CHEST

Official publication of the American College of Chest Physicians

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Chest 1976;69;283-284
DOI 10.1378/chest.69.2_Supplement.283

tion. This particulate is rapidly degraded to soluble products which immediately enter the circulation as macromolecules. Intact antigenic material which persists in the lung stimulates the accumulation of antibody-forming cells in respiratory tract-associated lymphoid tissue. Despite the circulation of macromolecular breakdown products of the SRBC, neither the antigen nor antibody-forming cells accumulate in systemic tissue. These results may be relevant to the mechanisms involved in disposal of and the response to inhaled organic antigens.

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Session 8: Hypersensitivity Pneumonitis (A)

Family Studies in Hypersensitivity Pneumonitis*

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Hypersensitivity pneumonitis was first described over 40 years ago, almost simultaneously in maple bark strippers and in farmers exposed to moldy hay. A wide variety of organic dusts were subsequently shown to produce this syndrome. Precipitating antibodies were demonstrated in the sera of persons exposed to organic dusts, but only recently was it recognized that there is activation of the cell-mediated,[1] as well as the humoral arm of the immune response in hypersensitivity pneumonitis.

An important question is why only a small percentage of those exposed to organic dusts develop hypersensitivity pneumonitis. It is likely that those who develop the disease are in some way predisposed. This is strongly suggested by the fact that occurrence of the disease is not necessarily related to degree of exposure to antigen and can indeed occur after minimal exposure. In addition, less than 5 percent of pigeon breeders as a group, for example, develop hypersensitivity pneumonitis. An attempt to explore the concept of predisposition by systematic examination of the families of patients with hypersensitivity pneumonitis was carried out. In addition, specific cell-mediated and humoral immune responses to the causative antigens were studied, both in patients with disease and in groups of relevant controls.

Six families were studied and a total of 15 members had clear evidence of the disease. Four patients had clinically mild disease and two were completely asymptomatic. This observation suggests that there may be a genetic or an environmental predisposition. To investigate the genetic factor, histocompatibility antigen status of each family member was determined in order to assess whether disease susceptibility was associated with a certain haplotype. Many studies, largely in experimental animals, and to a lesser extent in man, suggest that the genes controlling immune responsiveness and those determining histocompatability status are closely linked on the same pair of chromosomes.[2-4]

A family of pigeon breeders is shown in Figure 1, three of whom developed hypersensitivity pneumonitis within a period of 12 months. Three of four family members with the haplotype 2, W15, who were significantly exposed to antigen developed disease. The fourth member, although lacking evidence of pneumonitis, had a history of asthma on exposure to the birds which may well have resulted in antigen neutralization within the airways, therefore protecting him from a more delayed response. Thus, although the presumed immune response (Ir) gene increased the susceptibility to disease, it was not sufficient for development of disease. In the other five families, a common haplotype could be detected in at least two members of each family. The haplotypes varied from family to family. Levine[2] has shown that atopic ragweed sensitivity is haplotype-associated within a given family. As in our study, Levine also found that the presumed Ir gene was not expressed by all family members who carried it. Other factors, including exposure to antigen, determine whether an Ir gene is expressed or not. Therefore, it is suggested that this marked familial incidence detected in six families may be due to an immune response gene, closely linked to the histocompatibility antigen system. However, it should be pointed out that in no individual family could these results be analyzed statistically.

In the second part of this study, the immunologic mechanisms of disease production were investigated. The finding of precipitating antibodies in the sera of most patients with disease has led to the suggestion that hypersensitivity pneumonitis is due to a local Arthus reaction in the lungs. Some doubt is thrown on the validity of this assumption when one considers that up to 40 percent of normal individuals exposed to an organic dust have detectable precipitins to that dust in their sera. The possible importance of cell-mediated immunity in the pathogenesis of this disease has been suggested by

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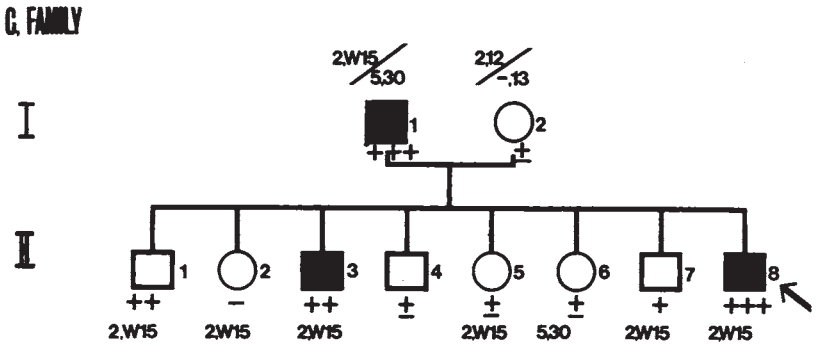

FIGURE 1. Pedigree of a family of pigeon breeders demonstrating the inheritance of HL-A haplotypes in relation to disease and degree of exposure to antigen. Family members with disease are indicated by black symbols. Degree of exposure to the pigeons is expressed as "+++" for heavy and continuous, "++" for moderate and continuous or heavy and intermittent, "+" for mild, "±" for incidental and "–" for non-exposed individuals. Each individual has two haplotypes, one inherited from each parent. Both haplotypes of the parents are shown above their respective symbols, but only the paternal haplotype inherited by each child is indicated below his or her respective symbol.

Table 1—*Specific Immunologic Studies in 14 Patients with Pigeon Fancier's Disease and 4 Patients with Budgerigar Fancier's Disease*

	MMI +VE	Precipitins +VE	MMI or Precipitins +VE
Pigeon fancier's disease	12/14	8/14	14/14
Budgerigar fancier's disease	3/4	3/4	4/4
Total	15/18	11/18	18/18

recent human[1,5] and animal[6] studies and the usual histopathologic changes are consistent with a cell-mediated response. Both the humoral and the cell-mediated arms of the immune response have been examined in a group of 18 patients with the bird fancier's variety of hypersensitivity pneumonitis. Cell-mediated sensitivity was assessed by macrophage migration inhibition (MMI) to dilute solutions of pigeon or budgerigar serum. Humoral immunity was assessed by the Ouchterlony method and negative sera have also been examined by crossover electrophoresis. Diagnosis in this group of patients was validated by a clear history of provocation on exposure to allergen, inhalation challenge or histopathology. The results of these studies are shown in Table 1. The MMI test had a better correlation with disease overall and especially so in the group with pigeon breeder's disease.

The specificity of the MMI test was assessed in two ways. First, in a group of 25 pigeon breeders with no evidence of lung disease, three had a positive MMI test. In a group of four asymptomatic breeders with serum precipitins, but normal lung function, none had a positive MMI. A group of ten patients with sarcoidosis were used to check the specificity of the antigen. No patient in this group had a positive MMI to pigeon serum, but seven of the ten had a positive MMI to Kveim antigen. Thus, the better correlation of the MMI test with lung disease did not result in an unacceptably high false positivity rate in our control groups. The activation of a specific cell-mediated response supports our hypothesis that an immune response gene may be required for the development of disease in view of the known association between T lymphocyte responsiveness in both mouse[4] and man.[3]

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Immune Complex Disease in the New Zealand Black/White Hybrid Mouse Lung*

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There is increasing clinical, physiologic, histologic and immunologic evidence that diffuse pulmonary interstitial disease develops in patients with systemic lupus erythematosus (SLE), a disease associated with circulating antigen-antibody complexes.[1-10] Several investigators believe that immune complexes of the type III reaction of Gel and Coombs contribute to the pathogenesis of SLE.[11] Diffuse interstitial pulmonary disease in SLE may therefore be due to the deposition of immune complexes in the pulmonary vasculature.

Insight into the pathogenesis of these human pulmonary lesions may be obtained from New Zealand black/white (NZB/W) hybrid mice who are known to spontaneously develop a positive reaction to the test for antinuclear antibodies, DNA antibodies, an autoimmune

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Supported by USPHS Training Grant HL 05917.

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