Hypersensitivity Pneumonitis

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Objectives:

1. To discuss the features of dusts and particulate matter that dictate possible clinical manifestations.
2. To identify the most common causes and the usual clinical presentation of hypersensitivity pneumonitis.
3. To describe those clinical syndromes that are similar to hypersensitivity pneumonitis but are clinically distinct entities.
4. To review the most likely pathogenetic mechanisms and the continuing gaps in our understanding.
5. To outline an approach to the diagnosis of the disease.

Key words: allergic alveolitis; farmer's lung; inhalation fever; organic dust toxic syndrome; pigeon breeder's disease

Inspired air may contain a wide variety of potentially harmful substances. These substances may be in the form of aerosols, gases, vapors, fumes, or particulate matter. Inhaled particles may cause respiratory system dysfunction due to an irritant, toxic, or hypersensitivity effect. Hypersensitivity pneumonitis (HP) is one type of hypersensitivity reaction caused by the inhalation of particulate matter. The type of hypersensitivity reaction that develops in response to inhaled particles is dependent on a number of factors : the size of the particle, the concentration of the particles, the duration of exposure, the frequency of exposure, the nature of the substance, and individual susceptibility.

A major factor is the size of the particle. Inhaled particles of >10 μm in diameter are intercepted by the nose and never reach the tracheobronchial tree. In the nose, they are cleared by the usual mechanisms or cause such problems as allergic rhinitis. Particles between 5 and 10 μm impact on the tracheobronchial mucosa. Here, they may be cleared by the ciliary transport mechanism or cause extrinsic asthma. Particles between 0.3 and 5 μm may escape deposition and reach the alveolar spaces. Here, they may be cleared by pulmonary macrophages or cause a hypersensitivity reaction. The hypersensitivity reaction that develops in the alveoli and terminal bronchioles is HP. Particles <0.3 μm will normally act as vapors or fumes and are exhaled in the expired gas.

Definition

HP is an immunologic-induced, non-IgE-mediated inflammatory lung disease resulting from the sensitization and subsequent recurrent exposure to any of a wide variety of inhaled organic dusts. The disease is a diffuse, predominantly mononuclear inflammation of the lung parenchyma, particularly the terminal bronchioles, interstitium, and alveoli. There is little, if any, involvement of the larger airways. The inflammation often organizes into granulomas and may progress to fibrosis. The disease is caused by the inhalation of an organic dust in a sensitized individual. Recently, the definition has been broadened to include some diseases caused by inorganic chemicals that are capable of serving as haptens. These reactive chemicals join native airway proteins to form the complete antigen. HP is also known as extrinsic allergic alveolitis (EAA). Previously considered a rare disease, HP may be more common than previously estimated.

Etiology

Since the original description of farmer's lung by Campbell in 1932, over 50 different occupational and environmental sources of antigen exposure have been identified. HP was once thought to be primarily an occupational hazard. The disorder is now known to be a recreational, avocational, and general environmental hazard, as well. The list of offending agents seems to be ever-expanding. The associated diseases have often been given colorful and descriptive names. For example, bagassosis is caused by exposure to moldy sugar cane, maple bark stripper's disease is due to exposure to a fungus found under the bark (*Cryptostroma corticale*), dheese washer's disease is due to Penicillum species, paprika slicer's lung is due to exposure to *Mucor stolinfer*, and duck fever is due to exposure to duck feathers. The main etiologic agents are microbial spores and avian-related antigens.

Farmer's lung is the best known of the HP syndromes. Farmer's lung is caused by the inhalation of one of the thermophilic actinomycetes,

such as *Faenia rectivirgula* (formerly known as *Micropolyspora faeni*) and *Thermoactinomyces vulgaris*. These ubiquitous unicellular organisms are usually thought of as fungi but, in reality, are bacteria. These organisms grow exuberantly in hay that has not been properly dried or stored. Farm workers are exposed when the stored hay is subsequently raked or turned over. Thermophilic actinomycetes have also been isolated from the soil, manure, and grain compost.

The thermophilic actinomycetes also grow in air conditioners, home humidifiers, hot air furnaces, swimming pools, hot tubs, and fireplace flues. When HP is acquired by these routes, the disease may be termed forced air disease or more commonly humidifier lung. Common to all is the presence of stagnant water and a temperature of approximately 60°C. Humidifier systems have also been shown to support the growth of amebae. These organisms or their products may be inhaled and cause a similar illness.

Another common mode of acquiring HP is the inhalation of animal products (*eg,* serum proteins, urine proteins, dried excrement, feathers, egg whites, and bloom). The best known example is pigeon breeder's disease (or bird fancier's lung), but also gerbil keeper's lung, turkey handler's lung, and pituitary snuff taker's lung. Free living amebae and nematodes in contaminated water or ventilation systems may cause the disorder

HP may be caused by exposure to true fungi. Examples include the following: malt worker's lung is caused by *Aspergillus clavatus*; cheese worker's lung is caused by *Penicillium caseii;* and suberosis is caused by *Penicillium frequetans* growing on moldy cork. A unique form of disease has been recently described in Japan occurring in summer. Summer-type HP is associated with contamination of homes with *Trichosporon cutaneum*.

Highly reactive chemicals that are capable of forming hapten-protein complexes with airway proteins have been shown to cause HP. HP associated with exposure to toluene diisocyanate, diphenyl methane diisocyanate, hexamethylene diisocyanate, and trimellitic anhydride have been described.

A number of ingested drugs have also been shown to cause an "HP-like illness." The best characterized is probably amiodarone but also, gold, minocycline, procarbazine, hydrochlorothiazide, among others. In general, these reactions are not considered HP as the inciting agent is administered systemically and the pathogenesis is likely different.

During the past several years, >100 cases of HP have been reported in workers utilizing water-based metalworking fluids in the automotive industry. A microbial contaminant is suspected to be the cause although the fluid itself has not been ruled out.

Epidemiology

The incidence of HP in exposed populations varies widely. A survey of >1,000 farmers in Wisconsin revealed precipitins in 8.5%. Clinical manifestations of the disease occurred in nearly one half of the latter group. The prevalence of farmer's lung in three agricultural areas of Scotland ranged from 2.3 to 8.6%. Studies of pigeon breeder clubs have found precipitins in 40 to 50% of members and disease in from 6 to 21%. Reports of outbreaks of HP due to microbially contaminated office buildings and industrial sites have described attack rates of 15% and up to 70% of those exposed.

Since only a small minority of identically exposed individuals develop the disease, host factors must be important. The reason for individual sensitivity is unknown. A number of studies have confirmed that HP occurs more frequently in nonsmokers than in smokers. The mechanism for this effect is not known. Atopic patients are not at increased risk. Concomitant viral infections with exposure may play a role

A related unanswered question is the frequency with which undiagnosed HP presents as end-stage idiopathic pulmonary fibrosis (IPF). It has been estimated that 10% of patients referred to National Jewish in Denver with IPF had histologic features suggestive of HP.

Related Disorders

Several disorders are often confused with HP; what follows is a mention them in brief to highlight the difference. Silo filler's disease (not to be confused with farmer's lung) is an acute toxic lung injury due to the inhalation of nitrogen dioxide. Nitrogen dioxide develops as a result of an interaction of nitric oxide and freshly stored silage. This chemical, when inhaled, will affect the terminal airways of all who are sufficiently exposed, regardless of prior exposure or sensitization. This is, in

essence, a chemical burn manifesting as bronchitis, bronchiolitis, or ARDS.

Organic dust toxic syndrome (ODTS) is an inflammatory pneumonitis that develops when a massive dose of organic dust is inhaled. This disorder was originally termed "pulmonary mycotoxicosis" by Emanuel in 1975 to describe fever and cough in Wisconsin dairy farmers. The term ODTS has been described as "clumsy and ugly." As a result, some prefer to use the term "inhalation fever" to describe this and related illnesses. Clinically, ODTS resembles HP with symptoms that are "flu-like" and dominated by fever and chills. ODTS, however, does not require prior sensitization and most subjects sufficiently exposed will develop the disorder. The attack rate can be 70% or higher given sufficient exposure. No long-term effects have been documented and complete recovery may be expected. In fact, the afflicted worker should be able to work with the dust again, if the levels are kept low. This may be very important in employment advice. Bacterial endotoxins, mycotoxins, or spores that reach the terminal airspaces may provoke an intense inflammatory reaction. This reaction may be due to direct activation of the alternate complement pathway and/or stimulation of the production of proinflammatory cytokines. ODTS is most commonly noted in an agricultural setting. Exposure to dusts in swine-confinement and poultry-raising buildings and exposure to grain dust, resulting in grain fever are common forms of the disorder. The National Institute of Occupational Safety and Health has estimated that up to 30 to40% of all heavily exposed workers, predominantly in the agricultural sector, might experience ODTS following organic dust inhalation. ODTS is distinct from HP and far more common.

ODTS, or inhalation fever, has also been reported with exposure to contaminated humidifier water as found in industrial humidifiers, air conditioning units, central heating and humidification systems, and cool mist home vaporizers. Although HP (termed humidifier lung) has been acquired by this route, sufficient evidence has shown that inhalation fever (termed humidifier fever) is a separate and distinct entity. Humidifier fever is an ill-defined feeling of malaise, fever, cough, and myalgia. These "flu-like" symptoms resolve within 24 h. Symptoms tend to be worse at the beginning of the work week (much like byssinosis). There are no radiographic changes or long-term effects. One theory of pathogenesis has recirculated water becoming contaminated by Gram-negative organisms that produce endotoxin. Subsequent inhalation of the endotoxin triggers the clinical syndrome.

Metal fume fever is a nonspecific, self-limited acute illness that resembles an attack of influenza. The syndrome is chiefly caused by exposure to zinc oxide. The most common modern industrial activity associated with zinc oxide fume inhalation is electric arc welding on galvanized steel. Although the data are sparse, metal fume fever has also been reported to occur after exposure to copper, magnesium, antimony, and iron. The pathogenesis is believed to be a direct toxic effect rather than a hypersensitivity reaction. Polymer fume fever is a similar syndrome resulting from exposure to combustion products of polymers and reactive chemicals used in polymer production.

Ornithosis (not to be confused with pigeon breeder's disease) is an infectious disease acquired by inhaling contaminated droppings. The illness is usually caused by *Chlamydia psittaci*. The disease usually resembles a flulike illness but may be a fulminant toxic syndrome.

Clinical Presentation

The clinical picture of HP is very similar regardless of the inciting agent. Although there is considerable overlap and an individual patient may be difficult to categorize, it is conceptually easy to describe three forms of the disease, namely acute, subacute, and chronic. Some authors list two forms by lumping the acute with the subacute form. The chronic form, in turn, appears to be the final common pathway for either multiple episodes of acute HP or prolonged subacute disease.

Acute HP is commonly due to a brief but intermittent intense exposure. Abrupt onset of symptoms occurs 4 to 8 h after exposure. The illness resembles the "24 hour flu" with cough, dyspnea, tachypnea, diffuse end inspiratory rales, chills, fever, malaise, diaphoresis, headache, and myalgias. The clinical picture is often mistaken for a viral or Mycoplasma pneumonia. Symptoms last for 12 to24 h with a peak at 8 to 12 h after exposure. Between attacks, the patient is usually asymptomatic. In most instances, the acute febrile episode occurs after each contact with the responsible antigen.

Subacute HP is likely due to a less intense but more prolonged exposure. The disease is insidious

and symptoms resemble progressive chronic bronchitis with chronic cough, exertional dyspnea, malaise, anorexia, fatigue, and weight loss. Symptoms are much less specific and do not readily associate themselves with exposure to inhaled substances. This form of the disease presents a diagnostic challenge to even the most astute clinician. Nevertheless, subacute disease must be recognized as it may progress to the chronic form if avoidance of the responsible agent is not practiced.

Chronic HP may be the final result of inadequately treated or unrecognized acute or subacute disease. Signs and symptoms of chronic HP are those of any chronic interstitial pulmonary fibrosis in which irreversible lung damage has occurred. At this stage, the entire picture is indistinguishable from end-stage IPF of any cause.

Pathogenesis

The pathogenesis of HP is complex and incompletely understood. This is an area of intense controversy and ongoing research. The final story is not in at this time but there is much speculation. In fact, several mechanisms may be involved. We do know that HP occurs in the setting of exposure to dust and particles of the correct size and composition. Particles must be approximately between 0.5 and 5 μm. Particles must be capable of providing an antigenic stimulus for not all particles of this size will cause the syndrome. Particles must be relatively resistant to degradation so that the antigen can persist long enough in lung tissue to allow sensitization. The patient must have been sensitized during a prior exposure. The period of sensitization is variable and may be as short as several months or may require a number of years of exposure. Not all of those exposed will become sensitized and not all who become sensitized will develop the disease on reexposure. Individual susceptibility is important but not well characterized.

Current evidence suggests that the pathogenesis may involve both immune-complex mediated disease and cell-mediated immunity, perhaps in a sequential fashion. Immune complex mechanisms initiate and mediate the acute syndrome. Direct activation of complement by the alternate pathway with resulting generation of chemotactic factors may be involved as well. Delayed-type reactions mediate the subacute and chronic phases. There is little to suggest that type I or type II immune mechanisms are involved.

Originally, HP was thought to be due exclusively to a type III reaction. A type III or Arthus-type reaction is the deposition of antigen-antibody complexes in vascular or alveolar walls. Immune complexes form *in situ* in the lung interstitium as a result of the interaction of the inhaled antigen and serum-derived IgG that is present in lung tissues and alveolar spaces. Local deposition of the complexes initiates an acute interstitial and alveolar injury characterized by an intense neutrophilic alveolitis and increased vascular permeability. Evidence in support of this theory includes the 4- to 8-h lag between inhalation and the onset of symptoms. This lag time is consistent with deposition of immune complexes, complement activation, and neutrophil recruitment. Additional supportive features include the demonstration of antigen-specific complement-fixing antibodies in both the blood and lung of patients; histopathologic studies revealing interstitial IgG, complement, and antigen; Arthus skin reactions; and neutrophils, complement, and antibody in BAL fluid analysis obtained during an acute episode. Several observations, however, cast doubt on the immune complex etiology as the sole mechanism. For example, only a minority of precipitin-positive individuals develop the disease; there is no evidence of vasculitis in biopsy specimens (vasculitis is characteristic of an Arthus reaction); and granulomas are often noted (this is more characteristic of a type IV reaction).

Could a type IV reaction be responsible? Type IV hypersensitivity is cell-mediated immunity. Evidence favoring cell-mediated mechanisms includes the presence of an intense lymphocytic and mononuclear interstitial infiltrate, immune-type granulomas, and interstitial fibrosis in the lungs of patients. Additional supportive features include passive transfer of disease to animals by CD4 lymphocytes and subsequent exposure and lymphokine production with stimulation of peripheral and BAL lymphocytes. However, the time course is not right. Cell-mediated reactions usually require 24 to 48 h to develop. In addition, delayed-type skin reactions are rarely, if ever, observed.

BAL studies in humans have provided some insights into possible pathogenetic mechanisms. Fluid analysis <48 h after the last exposure is characterized by neutrophilia. Fluid analysis, >5 days after last exposure, may reveal T-cell differential counts of as high as 70 to 80%. In afflicted individuals, there appears to be a preferential expansion

of CD8+ cells (suppressor/cytotoxic T cells). HP has therefore been termed a "T suppressor cell alveolitis."

BAL studies in antigen-exposed individuals but without clinical manifestations of HP may also demonstrate a "T suppressor cell alveolitis." This finding in symptomatic and asymptomatic patients suggests that T suppressor cells may be present in the alveoli in an attempt to control and/or dampen the inflammatory response. In turn, clinical disease may be due to an abnormality in T suppressor cell function (immunoregulatory imbalance). Here, immune reactions are not appropriately suppressed and therefore progress unimpeded. This may be a genetically determined susceptibility. Studies of BAL fluid in patients with HP have shown increases in NK lymphocytes, IgG, IgA ,and IgM, and recovery of foamy macrophages. In fact, in some cases, most recovered cells may be macrophages.

In summary, it is clear that a type III or a type IV reaction alone cannot explain all the observed phenomena and there is little evidence for a type I or type II reaction. As a result, a possible scenario is that an immune complex-mediated hypersensitivity reaction initiates acute lung injury and induces the syndrome. This is followed by T-cell-mediated hypersensitivity mechanisms that perpetuate the acute injury and induce the inflammation, granuloma formation, and interstitial fibrosis seen in subacute and chronic disease. Once again, this is an active area of ongoing research. The pathogenetic mechanisms discussed may or may not prove to be correct.

Diagnosis

No single clinical feature or laboratory test result is diagnostic of the disease. The diagnosis should therefore be made from a combination of characteristic symptoms, physical findings, radiographic changes, pulmonary function test results, and immunologic test results. Of prime importance is a high index of suspicion. In patients with recurrent bouts of an influenza-like illness or in patients with active interstitial lung disease, a complete occupational, avocational, and environmental history is vital.

Laboratory studies are neither sensitive nor specific. In the setting of acute disease, a mild leukocytosis (25,000/mm^3) with a left shift is usually seen. Eosinophilia is variable. Increased erythrocyte sedimentation rate, rheumatoid factor, and antinuclear antibody levels are common. A nonspecific polyclonal rise in gamma globulins is often noted. IgE levels are normal.

The chest radiograph is variable and normal films do not rule out the disease. In one study, 4% of acute cases of farmer's lung had normal films and another 40 to 45% had minimal changes that might have otherwise been overlooked. In acute or subacute disease, a fine soft poorly defined reticulonodular pattern (often described as "alveolar mottling") is noted. The mottling is less distinct than miliary tuberculosis and is widespread or predominantly located in the lower lung fields. Another common picture is scattered patchy interstitial infiltrates that may coalesce. Segmental or lobar consolidation is unusual. Pleural effusions, thickening, and hilar adenopathy are rare. The degree of radiographic abnormalities correlates poorly with symptoms. The symptoms are often worse than the chest radiograph as opposed to Mycoplasma pneumonia in which the chest radiograph may look "worse" than the patient. The chest radiograph usually returns to normal in several days to weeks after an acute episode.

High-resolution CT (HRCT) may be helpful, although no single pathognomonic feature identifies the syndrome. In a 1995 study from Denver and Vancouver, investigators concluded that HRCT can be used to distinguish IPF from HP in most, but not all cases. Desquamative interstitial pneumonitis looked like acute or subacute HP. Chronic HP looked like IPF. The investigators concluded that a lung biopsy specimen was still the gold standard for diagnosis. Characteristic findings in HP on HRCT included the following: poorly defined micronodules, widespread ground-glass attenuation, and predominance of disease in upper and middle lung zones. A pattern of centrilobular ground-glass nodules is fairly specific for the diagnosis of HP with the appropriate clinical history

In chronic stages, the chest radiograph is indistinguishable from diffuse interstitial fibrosis of any cause. A reticular pattern throughout the lung fields and/or honeycombing is common. Diffuse volume loss is evident and features of right ventricular enlargement and pulmonary hypertension may dominate the film. In some cases, upper lung zones contract with upward retraction of the pulmonary arteries. The final appearance may be indistinguishable from tuberculosis, sarcoidosis,

ankylosing spondylitis, and eosinophilic granuloma, all of which are in the differential for upper lung zone fibrosis.

Pulmonary function testing most commonly suggests a restrictive ventilatory impairment. In acute disease, the forced vital capacity is commonly about 80% of predicted. Decreased flow rates in concert with volumes (*ie*, normal ratio) are usually noted. The diffusing capacity is reduced (commonly about 60% of predicted). Decreased lung compliance and a decreased PO_2 with an elevated A-a gradient are noted. Pulmonary function usually returns to normal between episodes of acute disease but may require several weeks to completely recover. Progressive and irreversible restrictive changes are found in the chronic form of the disease.

Skin testing is neither appropriate nor practical in most patients. Few antigens are available and where available, they are often nonspecifically irritating, not well standardized, and/or impure. Where good antigens are available, an immediate wheal-and-flare reaction is seen in 80%. This reaction is not IgE mediated and is either nonspecific or IgG4 mediated. A classic Arthus skin reaction may be noted 6 to 8 h after placement but delayed skin reactions are rarely, if ever, seen

Precipitating antibodies were once believed to be the *sine qua non* of the disease. They are now more useful in establishing evidence of exposure to specific antigens. Serum precipitins are antigen-specific complement-fixing antibodies of the IgG class, although IgM and IgA have also been detected. They are usually detected by gel diffusion or immunoelectrophoresis. More sensitive methods, such as enzyme-linked immunosorbent assay and counterimmunoelectrophoresis may be used but offer no clinical benefit in separating those with disease from those with exposure alone. Precipitating antibody to the offending agent is found in 90 to 100% of patients with clinical disease. False negatives are likely to be due to methodologic problems or an inability to define the relevant antigen. Serum precipitins may disappear over time. Antibodies persist for at least a year and many are present at 3 years after cessation of exposure. There are a number of commercially available "Farmer's Lung" and "Bird Fancier" batteries. These are not for screening purposes nor are they useful in the absence of a clinical suspicion of HP. Reference laboratories may be able to prepare antigens for testing from dust extracts or fungal cultures.

Although the composition of BAL fluid varies with the stage of the disease, certain findings have been suggested as being of clinical use. There is an increase in lymphocytes in HP vs in normals (65% vs 6%). Moreover, HP appears to be mainly characterized by a low CD4+/CD8+ ratio. In contrast, a high CD4+/CD8+ ratio is frequently found in sarcoidosis. The presence of plasma cells in BAL fluid samples is highly suggestive of HP. BAL has also been touted as useful in separating IPF from HP. BAL fluid analysis in patients with IPF commonly reveals a neutrophil predominance as opposed to the lymphocyte predominance in HP. Unfortunately, BAL findings do not distinguish disease from exposure, CD4+/CD8+ ratios vary widely (and are not stable over time), do not correlate with disease activity, and do not serve as prognostic indicators. These latter findings would suggest that BAL analysis may not fulfill its early diagnostic promise. Drent et al, however, have recently reported a validated general discriminant model based on polychotomous logistic regression analysis. They were able to correctly classify 94.5% of cases of IPF, HP, and sarcoidosis using variables such as yield of recovered BAL fluid, total cell count, and percentages of alveolar macrophages, lymphocytes, neutrophils, and eosinophils.

A biopsy may not be necessary but is often useful in establishing a diagnosis. Unfortunately, histopathology varies depending on the stage of the illness and is distinctive but not diagnostic. Lung tissue is usually obtained by open biopsy rather than transbronchial lung biopsy. Very few biopsies have been done during the acute form of the disease. Where available, they have shown alveolar and interstitial accumulation of polymorphonuclear leukocytes, fluid, and macrophages. One of the most characteristic features is a centrilobular distribution of changes.

More often, biopsies are done in the subacute or chronic phases. At this stage of the disease, all biopsy specimens show a predominant lymphocyte, plasma cell, and macrophage infiltration in the alveolar wall and interstitium. Seventy percent show noncaseating granulomas described as less compact and less well defined than those seen in sarcoidosis. Sixty-five percent show varying degrees of fibrosis. Foam cells are seen in 65%. Foam cells are large foamy histiocytes representing activated macrophages. Fifty percent show bronchiolitis obliterans. Vasculitis and eosinophils are

distinctly unusual. The typical biopsy specimen is best described as a granulomatous interstitial pneumonitis with variable degrees of bronchiolitis obliterans.

Inhalation challenge tests are rarely performed but may be available in specialized centers. These challenge tests are not as well standardized as is the case for asthma and each test must be individualized. The test is not to be taken lightly as the reaction may be quite severe. Once a reaction is established, bronchodilators are of little benefit. Corticosteroids must be used. Outside of research settings, it would be difficult to recommend testing. In general, after a simulated exposure, the patient is observed for 12 to 24 h. Reproduction of the clinical syndrome is a positive test. Some or all of the following parameters are monitored: temperature, WBC count, lung volumes, physical examination, carbon monoxide diffusing capacity, arterial blood gases, and spirometry.

In summary, the diagnosis of HP may be challenging. A high degree of suspicion bolstered by a compatible history may permit a presumptive diagnosis. Removal of the suspected antigen source or avoidance by the patient followed by resolution of symptoms is very strong circumstantial evidence. Several recent articles have emphasized the difficulties encountered in making the diagnosis. Schuyler and Cormier have suggested six major and three minor criteria for the diagnosis. A diagnosis of HP may be confirmed if four of the major and two of the minor criteria are present. Major criteria are as follows: symptoms compatible with HP, evidence of exposure to appropriate antigen by history or detection of antibody in serum and/or BAL fluid, findings compatible with HP on chest radiograph or HRCT, BALF lymphocytosis, histologic changes compatible with HP, positive "natural challenge" (*ie*, reproduction of symptoms and laboratory abnormalities after exposure to the suspected environment). Minor criteria are as follows: bibasilar rales, decreased diffusing capacity, and arterial hypoxemia. Time will tell if this diagnostic definition will prove to be useful.

Treatment

The key is prevention and avoidance of reexposure is the top priority. This may require a job change, discarding a hobby, or moving to a new home. This is often not well received by the patient. In one study, 75% of pigeon breeders with disease were still breeding (pigeons, that is) at a 10-year follow-up. Changes in industrial procedures have proven beneficial. For example, maple bark stripper's disease has all but vanished due to the adoption of alternate work procedures. Spraying bagasse with dilute proprionic acid has decreased the incidence of bagassosis. Improvements in ventilation, air filtering systems, or masks may help in some circumstances.

For symptomatic relief of the inflammatory pneumonitis, antipyretics and supplemental oxygen may be needed. Bronchodilators are generally not beneficial. Corticosteroids, such as prednisone at 1 mg/kg/d for 1 to 2 weeks may decrease toxicity of the acute form but probably offer no long-term advantage. Longer periods of treatment may be necessary for the subacute form (up to 3 to 6 months) but once again, these are of variable and questionable benefit. Once the chronic phase has developed, any treatment is of marginal benefit.

Prognosis

Prognosis is incompletely understood. In the acute form, recovery is usually complete. Symptoms have usually disappeared in 12 to 48 h, but fatigue, lassitude, and exertional dyspnea may last for several weeks. The patient is usually asymptomatic between attacks. In the subacute form, recognition is crucial. With avoidance, signs and symptoms may completely disappear. In one study, 30 to 60% of patients with farmer's lung who continued to be exposed were disabled in 5 years and 10 to 15% were dead. But this also means that 40 to 70% did not suffer clinical deterioration despite continued exposure. A study in pigeon breeders in Mexico demonstrated a 5-year mortality of 30%. Some patients with HP, for example pigeon breeders, may experience progression of the disease despite avoidance of repeated exposure. In the chronic form, progressive functional deterioration to respiratory insufficiency is likely, but progression to end-stage disease is not a uniform finding.

Building-Related Lung Disorders

Americans generally spend over 90% of their time indoors and more than half of the workforce now works primarily in offices or commercial buildings. So it is not surprising that the qual-

ity of indoor air has become an important public concern. A number of well-publicized outbreaks of work-related illness acquired from the indoor work environment have heightened the public awareness of this issue.

Unfortunately, the popular media has begun to lump all signs and symptoms related to the indoor working environment under the catchy but somewhat inflammatory term, "sick building syndrome." There are, however, a number of clinical syndromes associated with indoor working environment that are distinctly different in terms of diagnosis, prognosis, and management. The "sick building syndrome" is but one of these syndromes. A more inclusive term, building-related Illness, better describes the entire spectrum of disorders acquired in the indoor working environment.

The building-related Illnesses may be further divided into the following: (1) specific disorders; and (2) nonspecific disorders (*ie,* "sick building syndrome). Specific disorders are characterized by well-defined signs, symptoms, and laboratory findings. A specific cause can be established and a long recovery time is the norm. Examples would include HP, humidifier fever, asthma, and various respiratory tract infections. Conversely, nonspecific building-related disorders are characterized by nonspecific symptoms and variable signs. There are no characteristic laboratory findings and no single cause can be identified. Symptoms appear soon after arriving at work, worsen during the day, and dramatically disappear upon leaving the building.

Worldwide, it has been estimated that in 25% of the investigations of apparent outbreaks of building-related illness, a specific cause can be identified, such as microbial contamination of humidification systems or the accumulation of motor-vehicle exhausts. The remaining 75% of outbreaks are unexplained and are considered to be due to the sick building syndrome. In a review of 356 cases of building-related illness in the United States, the National Institute for Occupational Safety and Health found that 39% involved identifiable contaminants and 50% were associated with inadequate provision of fresh air with no identifiable contaminants. In 11%, no cause was found.

Building-Related Illness: Specific Disorders

These disorders are conditions with a uniform clinical picture attributable to a specific identifiable cause. The symptoms of specific building-related disorders are due to identifiable allergens, toxins, or infectious agents that may be identified by appropriate laboratory tests or identification of the source in the building. In turn, the treatment of these disorders hinges on removing the source rather than merely altering building ventilation. The etiology of the specific disorders may be categorized into those caused by the following: (1) antigens and organic dusts; (2) infectious agents; and (3) toxins and irritants.

Building-Related Illness: "Sick Building Syndrome"

In the 1970s, a remarkably consistent pattern of complaints from office workers began to surface: dry eyes, dry skin, stuffy nose, fatigue, and headache. This was the time of the energy crisis and newly constructed or remodeled buildings were being designed with energy efficiency in mind. Most of these buildings had no windows that opened and outside air was provided only through a recirculating air-conditioning system. Moreover, ventilation standards had been lowered from 20 cubic feet of outdoor air per minute per occupant to 5 cfm per occupant. This lower standard is below the circulation rate of 15 cfm oer occupant which is necessary to ensure a CO_2 level of less than 1,000 ppm. A CO_2 level of <1,000 ppm is generally believed to indicate an adequate fresh air supply. As a result, the building-related symptoms were assumed to be attributable to lower rates of ventilation that resulted in inadequate dilution of irritants. The eye, nose, and throat irritation, headache, and difficulty concentrating that occurred in workers in these buildings came to be called the "sick building syndrome."

In the 1990s, similar complaints are being heard from occupants of many buildings, regardless of design, age, or geography. The World Health Organization has estimated that 30% of newly constructed or remodeled buildings are associated with health and discomfort problems and that between 10% and 30% of the occupants of these buildings may develop symptoms of sick building syndrome.

The World Health Organization has defined the "sick building syndrome" as follows: an excess of work-related irritations of the skin and mucous membranes and other symptoms, including headache, fatigue, and difficulty concentrating, reported by workers in modern office buildings. Because most of these symptoms are commonly experienced by the general population, an outbreak of sick building syndrome is defined by an excessive reporting of one or more symptoms by the occupants of a building. Excessive is defined as in excess of what would ordinarily be expected as the "background" level of such complaints. It has been estimated that the "background rate" of similar vague symptoms in any population of people is 10 to 20%. In addition, symptoms must be work-related. Symptoms must develop after coming to work, worsen during work, and disappear upon leaving work. Finally, there should be no evidence of apparent nonoccupational cause (such as a preexisting medical condition) nor an obvious exposure to occupational toxic materials.

Core symptoms of sick building syndrome are remarkably consistent and consist of lethargy, mucous membrane irritation (dry throat, stuffy nose), headache, eye symptoms (itchy, irritated, watery), and dry skin. These symptoms are not the result of tissue damage detectable by physical examination or laboratory tests. Burge and coworkers, in a study of over 4,000 office workers, found the most commonly reported symptoms were mucous membrane irritation (46%), headache (43%), and lethargy (57%). These symptoms, although not threatening, can be very unpleasant, disruptive to work and home life, cause lost work time and decreased productivity, and create distress about more serious health problems.

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Zacharisen MC. Hypersensitivity pneumonitis: knowing what to look for. J Respir Dis 1999; 20:523-533

Book Chapters

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This chapter from the third edition of Morgan and Seaton is strong on the many and varied individual syndromes.

Pickering CAC, Newman-Taylor AJ. Extrinsic allergic bronchioloalveolitis (hypersensitivity pneumonitis). In: Parkes WR, ed. Occupational lung disorders. Oxford: Butterworth/Heinemann, 1994; 667-709

This chapter from the most recent edition of a classic textbook of occupational lung disease discusses the disorder from a distinctive British/European viewpoint.

Rose C. Hypersensitivity pneumonitis. In: Harber P, Schenker MB, Balmes JR, eds. Occupational and environmental respiratory disease. St. Louis: Mosby, 1996; 201-215

Concise, complete, and readable overall review of the subject from a well- respected textbook.

Diagnosis

Krasnick J, Meuwissen HJ, Nakao MA, et al. Hypersensitivity pneumonitis: problems in diagnosis. J Allergy Clin Immunol1996; 97:1027-1030

Through a discussion of a challenging case, the authors describe the difficulties encountered in the diagnosis of HP.

Lynch DA, Newell JD, Logan PM, et al. Can CT distinguish hypersensitivity pneumonitis from idiopathic

pulmonary fibrosis? Am J Roentgenol AJR 1997; 165: 807-811
There are several high-resolution CT findings that are typical of HP.
Richerson HB, Bernstein IL, Fink JN, et al. Guidelines for the clinical evaluation of hypersensitivity pneumonitis. J Allergy Clin Immunol 1989; 84:839-844
Consensus expert opinion guidelines for the clinical evaluation of HP.
Schuyler M, Cormier Y. The diagnosis of hypersensitivity pneumonitis. Chest 1997; 111:534-536
Since the clinical and laboratory findings of HP overlap with those of many other pulmonary disease, the diagnosis can be difficult,. The authors of this editorial suggest major and minor criteria that should be present in a patient with this disorder.

Pathology

Coleman A, Colby TV. Histologic diagnosis of extrinsic allergic alveolitis. Am J Surg Pathol 1998; 12:514-518
Discussion of the pathologic features of this disease.

Editorials

Merrill W. Hypersensitivity pneumonitis: just think of it. Chest 2001; 120:1055-1057
Rose C, King TE. Controversies in hypersensitivity pneumonitis. Am Rev Respir Dis 1992; 146:1-2
Both are excellent short editorials that succinctly highlight a number of the controversial aspects of this disorder.

Mechanisms

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Useful discussion of the current thinking on pathogenesis.
Fink J. Immunologic orchestration of hypersensitivity pneumonitis. J Lab Clin Med 2000; 16:5-6
Schuyler M, Gott K, Cherne A. Mediators of hypersensitivity pneumonitis. J Lab Clin Med 2000; 136:29-38
Schuyler and Fink outline recent thoughts on the still incompletely understood pathogenesis.

Inhalation Fever (ODTS)

Blanc PD. Inhalation fever. Pulmonary Critical Care Update (PCCU) 1997; 12:1-11 (http://www.chestnet.org)
Highlights the distinct nature of these disorders.
Von essen S, Donman K. Illness and injury in animal confinement workers. Occup Med 1999; 14:337-350
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Building-Related Illness

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Bardana EJ. Sick building syndrome--a wolf in sheep's clothing. Ann Allergy Asthma Immunol. 1997; 79:283-293
Menzies D, Bourbeau J. Building-related illnesses. N Engl J Med 1997; 337:1524-1530
All three are short reviews of the entire spectrum of building-related illnesses, including the sick building syndrome.
Jones TF, Craig AS, Hoy D, et al. Mass psychogenic illness attributed to toxic exposure at a high school. N Engl J Med 2000; 342:96-100 (editorial: Wessely S. Responding to mass psychogenic illness. N Engl J Med 2000; 342:129-130)
Report and discussion of a building-related nonspecific disorder. Excellent discussion of physiologic symptoms in a psychogenic disorder.

Notes

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