INDOOR AIR QUALITY AND NON–IGE-MEDIATED IMMUNOLOGIC RESPIRATORY DISEASE

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Respiratory or inhalation exposures to a wide variety of airborne organic materials have long been known to cause illness.[11, 51] Respiratory diseases, such as asthma, acute and chronic bronchitis, and hypersensitivity pneumonitis, as well as infectious and noninfectious febrile illnesses, have been described following exposures to organic dusts in both the occupational and environmental settings.[5, 10, 28] The indoor air environment is no exception. In an effort to provide more comfortable working and living conditions, extensive heating, cooling, and ventilation systems have been developed to control building temperatures and humidity. Ventilation and humidification systems commonly utilize water and moving currents of air. Baffle plates are strategically placed to reduce large water droplets that may accumulate in these systems. Organic dusts can deposit on the plates and provide a source for bioaerosols to be nebulized throughout ventilation or forced air systems.[1]

Indoor air environmental conditions, created through mechanisms similar to those previously described, can produce microbial and antigenic exposures capable of causing the clinical entities commonly known as *humidifier fever*[6, 30] and *humidifier lung*.[5]

Humidifier fever is a prototypical inhalation fever causing an influenza-like illness with fever, chills, malaise, headache, and at times weight

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loss and anorexia.[53] The disorder may have respiratory symptoms, such as dyspnea, cough, and chest tightness, although these are typically less prominent than the systemic features.

Humidifier lung is a form of hypersensitivity pneumonitis (HP). HP, also known as extrinsic allergic alveolitis, is an immunologically mediated inflammation of the lung parenchyma and alveoli associated with repeated exposures to a variety of microbial or organic antigens and low molecular weight chemicals.

Humidifier fever and humidifier lung share many clinical features, including similar exposure settings and clinical symptoms. Humidifier fever may not be mediated by the same immunologic mechanisms as humidifier lung. The separation of these two disorders is often difficult clinically but is at times important because recurrent acute or subacute episodes of HP are a risk factor for the development of chronic lung disease, whereas humidifier fever may not present the same long-term health sequelae. In this article, both entities are discussed, and the similarities and differences of these disorders are reviewed.

HUMIDIFIER FEVER

A number of clinical descriptions of fevers following inhalation exposures to a variety of substances have been reported. Examples include grain fever,[18] pulmonary mycotoxicosis,[21] organic dust toxic syndrome,[17, 31, 52] metal fume fever, mill fever, and silo unloader's syndrome.[50] These illnesses are typically related to intense exposures to organic dusts, microbial organisms, metal oxides, or other polymers or fumes. Humidifier fever is another syndrome caused by exposure to contaminated air conditioners or humidifiers.

As previously described, humidifiers and air conditioning systems can act as aerosol generators, creating atmospheres contaminated with fungi, ameba, bacteria, and associated products, such as endotoxin.[19, 39, 44, 46, 48, 59] Individuals associated with outbreaks of humidifier fever (both symptomatic and asymptomatic) are often found to be seropositive to extracts of specific organisms isolated from the offending humidifier or air conditioning system.* The majority of these studies have shown no correlation between disease and seropositive reactions. The presence of specific antibodies against these organisms appears to be more important as a marker of exposure rather than specific IgG-mediated disease.

Humidifier fever shares many features with organic dust toxic syndrome, which was initially associated with agricultural environments.[45] Humidifier fever is an indoor air–related example of a toxic or systemic response to inhaled organic dusts and contaminating microbial organisms. These are inflammatory disorders in which neutrophils are recruited into the lung and cytokines, reactive oxygen species, and other nonspecific cellular components are elaborated, resulting in febrile, flu-

*References 7, 19, 23, 43, 44, 46, 59, 68.

like symptoms. This reaction is dose-dependent and resolves in several days when the individual is removed from the offending environment. Although humidifier fever is less common than sick building syndrome,[76] it is often reported as clusters of affected individuals from the same building or indoor environment.

The detailed pathogenic mechanism or biologic pathway responsible for the development of inhalation fevers remains to be precisely defined; however, characteristics of both humidifier fever and organic dust toxic syndrome, when contrasted with hypersensitivity pneumonitis and other classic immune mediated disorders, suggest a toxic mechanism[42] rather than a typically "allergic" or immunologic response. Commonly affected individuals may have no asymptomatic exposure period, and the outbreaks of reported cases often occur in dramatic clusters, suggesting that little (if any) host factor or susceptibility is required.

Clinical Presentation

Humidifier fever usually presents clinically as an acute febrile illness that occurs 4 to 12 hours after exposure to bioaerosols from contaminated air conditioning or humidification systems. Clusters of illness may be observed if several workers are similarly exposed. An exaggerated response may be noted on the first day back at work after several days away from the place of employment; however, this "Monday" pattern appears to be less common with humidifier fever than was historically reported with byssinosis in cotton workers. This is likely related to less predictable exposures generated by building ventilation and humidification systems than was present in cotton mills.

Full-blown humidifier fever can cause temporary debilitating symptoms and an influenza-like illness with fever, chills, malaise, and headache. Respiratory symptoms, such as dyspnea, cough, and chest tightness, may be present, although these symptoms are typically less prominent than systemic features. These symptoms usually last less than 24 hours but may persist for several days.

Physical Examination

Due to the spontaneous resolution of symptoms, many affected individuals with humidifier fever do not seek medical attention; however, when assessed by a physician, physical findings frequently include fever, tachycardia, and tachypnea. Lung crackles are infrequently heard.

Laboratory Studies

The white blood count may be elevated with a left shift. Arterial blood gases may be normal or reveal mild respiratory alkalosis. Serum

precipitins may be found, perhaps primarily as a marker of exposure, highlighting the similarity to HP. Radiographic pulmonary infiltrates have been reported but are certainly rare and may represent cases of HP.[6] Although they have been infrequently reported, pulmonary function tests may be normal or occasionally show a restrictive impairment with a diminished diffusing capacity.[20, 52]

HYPERSENSITIVITY PNEUMONITIS

The variety of organic particles that may cause HP accounts for the many descriptive names for this disorder that appear in the literature. Farmer's lung disease and bird fancier's disease are the two most extensively studied forms of HP. Farmer's lung disease, first described by Campbell in 1932, is associated with exposure and sensitization to *Thermoactinomyces vulgaris* and *Micropolyspora faeni* found in moldy grains and mulch materials. Bird fancier's lung disease was first described in the mid-1960s and is associated with exposure to certain avian proteins.[54]

The reported incidence of HP in individuals chronically exposed to potential antigens is generally low and consistent with a hypersensitivity reaction. Data have shown a prevalence of 0.03% in Swedish farmers[38] and 0.42% in a Wisconsin farming population[25] but as high as 15% or more in office workers exposed to contaminated ventilation systems.[24] HP has been reported in many parts of the world and in both occupational and nonoccupational settings. Although most reported cases are in adults with a median age in the sixth decade, HP in children also has been reported.[47] HP occurs more often in the winter and early spring and for unknown reasons is slightly but significantly less often noted in smokers than in nonsmoking adults.[25] Patients may present with acute recurring or acute HP following intense exposures to sensitizing agents, or with chronic HP, an illness that develops insidiously following frequent low-level exposures.

Exposure to microorganisms or other antigens aerosolized from contaminated humidifiers or ventilation systems in the indoor environment also can result in respiratory disorders consistent with HP.[4, 41, 58, 68] Other agents known to induce HP include thermophilic actinomycetes, fungi, arthropods, pigeon protein, and chemicals, such as isocyanates.[45] This discussion also includes several studies of HP cases not associated with indoor air (i.e., farmer's lung and pigeon breeder's disease) because the clinical picture and underlying disease mechanisms are probably similar to HP induced by contaminants of indoor air.

HP was originally thought to be an immune complex disease.[49] Experimental HP using animal models and histopathologic studies have implicated the cellular immune system and cast doubts on the immune complex theory. These studies are discussed in depth later in this article.

Hypersensitivity pneumonitis is a diffuse mononuclear inflammatory, granulomatous disease of the lung involving mainly the terminal bronchiole, interstitium, and alveoli. The disease may progress to fibrosis.

Clinical Picture

The patient with acute hypersensitivity pneumonitis typically presents 4 to 6 hours after respiratory exposure to the offending antigen with "flu-like" symptoms of fever, myalgias, and, at times, headaches. Dyspnea is the most prominent respiratory symptom, and a mildly productive cough and chest tightness may also be present. The patient with acute or subacute recurring HP experiences similar but sometimes less severe complaints, although the dyspnea may not completely resolve between the episodes of exposure. Patients with chronic HP may never experience episodes of fever or acute dyspnea but will note progressively worsening exertional dyspnea, fatigue, and weight loss.

The clinical examination in acute and in acute recurring HP often features an elevated temperature, heart, and respiratory rate. Inspiratory crackles in the lower chest are common in both acute and chronic forms of HP.

Laboratory Studies

Patients presenting with acute HP may initially have leukocytosis with a left shift. Also, clinically significant hypoxia may be present. Pulmonary function studies in the acute and chronic forms often demonstrate restriction and a reduction in diffusing capacity. These data are consistent with abnormalities of the gas exchanging units of the lung. The presence of serum precipitins to potential causative antigens may represent evidence of exposure but is neither sensitive nor specific for HP.

Radiographic Abnormalities

Radiographic findings in patients with HP are variable and are influenced by the severity of an acute episode and the timing of the film. During an acute episode, ill-defined patchy parenchymal shadowing is common, although the upper lobes appear to be spared. In chronic disease, diffuse fibrosis and even honeycombing can be seen.

High-resolution CT scanning has not demonstrated pathognomonic lesions for HP but does demonstrate a global increase in lung density often with well-defined miliary nodules.[26]

Diagnostic Criteria

Terho defined major and minor diagnostic criteria for HP.[72] His proposed major diagnostic criteria include a history of exposure, "flu-like" symptoms, and radiographic infiltrates. The minor diagnostic criteria include crepitant rales, reduction in diffusing capacity and PO_2,

evidence of restriction on pulmonary function testing, granulomas in the lung biopsy specimen, and positive response to rechallenge. These diagnostic criteria are still awaiting clinical validation.

Pathology

Open lung biopsy in patients with acute HP typically shows alveolar and interstitial infiltration with macrophages and lymphocytes. Sarcoid-like granulomas with lymphocytic infiltrates and Langhans' giant cells also are seen. The locations of granulomas occurring in HP are usually intra-alveolar and parenchymal as opposed to the peribronchial and perivascular locations in sarcoidosis.[55]

In more chronic HP, parenchymal changes, including thickened bronchiolar walls, granulation tissue, scattered granulomas, destruction of alveolar walls, and honeycombing are characteristic. Granulomas are not always present in chronic HP.

Bronchoalveolar Lavage Cells

Several studies have employed bronchoalveolar lavage (BAL) and examined the CD4/CD8 (helper/suppressor T lymphocyte) composition of the BAL mononuclear cells. An increase in BAL mononuclear cells, which are mostly T lymphocytes, is found in patients with HP. The origin of the increase in T lymphocytes may be due to the influx of circulating cells and proliferation in situ.[67] Several studies have reported that the CD8 was the predominate phenotype in the BAL of symptomatic HP individuals.[65, 74, 82, 84] An exception to this finding was reported by Ando et al[2, 3] in a nationwide epidemiologic study of HP in Japan in which they found that the phenotypic profile of BAL T lymphocytes was highly dependent on the causative agent. Summer-type HP, farmer's lung, ventilation pneumonitis, and bird fancier's lung were the types of HP examined in this study. Only summer-type HP, which is caused by exposure to the yeast *Trichosporon cutaneum* contaminating homes during the hot, humid summer season, displayed a CD4/CD8 phenotypic ratio less than 1. In contrast, a study by Semenzato et al[65] that included 14 subjects with farmer's lung, 1 with mushroom worker's lung, and 1 with pigeon breeder's disease found a significant increase in BAL suppressor cell number in HP patients and a CD4/CD8 ratio of 0.47. It is possible that the farmer's lung may be of different etiologic origin in the two studies, because they are from different geographic areas. The fact that summer-type HP has been reported only in Japan is consistent with the notion that geographic locale may be important in the types of biologic agents associated with HP. Epidemiologic studies also have demonstrated that the prevalence of the type of HP varies with different regions.[22, 37]

Although an increase in BAL suppressor cells has been identified in

several types of HP, the role of the suppressor cell activity is unclear. Suppressor cell activity from BAL of symptomatic and asymptomatic HP subjects is not different.[65] The proliferative response to phytohemagglutinin (PHA) or concanavalin A (ConA) of summer-type HP BAL lymphocytes was reported to be less than that of peripheral blood lymphocytes of these individuals. This lower response was found not to be due to suppressor cell activity.[82] An increase in BAL natural killer (NK) lymphocytes with the HNK-1+ cell surface marker in HP subjects but not in corresponding biopsy specimens was also reported by Semenzato et al.[65] Denis et al[13] found significant NK activity in BAL of HP patients that was enhanced with corticosteroid treatment.

BAL Cytokines

The presence or elaboration of cytokines from BAL cells in HP also has been an area of some investigation. Alveolar macrophages from symptomatic HP individuals have a higher spontaneous secretion rate of both IL-1 and TNF-α,[13] suggesting that the macrophages are in an active state.

The role of the T-cell cytokine IL-2 is still unclear. Bouic et al[9] found that peripheral blood lymphocytes from symptomatic pigeon breeders proliferated in response to antigen and this proliferative response was enhanced by IL-2. Asymptomatic pigeon breeders' lymphocytes required the presence of IL-2 to respond to antigen. A strong role for IL-2 in the presence of increased number of lymphocytes in the lung of HP subjects was also suggested by a study of farmer's lung.[74] The BAL lymphocytes from subjects with farmer's lung displayed CD3+, CD8+, CD16−, and CD56+ phenotype and expressed several activation markers, including the p75 chain of IL-2R, VLA-1, and HLA-DR antigen. These cells produced IL-2 in response to stimulation by PHA and proliferate in the presence of IL-2 (but not IL-4). BAL chemotactic factors in subjects with HP (mainly summer-type) were those directed at recruiting polymorphonuclear leukocytes rather than mononuclear cells.[84] The possible role of IL-2 as well as the identification of "proliferation-associated" markers (Tac and T9 antigens) supports the concept that the lymphocytes may be proliferating locally within the lung in patients with HP. Yamasaki et al[82] studied the production of IL-2 and IL-2 receptor induction in summer-type BAL and peripheral blood monocytes. The BAL cells demonstrated lower IL-2 secretion, IL-2 mRNA induction, and receptor expression to a variety of agonists when compared with blood monocytes.

HP and Lung Lipids

Smokers appear to develop HP less often than nonsmokers.[25, 40] Smoking is known to affect the immune system and also to alter lipid composition in the lung. The lung's lipid environment also has been

reported to be altered in HP. Jouánel et al[33] reported decreased phosphatidylcholine and increased phosphatidylethanolamine and cholesterol in HP BAL. Lipid lining of the lung may have an immunoregulatory function because it has been found to regulate lymphocyte proliferation.[79–81] Hughes and Haslam[29] compared the lipid composition of BAL from smokers and HP subjects and found differences in several "immunostimulatory lipids." Levels of these immunostimulatory lipids correlated with the numbers of lymphocytes, mast cells, neutrophils, and foamy macrophages found in the BAL of HP subjects. A strong correlation between cholesterol, lymphocyte count, and foamy macrophages was observed. The immunoregulatory role of pulmonary lipids in the pathogenesis of HP is not yet fully appreciated.

Fibrosis

Markers of ongoing fibrosis also have been identified in subjects with active HP. Teschler et al[73] found elevated levels of both vitronectin and fibronectin fibroblast adhesion molecules in BAL of recently exposed HP patients. Larsson et al[36] also found high levels of fibronectin as well as albumin, angiotensin converting enzyme (ACE), hyaluronic-acid, and procollagen-3-N-terminal-peptide (PC3P) in BAL of symptomatic HP subjects. Asymptomatic HP subjects also had levels of BAL fibronectin, albumin, and ACE that were greater than non-HP subjects but less than the symptomatic individuals. Hyaluronic-acid and PC3P were not elevated in the nonsymptomatic subjects. The mast cells have been implicated in interstitial lung disease, including HP. Mast cells and their granule-associated products, histamine and tryptase, have been reported to be elevated in interstitial lung diseases.[75]

Experimental HP

Several animal models of HP have been developed over the past several years to investigate the pathologic mechanisms that lead to this disease. Antigens that have been associated with HP, e.g., pigeon dropping and thermophilic actinomycetes, have been shown to produce pulmonary lesions in mice,[71] rats,[56] guinea pigs,[83] rabbits,[57] calves,[77] and nonhuman primates[35] when administered by the pulmonary route. Detailed analyses of these models have greatly enhanced our understanding of the pathogenesis of HP and the mediators involved in the progression of the disease.

The murine models of HP have been probably the most intensively studied, largely because they are very reproducible and a number of immunologic tools exist that allow for more detailed analysis of the response. Numerous studies have documented that BAL fluid in humans with HP has an increased number of lymphocytes, especially CD8+ T cells. The importance of T cells has been confirmed in animal models of

HP. Takizawa et al[70] showed that intranasal (IN) instillation of *T. vulgaris* antigen to athymic nude mice (C57 Black/nu/nu) failed to induce pulmonary lesions, whereas thymus-intact litter-mates did develop HP-like lesion as did C57 Black/6 mice. Transfer of sensitized spleen cells to the nude mice and IN challenge with the *T. vulgaris* antigens resulted in the appearance of HP-like lesions in the nude mice. Adoptive transfer studies also have been accomplished in the guinea pig. In a series of papers of experimental HP (EHP), Schuyler et al[62–64] demonstrated that spleen and lymph node cells from guinea pigs systemically immunized with *M. faeni* (now called *Faeni rectivirgula*) in Freund's adjuvant could transfer sensitivity to naive animals. Intratracheal (IT) instillation of the *M. faeni* antigen to the passively immunized animals increased the extent of pulmonary abnormalities as judged histopathologically. Successful transfer required that the spleen or lymph node cells be cultured in vitro with a soluble extract of the antigen for 48 hours and was dependent upon the donor sensitization protocol. Lymph node cells from animals immunized with *M. faeni* followed by two weekly IT challenges with *M. faeni* could transfer EHP, whereas cells from immunized animals given eight weekly IT challenges were markedly reduced in their capacity to transfer EHP, suggesting that suppressor cells may be arising in these animals. In a later report, these same investigators[61] demonstrated that nylon wool adherent CD5-negative cells were capable of transferring EHP, indicating that non-T cells may be responsible for the transfer; however, the nylon wool adherence and CD5 depletion may not have completely removed all T cells, and the lack of well-defined markers for guinea lymphocyte subsets did not allow for definitive analysis of the role of T cells and T-cell subsets in this model system.

Additional studies have been conducted in mice that directly addressed the cell types required.[60] They found that depletion of CD3+ or CD4+ but not CD8+ T cells ablated the transfer of EHP sensitivity to naive mice. Again, cells from immunized animals given eight weekly IT antigen challenges had diminished capacity to transfer sensitivity, but no differences in T-cell phenotypes were noted in the cultured cells before transfer.

Other cell types that have been implicated in the EHP models include mast cells and NK cells. Using mast cell–deficient mice, Takizawa et al[69] found that IN instillation of *T. vulgaris* antigen produced less severe lung injury in the deficient mice than in their normal litter-mates. Adoptive transfer of mast cells to the deficient mice enhanced the severity of the EHP lesions, and mast cells were found in the lungs. These findings are consistent with the observation of increased numbers of mast cells or mast cell markers in the BAL fluid of HP patients.[27] Increased numbers and activity of NK cells have been noted in human HP,[66] and the potential role of these cells has been evaluated in the mouse EHP model.[12] Mice sensitized by repeated IN instillation of *F. rectivirgula* developed alveolitis and fibrosis as evidenced by an increase in the lung hydroxyproline content; however, the fibrotic response tended to wane after 6 weeks of antigen administration. Depleting the NK cell population in these mice by infusion of an anti-NK antibody resulted in disease

progression and a more severe fibrotic response that did not diminish with time. These results suggest that NK cells may play a role in the down-regulation of the inflammatory response and inhibition of fibrosis.

These studies strongly support the role of T cells and cell-mediated immunity (CMI) in the chronic inflammatory state that is characteristic of HP. Expression of a CMI response is mediated by a variety of cytokines, and understanding of both the types of cytokines produced and how the cytokines interact with each other and with various cell types is critical to understanding a CMI response. A mouse model system has been developed in which repeated IN instillation of a thermophilic actinomycete (*T. vulgaris*) results in alveolitis, granuloma formation, and fibrosis.[71] Denis and Ghadirian[15] used this model and selectively depleted or infused cytokines to determine the role of a particular cytokine in the disease progression. Studies using either antisera to interferon gamma (INFγ) or the infusion of INF have found that this cytokine could have pro-inflammatory (enhancing tumor necrosis factor [TNFα] production) or anti-inflammatory effects (inhibiting cellular proliferation and collagen production), depending upon the quantity produced and the stage of the disease. Administration of a monoclonal antibody to TNFα prevented both the alveolitis and fibrotic process seen in this model, indicating that TNFα plays a critical role in both the early and later stages of the disease process. Earlier studies had shown that the direct instillation of either TNFα or interleukin 1 (IL-1) coupled to agarose beads could cause granuloma formation in mouse lungs.[34] Recent studies have indicated that the fibrotic response seen late in both the human disease and the animal models may be modulated by another cytokine, transforming growth factor beta (TGFβ).[16] Alveolar macrophages recovered from sensitized mice at the initial stages of pulmonary fibrosis were found to secrete high levels of TGFβ. The known effects of TGFβ include enhancement of the synthesis of collagen, fibronectin, and proteoglycans;[32] thus it is conceptually reasonable to postulate that macrophage-derived TGFβ plays a role in the fibrotic response seen in HP. In the study by Denis and Ghadirian, the stimulus for TGFβ production was not identified, but the authors speculated that the *F. rectivirgula* antigens initiate a sustained cytokine cascade that includes TNFα, IL-1, and possibly other cytokines, which leads to a strong TGFβ response.

Other models of HP have shown that the antigens frequently associated with the disease appear to have their own "adjuvant" activity, that is they could stimulate cytokine production or cellular proliferation in an immunologically nonspecific manner.[8, 14, 78] Richardson et al[57] showed that repeated aerosol exposure of rabbits to ovalbumin lead to a waning of the disease ("desensitization"), but that the addition of a known immunologic adjuvant, muramyl dipeptide (MDP), to the antigen lead to a chronic granulomatous interstitial pneumonitis. It is possible that the adjuvant effect may be a heightened or prolonged activation of the immune cells, particularly macrophages, which leads to the overproduction of cytokines involved in wound repair and tissue remodeling, resulting in fibrosis or granuloma formation. Additional research is

needed to understand both the nature of the antigens and the network of cytokines that are associated with HP.

Therapy for HP

The primary treatment of HP, typical of most occupational and environmental lung diseases, is avoidance of the offending antigen. This may be difficult to achieve in many indoor exposure settings; however, when humidifier lung is suspected, the careful evaluation of heating, ventilation, and air conditioning systems for microbial contamination is warranted. Cleanup, routine maintenance and inspection, as well as replacement of drain pans, filters, and other system components likely to be contaminated are mandatory.

In severe acute HP, the use of oral glucocorticoids continues to be the most widely applied therapy. Initial daily prednisone doses of 60 to 80 mg are used in cases with markedly abnormal gas exchange; however, corticosteroids may be tapered quickly after clinical improvement is seen. Improvement can be quite dramatic, and the length of therapy and dose should be tailored to the individual response. Relapses often represent repeated exposures, and careful environmental investigation to eliminate antigen exposure totally is crucial to successful management.

HUMIDIFIER FEVER AND HUMIDIFIER LUNG: SIMILARITIES AND DIFFERENCES

The similarities in exposure settings for these two disorders and the overlapping clinical presentations and findings are quite apparent. Certainly, any acute febrile illness occurring 4 to 12 hours after exposures to bioaerosols from contaminated air conditioning or humidification systems presents a differential diagnosis that includes these two diseases. Indeed, even after careful clinical evaluation and extensive characterization of the exposure environment, it may be difficult to differentiate the two disorders in a single affected individual; however, differences are also noteworthy and may be helpful in distinguishing between the two disorders.[6] Humidifier fever has higher attack rates in exposed populations. Humidifier fever has very dramatic systemic or constitutional symptoms with fewer severe reports of respiratory symptoms of dyspnea and cough. Lung function and chest radiographs are generally normal in humidifier fever. In contrast, the diagnosis of HP is more likely in the presence of extensive clinical, physiologic, and radiographic lung abnormalities, high titers of specific antibodies, and a prolonged illness with incomplete recovery.

Despite these differences, the considerable overlap in symptoms, signs, laboratory findings, and exposure settings continues to raise the possibility that these illnesses may represent extreme poles of a common syndrome. Could some episodes of humidifier fever be inciting episodes

of future humidifier lung or forme fruste presentations of HP? For example, the BAL findings in organic dust toxic syndrome and other inhalation fevers frequently show an initial neutrophilic alveolitis that often becomes lymphocytic over time, indeed quite analogous to HP.

Future research will be helpful in determining whether these disorders represent pathogenetically distinct entities or rather may be the "bookends" of a broad clinical spectrum of inflammatory and immunologic responses to the inhalation of organic materials.

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