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section 18 Respiratory disorders 4244 Hare SS, et al. (2012). The radiological spectrum of pulmonary lymphoproliferative disease. Br J Radiol, 85, 848–64. Jaffre S, et al. (2006). Fatal haemoptysis in a case of lymphomatoid granulomatosis treated with rituximab. Eur Respir J, 27, 644–6. Katzenstein AL, Doxtader E, Narendra S (2010). Lymphomatoid granulomatosis: insights gained over 4 decades. Am J Surg Pathol, 34, e35–e48. Kido T, et al. (2012). Detection of MALT1 gene rearrangements in BAL fluid cells for the diagnosis of pulmonary mucosa-associated lymphoid tissue lymphoma. Chest, 141, 176–82. Makol A, et al. (2009). Lymphomatoid granulomatosis masquerading as interstitial pneumonia in a 66-year-old man: a case report and re- view of literature. J Hematol Oncol, 2, 39–45. Tian X, et al. (2012). Lymphocytic interstitial pneumonia and other benign lymphoid disorders. Semin Respir Crit Care Med, 33, 450–61. Verschuuren EAM (2009). Post-transplant lymphoproliferative dis- ease and other malignancies. Eur Respir Mon, 45, 226–37. 18.14.4 Hypersensitivity pneumonitis S. J. Bourke and G.P. Spickett ESSENTIALS Hypersensitivity pneumonitis is an immune-mediated lung disease in which the repeated inhalation of certain antigens provokes a hypersensitivity response, with granulomatous inflammation in the distal bronchioles and alveoli of susceptible people. A diverse range of antigens including bacteria (Thermophilic actinomycetes), fungi (Trichosporon cutaneum), animal proteins (bird antigens), mycobac- teria, and chemicals may cause the disease. The commonest forms are bird fancier’s lung, farmer’s lung, humidifier lung, and metal- working fluid pneumonitis. In some cases no antigen is identified. Acute disease is characterized by recurrent episodes of breath- lessness, cough, fevers, malaise, and flu-like symptoms occurring
4–8 hours after antigen exposure. Fever and basal crackles are the main physical signs. This form of hypersensitivity pneumonitis is most commonly seen where there is intermittent high-level antigen exposure, as in the case of pigeon fancier’s lung or farmer’s lung. Most patients recover fully from each acute exacerbation within a day or so, and if the cause is recognized and further

exposure avoided there is little risk of persisting pulmonary dysfunction. Chronic disease is characterized by the insidious development of dyspnoea and persistent pneumonitis, sometimes progressing to lung fibrosis. This form of the disease is typically seen following long- standing low-level antigenic exposure, such as occurs in a person who keeps a single budgie (parakeet) in the home. Clinical features are similar to those of other varieties of pulmonary fibrosis, but clubbing is uncommon. Permanent fibrotic lung damage can eventually lead to hypoxaemia, pulmonary hypertension, right heart failure, and death. Investigation—the chest radiograph may be normal or show a ground-glass appearance; in subacute disease small reticular opacities may be seen; in chronic disease there is fibrosis. CT char- acteristically shows centrilobular nodules, mosaic air trapping, and ground-glass shadowing. Lung function studies typically show a re- strictive pattern with impaired gas diffusion. IgG antibody against the provoking antigen indicates sufficient exposure for the disease to de- velop, but such antibodies are frequently found in subjects who are similarly exposed but clinically unaffected. Bronchoalveolar lavage typically shows a lymphocytic alveolitis, and lung biopsy shows peri-bronchocentric lymphocytic inflammation with poorly formed granulomas and sometimes fibrosis. Management—complete cessation of contact with the provoking antigen is the safest advice for patients with hypersensitivity pneu- monitis. This usually leads to resolution of the acute form of the dis- ease. Corticosteroids hasten the rate of recovery, but do not alter the long-term outcome. Some patients with chronic hypersensitivity pneumonitis progress to severe fibrotic lung disease resembling idio- pathic pulmonary fibrosis. If these patients fail to respond to cortico- steroids and other immunosuppressive agents, lung transplantation is sometimes appropriate. Introduction Hypersensitivity pneumonitis (HP), previously known as extrinsic allergic alveolitis, is an immune-mediated lung disease in which the repeated inhalation of certain antigens provokes a hypersensitivity reaction with granulomatous inflammation in the distal bronchioles and alveoli of susceptible people. The essence of the disease is an interaction between specific inhaled antigens and the patient’s im- mune system. It is therefore an allergic lung disease and it should be distinguished from several nonallergic inflammatory reactions such as inhalation fevers, toxic alveolitis, and organic dust toxic syn- drome, which occur after a single exposure to an unusually high level of organic dust by toxic rather than immune mechanisms. By con- trast, individual susceptibility is a characteristic feature of immune- mediate disease such as HP, and only a small percentage of those repeatedly exposed to the antigen develop the disease. Aetiology HP can be caused by a diverse range of antigens including bac- teria (Thermophilic actinomycetes), fungi (Trichosporon cutaneum, Aspergillus fumigatus), animal proteins (bird antigens), mycobacteria (Mycobacterium immunogenum), and chemicals (di-isocyanates). Geographical, social, and occupational factors determine the particular types of HP found in different parts of the world (Table 18.14.4.1). Because of the great diversity and distribu- tion of these antigens, many individuals are exposed to potential causes of HP as part of their occupational, home, or recreational environments. Farmer’s lung is regarded as the prototype of HP since the classic description by Campbell et al. in 1932. Occupations in which there is contact with mouldy vegetation are particularly associated with the disease, and specific syndromes have therefore been described, for example, in respect of farmers, mushroom workers, and sugar cane workers (bagassosis). Those exposed to raw wood products have been

18.14.4 Hypersensitivity pneumonitis 4245 Table 18.14.4.1 Agents reported to cause hypersensitivity pneumonitis Agent Source Appellation (if any) Microorganisms Acinetobacter woffii Metal-working fluid Machine worker’s lung Alternaria Paper-mill wood pulp Wood pulp worker’s lung Aspergillus sp. Farm produce, maize (corn) Farmer’s lung Aspergillus clavatus Whisky maltings Malt

worker’s lung Aspergillus fumigatus Vegetable compost, cork Farmer’s lung, suberosis Aspergillus versicolor Dog bedding (straw) Dog house disease Aureobasidium pullulans Redwood/domestic cellar Sequoiosis Bacillus subtilis Wood/cleaning preparations Candida albicans Heated swimming pool; saxophonist lung Saxophonist lung Cephalosporium Sewage Sewage worker’s lung Cryptococcus albidus Asian homes in humid summers Summer-type hypersensitivity pneumonitis Cryptostroma corticale Maple Maple bark stripper’s lung Debaryomyces hansenii Home ultrasonic nebulizer Eurotium sp. Metal-working fluid Machine worker’s lung Fusarium sp. Metal-working fluid/home Machine worker’s lung Graphium Redwood Sequoiosis Grifola fondosa Maitake mushrooms Mushroom worker’s lung Humicola fuscoatra Domestic home Hypsizigus marmoreus Mushrooms Mushroom worker’s lung Lentinus edodes Mushrooms Mushroom worker’s lung Lycoperdon Puffballs Lycoperdonosis Lyophyllum aggregatum Mushrooms Mushroom worker’s lung Merulius lacrymans Domestic wood Mucor stolonifer Paprika Paprika splitter’s lung Mycobacterium sp. Metal-working fluid Machine worker’s lung Paecilomyces sp. (nivea/variotii) Hardwood, oil heater Penicillium camemberti Salami production P. casei Cheese Cheese washer’s lung P. chrysogenum/cyclopium Domestic wood P. citrinum Enoki mushroom cultivation P. frequentens Cork Suberosis P. nalgiovense Pork sausage mould P. verrucosum Gorgonzola cheese Peziza domiciliana Flooded basement El Niño lung Pleurotus ostreatus/eryngii Mushrooms Mushroom worker’s lung Pseudomonas fluorescens Metal-working fluid Machine worker’s lung Rhodotorula sp. Ultrasonic humidifier Saccharomonspora viridis Logging plant Sphingbacterium spiritvorum Domestic steam iron Sporobolomyces Horse barn straw Streptomyces albus Soil/peat Thermophilic actinomycetes (Saccharopolyspora rectivirgula, Thermoactinomyces vulgaris) Hay/straw/grain/mushroom compost/bagasse/heated water/domestic cellar/esparto grass Farmer’s lung Mushroom worker’s lung Bagassosis Esparto plasterer’s lung Trichosporon cutaneum/ovoides Asian homes in humid summers Summer-type hypersensitivity pneumonitis (continued)

section 18 Respiratory disorders 4246 affected as maple bark stripper’s lung, sequoiosis, and suberosis (cork worker’s lung). Office and factory workers may be exposed to aetio- logical agents via humidifier or ventilation systems that have become contaminated with a variety of agents including bacteria, mycobac- teria, fungi, protozoa (amoebae), and metazoa (nematode debris). Workers exposed to some reactive chemicals, such as di-isocyanates, may also develop HP, and here the chemical acts as a hapten com- bining with body proteins to produce larger antigenic molecules. As practices change, some classic causes of HP have faded, but new syndromes are constantly being identified. Metal-working fluid pneumonitis has recently come to prominence because of outbreaks of HP in workers in car manufacturing, due to contamination of coolant and lubricant fluid. The home environment may also be a rich source of the antigens of HP. Budgie fancier’s lung may be the commonest form of the dis- ease in the United Kingdom due to pet birds kept in homes. Mould contaminating houses may also provoke HP: summer-type HP is common in Japan and due to contamination of the home environ- ment by fungi such as Trichosporon cutaneum or Cryptococcus albi- dus. Mould contamination of domestic environments (e.g. cellars,

Agent	Source	Appellation (if any)
Miscellaneous bacteria/mycobacteria/fungi/ amoebae/nematode debris	Air conditioners/humidifiers/tap water/showers/heated pools, saunas, tubs/metal fluids	Humidifier lung Ventilation pneumonitis Sauna taker’s lung Unknown
Roof thatch	New Guinea lung	
Animals Arthropods (Sitophilus granarius)	Grain dust	Wheat weevil disease
Birds Feather bloom/droppings	Bird fancier’s lung	
Fish	Fish meal	Fish meal worker’s lung
Mammal pituitary (cattle, pig)	Pituitary extracts	Pituitary snuff taker’s lung
Mammal hair	Fur	Furrier’s lung
Mollusc		

shell Nacre-button manufacture Urine (rodents) Urinary protein Rodent handler’s lung Vegetation Cabreuva Wood dust Coffee Coffee bean dust Coffee worker’s lung Esparto grass Plaster Esparto plasterer’s lung Amorphophalus konjac Konjac flour Konnyaku maker’s lung Peat moss Peat moss packaging plant Shimeji Shimeji cultivators Tiger nut Tiger nut dust Wood (Gonystylus bacanus) Wood dust Wood worker’s lung Chemicals Bordeaux mixture (fungicide) Vineyards Vineyard sprayer’s lung Cobalt dissolved in solvents Tungsten carbide grinding Diphenyl methane diisocyanate Plastics industry Hexamethylene diisocyanate Plastics industry Methyl methacrylate Dentistry Pauli’s reagent Laboratory Phthalic (or trimellitic) anhydride Epoxy polyester powder paint Pyrethrum Insecticide spray Tetrachloroethylene Dry cleaning Toluene diisocyanate Plastics industry Triglycidyl isocyanate Plastics industry Trimellitic anhydride Plastics industry Vanadium catalyst Maleic anhydride manufacture Miscellaneous Hijikia fusiforme (algae) Konjac flour Konnyaku maker’s lung Pet fish food Table 18.14.4.1 Continued

18.14.4 Hypersensitivity pneumonitis 4247 ultrasonic nebulizers, steam irons, oil heaters, air conditioners) is a less common cause of HP worldwide, but there are many con- vincing case reports of domestic causes. Composter’s lung has been described in relation to inhaling Aspergillus fumigatus from a compost heap. Recreational exposure to antigens occurs in the case of pigeon fancier’s lung, where pigeons are kept for the sport of pigeon racing. The widespread nature of provoking antigens is illustrated by ex- amples of the syndrome being attributed to contamination of water by a pullularia fungus in sauna taker’s disease (hot tub lung), and the mouthpiece of wind instruments by Candida albicans in saxopho- nist lung and trombone lung. Farmer’s lung Farmer’s lung results from the repeated inhalation of thermophilic actinomycetes from mouldy organic dust such as hay, straw, or crops. When hay is harvested during a wet summer it has a high mois- ture content of 30–60%, such that it undergoes moulding during storage with proliferation of thermophilic actinomycetes such as Saccharopolyspora rectivirgula (formerly Micropolyspora faeni) or Thermoactinomyces vulgaris. When that hay is then used for feeding cattle or animal bedding during the winter, spores are inhaled, pro- voking HP. It has been estimated that up to 1.6×109 spores may be present in the air after disturbing mouldy hay, and that a farmer working in a confined space, such as a poorly ventilated barn, might inhale 750 000 spores per minute. The prevalence of farmer’s lung varies in different regions from approximately 0.5–5%, and this relates to differences in climate and farming practices in the harvesting, drying, and storage of hay and crops. Farmer’s lung as a HP must be distinguished from other dis- eases such as inhalation fever, silo-filler’s lung, and organic dust toxic syndrome, which can arise from the inhalation of endotoxins and other substances on farms. It can be difficult for patients diagnosed as having farmer’s lung to leave their work, and many continue to work on the farm using precautionary measures such as respiratory protection devices and avoidance of situations with high antigen exposures. In areas of heavy rainfall, the prevalence of farmer’s lung can be reduced by improved farming techniques, involving the artificial drying of crops and hay using a blower, better barn ventilation, and the addition of propionic acid to hay to reduce moulding. There have been many changes in the practice of farming over the years, and less than 2% of the population in the United Kingdom now works in agriculture, such that farmer’s lung is much less common than previously. Bird fancier’s lung Bird fancier’s lung remains one of the most common forms of HP throughout the world. Although it has been described in people ex- posed to avian antigens in many different circumstances, it is more common in those exposed to flying birds such as budgies or pigeons, whose feathers are covered by a fine powdery substance called bloom, than in those working with nonflying poultry, such as ducks or turkeys, whose feathers are not well developed and lack bloom.

In bird breeder's HP, multiple antigens have been extracted from bird droppings, feathers, serum, egg yolk, egg white, and gut wall. Many of these antigens are dispersed in the air from bloom or droppings and easily inhaled. In the United Kingdom, pigeons are mainly bred for the sport of pigeon racing, and fanciers typically keep 100–200 pigeons in a loft. The resultant high-intensity intermittent antigen exposure seems to favour the development of acute HP and particularly affects men. By contrast, small numbers of pigeons, typically 1–10, are kept in homes in Mexico as pets, and this chronic low-level antigen ex- posure is associated with chronic HP progressing to severe lung fi- brosis, particularly in women. In some unusual circumstances, where there is particularly close contact, bird fancier's lung can occur in relation to wild pigeons. Occasionally bird antigens give rise to HP from a hidden source, such as feathered duvets or pillows. A variety of different lung diseases are associated with bird keeping, including inhalation fevers, asthma, psittacosis (infection with Chlamydia psittaci) and HP. Although it is often relatively easy to remove exposure to a pet bird, pigeon fanciers are frequently very committed to their sport and reluctant to stop contact with their pigeons. Many continue to keep pigeons despite a diagnosis of HP, using antigen avoidance and respiratory protection to reduce their level of contact. Metal-working fluid HP Metal-working fluids (MWF) are a mixture of water-oil emulsion containing biocides and lubricants which are sprayed onto metal and machines to act as a lubricant and coolant in industries such as car manufacture. The MWF is usually collected and recirculated from a sump or reservoir, and can become contaminated with a var- iety of bacteria, fungi, and environmental mycobacteria. Several respiratory diseases may result from the inhalation of the mist of MWF, including lipoid pneumonia, inhalation fevers, asthma, and HP. Several outbreaks of MWF-HP have been re- ported in metal workers in the United Kingdom, United States, and Europe. Some cases have been attributed to a specific antigen, such as Mycobacterium immunogenum, but in other cases workers have demonstrated high IgG levels to a range of bacteria and fungi, hence the precise causative antigen is uncertain and likely to differ between outbreaks depending on the exact circumstances. The diagnosis of a case of MWF-HP should prompt an inspection of the workplace to review risk management and exposure control, and a survey of other workers who might also be affected. Prevention can be achieved by exhaust-ventilation to reduce the escape of the MWF mist into the air, by monitoring and reducing microbial con- tamination of the fluid, and sometimes by use of respiratory protec- tion masks by the workers. Idiopathic HP (no antigen identified) It is common for CT imaging or lung biopsies to show features sug- gesting HP in patients attending specialist hospital clinics with inter- stitial lung disease who have no apparent contact with an antigen or environment known to cause HP. The CT features suggesting HP in- clude centrilobular nodules, mosaic air trapping, and ground-glass shadowing with an upper lobe distribution. Biopsy features sug- gesting HP include bronchiolocentric distribution of inflammation and fibrosis with poorly formed granulomas. Up to 30% of patients with CT and biopsy features suggesting HP have no identifiable antigen exposure. Clearly when the potential diagnosis of HP is suggested, a detailed history should be taken from the patient, looking for any potential antigens or environments.

 A visit to the patient's home and work environment may identify potential sources of antigens such as mould, humidifiers, or aero- sols. It is also common for pigeon fanciers to be reluctant to inform doctors that they keep pigeons, because of a perception that doctors disapprove of the sport. It may be useful to measure antibody responses to avian antigens, Aspergillus, and thermophilic actinomycetes to detect evidence of unrecognized exposure to these antigens. Some cases of idiopathic HP have subsequently been attributed to

previously undetected contact with avian antigens from feathers in duvets or pillows. Measurement of auto-antibodies may provide clues to alternative diagnoses such as interstitial lung disease associated with connective tissue disease. The lack of an identifiable antigen casts doubt on the provoking factors and mechanisms of disease in cases of idiopathic HP, and it is important to realize that HP is not fundamentally a histopatho- logical or radiological diagnosis, but rather a clinical syndrome. The histopathology describes the pattern of disease rather than the pre- cise causation. Patients with idiopathic HP (no antigen identified) appear to have a worse prognosis than patients with HP and an identifiable antigen. It is possible that failing to identify an antigen perpetuates exposure that drives disease progression. It is also possible that pa- tients classified as having idiopathic HP may have a disease process driven by other mechanisms, and there is sometimes difficulty in differentiating HP from other diseases such as nonspecific intersti- tial pneumonia, idiopathic pulmonary fibrosis, airways centred fi- brosis, and connective tissue disease. In practice, patients classified as having idiopathic HP (no antigen identified) are usually given trials of treatment with corticosteroids and other immunosuppres- sive agents, but there is some evidence that their response to treat- ment is poorer than those in whom an antigen has been identified. Epidemiology The epidemiology of HP is difficult to define because of the diverse circumstances in which the disease occurs, the complex dynamic nature of the clinical syndromes, and the different forms of the dis- ease. Very different patterns of disease are seen when studies are undertaken at community level in patients at home, in workplace- based outbreaks, in primary care, or in specialist hospital settings (Fig. 18.14.4.1). Prevalence rates vary widely between countries and are influenced by factors such as climate, local customs, smoking habits, and dif- ferent work practices and processes. The most common types of HP in several series are bird fancier’s lung from a pet bird in the home or the sport of pigeon racing, farmer’s lung due to fungi in mouldy hay or straw, and various types of humidifier lung due to fungi or bacteria in water aerosols in the home or workplace. A study by the international HP research group showed that 61% of cases were due to birds, 21% to farming, and 12% to various fungi encountered in the home or workplace. In the United Kingdom it is estimated that 1 million homes have a pet bird, 2% of the population work in agriculture, and there are approximately 43 000 registered pigeon fanciers. Only a small per- centage of those of those exposed to an antigen of HP develop the disease. It is estimated that 3.4% of budgie fanciers, 10–15% of pigeon fanciers and up to 5% of farmers develop HP. A study of pri- mary care data in the United Kingdom estimated that there were about 600 new cases of HP in the United Kingdom each year, giving an incidence of HP of 1 per 100 000 person-years with a mean age of diagnosis of 51 years. HP accounts for only about 6% of occupational lung disease re- ported to the United Kingdom surveillance scheme, of which almost 50% of reported cases involved farmers or farm workers, followed by 15% affecting workers in material, metal, or electrical processing trades. However, in recent years there has been a change, with metal- working fluid HP becoming the most commonly reported cause of occupational HP. In reported outbreaks of humidifier lung in offices and factories in North America the prevalence rates among workers have varied from 15 to 70%. The risk of developing HP from metal- working fluids varies substantially according to the degree and na- ture of microbial contamination, and the ease with which aerosols of the fluids are released into the working environment. Up to one- third of workers have been affected in some outbreaks. Smaller numbers of people are employed making whisky from germinating barley (maltings), raising mushrooms on a variety of antigenic composts, or handling bagasse (the fibrous stem that re- mains when sugar is extracted from sugar cane), but within some of these populations HP was a common problem until excessive ex- posure levels were controlled. In Japan, the seasonal summer growth of T. cutaneum

in the home is a common cause of HP. Pathogenesis Antigens of HP The antigens which provoke HP have important characteristics that distinguish them from the antigens that provoke asthma.
Hypersensitivity pneumonitis Population studied Form of HP Death Specialist
Chronic Fibrosis Recurrent alveolitis Hospital Subacute Acute severe alveolitis Acute Community
Acute mild stable symptoms Normal Asymptomatic antigen sensitization Fig. 18.14.4.1
Hypersensitivity pneumonitis is a heterogeneous dynamic clinic syndrome which varies in its initial presentation and clinical course. Traditionally the disease is classified into acute, subacute, and chronic forms. The clinical features depend on the population studied. Community-based studies often identify subjects with mild intermittent acute symptoms, and subjects who have an immune response to the antigen but who have not developed disease. In hospital practice, patients may present acutely with severe alveolitis. Studies from specialist interstitial lung disease services tend to have selected populations of patients who have developed chronic disease with progressive fibrosis.

18.14.4 Hypersensitivity pneumonitis 4249 These characteristics include their size, solubility, particulate na- ture, and their capacity to provoke a nonspecific inflammatory response and a specific immune reaction. They are usually small, with a particle size less than 3 μm in diameter, such that they can be inhaled into the distal bronchial tree and alveoli, where they are cleared via local lymphatics to the hilar nodes, which seems to be important in producing IgG antibody responses. By contrast, antigens more typically associated with asthma are larger at about 30 μm in diameter, and are preferentially deposited in the proximal airways, where they tend to provoke an IgE antibody response in atopic subjects. The antigens of HP have powerful adjuvant prop- erties, with a capacity to activate complement by the alternative pathway, to stimulate macrophages, and to enhance delayed cel- lular responses, with the release of interleukin (IL)-1 and tumour necrosis factor (TNF)α. Susceptibility and environmental factors Individual susceptibility is important in determining the immune response: less than 10% of subjects repeatedly exposed to antigens of HP develop the disease. Host risk factors are poorly under- stood. 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, HLA B8 in farmer’s lung and pigeon fancier’s lung in Caucasians, and HLA-DQw3 in Japanese summer- type HP, but other studies have found no association. Genetic factors are known to influence immune response. Gene polymorphisms resulting in high-responders for TNFα result in a greater risk for developing HP. 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 inflammation. Environmental factors, including antigen concentration, dur- ation, and frequency of exposure, particulate size, antigen solubility, and variability in work practices may influence the prevalence, se- verity, and course of HP. It has been repeatedly shown that HP is less common in current smokers, and smoking reduces the IgG response to inhaled antigens, influences cytokine production and impairs macrophage function. Smoking may also reduce the risk for other T-cell-mediated immunological disorders such as sarcoidosis, ul- cerative colitis, and some types of occupational asthma. The key cell in a complex series of interactions is probably the alveolar macro- phage, which is critical in presenting antigen to CD4+ T lympho- cytes and so to activating cellular immune mechanisms. Although smoking increases macrophage numbers and their metabolic ac- tivity, the activated cells show impairment of both the expression of surface major histocompatibility (MHC) class 2 antigens and the production or release of IL-1 and inflammatory mediators derived from arachidonic acid metabolism (leukotriene B4, prostaglandin E2,

thromboxane B2). It is also argued that the increased macrophage numbers down-regulate pulmonary immune responses in a purely nonspecific fashion by impairing antigen access to more effective blood monocytes. There is some evidence that the onset of HP may be precipitated by additional nonspecific lung inflammation. 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 it has been shown that Sendai virus infection enhances the lung response to antigenic challenge with Saccharopolyspora rectivirgula. Other 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. Immunopathogenesis The immunopathogenesis of HP is complex and incompletely understood. Patients have high levels of antigen exposure and dem- onstrate complex immune responses involving antibody and cellular immune mechanisms. An outline of the possible immunopathology of HP is illustrated in Figs. 18.14.4.2 and 18.14.4.3, and it is likely that different mechanisms are important at different stages of the process, depending on whether the patient is presenting with acute HP, chronic HP, or progressive pulmonary fibrosis. Initially it was thought that HP was an immune complex-mediated disease, but greater emphasis has subsequently been placed on the role of cellular immune responses. The evidence for deposition of immune complexes is not convincing, and neither IgG nor IgM anti- bodies are uniformly demonstrated in the sera of affected subjects unless sensitive detection techniques such as the enzyme-linked im- munosorbent assay (ELISA) or radioimmunoassays are used. More importantly, these antibodies are frequently found in subjects who are similarly exposed but clinically unaffected. A closer association of disease with the IgG4 antibody subclass has been suggested, but the significance of this is not yet apparent. It is clear, however, that vasculitis—a cardinal feature of the experimental Arthus reaction— is not a characteristic feature. The inflammatory reaction is dominantly lymphocytic or mono- nuclear rather than polymorphonuclear, although a transitory poly- morphonuclear leucocyte response is typical immediately following exposure. 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 produces lesions closely resem- bling those seen in HP. Immediately after antigen challenge there is an influx of neutrophils into the alveoli. This may be stimulated by the formation of immune complexes and direct activation of Smooth muscle constriction Air space Spores +C3bi Activated macrophage T lymphocyte IL-2 Activated endothelium Bloodstream Neutrophil Alternate pathway complement C3bi (opsonin) C3a + C5a (chemotactic factors; bronchoconstriction) Cell recruitment and activation Cytokines IL-1/TNF Systemic effects of cytokines (fever, malaise) Antigen presentation Mediator release (leukotrienes, prostaglandins) Fig. 18.14.4.2 Possible immunopathogenesis: acute phase.

section 18 Respiratory disorders 4250 complement by the alternative pathway. This neutrophilic alveolitis is transient and is followed by the influx of activated T-cells with a preponderance of CD8 T-cells. As time passes from antigen ex- posure, the number of CD8 cells decreases and there is an increase in CD4 T-cells. Alveolar macrophages are activated and an array of pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α, interleukin (IL)-6, IL-17 and interferon (IFN)-γ is pro- duced. Regulatory cytokines such as IL-10 are also secreted and may play a role in damping down the inflammatory response. Toll- like receptors (TLR) may also be involved. These recognize par- ticular bacterial and fungal lipoproteins. TLR2 and TLR9 appear to be important in the initial response. The factors governing granulomatous inflammation are uncer- tain, but animal models of schistosome-induced granulomatous inflammation show that certain factors, such as T-suppressor

ef- fector factor and cyclo-oxygenase products, inhibit macrophage expression and granuloma formation, whereas other factors such as lipoxygenase products enhance granuloma formation. There are therefore certain modulating factors which may enhance or sup- press the disease process at various stages. Bronchoalveolar lavage in subjects exposed to HP antigens has shown excess numbers of T lymphocytes, whether they were clinically affected or not, although the proportions of T-cell subpopulations have varied according to disease activity and the circumstances of exposure. It is known that different antigenic de- terminants from a given inducing microbial source may lead to dif- ferent immunological responses, and it seems likely that cytotoxic activity and released cytokines (e.g. IL-6 and TNFα) play some role, possibly by activating the vascular endothelium and thereby recruiting and activating further macrophages and inflammatory cells. In experimental models IFN-γ has been shown to play a major role (an excess of IFN-γ-producing T-cells is present in the lungs), and IL-10 ameliorates the disease. Other studies implicate IL-6, IL-8, IL-12, IL-17, IL-18, and IL-22, monocyte chemotactic protein-1 (MCP-1), intercellular adhesion molecule 1 (ICAM-1), mast cells, and NK cells. Cytokines, possibly together with anaphylatoxins from the deg- radation of complement components (C4, C3, C5), are likely to be responsible for the systemic influenza-like symptoms that are so characteristic of the acute form of HP. These symptoms are indistin- guishable from those of grain fever in grain workers, ‘Monday fever’ in cotton workers, humidifier fever in subjects exposed to contamin- ated humidifiers, and metal fume fever in welders. In these situations the febrile disorder is not characteristically associated with clinical alveolitis, raising the possibility that its occurrence with the acute form of HP is an independent phenomenon, rather than an integral part of the disease progression. In favour of this hypothesis has been the finding of high levels of endotoxin from Gram-negative bacteria (which are known to provoke these symptoms) in grain dust, cotton dust, contaminated humidifiers, and many of the ‘mouldy’ vegetable dusts that cause HP. Pulmonary fibrosis may represent a common pathway for many interstitial lung diseases. The precise links between inflammation and fibrosis in interstitial lung disease are also poorly understood, but may relate to the extent of injury to epithelial cells and base- ment membrane, and factors governing fibroblast activation, col- lagen deposition, and collagen degradation. The onset of fibrosis is associated with a poor response to treatment and increased mor- tality. The mechanisms for profibrotic and antifibrotic regulation by various cytokines and cell surface markers are uncertain. In ad- vanced fibrotic disease it is often difficult to differentiate HP from idiopathic pulmonary fibrosis. However, there are different gene expression signatures in these diseases. In HP, the gene expres- sion signature on oligonucleotide arrays are is of those function- ally associated with inflammation, T-cell activation, and immune responses, whereas idiopathic pulmonary fibrosis is character- ized by the expression of tissue remodelling, and epithelial and myofibroblast genes. In summary, the immune mechanisms underlying HP are com- plex and may differ at different stages of the disease. This diversity is reflected in a dynamic heterogeneous clinical syndrome which varies greatly in its initial presentation and subsequent clinical course. Air space Spores CD4+ lymphocytes Cytokines Bloodstream Activated endothelium CD8+ lymphocyte Efferent lymph Regional lymphoid tissue Precipitating antibodies [IgG] Multinucleate giant cell Activated CD4+ lymphocytes Antigen transported to lymph node in afferent lymph Follicles [B cells] Fig. 18.14.4.3 Possible immunopathogenesis: subacute/chronic phase.

18.14.4 Hypersensitivity pneumonitis 4251 Clinical features The clinical features of the disease depend greatly on the population studied, the clinical circumstances of antigen exposure, and the pat- tern of the disease in an individual patient. The clinical spectrum varies from mild recurrent

symptoms, often managed by patients themselves at community level, to acute severe pneumonitis pre- senting to hospital, and to progressive fibrotic lung disease in pa- tients seen in specialist interstitial lung disease clinics. Traditionally HP is classified into acute, subacute, and chronic forms, although patients do not always fit neatly into this classifica- tion, and different patterns emerge over time. Acute hypersensitivity pneumonitis Acute HP is characterized by recurrent episodes of breathlessness, cough, fevers, malaise, and flu-like symptoms, occurring 4–8 hours after antigen exposure. Lung function tests, chest radiographs, and CT images may be abnormal after exposure but usually return to normal between episodes. Characteristically there is a latency period, which may vary from weeks to years, during which there are no symptoms, as sensitization to the antigen develops before the onset of disease. The severity and duration of symptoms depend critically on ex- posure dose and individual susceptibility. With low levels of acute exposure, symptoms are mild and persist for a few hours only. When occupation is responsible, the affected worker may feel unwell only at home during the following evening or night, and be fully recovered by the next morning, such that the relevance of the workplace envir- onment may not be initially obvious. In hospital practice, patients may present acutely with severe HP with fever, breathlessness, hypoxia, and diffuse shadowing on a chest radiograph or CT. Initially these patients may be suspected to have developed infective pneumonia and may receive antibiotics. The symptoms may resolve as admission to hospital removes them from further antigenic contact, but they may present again with recurrent episodes. It is crucial to ask about potential antigenic exposure to identify the correct diagnosis in such cases. Chronic hypersensitivity pneumonitis Chronic HP is characterized by the insidious development of breathlessness and persistent pneumonitis. It is typically seen in a person who keeps a single budgie in the home. The level of antigenic exposure to avian dust is comparatively small compared with that of the farm worker forking bales of heavily contaminated hay in a poorly ventilated barn, but it is encountered almost continuously, particularly if the affected individual is housebound. Subacute hypersensitivity pneumonitis In subacute HP patients may demonstrate chronic pneumonitis with episodes of acute symptoms after antigen exposure. Diagnostic criteria and investigation No single clinical feature or laboratory test is diagnostic of HP, and the diagnosis is made from a combination of characteristic clinical features, radiographic abnormalities, lung function tests, immunological tests and (in some cases) lung biopsy, and the exclu- sion of alternative disease processes. The diagnostic approach should be adapted to the circumstances of the clinical problem, and very few patients will demonstrate all features of the disease at any one point in time. In many cases the diagnosis can be established from clinical features supported by chest radiography, CT, serology, and lung function tests. In those with lung fibrosis the difficulty is in differentiating chronic HP from idiopathic pulmonary fibrosis, and invasive tests such as bronchoalveolar lavage, lung biopsy, and antigen challenge tests may be appropriate. Suspicion of an association between symptoms and contact with a provoking antigen is a key step in the diagnostic process. In the acute form of HP this association may be readily apparent. In the chronic form symptoms often do not show a temporal relationship to antigen exposure, and sometimes no antigenic source is apparent. An important step is the demonstration of either an antibody or cellular immune response to the provoking antigen. However, this merely confirms that that the patient has had a sufficient level of ex- posure to the antigen to develop sensitization, and this is not suf- ficient to establish a diagnosis of HP, since many asymptomatic subjects show similar antibody or cellular responses. Serological tests for antibodies to avian antigens, thermophilic actinomycetes, and Aspergillus may be useful in identifying exposure to a relevant antigen. Radiological imaging With the acute form of the disease the chest radiograph commonly shows no

abnormality between episodes. When the radiograph is abnormal, there is a widespread ground-glass appearance or an al- veolar filling pattern, particularly in the lower and mid-zones. This may resolve within 24–48 h once exposure has ceased. In more sub- acute forms small reticular opacities may persist for several weeks despite cessation of exposure. Occasionally a more nodular pattern occurs. In practice, the radiographic appearances vary considerably from patient to patient and correlate poorly with the clinical severity of the disease. High-resolution CT is more sensitive than chest radiography in demonstrating parenchymal changes. The typical features are diffuse bilateral ground-glass attenuation with small centrilobular nodules with a mid and lower zone distribution. A characteristic finding is of a mosaic pattern due to focal areas of air trapping, often with a clear lobular distribution, within diffuse areas of ground-glass attenu- ation. The extent of air-trapping on expiratory CT correlates with an increase in residual volume on pulmonary function tests. In more advanced chronic HP, the CT findings are of pulmonary fibrosis with linear opacities, architectural distortion, and honeycombing, often indistinguishable from other causes of pulmonary fibrosis. Features which suggest HP rather than idiopathic pulmonary fi- brosis include a relative sparing of the lung bases, lack of peripheral subpleural distribution of fibrosis and the presence of centrilobular nodules (Fig. 18.14.4.4). Lymph node enlargement and/or pleural involvement are not characteristic. Lung function studies The results of lung function studies vary according to severity of the disease and the interval to last antigen exposure. When lung function is impaired, the pattern suggests parenchymal and interstitial disease,

section 18 Respiratory disorders 4252 but is otherwise nonspecific. There is a restrictive defect with reduced lung volumes and impaired carbon monoxide gas transfer (dimin- ished TLco and Kco), decreased compliance, and in more severe cases arterial hypoxaemia. Although total lung capacity is reduced, residual volume is often increased, suggesting air trapping as a result of bronchiolar involvement. Occasionally there is also evidence of obstruction of the large and peripheral airways. Serial measurements of lung function may be particularly useful in demonstrating that im- pairment is closely related to the relevant exposure. Bronchoalveolar lavage Bronchoalveolar lavage characteristically shows a lymphocytic alve- olitis with a predominance of CD8 T-cells, but the cell profile is de- pendent upon the interval from last antigen exposure. A neutrophilic alveolitis is seen immediately after antigen challenge and the number of CD8 T-cells falls after cessation of antigen contact. A lymphocytic alveolitis is seen in asymptomatic subjects exposed to an antigen and in patients with organic dust toxic syndrome. Sarcoidosis is also characterized by lymphocytosis in bronchoalveolar lavage fluid, but B-lymphocyte numbers are decreased and the excess T lymphocytes are typically CD4 + helper cells, with the CD4 + to CD8 + ratio nor- mally exceeding 1. By contrast, the ratio is typically reversed in HP, CD8 + cells outnumbering CD4 + cells, and B-lymphocyte numbers are not decreased. Lymphocyte markers may therefore help distin- guish sarcoidosis from HP. Lung biopsy Lung biopsy typically shows lymphocytic infiltration, foamy macro- phages, poorly formed granulomas, and bronchiolitis, but this depends on the stage of the disease and in more advanced disease the predominant feature may be pulmonary fibrosis resembling usual interstitial pneumonia of idiopathic pulmonary fibrosis. Close correlation with all the clinical details is required to differentiate the granulomatous inflammation of HP from other disease processes such as sarcoidosis. There has been little opportunity to characterize the pathology of the acute form of HP histologically because biopsies are very rarely taken within 24–48 h of a provoking exposure. Initially there is a nonspecific diffuse pneumonitis with inflammatory cellular infiltra- tion of the bronchioles, alveoli, and interstitium, accompanied by oedema and luminal exudation. With

ongoing exposure, whether continuous or intermittent, the more familiar appearances of the subacute forms of HP evolve. The typical histological appearance of subacute HP is illustrated in Fig. 18.14.4.5. The most characteristic feature is the formation of epithelioid noncaseating granulomas. These are generally less well formed than in sarcoidosis, less profuse, and often evanescent. They can be recognized within 3 weeks of the initiating exposure, and generally resolve within 6–12 months. In parallel, fibrosis evolves alongside cellular infiltration of the interstitium with histiocytes, lymphocytes, and plasma cells. Macrophages with foamy cytoplasm may be prominent in the alveolar spaces, and organization of the in- flammatory exudate may lead to intra-alveolar fibrosis. Obstruction or obliteration of bronchioles is common. Foreign-body giant cells may reflect the dependence of HP on antigens derived from inhaled foreign material, as does a peribronchial predominance of the in- flammatory response. Vasculitis is notable by its absence. Immunological tests The demonstration of a serum IgG antibody response to the inducing organic dust is the most widely used method of confirming an im- mune response to an inhaled antigen. Although affected subjects tend to have higher antibody levels than those who are exposed but unaffected, the antibody response tends to correlate more closely with exposure than with disease. If the more sensitive ELISA is used, rather than the traditional Ouchterlony double-gel diffusion test, even higher rates of false-positive results are obtained. Fig. 18.14.4.5 Histological appearance: subacute disease. There is bronchocentric interstitial fibrosis and chronic inflammation, with poorly formed interstitial granulomas including giant cells. (Haematoxylin and eosin stain at medium magnification.) Courtesy of Dr T. Ashcroft. Fig. 18.14.4.4 (a) CT scan of a woman aged 44 years who had never smoked whose lung biopsy showed the typical appearances of subacute HP. She kept two budgies in her home and had serum precipitins to avian antigens. The scan shows marked ground-glass attenuation of the lung parenchyma, which is nodular in some areas due to characteristic peribronchiolar (and centrilobular) foci. In other areas there is increased translucency because of bronchiolar obstruction and air trapping. Both the ground-glass attenuation and the increases in translucency are exaggerated in the expiratory film (b), giving a ‘mosaic’ pattern. She recovered fully after the birds left her home.

18.14.4 Hypersensitivity pneumonitis 4253 In practice, the absence of an IgG precipitin response is un- common in subjects eventually proven to have HP. This is of con- siderable value in that a negative test generally makes the diagnosis unlikely. The proliferative response of peripheral blood lymphocytes to specific antigens has been used in some research studies as a measure of a cellular immune response in establishing a diagnosis of HP in patients with interstitial lung disease, but these tests are not widely available and their sensitivity and specificity for diagnosing HP are not established. Challenge tests When the diagnosis remains in doubt, some form of inhalation challenge test may be necessary. The simplest method involves com- parison of experimental periods spent away from the suspected causative environment with similar periods of continuing exposure. This can be done in workplace-based settings or in the setting of a pigeon loft, for example, where subjects undertake their usually activities, with monitoring of symptoms, clinical signs, and lung function. The acute form of the disease is likely to be recognized in this way. When a definitive diagnosis is particularly important, laboratory- based inhalation challenge tests can be used. These employ a variety of techniques, ranging from nebulizing soluble extracts to recre- ating natural environmental exposures in an exposure chamber. However, the use of such 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. The influenza-like component of

positive reactions is often uncomfortable, and if excessive doses are administered these tests can be hazardous. Furthermore, objective evidence for posi- tive reactions may be difficult to obtain from conventional lung function tests. Table 18.14.4.2 outlines the sensitivity and specificity of certain parameters from a study of 144 inhalation challenge tests. Together they provide high specificity and high sensitivity. Auscultation, chest radiography, measurements of gas transfer, and arterial blood gas analyses are often too insensitive to provide useful diagnostic information. Differential diagnosis The differential diagnoses to be considered depend on the popula- tion studied and the circumstances of the disease. The acute form of HP needs to be distinguished from organic dust toxic syndrome and mere sensitization to the antigen. The chronic fibrotic form may mimic idiopathic pulmonary fibrosis or nonspecific interstitial pneumonia. Organic dust toxic syndrome Systemic influenza-like symptoms and respiratory distress may also follow an unusually heavy exposure to contaminated vegetable pro- duce. In 1986 an international symposium considered a further dis- order that occurs within hours of heavy respiratory exposure to dusts containing fungal toxins, especially those released on decapping silos. The condition typically occurs after a single exposure to an un- usually high level of organic dust, and may arise in subjects who have not had previous exposure. All subjects that have a similar degree of exposure develop a similar clinical illness. It is the result of direct toxicity rather than hypersensitivity, and the term ‘organic dust toxic syndrome’ was recommended to describe it. Its effects are usually mild and self-limiting, but severe respira- tory embarrassment can occur. Not only does organic dust toxic syndrome occur in circumstances which favour the occurrence of HP (particularly silos and swine/poultry confinement buildings), but its clinical features have much in common with HP, and to a lesser extent with nitrogen dioxide toxicity, which may also affect silo workers (Table 18.14.4.3). Most organic dusts contain an array of bacteria, fungi, and en- dotoxins, which can give rise to this direct toxic lung inflamma- tion. These are sometimes associated with systemic febrile reactions without impairment of lung function, as in the case of farmer’s fever, grain fever, swine fever, and humidifier fever. These patients do not usually have antibodies to relevant antigens. Nitrogen dioxide toxicity In the agricultural silo, decomposing grain or silage releases ni- trogen dioxide into the confined space immediately above the level of the stored produce. Since this is denser than air it disperses slowly and may reach sufficiently high concentrations to cause asphyxia. Silo-fillers lung is a toxic pneumonitis resulting from inhalation of nitrogen dioxide. It can produce severe pneumonitis with pul- monary oedema and death. Treatment and prognosis Antigen avoidance Removal of exposure to the provoking antigen is the key treatment for patients with HP, and complete cessation of contact is the safest advice for these patients. In patients with the acute form of HP ces- sation of antigenic exposure usually results in rapid resolution of the disease. In patients admitted to hospital with more severe acute pneumonitis there is often an apparent beneficial response to cor- ticosteroids, although it is difficult to distinguish between the effects of treatment and the effects of antigen avoidance brought about by the admission to hospital. Table 18.14.4.2 Diagnostic features of positive inhalation challenge tests Diagnostic changes within 36 h of challenge exposure Sensitivity (%) Increase in body temperature to >37.2°C 78 Increase in circulating neutrophils by ≥2.5 × 109/litre 68 Decrease in circulating lymphocytes by ≥0.5 × 109/litre,
with lymphopenia (<1.5 × 109/litre) 52 Decrease in forced vital capacity by ≥15% 48 Increase in exercise minute volume by ≥15% 85 Increase in exercise respiratory frequency by ≥25% 64 The data were taken from a series of 144 antigen and control challenge tests in 31 subjects. Diagnostic endpoints were chosen to produce specificities of approximately 95% after mean changes associated with positive challenge tests were shown to be highly significant. When each monitoring

parameter was given a score of 1 for a significant result, a total score of 2/6 or more was associated with a specificity of 100% and a sensitivity of 78% for the 144 challenge tests.

section 18 Respiratory disorders 4254 Some patients have had mild stable symptoms for several years, but have not consulted doctors because they fear that their liveli- hood is at stake in the case of farmers, or that their commitment to their sport will not be appreciated in the case of pigeon fanciers. Sometimes it is unrealistic for the affected individual to change the relevant working, domestic, or recreational environment com- pletely, and many such patients continue some exposure, and sur- prisingly this does not inevitably result in progressive disease. Many patients will have adopted strategies to reduce antigen exposure, and further advice can be given in that regard. For ex- ample, pigeon fanciers can be encouraged to spend less time in the loft, to avoid activities where there is a high level of antigen, 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 car- ried on clothing or in hair. In particular, pigeon fanciers should be specifically advised not to transport pigeons on the back seat of their car, as this can result in intense exposure in a confined space. Farmers can use silage rather than hay for feeding animals, and can adopt modern practices with drying systems which reduce the moisture and mould content of hay. An alternative is some form of ‘pickling’, so that the produce is preserved chemically. With silage, for example, newly cut grass is kept under impervious covering in relatively sealed conditions. Initial enzymatic and moulding pro- cesses use up available oxygen, and produce aldehydes and other preservative chemicals. These create nearly anaerobic conditions and protect the produce until it is used. Similarly, hay may be sealed in plastic bags, or grain or bagasse may be treated with propionic acid. Occupational aspects Where outbreaks of HP occur in workplaces, it is important that an industrial hygienist and occupational physician work with the management and employees to identify the process involved and to reduce or remove the risk to the affected individual and fellow workers. If workers suffer disability or have to stop work because of occupational HP, they are entitled to compensation either through governmental compensation schemes or through pursuit of a legal claim via the civil courts. Sometimes, as in the case of contamin- ated metal-working fluid or a humidifier system, the source of the antigen can be identified and removed. Assessment and surveillance of other workers is important as often they may have been affected but not diagnosed correctly. The affected individuals who continue to work in the occupation respon- sible for their disease can often reduce their exposure substantially by changing the pattern of their particular duties, or working in Table 18.14.4.3 Characteristics of nitrogen dioxide toxicity (silo-filler’s disease), organic dust toxic syndrome, and acute farmer’s lung Nitrogen dioxide toxicity Organic dust toxic syndrome Acute farmer’s lung Susceptibility in smokers Unknown Unknown Decreased Relation to time of harvest Days Months to years Months to years Microbial decomposition of harvest product Little Marked Variable Confined exposure space +++ + + Previous episodes – + ++ Symptoms Dry cough ++ ++ ++ Breathlessness ++ ++ ++ Wheeze – – – Systemic upset + + ++ Signs Basal crackles + + + Fever + + + Time of onset after beginning exposure 1–10 h 1–10 h 1–10 h Duration Hours to days Hours to days Hours to days Investigations Leucocytosis + + + Radiograph–small irregular opacities, alveolar shadows + ± + Restricted ventilation + ± + Reduced gas transfer + ± + Hypoxaemia + ± + Fungi from secretions/biopsy – ++ + Methaemoglobinaemia + – – Serum precipitins – –

- (?– in smokers) Response to steroids
-

– ++ Life-threatening Not uncommonly Rarely Rarely

18.14.4 Hypersensitivity pneumonitis 4255 different areas of the factory. Modifications can always be made to the environment to lessen the level of exposure, but their extent will be limited by expense and should be justified by need. When ventila- tion and humidification systems are themselves responsible for HP, major mechanical alterations may be necessary, and the methods of humidification and temperature control may need to be changed. The crucial need is to reduce the ease with which normal airborne microbial contaminants are able to proliferate in stagnant, reservoir, collections of water. For this there may be a role for 'biocide' steril- izing agents, but these are also likely to become airborne and respir- able and so must have low intrinsic toxicity and sensitizing potency. Respiratory protection masks have been shown to improve symp- toms and prevent a reaction to an antigen challenge, but these have to be of sufficient quality to filter out small particles of respirable dust, and they have to be worn regularly and have a close fit to the face to prevent antigens being inhaled. Continued exposure Where a patient with HP decides to continue exposure to the antigen, there is a risk of recurrent episodes of acute HP and some- times progression of the disease to lung fibrosis. Complete cessation of antigen exposure remains the safest advice, but where this is not possible methods to reduce the level of antigen exposure should be recommended, and measuring the level of circulating antibody to the antigen may be a useful guide to the effectiveness of avoidance measures. Ongoing medical supervision of symptoms, lung func- tion, and chest radiographs is advisable. Surprisingly, acute HP does not usually progress to chronic fi- brotic disease, even when there is continued antigen exposure.
A long-term follow-up study of 92 farm workers presenting with acute farmer's lung showed that while most continued to live on farms, only some developed radiographic evidence of pulmonary fi- brosis (39%) or impairment of carbon monoxide gas transfer (30%), but 28% gave histories of chronic productive cough and 25% had airway obstruction. A similar 10-year outcome has been reported in pigeon fanciers with acute HP; again, most elected to continue their antigenic exposures despite medical advice to the contrary, but symptoms tended to improve and only a few had residual abnormal- ities on chest radiographs or lung function tests. Some patients seem to remain in a state of equilibrium with the antigen over long periods of time without developing progressive disease. This intriguing phe- nomenon has also been reported in animal models of the disease, where repeated antigen challenges result in a waning of the immune response rather than progression of the disease. The interaction of the antigen and the host response in HP is complex, and it is clear that there are several factors which modulate the response. This also suggests that the underlying pathogenic mechanisms differ between acute HP and chronic fibrotic disease. Acute severe alveolitis Patients presenting to hospital with acute severe alveolitis are usually treated with corticosteroids. A randomized, double-blind, placebo- controlled study of corticosteroids in patients with acute farmer's lung showed more rapid improvement in lung function, with a sig- nificantly higher transfer factor for carbon monoxide (TLco) and transfer coefficient (Kco) at one month compared to the control group, but there was no difference in the long-term outcome be- tween the two groups. Chronic fibrotic hypersensitivity pneumonitis Patients with chronic fibrotic HP have severe disease which is often progressive, and it is essential for these patients to avoid further con- tact with the provoking antigen. Sometimes this fibrotic form of HP progresses even after cessation of antigen exposure, suggesting that the disease mechanisms giving rise to fibrosis may be progres- sive and not dependent on ongoing antigenic stimulation. Many of these patients improve on corticosteroids, particularly where a lung biopsy shows a nonspecific pneumonia or cryptogenic organizing pneumonia pattern of disease rather than a usual interstitial pneu- monia pattern. Evidence of lung fibrosis on biopsy or CT imaging is an adverse feature and is associated with a

high likelihood of pro- gressive disease and death from respiratory failure. Some of these patients show a similar pattern of disease progression as is seen in idiopathic pulmonary fibrosis. Acute exacerbations of chronic HP may also occur, and are charac- terized by an acute deterioration in breathlessness, oxygenation, and lung function. As is the case with acute exacerbations of idiopathic pulmonary fibrosis, these patents are usually treated by corticoster- oids during exacerbations. Where patients fail to respond to cor- ticosteroids other immunosuppressive drugs, such as azathioprine, cyclophosphamide, or mycophenolate, are often tried, but evidence of benefit is based on case reports rather than formal clinical trials. Rituximab, a B-cell depleting anti-CD20 antibody, has also been re- ported to have a beneficial effect, suggesting an immunopathogenic role for B cells in some patients with severe HP. Lung transplantation may be necessary in patients with progres- sive HP who have failed to respond to antigen avoidance and im- munosuppressive treatments. Although patients with HP have an exaggerated immune response to certain inhaled antigens, they have lower rates of acute rejection of transplanted lungs and a better prog- nosis than patients with idiopathic pulmonary fibrosis. There have been reports of recurrence of the disease in the transplanted lungs if there is re-exposure to the antigen. FURTHER READING

Anderson K, et al. (1989). The long-term effect of a positive pressure respirator on the specific antibody response in pigeon breeders. Clin Expt Allergy, 19, 45–9. Bourke S, Boyd G (1997). Pigeon fancier’s lung. Brit Med J, 315, 70–1. Bourke SJ, et al. (1989). Longitudinal course of extrinsic allergic alve- olitis in pigeon breeders. Thorax, 44, 415–18. Bourke SJ, et al. (2001). Hypersensitivity pneumonitis: current con- cepts. Eur Respir J, 32 (Suppl), 81–92. Braun SR, et al. (1979). Farmer’s lung disease: long-term clinical and physiologic outcome. Am Rev Respir Dis, 119, 185–91. Camarena A, et al. (2001). Major histocompatibility complex and tu- mour necrosis factor-alpha polymorphisms in pigeon breeder’s dis- ease. Am J Respir Crit Care Med, 163, 1528–33. Cormier Y, et al. (1994). Long-term viral enhancement of lung re- sponse to Saccharopolyspora rectivirgula. Am J Respir Crit Care Med, 149, 490–4.

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