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REVIEW

Hypersensitivity pneumonitis: current concepts

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Hypersensitivity pneumonitis: current concepts. S.J. Bourke, J.C. Dalphin, G. Boyd, C. McSharry, C.I. Baldwin, J.E. Calvert. ©ERS Journals Ltd 2001.

ABSTRACT: Hypersensitivity pneumonitis (HP), or extrinsic allergic alveolitis, is due to a hypersensitivity reaction after repeated inhalation of finely dispersed antigens, mainly organic particles or low molecular weight chemicals. The essence of this disease is an interaction between the host's immune system and external antigen, influenced by both genetic and environmental factors. In susceptible subjects, it leads to a combined type III allergic reaction of Gell and Coombs (with formation of precipitines) and a type IV lymphocytic reaction (with a granulomatous inflammation in the distal bronchioles and alveoli).

This review gives an update on epidemiology, antigens, pathogenesis, host susceptibility, environmental factors, clinical features, diagnosis and treatment in HP. The list of aetiological agents is long and new sources of antigens are constantly being identified. Host risk factors are poorly characterized, with the exception of those linked to exposure factors. Environmental factors and cofactors may be critical for the pathogenesis of the disease.

HP is not a uniform disease entity, but a complex dynamic clinical syndrome such that different patterns of disease emerge over time. The diagnosis is made from a combination of clinical features, radiographic abnormalities, lung function tests and immunological tests. The use of inhalation challenge tests for the diagnosis has been hampered by the lack of standardization.

Antigen avoidance is the key element in the treatment. There is often an apparent beneficial response to corticosteroids, but it may be difficult to distinguish between the effects of treatment, the natural course of the disease and the effect of antigen avoidance.

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Hypersensitivity pneumonitis (HP), or extrinsic allergic alveolitis, is a group of immunologically mediated lung diseases in which the repeated inhalation of certain finely dispersed antigens of a wide variety, mainly including organic particles or low molecular weight chemicals, provokes a hypersensitivity reaction with granulomatous inflammation in the distal bronchioles and alveoli of susceptible subjects [1]. The essence of this disease is an interaction between an external antigen and the host's immune system. It must be clearly distinguished from a number of nonallergic, inflammatory reactions, such as "inhalation fevers", toxic alveolitis and organic dust toxic syndrome, which are also associated with the inhalation of organic dusts [2–4]. These reactions typically occur after a single exposure to an unusually high level of organic dust, and they may occur in "naïve" subjects without previous exposure. In such toxic reactions, individual susceptibility is less apparent and all subjects that have the same degree of exposure develop a similar clinical illness. In contrast, individual susceptibility is a characteristic feature of an immune-mediated disease such as HP, such that only a small percentage of those exposed to the antigen develop the disease. In HP, the provoking antigens have certain important characteristics, the patients who develop the disease have some susceptibility and the interaction between host and antigen is influenced by both genetic and environmental factors (fig. 1).

Epidemiology

Epidemiological studies of the prevalence of the various forms of HP in different populations are

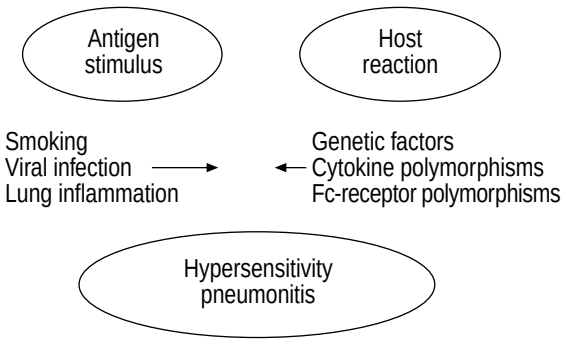

Fig. 1. – In hypersensitivity pneumonitis, the interaction between the external antigen and the host's immune response is influenced by both genetic and environmental factors. Fc: fragment crystallizable.

fraught with difficulties [5]. The list of aetiological agents is long and new sources of antigen are constantly being identified. Prevalence rates vary widely between countries and are influenced by factors such as climatic, seasonal and geographical conditions, local customs, smoking habits and differing work practices and processes. There is no consistent, standardized epidemiological approach for assessing the various forms of HP. Most large surveys have relied upon questionnaires of symptoms and measurement of precipitating antibodies, but these methods correlate poorly with more comprehensive assessments of HP. Conversely, studies based on patients admitted to hospital and undergoing comprehensive investigations leading to a definitive diagnosis of HP, are likely to underestimate the true prevalence of the disease. The diverse and dynamic nature of HP makes it difficult to define precise diagnostic criteria and this may account for the large differences that have been observed in the classification of respiratory diseases among farmers, for example, by physicians from different European countries [6], and the inaccuracies in the diagnosis of farmer's lung in hospital discharge data [7].

Most epidemiological studies have used cross-sectional surveys to assess the prevalence of the disease and have relied on questionnaires to obtain data about symptoms and antigen exposure. Such questionnaires have sometimes been used alone, or more often, in association with further investigations, such as measurement of precipitating antibodies, chest radiography and/or pulmonary function tests. Although HP may develop insidiously without manifesting classic symptoms [8], questionnaires are probably quite sensitive in detecting the acute form of HP, although they may underestimate the chronic form of the disease. However, questionnaires lack specificity, since the symptoms of HP may be confused with the symptoms of other forms of reaction to inhaled materials, such as organic dust toxic syndrome, chemical pneumonitis, inhalation fevers or late asthmatic reactions. The demonstration of an antibody reaction against the provoking antigen may assist in establishing the diagnosis, but such antibody reactions are not present in all cases of HP and they lack specificity for the disease because they are often present in asymptomatic subjects exposed to the antigen [9–11]. Pulmonary function testing may also not be definitive, since the typical restrictive pattern in spirometry may be transient and is not always present. A decrease in the transfer factor of the lung (diffusing capacity) for carbon monoxide ($T_{L,CO}$) is more sensitive in detecting the acute form of HP, but this test is difficult to apply in large screening surveys [12]. Imaging techniques also have their limitations. A meta-analysis of available reports showed that only 80% of subjects with acute HP had abnormal chest radiographs [13]. Radiological abnormalities may resolve rapidly after an acute episode. Thus, both pulmonary function tests and radiography can underestimate the true prevalence of the disease, especially if they are performed at a preset time, rather than at the time of acute symptoms. High-resolution computed tomography and bronchoalveolar lavage cell analysis are the most sensitive tests, which are probably always abnormal in the acute stages of HP, but neither of these techniques are suitable for use as an epidemiological screening method [5, 14, 15].

Thus, questionnaire-based surveys often overestimate the prevalence of HP, whereas the use of more comprehensive investigations, such as chest radiography, pulmonary function tests and serological tests, may improve the accuracy of diagnosis but underestimate the true prevalence of the disease. These difficulties account for the wide range of reported prevalence and incidence rates for HP that depend upon the diagnostic criteria and methods used in any particular study, as well as on the nature and intensity of antigen exposure. These difficulties are illustrated in table 1, which presents a selection of recent prevalence studies (*i.e.* after 1980) carried out in various settings.

Very few cohort studies of incidence rates of HP have been published. One of the largest of such studies was performed amongst farmers in six districts in Finland and found the standardized annual incidence of farmer's lung leading to admission to hospital during 1980 was five per 10,000 farmers [34]. In Sweden the incidence of hospital-diagnosed cases of farmer's lung was estimated at two to three per 10,000 farmers per year [22]. A Japanese survey performed *via* nationwide questionnaire identified 835 cases of HP between 1980–1989; 75% of these cases were due to summer-type HP [35]. Although this study was not truly an incidence study, it gives an estimate of the annual incidence of HP in Japan.

The antigens of hypersensitivity pneumonitis

HP can be provoked by a diverse array of antigens, including bacteria (*e.g.* thermophilic actinomycetes), fungi (*e.g. Trichosporon cutaneum*), animal proteins (*e.g.* avian) and chemicals (*e.g.* di-isocyanates) [1]. Geographical, social and occupational factors determine the particular types of HP found throughout the world. Because of the great variety and distribution of these antigens, many individuals are exposed to potential causes of this syndrome as part of their occupational, home or recreational environments. Occupations in which there is contact with mouldy vegetations are particularly associated with the disease, so that specific syndromes have been described, for example, for farmers, mushroom workers, and sugar cane workers [21, 36, 37]. Those exposed to raw wood products are commonly affected by sequoiosis, suberosis, and maple bark strippers's disease [37]. Office and factory workers may be exposed to provoking antigens, such as thermophilic actinomycetes, *via* contaminated air conditioning systems [37]. Workers exposed to chemicals such as di-isocyanates may also develop HP [30, 38]. As working practices change, some syndromes are eradicated, and as new agents are introduced, new diseases are described. The home environment may also be a rich source of antigens of HP. In the UK, budgerigar fancier's lung may be the commonest variety, whereas in Japan, summer-type HP is the most prevalent form of the disease and is caused by contamination of homes by *T. cutaneum*

Table 1. – Selection of recent epidemiological studies of hypersensitivity pneumonitis, focusing on differences in prevalence rates in relation to diagnostic methods and type of exposure

Author [Ref.]	Location	Subjects studied n	Prevalence (%)		
			Q	Q + S	Q + S + further tests
Farmers					
BABBOTT [16]	Vermont, USA	210		0.48	
GRUCHOW [17]	Wisconsin, USA	1444		0.42	
MARCER [18]	Italy	2932	2.6		1.2
SAIA [19]	Italy	249			1.4
MALMBERG [20]	Sweden	512	19*		
DEPIERRE [21]	France	1763	15.3	4.4	~0.5–1
MALMBERG [22]	Sweden	6702			~0.25
STANFORD [23]	Ireland	380	10.4	1.7	0.5
VOHLONEN [24]	Finland	6790	1.7		
DALPHIN [25]	France	5703	1.4		
Pigeon breeders					
BANHAM [26]	Scotland	277	10.4	7.5	
BOURKE [27]	Scotland	208	31		
DE CASTRO [28]	Canary Islands	343	8	6.4	
Tobacco industry					
HUUSKONEN [29]	Finland	57	26	14	5.3
Isocyanates					
VANDENPLAS [30]	Canada	167			4.7
BAUR [31]	Germany	1780	0.9	~0.6	~0.9
Nacre factory					
ORRIOLS [32]	Spain	26	~40–50	23	~20
Machine operators					
BERNSTEIN [33]	Ohio, USA	16	37.5	37.5	~31

Q: questionnaire; S: serology. *: febrile reactions after exposure to organic dust.

[39, 40]. Recreational exposure to antigens of HP occurs in those participating in the sport of pigeon racing, and the widespread nature of provoking antigens is illustrated by examples of the syndrome being attributed to contamination of water by a pullularia fungus in sauna taker's disease and to contamination of a mouthpiece by *Candida albicans* in saxophonist lung [28, 41, 42].

Although there is a diverse array of antigens that provoke HP, they share certain important characteristics that distinguish them from the antigens that provoke asthma for example, and not all inhaled antigens have the capacity to provoke HP. These characteristics include their size, solubility, particulate nature and their capacity to provoke a nonspecific inflammatory response and a specific immune reaction. Antigens provoking HP are usually <3 μm in diameter and can, therefore, be inhaled into the distal bronchial tree and alveoli, where they may be cleared *via* local lymphatic drainage to the hilar nodes, which seems to be important in inducing an immunoglobulin-G (IgG) antibody response [43]. In contrast, antigens more typically associated with asthma are larger, ~30 μm in diameter, and are preferentially deposited in the proximal airways, where they tend to provoke an IgE antibody response in atopic subjects. Nevertheless, a single antigen may sometimes produce both types of response [30, 38] and occasionally, larger particles may reach the alveoli after degradation or being dissolved in lung secretions. The antigens of HP also have powerful adjuvant properties with a capacity to activate complement by the alternative pathway, to stimulate alveolar macrophages and to enhance delayed cellular responses [44, 45]. For example, the cell wall of many moulds and yeast spores contain β-(1–3)-D-glucan, which can activate alveolar macrophages following interaction with a specific receptor causing the release of interleukin (IL)-1 and tumour necrosis factor (TNF)-α [4]. Many of the antigens of HP may also be resistant to degradation. For example, pigeon intestinal mucin has been identified as a major antigen in pigeon fancier's lung [46]. This antigen is a high molecular weight glycoprotein comprising 70–80% carbohydrate with a heavily glycosylated protein core and is resistant to degradation [1, 46]. Similarly, the causative agent of Japanese summer-type HP has been identified as *T. cutaneum* and it is the high molecular weight, polysaccharide component of the antigen that provokes an antibody response [47].

Genetic susceptibility and host factors

A characteristic feature of HP is that only 5–15% of subjects exposed to a provoking antigen develop the disease [48]. For example, ~3.4% of budgerigar fanciers, 8% of pigeon fanciers, and 4.3% of farmers develop HP [21, 28, 39]. A much larger number of subjects exposed to the antigen develop sensitization in the form of a humoral or cellular immune response, but do not progress from sensitization to overt disease.

Host risk factors are poorly characterized, with the exception of those linked to exposure factors. HP is

more common in males than females with an over-representation of middle-aged individuals. This is likely to represent differences in exposure to the provoking antigens. HP has been diagnosed in patients of all ages, including infants and children. Pregnancy and delivery appear to trigger symptoms and illness in females with pigeon fancier's lung [49], with no evidence that hormonal or immunological status play a role. Familial forms of HP have been described for both bird fancier's lung and farmer's lung [50, 51] but genetic investigations have failed to confirm hereditary factors for HP [52, 53]. For many other immune-mediated lung diseases there is evidence of a genetic predisposition, which, in conjunction with a specific environmental factor, leads to disease expression. Beryllium lung disease is the classic example of this phenomenon, where subjects with a particular human leukocyte antigen (HLA) type, HLA-DPB1 Glu-69, are particularly susceptible to developing the disease because of the important role played by this HLA type in the binding of beryllium and in its presentation to T-cell receptors [54]. Several studies have suggested links between HLA types and HP, with an increased occurrence of HLA DR7 in pigeon fancier's lung in a Mexican population [55], HLA B8 in farmer's lung and pigeon fancier's lung in Caucasians [56–58], and HLA-DQw3 in Japanese summer-type HP [40]. Other studies have found no association with HLA type [59].

Differences between studies may provide clues to additional environmental or genetic factors determining disease outcome. For example, pigeon fancier's lung in Mexican patients, with a high prevalence of HLA-DR7, produces a disease similar to idiopathic pulmonary fibrosis, with clubbing, fibrosis and a poor prognosis, which contrasts with a more benign clinical course in Caucasian populations [60, 61]. Discrepant results between studies may reflect spurious associations, the diversity of the clinical syndrome, the complexity of genetic factors involving polygeneic inheritance (several genes influencing the trait) or genetic heterogeneity (different genes operating in different populations), or the influence of additional environmental factors.

Genetic factors are known to influence various components of the immune response in different diseases, as outlined in detail in the report by NEMERY *et al.* [62] in this Supplement. For example, atopy is linked to a locus on chromosome 11 close to genes coding for the high affinity IgE receptor, and cytokine gene polymorphisms are related to rejection of transplanted organs, with the high-producing TNF-α genotype being associated with acute rejection [63, 64]. In HP there are preliminary reports of such gene polymorphisms playing an important role, with high-responders for TNF-α being at greater risk for developing farmer's lung and pigeon fancier's lung [65, 66]. Polymorphisms of the fragment crystallizable (Fc)-receptor may also be important in determining the relevance of a specific antibody response to an antigen [1, 67]. Similarly, animal models of HP suggest that multigenic factors are important in determining the susceptibility of certain strains of mice to the development of granulomatous lung inflammation [68].

Environmental factors and cofactors

HP is probably the allergic disease in which the role of exposure factors is most important. Environmental risk factors, including antigen concentration, duration of exposure, frequency (or intermittency) of exposure, particle size, antigen solubility, use of respiratory protection, and variability in work practices may influence disease latency, prevalence, severity and course [69].

It is generally believed that acute HP usually results from very intense, intermittent exposure to inhaled antigens and that subacute HP results from a less intense but continuous exposure, although this relationship is not fully established [70]. Chronic HP may develop from acute or subacute forms of the disease, but may also arise directly as a consequence of prolonged low level exposure [48]. Although HP may occur after indirect [71] or apparently trivial exposure [72], in acute and probably subacute forms, there may be a direct relationship between the intensity of antigen exposure and the development of the disease.

These exposure factors have been well described in farmer's lung. The risk of developing farmer's lung bears a close relationship to the concentration of airborne micro-organisms [4, 73]. This explains why farmer's lung is most common in late winter, when stored hay is used to feed cattle, and in regions with heavy rainfall, where feed is likely to become damp, forming a substrate for microbial proliferation. In a large French study, a close linear relationship between the prevalence of farmer's lung and altitude was observed [25]. Altitude was closely related to the amount of rainfall during haymaking and consequently, with the quantity of mould formation. In a Finnish hospital-based study, the incidence rates of farmer's lung were significantly correlated with the amount of daily rainfall during the haymaking period [34]. These findings confirm earlier data [74], and have also been observed recently in Ireland [75].

Although less clearly documented, similar observations have been made in pigeon fancier's lung. Comparisons of prevalence rates in different areas or types of exposure suggest that the occurrence of the disease is partly related to the intensity and perhaps the duration of contact with the pigeon antigens [26–28, 76]. Thus, there is a seasonal variation in specific antibody levels in subjects with pigeon fancier's lung, with a peak in antibody production during late summer, when maximum avian exposure is associated with the sporting season [77]. A relationship between sensitization to avian antigens and intensity [28], as well as duration of exposure [26], has been demonstrated.

In HP of other aetiologies, such relationships are less obvious because there are few epidemiological studies with a sufficient number of patients. However, the considerable differences in the reported prevalence of HP caused by isocyanates in two large studies, *i.e.* $<1\%$ [31] and $\sim 5\%$ [30], are also likely to be due to differences in exposure factors.

These studies, and studies in which respiratory protection devices have been used [78, 79], suggest

that there may be an exposure threshold that has to be exceeded before acute and perhaps subacute forms of HP develop. The risk of HP is low under this exposure threshold and high beyond it, with a dose/effect relationship between the level of antigen exposure and the occurrence of the disease in the latter situation.

It is known that additional environmental factors and cofactors may influence the basic interaction of antigenic stimulus and host immune response in HP. It has been shown that HP occurs more frequently in nonsmokers than smokers. Several explanations have been proposed: smoking, for example, has been shown to reduce the IgG response to inhaled antigens, influence cytokine production and impair macrophage function with a reduced risk of developing HP [80, 81]. There is some evidence to suggest that in sensitized subjects, the onset of HP may be precipitated by additional nonspecific lung inflammation, and this may, in part, explain why the disease may develop in some subjects after a long period of time, often many years, during which the subject seems to have remained in a state of equilibrium with the antigen, with no symptoms. For example, McGAVIN [82] described two farmers who had long-term exposure to hay but who developed farmer's lung only after infection with *Mycoplasma pneumoniae*. Similarly, DAKHAMA *et al.* [83] have shown that respiratory viruses, such as Influenza A, are commonly detectable by the polymerase chain reaction in the lower airways of patients presenting with acute HP and in a mouse model of HP. CORMIER *et al.* [84] have shown that Sendai virus infection enhances the lung response to antigenic challenge with *Saccharopolyspora rectivirgula*. It has long been accepted that most animal models of HP require the induction of nonspecific lung inflammation by adjuvants such as bacille Calmette-Guérin (BCG) or carrageenan, before HP can be provoked by antigen challenge [85]. The fact that many of the antigens of HP also have adjuvant properties that enable them to activate, complement and release cytokines directly may be important. In many circumstances, subjects who develop a specific immune-mediated disease in the form of HP are also exposed to an array of agents that have the capacity to induce nonspecific lung inflammation. Thus, pigeon fanciers are exposed to infectious agents such as *Chlamydia psittaci, C. pneumoniae and Cryptococcus neoformans*, endotoxins and pesticides, and farmers are exposed to various respiratory pathogens, dusts and toxins [49, 86–88]. It is accepted that airborne endotoxin exposure potentiates allergen-specific airway inflammation and allergic responses, thereby providing a potential link between the separate entities of organic dust toxic syndrome and HP [89].

Clinical features

HP is not a uniform disease entity, but rather a complex dynamic clinical syndrome that varies in its initial presentation and clinical course, resulting in the emergence of different patterns of disease over time (fig. 2).

Traditionally, HP has been described as occurring

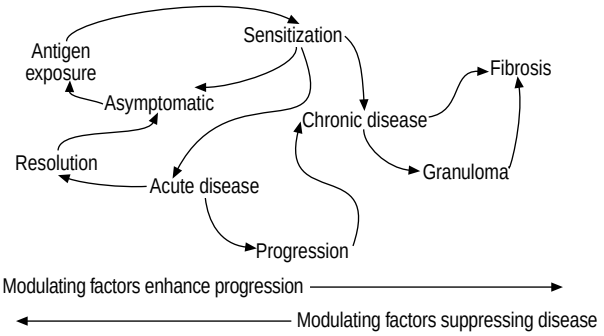

Fig. 2. – Hypersensitivity pneumonitis is a complex dynamic clinical syndrome which varies in its initial presentation and clinical course such that different patterns of disease emerge over time. A variety of modulating factors may enhance or suppress the evolution of the disease.

in acute, subacute and chronic forms [90]. The acute form manifests as recurrent episodes of dyspnoea and cough with fever, chills and malaise occurring about 4–8 h after exposure to antigen, and usually resolving within about 24–48 h. Lung function tests typically show a restrictive defect with reduced gas diffusion and hypoxaemia, and a chest radiograph may show alveolar shadowing. The chronic form is characterized by the insidious development of dyspnoea and pulmonary fibrosis in a patient that has not experienced acute symptoms. The subacute form is similar to the chronic form in that dyspnoea develops insidiously, but these patients also have discrete episodes of acute symptoms after antigen exposure.

An alternative classification system has been proposed that emphasizes the dynamic nature of the disease and allows for the evolution of different clinical patterns over time [91]. Three main clinical patterns are recognized: "acute progressive", "acute intermittent nonprogressive" and "recurrent nonacute disease". In acute progressive disease, patients experience debilitating symptoms after antigen exposure and symptoms progress on each subsequent exposure such that the patient often recognizes the nature of the problem and stops antigen exposure. In acute intermittent nonprogressive disease, patients have similar classic symptoms after antigen exposure, but they are less intense. Many of these subjects continue to be exposed to the antigen and, paradoxically, symptoms may become less severe on recurrent exposure resulting in a long-term clinical picture that is often stable, with no deterioration in clinical status or lung function over years [61]. In recurrent nonacute disease, the symptoms are of a chronic nonspecific nature and their lack of a temporal relationship to antigen exposure may lead to a delay in diagnosis. In this form of the disease, the patient presents with permanent disability, chronic dyspnoea, impaired lung function, pulmonary fibrosis and emphysema.

Classification of HP into acute and chronic forms has tended to cause confusion as it is often assumed that there is an inevitable progression from acute to chronic disease if antigen exposure continues. However, the interaction of antigen exposure and host response in the initiation and progression of the

disease is considerably more complex than this and the clinical course of the disease is unpredictable. In some patients, continued exposure to the antigen results in a progressive loss of lung function and occasionally, the disease may progress even after contact with the antigen has ceased [92]. The paradoxical phenomenon of disease stability or regression despite continued antigen exposure has been documented in a number of studies. For example, patients with farmer's lung sometimes demonstrate spontaneous remissions or significant improvement in lung function, even if they continue to work on the farm with ongoing antigen exposure [12, 93]. Similarly, in the first description of pigeon fancier's lung by REED *et al.* [94] in 1965, the patient continued to keep pigeons without experiencing exacerbations, and long-term follow-up studies show that some fanciers have normal lung function despite having had acute intermittent nonprogressive HP for many years [61, 90]. This intriguing phenomenon remains difficult to explain adequately, but has been confirmed in animal models of the disease, where repeated antigen challenge often results in a decrease rather than a progression of the pulmonary inflammatory response [95]. The clinical picture is distorted by the self-regulatory effect of symptoms as patients with severe symptoms are likely to modify their antigen exposure [61, 91].

The factors that determine the initial clinical presentation and subsequent course of HP are uncertain, but are likely to involve both the circumstances of antigen exposure and a range of modulating factors governing the immune response in an individual. For example, in Mexico, pigeon fancier's lung usually occurs in females that have kept domesticated pigeons in their home. In this environment, antigen exposure is prolonged and low grade, and the disease usually pursues an insidious clinical course without acute episodes. In these circumstances, the disease resembles other chronic interstitial lung diseases, such as idiopathic pulmonary fibrosis [60, 96]. This is similar to the experience of budgerigar fancier's lung in the UK [39]. In contrast, individuals who keep 100–200 pigeons in a loft for the sport of pigeon racing have intermittent high intensity exposure, and acute intermittent nonprogressive HP is the commonest form of the disease in this population [61, 91].

Although HP is classically regarded as a disease of the distal gas exchange portion of the lung, the spectrum of lung involvement includes a bronchial component, with physiological evidence of both large and peripheral airway obstruction and histological evidence of bronchitis and bronchiolitis [26, 96]. Chronic bronchitis in the form of chronic cough and sputum production, is common in farmers and pigeon fanciers and shows a relationship with HP [21, 27, 28, 97]. However, it is not certain if the bronchial aspect of the disease is truly a specific, immunologically-mediated "hypersensitivity bronchitis" or whether it results from a direct inflammatory effect of inhaled organic dust. Similarly, many subjects exposed to organic dusts report symptoms such as cough, wheeze, sneezing and watering of the eyes within 30–60 min of antigen exposure [28]. These immediate symptoms are often found in association with the classic delayed symptoms of HP, but they form an indistinct clinical entity that probably results from a direct irritant effect, rather than a specific immune reaction. Nevertheless, such symptoms may cause confusion in clinical practice.

Diagnosis

When assessing respiratory disease in patients exposed to an antigen of HP, it may be difficult to differentiate HP from a variety of other common lung diseases, such as asthma or chronic obstructive pulmonary disease, which may be aggravated by the nonspecific irritant effect of inhaled particulate matter, and from nonimmunologically-mediated syndromes associated with the inhalation of organic dusts, such as organic dust toxic syndrome and inhalational fevers. The diverse and dynamic nature of HP makes it difficult to define precise diagnostic criteria for the disease [98].

No single clinical feature or laboratory test is diagnostic of the disease and the diagnosis is made from a combination of clinical features, radiographic abnormalities, lung function tests and immunological tests (table 2). Suspicion of an association between symptoms and contact with a provoking antigen is the first step in the diagnostic process. In the acute form of HP, this association may be apparent to the patient and the diagnosis may be quite straightforward. In the chronic form of HP, symptoms often do not show a temporal relationship to antigen exposure and errors occur if specific questions are not asked about exposure to antigens of HP. Sources of antigen may not always be apparent and it may be necessary to consider occult exposure to antigens from contaminated air conditioning or heating systems in the home or work environment, for example [37, 41, 42].

An important step in the diagnostic process is the demonstration of either an antibody or cellular immune response to the provoking antigen. The development of such an immune response confirms that the patient has had a sufficient level of exposure

Table 2. – Steps to diagnose hypersensitivity pneumonitis

1. Identify exposure to a provoking antigen
2. Demonstrate an immune response to the antigen
3. Establish the relationship of symptoms to antigen exposure
4. Assess the degree of impairment of lung function
5. Determine the extent of radiographic abnormality
6. Consider the need for lung biopsy or bronchoalveolar lavage
7. Consider the usefulness of a natural or laboratory-based challenge study
8. Exclude alternative diagnoses (*e.g.* sarcoidosis, inhalation fevers)

Because of the diverse and dynamic nature of hypersensitivity pneumonitis the diagnosis is made from a combination of features with judicious use of more invasive tests and exclusion of alternative diagnoses. The diagnostic approach should be adapted to the circumstances of the clinical problem.

to the antigen to develop sensitization, but this is not sufficient to establish a diagnosis of HP, since many asymptomatic subjects show a similar level of humoral or cellular responses to symptomatic patients. A variety of antibody or cellular responses show a greater degree of disease specificity than others, but the search for a single immunological test that is truly specific to the disease has not been successful and the concept of such a test probably underestimates the capacity of the immune system to respond in a complex and diverse way to inhaled antigens in HP [1].

Lung function tests in HP demonstrate the physiological consequences of immunologically-mediated events and typically show a reduction in lung volumes, impairment of gas diffusion and hypoxaemia [12, 61, 92, 93]. Chest radiography shows a range of abnormalities from an alveolar filling pattern to reticulonodular shadowing, depending on the combination of alveolitis and fibrosis. The chest radiograph may be normal even in the presence of significantly impaired lung function and in these circumstances computed tomography is more sensitive [99] (fig. 3). A particularly characteristic pattern is the presence of ground-glass shadowing with areas of decreased attenuation and air trapping on expiratory scans, but poorly defined nodules and honeycomb lung may be present, depending on the stage of the disease.

The chronic form of HP must be distinguished from other causes of interstitial lung disease, such as sarcoidosis or idiopathic pulmonary fibrosis, and in these cases, bronchoalveolar lavage and lung biopsy may be indicated. The most characteristic cell profile in lavage fluid is of a lymphocytic alveolitis with a predominance of CD8 T-cells. However, the cell profile is dependent upon the interval from last antigen exposure and a neutrophil alveolitis is seen immediately after antigen challenge and the number of CD8 T-cells falls after cessation of antigenic contact [100–103]. Furthermore, a lymphocytic alveolitis is also found in asymptomatic subjects exposed to an antigen and in patients with organic dust toxic syndrome so that, as with the antibody response, the demonstration of a cellular immune response is not sufficient to establish a diagnosis [100, 103]. Lung biopsy may show a spectrum of abnormalities, which are distinctive, but not pathognomonic, including lymphocyte infiltration, foamy macrophages, granulomas, bronchiolitis and fibrosis [96]. In advanced disease, where fibrotic changes predominate, the pathology features may be indistinguishable from other causes of lung fibrosis, such as idiopathic pulmonary fibrosis.

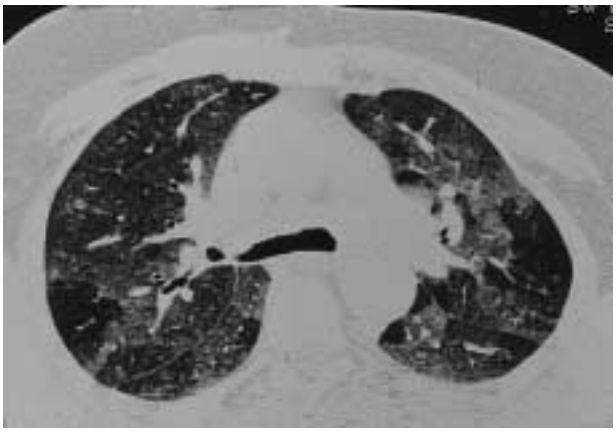

Fig. 3. – Computed tomography is more sensitive than the chest radiograph in detecting the changes of hypersensitivity pneumonitis. A characteristic pattern is of ground-glass shadowing with areas of decreased attenuation and air trapping on expiratory scans.

Observing the response to a natural exposure to the antigen or to a laboratory-based challenge study test may occasionally be useful [104]. Conversely, the response to a period of antigen avoidance can be studied. The use of inhalational challenge studies in the diagnosis of HP has been hampered by the lack of standardized antigens, the diversity of the clinical manifestations of the disease and the difficulties in defining objective criteria that characterize a positive test [98]. HENDRICK *et al.* [104] defined criteria for a positive "alveolar" response in a study of 144 antigen challenges in 31 subjects. Positive reactions were recognized subjectively from symptoms of a flu-like illness, and objective measurements included an increase in exercise minute ventilation, temperature, blood neutrophils and a fall in vital capacity. Measurement of gas diffusion was too insensitive to be useful. However, many of these criteria for a positive challenge test in HP overlap with the features of organic dust toxic syndrome and inhalational fevers, and, therefore, may not adequately differentiate between immunologically-mediated and nonallergic inflammatory responses [2, 98].

Although characteristic abnormalities of lung function, histology, radiology and immunological tests have been described in HP, very few patients demonstrate all these features at the same time, so that the diagnosis is established from the combination of features in a particular case. The diagnostic approach should be adapted to the circumstances of the clinical problem, depending on whether the patient presents with the acute or chronic form of the disease or an advanced interstitial lung disease of uncertain aetiology.

Pathogenesis

Initially, it was thought that HP was an immune complex-mediated disease, but subsequently, greater emphasis has been placed on the role of cellular immune responses. In experimental animal models of HP, the disease cannot be induced by the passive transfer of hyperimmune serum, but transfer of specifically sensitized lymph node cells intraperitoneally followed by antigen challenge *via* the respiratory tract, produces lesions closely resembling those seen in HP in humans [105]. However, separation of different components of the immune response is artificial, since the immune system is capable of responding in a variety of ways to a single antigen and immune responses are interlinked and subject to feedback loops and modulating factors that may enhance or suppress the inflammatory process. No single component of

the immune response accounts for the diverse and dynamic patterns of the disease seen in clinical practice and it seems likely that it is the relative balance between different responses and the influence of modulating factors that determine the nature of the disease as it evolves over time. Notions of HP have, therefore, moved from an initial simplistic concept of an "immune complex disease" to a realization that it is truly a "complex immune disease".

Immediately after antigen challenge there is an influx of neutrophils into the alveoli, which corresponds with the clinical phase of acute symptoms [101, 103]. This neutrophil alveolitis may be stimulated by the formation of immune complexes, direct activation of complement by the alternative pathway or by the endotoxic effect of inhaled antigen [1]. This neutrophil alveolitis is transient and is followed by influx of activated T-cells with a preponderance of CD8 T-cells. As time passes from antigen challenge, the number of CD8 cells decreases and there is a corresponding increase in CD4 T-cells [1, 100–103]. Alveolar macrophages are activated and an array of proinflammatory cytokines, such as TNF-α, IL-1 and IL-8, are produced. Regulatory cytokines, such as IL-10, are also secreted and may play a regulatory role in damping down the inflammatory responses [1, 100]. A number of other regulatory factors have been identified. For example, soluble TNF receptors are inhibitors of TNF and can block TNF bioactivity in HP [106]. In some patients, these humoral, cellular and cytokine responses lead to progressive inflammation and the formation of granulomas, which are a characteristic feature of the disease. The factors governing granuloma formation are poorly understood but animal models of schistosome-induced granulomatous inflammation show that certain factors, such as T-suppressor effector factor and cyclo-oxygenase products, inhibit macrophage expression and granuloma formation, whereas other factors, such as lipoxygenese products, enhance granuloma formation [100]. There are problems in translating these findings to human disease since there may be fundamental differences in immune function in different species, but such studies emphasize modulating factors which may up- or down-regulate the disease process at various stages. The precise links between inflammation and fibrosis in interstitial lung disease are also not completely understood, but may be related to the extent of injury to epithelial cells and basement membrane, the antioxidant status of the subject, and factors governing fibroblast activation, collagen deposition and collagen degradation [107].

A fundamental difficulty in understanding the pathogenesis of HP is that many of the immune responses are found both in patients with the disease and in asymptomatic antigen-exposed subjects [1, 100, 103]. Although sensitization to the provoking antigen is a key step in the pathogenesis of HP it does not equate with disease development. Some elements of the immune inflammatory response may be holding the disease in check and this may explain why in some animal models of HP, and in some patients, resolution of the disease may occur despite continued antigen exposure [60, 95].

At present, it is difficult to distinguish beneficial inflammatory responses, which may form part of normal antigen handling mechanisms, from deleterious inflammation leading to lung fibrosis. It may not necessarily be appropriate to consider all lung inflammation as a disease. The concept of a beneficial inflammatory response is well established as part of the host response to injury or infection, but is more controversial in interstitial lung disease. Nevertheless, lymphocytic alveolitis is common in asymptomatic antigen-exposed subjects and does not correlate with the development or progression of HP. Furthermore, in sarcoidosis, for example, patients with bilateral hilar adenopathy and erythema nodosum have the highest intensity alveolitis, and yet, the best prognosis in terms of disease resolution [108]. Curiously, although corticosteroids hasten the recovery of lung function in HP, they may be associated with more frequent recurrences of acute symptoms in patients with continued antigen exposure [109]. This suggests that anti-inflammatory drugs may interfere with both beneficial and deleterious components of the immune inflammatory response in HP.

Treatment

Antigen avoidance is the key element in the treatment of HP and complete cessation of exposure to the provoking antigen is the safest advice for these patients. In some circumstances, the recognition of a clinical syndrome can lead to changes in the occupational environment, so that the risk to workers is eliminated, as has occurred with sugar cane after the discovery of bagassosis [37]. Education of certain "at risk" populations may be helpful in the early recognition of symptoms and in encouraging them to adopt preventative strategies. Patients are sometimes reluctant to consult doctors when they fear that their livelihood is at stake, as in the case of farmers, or that their commitment to their sport will not be adequately appreciated, as in the case of pigeon fanciers. In order to gain the confidence of the patient, it is essential that the doctor is well informed about the different outcomes of the various forms of HP and has a sympathetic attitude to the difficulties a patient may have in achieving complete cessation of antigen exposure [91]. Patients with the acute progressive form of the disease have debilitating symptoms such that they are usually prepared to cease all exposure to the antigen once the diagnosis has been established. In contrast, patients with acute intermittent nonprogressive HP may have already developed their own antigen avoidance strategies to control their symptoms. Pigeon fanciers can be encouraged to spend less time in the loft, to avoid activities associated with high levels of antigen exposure, such as "scraping out", and to wear a loft coat and hat that are removed on leaving the loft so as to avoid continuing contact with antigen carried on clothing or hair [91]. Increasing the level of ventilation in the loft may also be helpful in reducing antigen counts [110]. In the case of farmer's lung, the risk of HP can be reduced by conversion to silage for foddering of animals and by the adoption of

modern farming practices, with drying and heating systems that reduce the moisture content of hay [111]. Spraying hay with proprionic acid can be useful in suppressing the growth of thermophilic actinomycetes [37]. Respiratory protection masks have been shown to improve symptoms, prevent a reaction to antigen challenge and reduce the level of circulating antibodies [112]. The protection provided by masks is not complete, however, since most masks permit penetration of particles <1 μm in diameter and leakage through defects in the fit of the mask to the face allows particles to by-pass the filter. Ongoing supervision of symptoms, lung function and chest radiographs is essential to ensure that the patient is not developing progressive disease, and sequential monitoring of the level of circulating antibody to the provoking antigen is a useful guide to the effectiveness of avoidance measures [91, 111].

Although there is often an apparent beneficial response to corticosteroids in HP, it is difficult to distinguish between the effects of treatment, the natural course of the disease and the effect of antigen avoidance. A randomized, double-blind, placebo-controlled study of corticosteroids in patients with acute farmer's lung found that patients given prednisolone showed more rapid improvement in lung function, with a significantly higher diffusing capacity at 1 month, compared to the control group, but there was no difference in the long-term outcome between the two groups [109]. Recurrence of acute farmer's lung was more common among corticosteroid treated patients than among controls if they had continuing antigen exposure, raising the possibility that corticosteroid treatment was also suppressing the counter-regulatory aspects of the immune response in these patients.

Conclusion

It is now clear that hypersensitivity pneumonitis is a complex dynamic clinical syndrome that varies in its initial presentation and clinical course. The prevalence rates of hypersensitivity pneumonitis in epidemiological studies vary widely and depend not only on exposure-related variables and host-related factors, but also on the chosen diagnostic criteria. The diverse and dynamic patterns of the disease seen in clinical practice are reflected in current concepts of pathogenesis, which recognize the inter-play of virtually all elements of the immune system in this disease and emphasize the evolution of the response over time and the importance of modulating factors that influence the interaction of antigenic stimulus and host immune response, either enhancing or suppressing the inflammatory process. The intensity of exposure to the antigen stimulus is a crucial factor in the risk of developing the acute and subacute forms of hypersensitivity pneumonitis. Reducing the level of exposure clearly decreases the frequency of hypersensitivity pneumonitis and is the most important element in treatment of the disease, even if many of the interactions between antigenic contact and the clinical presentation and course of the disease remain obscure.

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