Needs and Opportunities for Research in Hypersensitivity Pneumonitis

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Hypersensitivity pneumonitis (HP) develops after inhalation of many different environmental antigens, causing variable clinical symptoms that often make diagnosis uncertain. The prevalence of HP is higher than recognized, especially its chronic form. Mechanisms of disease are still incompletely known. Strategies to improve detection and diagnosis are needed, and treatment options, principally avoidance, are limited. A workshop recommended: a population-based study to more accurately document the incidence and prevalence of HP; better classification of disease stages, including natural history; evaluation of diagnostic tests and biomarkers used to detect disease; better correlation of computerized tomography lung imaging and pathologic changes; more study of inflammatory and immune mechanisms; and improvement of animal models that are more relevant for human disease.

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is a complex health syndrome of varying intensity, clinical presentation, and natural history. HP is the result of an immunologically induced inflammation of the lung parenchyma in response to inhalation exposure to a large variety of antigens. The prevalence and incidence of HP vary considerably, depending upon disease definitions, methods to establish the diagnosis, intensity of exposure, environmental conditions, and host/genetic risk factors that remain poorly understood. Despite the apparently large number of individuals exposed to potential HP-causing antigens, the prevalence and incidence of HP seem to be low. The reasons are unknown but may be at least partially related to some environmental or genetic cofactors present that are necessary to trigger development of the disease. Also, the putatively low prevalence and incidence may be somewhat artificial because a large number of individuals with mild or subclinical HP are not detected or are misdiagnosed. Despite its apparent low prevalence, the impact of HP on individuals of all ages continues to be a major concern. The lack of recognition and limited understanding of the mechanisms of the disease have contributed to the development of chronic/recurrent presentations where subjects remain exposed to causal antigen exposure for prolonged periods. Removal from exposure is the best treatment option, often resulting in partial improvement or disease resolution, but overall, treatment alternatives are limited and poorly studied. Because of both limited advances in understanding the pathogenesis of HP and recognizing the need to improve strategies for disease detection, management, and prevention, the National Heart, Lung, and Blood Institute, in collaboration with the Office of Rare Diseases of the National Institutes of Health, convened a group of investigators to identify opportunities for scientific advancement, including basic and clinical research. On May 10 and 11, 2004, this group met to review the current status of HP research and from these discussions provide the Institutes with recommendations and priorities for new research opportunities to improve the accuracy of clinical diagnosis and to investigate disease mechanisms and prevention.

DISEASE DEFINITION

Several different diagnostic criteria for HP have been proposed, and all have significant problems that limit their utility (1–3). HP is usually defined in terms of exposure, clinical features, and laboratory studies. Guidelines for the clinical evaluation of HP state that "identification of the source of exposure" is essential for a definitive diagnosis and future management; however, the working group recognized the difficulties in always identifying the responsible agent. Therefore, the group proposed revising criteria so that in some settings the presumptive diagnosis of HP could be established without the "identification of the source of exposure" when it is not possible to ascertain the causative agent. However, lacking source identification of exposure and specific antigen (e.g., undetermined bioaerosol disseminated in a swimming pool [4], or in contaminated metal working fluids [5]) restricts key management recommendations regarding avoidance of further exposure. The group believed that several important questions should always be included in the history, such as: circumstances surrounding the onset of the clinical manifestations; their severity and persistence; temporal relationships between relevant exposures and disease exacerbation; and the clinical course of disease. In some cases, requiring demonstration of a specific antigen may hold the research field back. For example, there have been clusters of HP in industrial environments and in wet buildings (6), but publication of reports has been difficult when the specific antigen is not determined. Thus, identification of a specific antigen should not be a *sine qua non* for diagnosis, because new knowledge about antigens is generated from identifying new sources of exposure. Also, it can be difficult to differentiate HP from other interstitial lung diseases, or occasionally from non–immunologically mediated syndromes associated with the inhalation of organic dusts and even from airways disorders such as asthma or chronic obstructive pulmonary disease (COPD) (7).

CURRENT CHALLENGES IN ESTABLISHING THE DIAGNOSIS

Although several diagnostic criteria for HP have been published (1–3, 8–10), these were based on an unclear definition of the

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disease. Recently, to validate diagnostic criteria for HP, investigators developed a clinical predictive rule for the diagnosis that may be useful for acute/subacute cases (11). Important diagnostic tools included bronchoalveolar lavage (BAL), high-resolution CT (HRCT) scans, provocation tests, and lung biopsies (11). Further characterization may also include finding an increase in BAL lymphocytes and neutrophils. Despite the effort to generate a good matrix to assess patients, the working group recognized limitations in this area and provided further recommendations to assist clinicians in characterizing patients with HP. Clinical assessment should include a high index of suspicion by the clinician, based on cough, fever, dyspnea, and weight loss (Table 1).

Challenge Studies

Inhalation challenge studies can be helpful in the context of research on new antigenic causes of HP or on immunogenic mechanisms of HP. Inhalation challenge has been used safely by experienced investigators in the past, both clinically and for research purposes. Inhalation challenge usually produces only a transient inflammatory response without long-term complications (12, 13). Safety precaution is an essential requirement with any inhalation challenge. In occupational asthma (OA), for example, specific inhalation challenge (SIC) with suspected agents conducted either in a laboratory or in the workplace has been used more widely than in HP to establish linkages between workplace exposures and the disease (13). In general, inhalation challenge of a suspected antigen is not commonly performed because of the lack of standardized antigens, and limited access to a specialized center to conduct the study (14). Aerosols prepared in laboratories may contain an imprecise mixture of the antigen or may be contaminated with nonspecific irritants. Ramirez-Venegas and colleagues (15) evaluated the diagnostic utility of a provocation test with pigeon serum in patients with subacute/chronic pigeon breeder's disease. Patients with other interstitial lung disease and exposed but asymptomatic individuals were challenged as control subjects. After the inhalation challenge, an increase in body temperature and a significant decrease in FVC, Pa_{O_2}, and SO_2 were observed in all patients with HP. There were no challenge test complications reported during the study. The findings suggest that the provocation test can identify patients with HP in the majority of the cases. Similar results have been reported in patients with farmer's lung after controlled exposure to moldy hay (16). Overall, this test is limited to experienced investigators in research centers with the appropriate setting.

HYPERSENSITIVITY PNEUMONITIS IN CHILDREN

Because pediatric cases of HP are rarely recognized or reported, knowledge is limited and is based mostly on case reports and small series of patients. Since 1960, 95 cases of HP in children have appeared in the literature (17–19). From these cases, the mean age of onset was 10 years. The youngest reported case had the onset of symptoms at 8 months. Fifty-nine percent of the cases were males and 25% had a family history of HP, usually involving a sibling or parent with the same exposure. From these cases the most common symptoms, when reported, included cough, weight loss, and fever. The most typical signs reported include crackles in 69% (43/62) and clubbing in 31% (10/32), suggesting that the disease was recognized late in its clinical course. An abnormal chest film was reported in 84% (79/94) of the cases. The exposures associated with the disease were mainly from birds in 75 cases and fungal bioaerosols in 19. Ninety-seven percent of the children were treated with removal from the exposure and 66% with corticosteroid therapy. The response to treatment was excellent, with clinical improvement in most of the cases. However, deaths from HP have been reported in children as well as adults (17–18). Also, an unknown proportion of cases of interstitial lung disease in children may represent undiagnosed HP.

OCCUPATIONAL AND ENVIRONMENTAL EXPOSURES

Because of the great variety and ubiquity of the potentially causative agents of HP, many individuals may be at risk for exposure in their occupational, domestic, or recreational environments. HP may be present in less traditional environments or settings associated with multiple exposures. A number of occupations have been associated with the risk of HP, including farmers, mushroom and tobacco workers, woodworkers, maple bark strippers, stucco workers, malt workers, millers, machinists, foundry workers, office workers, etc. (20–25) or hobbyists such

TABLE 1. ADVANTAGES AND DISADVANTAGES OF METHODS USED IN THE DIAGNOSIS OF HYPERSENSITIVITY PNEUMONITIS

Method	Advantages	Disadvantages
Clinical history	Simple, sensitive	Low specificity
Precipitins	Relatively sensitive	False negatives (lack of standardized extracts)
IgG ELISA	More sensitive	Identifies IgG production not disease
Radiologic evaluation		
Chest X-ray	Simple, affordable	Can be normal, nonspecific
CT scan	More sensitive	
Pulmonary spirometry	Relatively simple, affordable	Not specific for HP; HP not ruled out by a normal test
Gas exchange ($D_{L_{CO}}$)	Simple, sensitive	Not specific for HP; HP not ruled out by a normal test
Lymphocyte proliferation test with specific antigens	More reliable in distinguishing disease from mere exposure	Few specialized centers, lack of adequate reagents (antigens), not validated yet
Bronchoalveolar lavage	Assess inflammation, normal lymphocyte count rules out active HP	Different stages of inflammation; affected by time lapse since last antigen exposure; typical but not specific
Lung biopsy	Histopathology highly suggestive	Different stages of disease; not pathognomonic
Specific inhalation challenge in the laboratory	If positive, confirmatory	If negative, diagnosis not ruled out; few specialized centers; not standardized
"Natural challenge" with clinical and functional monitoring	If negative under usual exposure conditions, rules out diagnosis; but if positive, is confirmatory	Difficult to differentiate from ODTS; requires collaboration (patient and staff)

Definition of abbreviations: HP = hypersensitivity pneumonitis; ODTS = organic dust syndrome.

as bird fanciers. Factors such as concentration and duration or frequency of exposure to the antigen, particle size, and antigen solubility all may influence disease latency, prevalence, severity, and clinical course. Unfortunately, information is lacking on the exposure thresholds associated with sensitization and also with provoking an exacerbation of symptoms. Little is known about the effect of exposure to airborne endotoxins, glucans, and other contaminants or co-factors common in the environments associated with HP, which may potentiate antigen-specific inflammation (26).

As new types of HP and new causative agents continue to be recognized, ongoing recognition of new causative agents of HP is important in helping clinicians to identify possible causes of disease and to provide appropriate advice on treatment and avoidance (24, 25). Reactive low molecular weight chemicals, many of which are known causes of OA, may act as haptens (protein-free substances that, when coupled with a carrier protein, elicit an immune response) when inhaled, perhaps causing sensitization and HP (e.g., isocyanates). Exposure at home is also an important source of HP antigens, as exemplified by summer-type HP in Japan (27) and bird-associated lung diseases elsewhere. Accumulating evidence suggests that *Mycobacterium avium* complex may provoke an HP-like disorder in otherwise healthy individuals, mostly related with recent hot tub use (28).

RADIOLOGICAL APPROACH

Computerized tomography (CT) evaluation for HP should always include, as with other interstitial lung diseases, thin sections, spaced at 1- to 2-cm intervals, using high-resolution technique. Expiratory high resolution CT images must always be obtained (29). Prone images should be performed whenever there is opacity in the dependent lungs on the supine images. Scans showing respiratory motion artifact should be repeated.

CT Findings

The nodules of HP are typically profuse, round, poorly defined, centrilobular, and less than 5 mm in diameter (30, 31). The prevalence of micronodules seems to vary with the type of exposure. In Japanese summer-type HP they are seen in 100% of cases (32). Ground-glass attenuation is most common in acute HP, but may also be seen in subacute and chronic HP, especially if there is ongoing exposure (33). The ground-glass opacification may be patchy or diffuse, and some authors report middle lung-zone predominance (34).

In chronic HP, fibrosis is represented by irregular linear opacities, traction bronchiectasis, lobar volume loss, and honeycombing (35). Although a mid-lung zone predominance has been described as characteristic, the fibrotic appearance may also be seen in the upper or lower lobes (34). Honeycombing has been observed in up to 50% of patients with chronic bird fancier's lung (30) but appears to be much less common in chronic HP of other etiologies (36). Awareness is increasing of the obstructive manifestations of chronic HP on CT. These include mosaic attenuation (29), expiratory air trapping (29), cysts (37), and emphysema (30, 33, 38, 39). Several studies have found that emphysema occurs more commonly than fibrosis in chronic farmer's lung, even in nonsmokers (33, 38, 39). The available studies do not clearly describe or illustrate the pattern of emphysema, but it seems to be similar to smoking-related emphysema. The mechanism for the development of emphysema in HP remains unclear. Some authors have postulated it is the result of chronic bronchiolar inflammation and obstruction (33, 39). Potentially reversible findings in HP include the presence of centrilobular nodules and ground-glass attenuation (30, 31). Honeycombing and emphysema are usually irreversible.

Specificity of CT Findings

In a study of 90 patients with acute parenchymal lung diseases, including 18 with HP, Tomiyama and colleagues (40) found that a confident first choice diagnosis of HP was correct in 81% of cases. Profuse poorly defined nodules of ground-glass attenuation were very suggestive of HP (4), but were not seen in all cases. Patients with chronic HP may exhibit a histologic and imaging pattern of nonspecific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP) (41, 42). Imaging features which favor a diagnosis of HP over idiopathic pulmonary fibrosis (IPF) include upper or mid-zone predominance, presence of ground glass abnormality or air trapping, and absence of honeycombing (43).

Sensitivity of Imaging for HP

The sensitivity of HRCT for detection of HP is significantly better than that of plain radiographs (30, 31, 44), but less than that of lung biopsy (4). In a study of 31 individuals exposed to bio-aerosol at a swimming pool, 11 had biopsy-proven HP; of these, five (45%) had an abnormal CT and only one (9%) had an abnormal chest radiograph. No patient had a false-positive CT (4). It should be emphasized that this study was performed using relatively early CT scan technology, and has not been repeated with more modern scanners or with digital CT analysis techniques, which might yield greater sensitivity.

Correlation with Physiology

The extent of decreased attenuation on CT correlates with physiologic evidence of air trapping (elevated residual volume), while the extent of ground-glass and reticular abnormalities correlated independently with evidence of restrictive pulmonary function (45, 46). Centrilobular nodules do not correlate with pulmonary function abnormalities (30).

Correlation with Pathology

There is sparse information regarding the relationship between imaging features of HP and their pathologic correlates. Centrilobular nodules probably represent the peribronchiolar lymphocytic infiltration frequently seen on histology in HP. Ground glass abnormality is a nonspecific finding that may represent inflammatory infiltration or fibrosis (47, 48). Air trapping does not have a proven histologic correlate, but seems most likely to be due to bronchiolar obstruction (29, 49). However, further information on the pathologic correlation of the imaging features is required.

The evaluation of diffuse lung disease is a challenge to pathologists because lung tissue reactions to numerous stimuli are quite limited—essentially revealing varying degrees of fibrosis and inflammation. Because HRCT can accurately demonstrate gross anatomy and characterize abnormal findings, it has greatly improved radiologists' ability to delineate the location and extent of disease in the pulmonary parenchyma. The view of HRCT is essentially that of a 1 to 2× scanning magnification microscopically, which helps the pathologist recognize patterns that are difficult to see at high microscopic magnifications of tissue. For example, the centrilobular nature of HP may be difficult to recognize at high magnification microscopically but is more readily appreciated on HRCT. Plain films, standard computed tomography, and HRCT all provide views of the entire lung that can define types of abnormality and distribution of disease not apparent on a limited biopsy specimen. Thus, radiology and pathology have become complementary disciplines, and radiologic studies function as the "*in vivo* gross lung examination" for pathologists (50).

HISTOPATHOLOGICAL ASSESSMENT

Histologically, HP is characterized by bronchiolocentric, chronic interstitial inflammation composed predominantly of lymphocytes. Interstitial nonnecrotizing, usually poorly formed granulomas and intraalveolar foci of organizing pneumonia (Masson bodies) accompany the interstitial inflammation in approximately two-thirds of cases (51, 52). The bronchiolocentric distribution is the result of airways functioning as the portal of entry for the etiologic agent. On HRCT, the airway-centered involvement of acute and subacute HP is manifest as ill-defined centrilobular nodules. As the disease progresses, the airway-centered interstitial inflammation may spread to involve the parenchyma more diffusely; however, accentuation around airways is typically still evident. A number of cases of HP exhibit a NSIP pattern, that is, a diffuse and temporally homogeneous lung inflammation/fibrosis. Therefore, a pathologic diagnosis of NSIP should alert the clinicians to investigate for prior antigen exposure before classifying the disease as idiopathic. In chronic disease, the interstitial inflammation may progress to irreversible scarring, including dense fibrosis with honeycombing and fibroblastic foci compatible with the histologic diagnosis of UIP (41, 53). Although the UIP pattern of fibrosis is associated with both chronic HP and IPF, the distribution of fibrosis is different (54). Chronic HP shows patchy distribution predominantly in the upper lobes with central zones involved as much as the periphery, whereas IPF affects basilar and peripheral subpleural areas of the lung. This disparity in distribution may not be apparent on limited open lung biopsies, particularly those taken from only one lobe. Correlation with HRCT may provide the necessary clues to distinguish chronic HP from IPF.

ANIMAL MODELS

The first animal models of HP examined the effects of substances known to cause human HP, on the lungs of various animal species (e.g., rabbits, guinea pigs, mice, primates, calves). The route of antigen administration was usually intrapulmonary, but in some models was intravenous. Most of the pulmonary exposure was via intratracheal instillation, but a few used inhalations. Some of the experimental protocols included the use of adjuvants such as Freund's.

Much was discovered using the technique of intratracheal injection and later examination of the lung, including understanding the involvement of macrophages, T cells, mast cells, cytokines, chemokines, and vascular adhesion molecules in HP (55–57). Most recent work has used *Saccharopolyspora rectivirgula* (SR), the agent responsible for farmer's lung disease, injected intratracheally into mice (57–59).

In general, the response of the lung to intratracheal SR is dependent on IFN-γ (57), perhaps dependent on interleukin (IL)-12 (60, 61), and is associated with upregulation of vascular adhesion molecules such as E-selectin, P-selectin, and vascular cell adhesion molecule-1 (57, 61). Although most mouse strains respond similarly to SR (62), DBA/2 mice express less pulmonary inflammation (60), perhaps due to increased IL-4 mRNA stability, compared with C57Bl/6 animals (63). Chemokines (monocyte chemotactic protein-1, macrophage inflammatory protein-1α and -2) are increased in BAL (64, 65), but are not necessary for the expression of experimental HP (66). IL-10 appears to downregulate the inflammatory response (67). Viral infection (both RSV and Sendai virus) accentuates pulmonary inflammation (65, 68). Nicotine exposure decreases the pulmonary inflammatory response, which may partially explain why cigarette smoking seems to forestall the development of HP (69).

A slight modification of the above model uses repeated injections of antigen into mice. This better simulates the events that occur in humans which likely involve immune events, such as blockage of co-stimulatory signals by CTLA4-Ig to reduce pulmonary inflammation, specific antibody, and cytokine (IL-4, IL-10, IFN-γ) production (70). A common phenomenon in animals injected repetitively with intratracheal antigen is diminution of pulmonary inflammation, despite continuing injections (71, 72), that might be regulated by IL-10 (72).

Another very useful model, adoptive-transfer HP, can separate the direct effects of the HP-inducing agent from those caused by adoptive immunity. Adoptive-transfer HP can be accomplished by transfer of the putatively responsible cells or antibody into a recipient animal, before challenge of that animal with an agent that causes HP.

Adoptive-transfer HP in mice is not mediated by serum antibody (62), but by T cells (73). Both *in vivo* sensitization and *in vitro* culture of cells with antigen are required. CD4+ cells are responsible for transfer and interact with recipient CD4+ cells (71, 74, 75). The bulk of pulmonary inflammatory cells in the recipient animals originate from the host and are not the transferred cells (76). The transferring cells have the characteristics of Th1 cells (77) and express $\alpha4\beta7$. Th1 cell lines (capable of transfer) express more CD44 and less CD45Rb, compared with Th2 cell lines (incapable of transfer) (78).

As useful as these animal models have proven to be, they have significant limitations. These include administration of large amounts of antigenic material as an intratracheal bolus, the lack of ability (in general) to induce granulomata or produce ongoing fibrosis, and the obvious differences between the experimental animal (usually mice) and humans (79).

Given the current limited progress in the understanding of mechanisms of HP, development of new models should include the ability to monitor rapid changes of cellular and tissue events. Use of emerging technologies, such as proteomics and gene array techniques, will allow more detailed analysis of events that occur in animal models. The challenge will be to understand the very large amount of data that emerge from these techniques. Use of the animal models can be used to better understand the natural history of the disease.

CHALLENGES AND OPPORTUNITIES

The study of HP presents challenges for both the clinician and the bench researcher. To advance this field, detailed molecular characterization of the offending antigens, production of purified recombinant antigens for developing specific assays (antigen and antibody), and establishment of defined experimental challenge systems in animals and humans will be necessary to catalyze advancements in this area of investigation. The relative importance of innate immunity, humoral immunity, and adaptive T cell responses is not yet clear. Host susceptibility factors that may determine the occurrence, development, and severity of HP have not been elucidated. Likewise, the role of environmental promoting factors, such as viral infection, that may be critical for the pathogenesis of the disease are largely unknown.

Although there is widespread belief that the disease is mediated by T lymphocytes, the value of lymphocyte assays based upon proliferation or cytokine production in determining sensitization is not well established. These assays suffer from high background responses, often due to the presence of many immunostimulatory factors in complex antigen mixtures. This difficulty has been overcome in other fields recently with the use of fluorescent dye–based assays that enable investigators to quantitate the number of proliferating antigen-specific T cells and to simultaneously define their phenotype. The role of T regulatory cells in prevention of the development of disease in the vast majority of exposed individuals is an area of obvious appeal for future investigations (80). Lack of adequate responses of T regulatory cells is now suspected to be of importance in the development of a number of mucosal diseases. Studies of the phenotype of BAL lymphocytes using markers that identify T-regulatory cells (e.g., CTLA4, GITR, CD25, etc.) may well discriminate between those with disease and those without symptoms among exposed individuals.

Future studies for discovering genes associated with risk and severity of the disease are needed to define markers for susceptibility. Tissue level microarray analysis may provide differentiation of HP and other inflammatory lung diseases such as idiopathic interstitial pneumonias, or connective tissue disease–associated interstitial lung diseases.

Insight into the interaction of occupational and environmental exposures and host/genetic factors in risk for and outcome of HP will require a coordinated effort if the field is to see meaningful scientific advancement. This will require collaboration from epidemiologists, clinical researchers, and laboratory-based scientists. The establishment of an adequately funded multicenter collaborative network of investigators will enable the accumulation of adequate numbers of cases of HP, careful characterization of disease stage and phenotype, analysis of host and genetic risk factors, characterization of cases based on differences between antigens and exposure settings, and the use of consensus-based histologic and imaging data to better understand natural history and prognosis. Such an approach will likely also be required to design adequate controlled clinical trials for pharmacologic management of more intractable, progressive cases of HP. For example, the responsiveness of HP to glucocorticoids and other therapies, and the relative unresponsiveness of forms characterized by fibrosis, should be explored further.

Human experimental challenge models for further elucidating the cellular and molecular basis of HP may hold promise, but this approach awaits further consensus on antigens to be used, exposure conditions, outcome variables, and generalizability of findings to other antigens and to all disease stages. A collaborative effort to establish rigorously validated models should be made. Ideally such systems would use well defined purified or recombinant antigen.

RECOMMENDATIONS

The working group noted the need for better documentation of the incidence and prevalence of HP in a population-based study. Improved criteria for diagnosis are needed, and the group suggested classifying disease considered chronic HP as recurrent versus insidious, rather than acute, subacute, and chronic disease. Future studies should include symptomatic patients with well characterized stages of HP, asymptomatic but similarly exposed patients, and appropriate control subjects. Overall, the working group recommended the following:

- Establish a multicenter collaborative network, with appropriate ties to governmental agencies that share interest in HP, to enhance the recognition, diagnosis, and management of the disease, including a tissue and imaging repository to foster improved clinical and laboratory-based research.
- Define the risk factors (host/genetic and environmental) that affect the occurrence and natural history of the disease. Investigate gene regulation of inflammatory cytokine production and other markers of disease.
- Establish reasonable, acceptable, and validated case definitions for HP that reflect differing study designs. For example, the definition of HP used for epidemiologic research in at-risk populations will vary from that used in a pathologic/imaging analysis of HP cases. Research in HP will be enhanced by definitions based on histologic criteria, specifics of antigen exposure, and better characterization of disease phenotypes (e.g., recurrent versus insidious).
- Explore the use and validity of biomarkers of both exposure and disease. For example, nasal lavage, induced sputum, exhaled breath condensates, peripheral blood, and BAL mononuclear cells in antigen-specific lymphocyte proliferation assays could provide an additional diagnostic and research tool in HP.
- Develop and support population-based studies, particularly in settings where the disease is endemic, to provide additional insights into environmental and clinical characterization of such cases. This will require interdisciplinary exposure assessment and aerosol research expertise for understanding exposure/dose/response relationships.
- Define the natural history of the disease in the context of other diseases such as asthma and COPD. Investigate the relationship (e.g., immune and physiologic response) between HP and upper airway symptoms.
- Develop a battery of standardized antigens known to cause HP and make them available to clinicians and researchers for use in both diagnosis and investigations of pathogenesis.
- Use quantitative and high resolution CT in prospective evaluation and longitudinal follow-up studies of HP and other organic dust diseases.

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