours after exposure to the offending antigen. There is a decrease in forced vital capacity (FVC) and one-second forced expiratory volume (FEV_1), with a constant ratio between these two parameters. There is little change in expiratory flow rates. A decrease in compliance indicating increased lung stiffness and a fall in diffusion capacity also occurs during acute episodes. Determination of arterial blood gases usually demonstrates hypoxemia

which is accentuated by exercise. Closing volumes may also increase and maximal mid-expiratory flow rates decrease. As the attack subsides, these abnormalities resolve. If there is parenchymal damage, however, volume and flow abnormalities, as well as hypercapnia, may be found during asymptomatic phases.

Some individuals with hypersensitivity pneumonitis exhibit a two-stage reaction. Immediately after exposure, an asthmatic response occurs with a decrease in forced vital capacity, forced expiratory flow volume and expiratory flow rates. This response is followed by the late 4 to 6 hour response described above. Controlled laboratory challenge studies have demonstrated that the immediate pulmonary function response can be reversed with bronchodilators; the late response is resistant to these drugs. Pretreatment with corticosteroids blocks the late response, and cromolyn may block both responses. The findings suggest that different mechanisms may be involved in the two types of responses.

In patients with the more chronic forms of hypersensitivity pneumonitis, less reversible pulmonary function abnormalities may be detected. In the subacute form, a more persistent restrictive impairment and diffusion defect may be demonstrated during exposure and even for some time after cessation of contact with the antigen (58).

The most marked physiologic alterations have been found in patients with the chronic form of hypersensitivity pneumonitis—readily studied in individuals with pigeon breeder's disease (30) or farmer's lung (6). A severe restrictive impairment with a moderate-to-marked diffusion defect has been shown to persist in some of these patients and may be physiologically correlated to the pulmonary fibrosis demonstrable on chest x-ray and lung biopsy.

Other individuals with chronic hypersensitivity pneumonitis may demonstrate poorly reversible and progressive obstructive disease with hyperinflation and elevation of residual volume. A loss of pulmonary elasticity with increased static compliance can be detected in these individuals (58). Some of this latter group may also have decreased diffusion capacity. These findings may correlate with biopsy evidence of obliterative bronchiolitis and emphysema (30).

Radiologic Studies

Chest x-ray studies of patients with hypersensitivity pneumonitis can be normal if recurrent episodes are infrequent. Usually, however, there are detectable, fine, sharp nodulations and reticulations with general coarsening of bronchovascular markings. During an acute attack, soft, patchy, ill-defined, diffuse parenchymal densities—which tend to coalesce—may be seen in both lung fields. Chronic or end stage disease may present as diffuse fibrosis with parenchymal contraction or even honeycombing (64) (Figures IV-4 and IV-5).

Immunologic Studies

The characteristic immunologic feature of hypersensitivity pneumonitis is the occurrence of serum precipitating antibodies against the specific organic dust antigen. Agar gel diffusion techniques with a suspect antigen and patient serum can be used to demonstrate antibodies in almost all ill individuals. However, these tests must be evaluated in light of clinical findings since up to 50% of similarly exposed but asymptomatic individuals may also have moderate to high titers of serum precipitating antibodies. The antibodies in symptomatic and asymptomatic individuals belong largely to the IgG class of immunoglobulins, but IgA and IgM antibodies have also been detected in these sera.

Cell-mediated immunity to organic dust antigens has recently been detected in the peripheral lymphocytes of patients with hypersensitivity pneumonitis. While these tests may be more specific for hypersensitivity pneumonitis, and may more readily discriminate between ill and well individuals than do tests for humoral immunity, they are not generally available.

Skin tests with bird sera and some of the mold antigens may evoke a dual phased skin reaction. A positive response consists of an immediate wheal-and-erythema reaction followed 3 to 8 hours later by an area of dermal and subcutaneous swelling several centimeters in diameter. Other antigens such as the thermophilic antinomycetes are not suitable for skin tests as they evoke a nonspecific constant inflammatory response in nearly everyone.

Blood Studies

A polymorphonuclear leukocytosis of up to 25,000/mm^3 with a shift to young forms is the usual finding in the acute phase of hypersensitivity pneumonitis, but it resolves with recovery. Eosinophilia of up to 10% may be seen but is unusual. The leukocytosis is not evident between attacks.

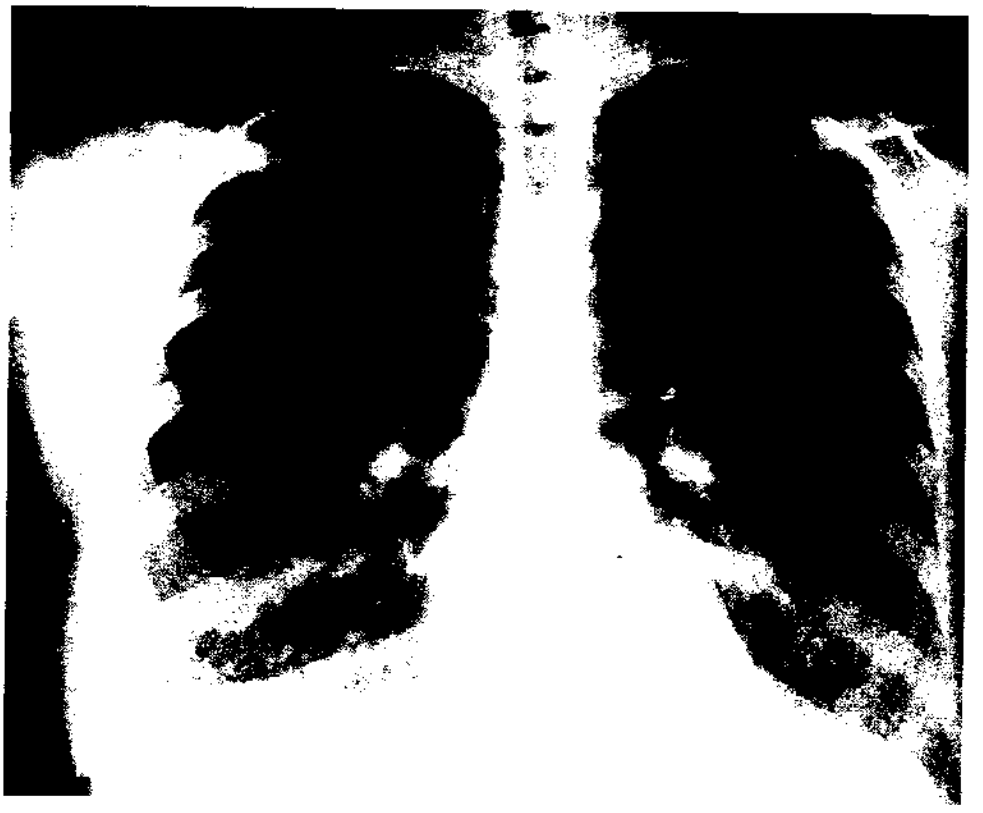

Figure IV-4. Chest x-ray of 35-year-old pigeon breeder with recurrent acute episodes of hypersensitivity pneumonitis. Nodular interstitial infiltrates are prominent at the bases.

There is generalized elevation of immunoglobulin levels, except for IgE. Rheumatoid factor tests are often positive during periods of illness, but become negative after prolonged avoidance.

Diagnostic Challenge

Inhalation challenge testing may be carried out by exposing the patient to the suspect environment, or by cautious inhalation challenge with the suspect antigen in a pulmonary function laboratory. The technique may confirm the diagnosis by reproducing a typical acute attack with fever, rales, leukocytosis, and pulmonary function abnormalities occurring four to six hours after exposure.

Treatment

The major therapy for hypersensitivity pneumonitis is the same as for all allergic disorders once the offending antigen is known—avoidance. Since many of these disorders are occupational, and the antigen size is known, the use of masks with filters capable of removing the antigen, appropriate ventilation of working areas, or as a last resort, changing of occupations may be necessary (24)(49).

In the acute or subacute forms of hypersensitivity pneumonitis, when avoidance cannot be quickly achieved, drug therapy can be instituted. Corticosteroids are the drug of choice and will abort and prevent the episodic illness. Antihistamines and bronchodilators have no effect. If the corticosteroids are administered while avoidance is practiced, reversibility of the clinical and laboratory abnormalities is usually possible. Immunotherapy, as used for treatment of atopic diseases such as asthma and allergic rhinitis, is contraindicated in hypersensitivity pneumonitis because of the possibility of immune complex vascular damage.

DIAGNOSTIC CRITERIA

The diagnosis of hypersensitivity pneumonitis is dependent on associating the pulmonary and/or systemic response of the patient with

Figure IV-5. Chest x-ray of 56-year-old farmer with severe pulmonary impairment as a result of chronic farmer's lung. Diffuse interstitial involvement is present.

the inhalation of a specific environmental dust. The disorder should be suspected in individuals with recurrent "flu"-like episodes, chronic unexplained cough, sputum and dyspnea, or in individuals with chronic progressive pulmonary impairment. The history may be important in differentiating hypersensitivity pneumonitis from other forms of interstitial pneumonitis in that it may bring out a temporal relationship between exposure (hobby or occupation) and symptoms. However, if the exposure is constant, the symptoms may be insidious and progressive and the diagnosis more obscure.

The physical examination is not specific for hypersensitivity pneumonitis. The acute attack is characterized by the presence of diffuse bibasilar rales indicative of an interstitial process. Fever and leukocytosis occur during the acute episode and these features disappear with recovery. This spontaneous recovery and subsequent recurrence should suggest an allergic phenomenon.

Pulmonary function abnormalities are not specific. An acute episode is associated with transient restriction, diffusion defects, and more persistent functional defects including high grade irreversible obstruction or severe restriction and diffusion impairment.

The chest x-ray features of hypersensitivity pneumonitis are variable, with findings ranging from no abnormality to diffuse interstitial fibrosis. The most common features are diffuse nodular infiltrates and coarse bronchovascular markings, which disappear with avoidance. Hilar adenopathy is rare.

The clinical features of hypersensitivity pneumonitis may be present in most other interstitial lung diseases such as chronic eosinophilic pneumonia, the collagen-vascular diseases, lymphogenous spread of carcinoma, desquamative pneumonitis, and sarcoid. The finding of extrapulmonary involvement (splenomegaly, lymphadenopathy) is rare in hypersensitivity pneumonitis. At times lung biopsy may be neces-

sary to confirm the diagnosis.

The most consistent feature of hypersensitivity pneumonitis is the presence of serum precipitating antibodies to an offending organic dust in affected individuals. However, these antibodies can also be detected in the serum of up to 50% of exposed but well individuals. Therefore, the finding of these antibodies must be evaluated in light of a patient's clinical features. Recent evidence has suggested that cellular immune responses to specific antigens may be more specific than humoral responses in the diagnosis of hypersensitivity pneumonitis. Additional studies are necessary to confirm these observations.

A suspected diagnosis may be confirmed by observation of the patients for clinical and pulmonary function changes following natural exposure to the environmental dust or following provocative challenge by controlled insufflation. Observation following removal of the individual from the suspect environment may also aid in confirming the diagnosis. These measures have been shown to be specific for the etiologic agent in hypersensitivity pneumonitis and are likely the key in confirming the diagnosis.

METHODS OF PREVENTION

The most effective control measure for abnormalities associated with hypersensitivity pneumonitis is removal of the affected worker from the occupational exposure—a step often quite disruptive to the individual involved. A more satisfactory approach would be prevention of the disease through the lowering of antigen levels in the work environment. In a few instances, such as in the lumbering industry, exposure of workers to potentially problematic dusts has been prevented by operational changes. For example, maple bark stripper's disease has been eliminated by altering handling of the logs (F.J. Wenzel, personal communication). The disease is caused by the inhalation of the spores of *Cryptostroma corticale*, a mold found growing beneath the bark of maple logs. The disease was first described in a group of bark peelers in northern Michigan in 1932 (63). The next report of the illness occurred in a paper mill in northern Wisconsin. At that site, out of 35 men tested, 5 had severe clinical disease, 9 had subclinical disease, and 4 others had serological evidence of exposure. The remaining 17 appeared normal (66).

High dust concentrations occurred in the wood room, and it was shown that most of the dust material consisted of spores of *Cryptostroma corticale*. Clouds of spores could be seen each time an infected maple log entered the saw area. The spore counts were particularly high in the winter because of the poor ventilation of the wood room. To combat these conditions, changes were made including: eliminating the saw area by installing debarking drums; spraying the drums continuously with water containing a detergent; isolating the chippermen from the wood room with a glass positive-pressure room; and cautioning the workroom crew against spending excessive time in areas of high dust concentrations. These changes resulted in a dramatic fall in spore counts during the winter of 1964, and there have been no further cases of maple bark disease at the plant since that time.

Attempts to prevent bagassosis have been made by drying the material or by treatment with proprionic acid to prevent growth of microorganisms (40). Bagassosis has also been reported to have been eliminated from a Louisiana paper mill by process changes (41). These involved both storage and processing modifications which retarded microbial growth and reduced the generation of organic dust.

Hypersensitivity pneumonitis due to the inhalation of microorganisms present in industrial air handling systems may also be amenable to engineering control. The microorganism reported to have been associated with this type of pneumonitis has varied presumably due to environmental conditions within the system. In an industrial context, contaminated humidifier water is most likely to cause problems. This type of pneumonitis may constitute a serious health problem occurring more frequently than is generally realized.

Where such preventive approaches are not possible or feasible, it would be helpful to be able to screen applicants for sensitivity to antigens and selectively prevent those susceptible from contacting the offending dusts. However, such testing is not currently available since factors (other than exposure) which lead to sensitization are not known.

Immediate, practical measures of hypersensitivity pneumonitis prevention and control include the education of individuals and industries at risk. Workers exposed to incriminated organic dusts must be made aware of potential hazards. Pertinent industries must be encouraged to

reduce sensitizing and challenging exposures. Industrial physicians, public health officials, primary care physicians, and consultants must be alerted to the importance of prevention as well as diagnosis and treatment of this group of diseases.

The limited, current control of hypersensitivity pneumonitis is primarily confined to manipulations of an afflicted individual's environment. Environmental factors have been clarified by studies of causative agents and their sources, and individual patients have benefited greatly by these studies. Of greater economic and epidemiological importance, however, will be predictive and preventive measures affecting whole environments and communities of workers which will result from an increased understanding of sensitizing events and host factors. Further research is required to establish knowledge necessary for the design of feasible preventive programs and the maintenance of a healthy, stable, work force in relevant environments.

RESEARCH NEEDS

The first research priority for hypersensitivity pneumonitis is pathogenetic cognizance. An almost infinite number of antigens are inhaled and enter pulmonary tissue, but only certain ones can apparently cause sensitization and disease—and only in certain exposed individuals. Factors and events essential for an inhaled antigen to induce disease need further investigation. Also essential is research into the roles of various peripheral and central humoral and cellular mechanisms—including immune complexes, specific immunoglobulin classes, and suppressor and helper T-cells.

A second priority should be the development of animal models to study a number of disease factors. These would include the immunopathogenesis, the conditions necessary for sensitization, and the evaluation of progressive damage to the lung. Animal models would also provide a means for screening antigens for their immunopathogenicity.

A third priority should be an intensive study of antigens known to cause disease. Immunochemical analysis of various antigens may determine possible common features between disparate organic dusts and may lead to the development of preventive or diagnostic tests. Studies are also needed to explore new antigens in the environment which may induce pulmonary disease. Such studies may require biochemical, microbiologic, and immunochemical techniques. Furthermore, antigen standardization investigations, utilizing reference dusts and human sera, are important.

Finally, it is necessary to determine the prevalence and natural history of these diseases, perhaps by a national cooperative study. Initial studies should be carried out in well defined populations such as farmers, malt workers, or pigeon breeders. Data collection should include quantitation of the environmental antigen load in order to correlate the level of exposure with the type of immune response.

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