

ALLERGY ROUNDS

Hypersensitivity pneumonitis

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Over the past several years increasing numbers of reports have indicated that hypersensitivity pneumonitis may occur in certain individuals who contact various species of birds.¹⁻¹⁴ The characteristic symptoms of the disease include chills, fever, cough, and dyspnea, which usually occur acutely 4 to 6 hours after exposure to the birds. Some patients may have a progressive illness manifested mainly by increasing dyspnea not clearly related to exposure to any avian species.

The population at risk is significant since, in the United States, approximately 100,000 individuals are engaged in the hobby of raising pigeons for show or for racing, while in Europe, approximately 250,000 are active in the hobby.¹⁵ Moreover, in the British Isles and in Canada, many individuals keep one or two lovebirds (budgerigars) in their homes.^{13, 16} The involvement of the bird fanciers in the care of their birds presents a situation in which variable amounts of bird-derived organic dusts may be inhaled for long periods of time.

CASE REPORT

H. S., a 54-year-old fish and game biologist, sought medical attention on May 15, 1969, because of a chronic cough and shortness of breath. He first became ill 6 months previously with a cough productive of small amounts of purulent sputum. His dyspnea progressed over the next few months so that he eventually had difficulty in climbing one flight of stairs. There had been no previous history of pneumonia, asthma, or hay fever or other respiratory illness. He had never smoked. He had lost about 10 pounds in weight, attributed to some loss of appetite. There were no other gastrointestinal symptoms.

Physical examination revealed only fine bibasilar end-inspiratory crackling rales. The hemoglobin was 14.8 Gm. per 100 ml., hematocrit, 42, white blood cell count, 8,000 per cubic millimeter, with 65% polymorphonuclear cells, 28% lymphocytes, 1% monocytes, and 4% eosinophils. The IgG level was 1,600 mg. per cent (normal $1,100 \pm 300$), IgM, 200 mg. per cent (normal 200 ± 60), and IgA, 180 mg. per cent (normal 100 ± 30). Normal laboratory results were reported for the urinalysis, SMA-12, VDRL, ECG, α_1 antitrypsin, rheumatoid factor, lupus erythematosus preparation, and upper and lower gastrointestinal series. Skin tests with 5 units of tuberculin were positive in 48 hours. Three sputum cultures for *Mycobacterium tuberculosis* were negative.

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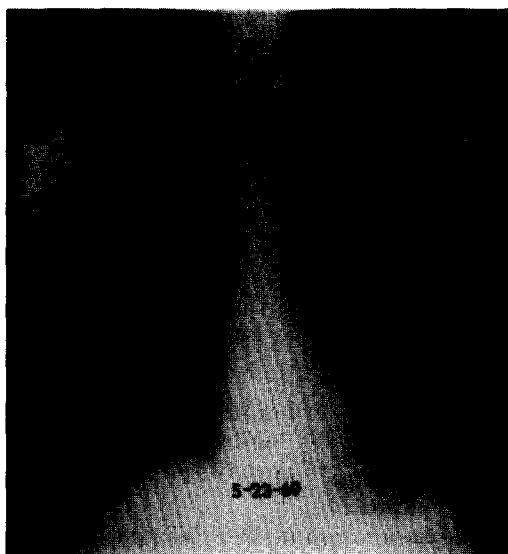


FIG. 1. Chest x-ray of Patient H. S. demonstrating fine nodular infiltrates in both bases.

Chest x-ray (Fig. 1) revealed fine interstitial nodular densities scattered throughout the lung fields. Pulmonary function tests demonstrated a $FEV_{1,0}$ (one second forced expiratory volume) of 68 per cent of predicted and a $FEF_{200-1,200}$ (forced expiratory flow rate between 200 and 1,200 ml.) of 72 per cent of predicted. These tests improved to 85 per cent and 82 per cent of predicted, respectively, following the administration of isoproterenol by aerosol. The forced vital capacity (FVC) was 63 per cent of predicted, and the diffusing capacity was 52 per cent of predicted. Arterial blood gas determinations were normal at rest, but the P_{O_2} fell to 73 mm Hg and the P_{CO_2} remained within normal limits following exercise.

The patient was placed on regular bronchodilators, saturated solution potassium iodide (SSKI), and was given a 14 day course of tetracycline. His sputum cleared, but he continued to have cough and his dyspnea continued. He was then placed on 300 mg. INH and 30 mg. prednisone per day, and all of his symptoms disappeared within 2 weeks. His chest x-ray and pulmonary function tests returned to normal over the next 60 days, but as the prednisone was reduced his symptoms, signs, and clinical abnormalities suggestive of respiratory disease all returned.

At this time, additional history obtained indicated that the patient had raised up to 150 pigeons for the past 6 years. He admitted spending up to 2 hours every day in the coop caring for the birds. On further questioning he stated that on two occasions, several hours after attending pigeon shows where as many as 1,000 birds might be exhibited, he had noted an increase in his cough, chills, and a feverish sensation and myalgia. These episodes disappeared within 12 hours.

At this time, an intracutaneous injection of 0.02 ml. of pigeon serum diluted 1:10 with saline demonstrated an immediate wheal-and-flare reaction graded 4+ (pseudopods) followed by a "late" reaction in 4 hours consisting of 60 mm. of erythema and edema surrounding the injection site. All skin reactions subsided by 18 hours, and no tuberculin-type reaction could be detected over the next 36 hours. Immunodiffusion studies of the patient's serum detected precipitating antibody against pigeon serum and pigeon dropping extract.

The patient was then allowed to spend one hour in contact with 200 pigeons in a coop and was returned to the hospital for observation. Within 6 hours he developed chills, a temperature elevation to 101° F., and a rise in white blood cell count from 8,000 per cubic millimeter to 16,000 per cubic millimeter. Physical examination at this time revealed an accentuation of his bibasilar rales. Pulmonary function tests demonstrated a 30 per cent

decrease in flow rates, 25 per cent decrease in vital capacity, and 40 per cent decrease in diffusing capacity over the pre-exposure values. All of the measured parameters returned to normal within the next 24 hours.

The patient was advised to avoid contact with pigeons. One year after achieving complete avoidance he was asymptomatic. His pulmonary functions and chest x-ray had returned to normal. Precipitating antibody to pigeon antigens could still be detected in the patient's serum, but the intensity of the reaction was reduced considerably.

The historical and clinical features of the present case are typical of the difficulties encountered in establishing the diagnosis of a hypersensitivity pneumonitis.

CLINICAL FEATURES OF AVIAN DUST PNEUMONITIS

It has become apparent that hypersensitivity pneumonitis due to inhalation of avian dusts may present in several forms, depending upon the circumstances under which the avian dusts have been inhaled.^{12, 16} The present case report demonstrates a number of these features.

Acute form

The most common and most easily recognized form of this disease occurs in individuals intermittently exposed to large amounts of avian dusts.^{1-14, 16} A pigeon breeder will often raise anywhere from 50 to 400 birds at one time and will spend several hours per day in contact with them in the coop. The length and degree of exposure necessary to cause illness varies considerably among breeders. Some individuals raise a few birds for only several months before becoming ill, while others require many years of extensive exposure before developing symptoms.

Symptoms occur typically 4 to 6 hours after exposure and are both respiratory and systemic. They consist of cough, malaise, dyspnea, chills, and fever to 104° F., reach a peak about 12 hours after exposure, and then gradually wane over the next 12 hours. The individuals are usually left weakened for a few hours, but gradually return to normal, only to have the cycle repeated after the next exposure. Frequent attacks may be associated with anorexia and some weight loss, but usually there are no progressive respiratory symptoms.

After several attacks the breeder usually becomes aware of an association between exposure to birds and the development of symptoms. He then tries to prevent the attacks by wearing a mask, spending less time in the coop, or by having another individual care for the birds. As long as the susceptible individual is exposed to birds for even short periods of time these protective measures are effective usually only to a limited degree, and the attacks continue to occur. Because of their extreme reluctance in giving up their hobby, the breeders may continue their contact with birds for many years, and may even deny themselves appropriate medical attention.

Chronic form

This form is more common in individuals inhaling organic dusts in a more constant manner from even a small number of birds, although it may be seen in a few pigeon breeders exposed to large numbers of birds for many years.^{12, 16} Thus, patients with this form of the disease can be found in England or Canada

where the raising of only one or two lovebirds (budgerigars) or parakeets within the home is common. In contrast to the acute form, such individuals are usually constantly exposed to small amounts of antigen over prolonged periods.

As in the present case, the symptoms and signs of this form are insidious and progressive. Acute episodes are infrequent. The patients develop mainly respiratory symptoms of chronic cough and progressive dyspnea.^{12, 16} Symptoms of anorexia, weight loss, and debilitation may also occur. Sometimes the cough may become productive of purulent sputum and a respiratory infection is suspected. Other patients present with dyspnea alone, progressing in severity as contact with the antigen continues.^{12, 16} Eventually pulmonary disability results and the patients take the course of individuals with chronic lung disease.

PHYSICAL FINDINGS

The most typical findings during the acute attack are those of an acutely ill patient with fever and shaking chills. The examination of the chest reveals diffuse bibasilar end-inspiratory crackling rales.^{1-14, 16} Wheezing is not heard unless the patient also has asthma due to reagin-mediated inhalant sensitivity to birds. In such patients, asthma occurs immediately after contact with the birds, and a typical acute attack occurs 4 to 6 hours later. The characteristic rales persist during the acute episode and then gradually disappear as the patient recovers. Physical examination of these patients is normal during asymptomatic phases of their disease. As in the case under discussion, these patients are often considered to have recurrent episodes of influenza or bronchitis, and are repeatedly treated for these disorders.

Examination of the patient with the chronic form of hypersensitivity pneumonitis is quite variable, depending on the degree of pulmonary impairment.^{1-14, 16} Some patients may demonstrate findings of chronic obstructive lung disease with hyperinflation, flat diaphragms, and depressed breath sounds. Other patients may have signs of interstitial lung disease with persistent basilar rales and depressed breath sounds. Features such as clubbing, cyanosis, edema, and right ventricular heave, all indicative of pulmonary decompensation or cor pulmonale, are unusual except in the most severe cases.

PULMONARY FUNCTION

The presence and degree of pulmonary function abnormalities detected in a sensitive pigeon breeder depend on the type of illness he has and whether or not he is symptomatic at the time the test is done.

Varying degrees of restriction, increased residual volume, and decreased diffusing capacity can be demonstrated after exposure to pigeon antigens in most patients with the acute form and some patients with the chronic form of the disease.^{12, 16-18} The changes are usually reversible, especially in the acute form. In patients with the more chronic and insidious type of disease, less reversible abnormalities may be demonstrated.¹⁶⁻¹⁸ In some cases, exercise studies with arterial blood gas determinations may be necessary to bring out the alteration in alveolar gas transfer. Airway obstruction, persistent restrictive respiratory impairment with diffusion defect, and progressive "stiffness" of the lung may

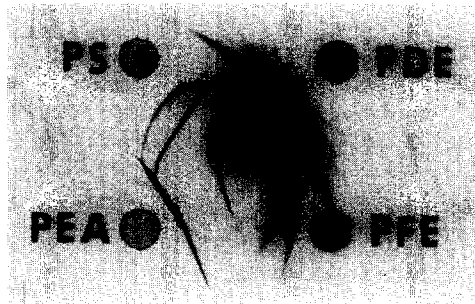


FIG. 2. Gel diffusion studies of serum from a symptomatic pigeon breeder (center well) versus several pigeon antigens. **PDE**, Pigeon dropping extract; **PS**, pigeon serum; **PFE**, pigeon feather extract; **PEA**, pigeon egg albumin. (From Fink, J. N., et al.: *Ann. of Intern. Med.*, **68**: 1211, 1968.)

all be found in individuals who have long-standing and less intermittent exposure to the antigens.¹⁶⁻¹⁸ Such abnormalities may suggest chronic obstructive lung disease, and reversibility may not be evident after long periods of avoidance or even after intensive corticosteroid therapy.

X-RAY FINDINGS

The chest x-ray features of patients with pigeon breeders' disease may vary, depending on the severity of the illness, the duration of, and length between, attacks, and the manner of exposure to the antigen.^{19, 20} During asymptomatic periods and in some symptomatic individuals, normal chest x-rays may be seen. Most patients demonstrate coarse bronchovascular markings, fine nodular infiltration, and reticulation indicative of an interstitial process.^{16, 19, 20} In some of the more severe cases, especially individuals exposed to small numbers of birds for prolonged periods, fibrotic changes with contraction of a lobe, hilar shifting, and tracheal displacement may be seen. Cardiac enlargement is unusual, but hilar adenopathy suggestive of sarcoid has been observed in a few cases.^{16, 19}

PATHOLOGIC FEATURES

Biopsy specimens obtained from patients with pigeon breeders' disease have demonstrated varying degrees of interstitial pneumonitis that tends to intensify about terminal bronchioles.^{20, 21} Clusters of lymphocytes and plasma cells surrounding foamy macrophages may be found within the thickened alveolar septa. Small numbers of sarcoid-like granuloma may be seen in the interstitium. Caseation and necrosis within the granulomas have not been described. Chronic cases of pigeon breeders' disease may demonstrate an obliterative bronchiolitis along with a diffuse interstitial pneumonitis, or, if the pathologic process is end stage, diffuse fibrosis and pleuritis may be found.^{20, 21}

IMMUNOLOGIC FEATURES

The characteristic immunologic features of pigeon breeders' disease, as detected in the present case, are: (1) the demonstration in most patients of an

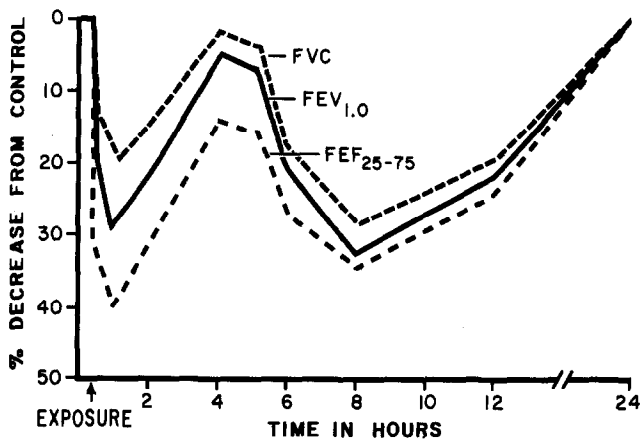


FIG. 3. Dual respiratory reaction occurring in sensitive breeder after exposure to pigeons. Note immediate and late components. (From Schlueter, D. P.: *Med. Times* **98**: 131, 1970.)

immediate wheal-and-flare skin reaction followed by a "late" skin reaction resembling the Arthus phenomenon and presenting in 4 to 6 hours as erythema and edema at the test site; (2) the finding of precipitins to pigeon materials in ill individuals; and (3) reproducibility of the systemic and/or pulmonary signs and symptoms by controlled or natural exposure to birds or bird antigens.^{1-14, 16}

When patients with pigeon breeders' disease are tested intradermally with a nonirritating dilution of pigeon serum, a wheal-and-flare reaction develops in about 80 per cent.^{4, 12, 16} This reaction is almost uniformly followed by a late edematous or boggy and erythematous reaction beginning at about 2 hours and persisting up to 8 to 10 hours, depending upon the severity of the inflammatory reaction. In the remaining 20 per cent of ill breeders, only the "late" reaction occurs.

The significance of these reactions, the antibodies involved (although IgE is most likely involved in the immediate reaction), and their relationship to the immunologic responsiveness of the host remain to be elucidated.

If the sera of patients with pigeon breeders' disease are examined by various gel diffusion techniques, numerous antibodies to a wide variety of pigeon antigens (including pigeon serum, droppings, feather extract, and egg albumin) can be detected, as shown in Fig. 2.^{2, 16, 22} However, up to 40 per cent of asymptomatic pigeon breeders may also have precipitating antibodies demonstrable in their sera.^{22, 25, 26} Some of the precipitin arcs seen with dropping extract may be nonspecific and may represent reactions with enzymes, staphylococcal teichoic acids, or C-reactive proteins present in the droppings.^{16, 24} Thus, in some cases, immunologic reactions with avian serum proteins may be more diagnostic.²⁷

The specific test for a hypersensitivity pneumonitis due to avian antigens is observation of the patient following natural exposure to birds in the coop or by careful inhalation exposure to a dilute antigen solution. After the exposure, the patient must be observed at frequent intervals within the hospital. Temperature

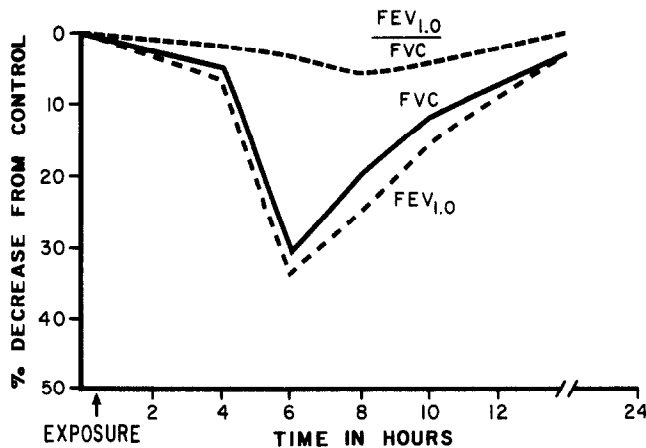


FIG. 4. Late onset respiratory reaction in symptomatic breeder after exposure to pigeons. Note only late component. (From Schlueter, D. P.: *Med. Times* **98**: 131, 1970.)

determination, pulmonary function, and clinical and laboratory examinations should be repeated at intervals for at least 12 hours. In some patients, an immediate respiratory reaction with a fall in flow rates may be noted (Fig. 3). This immediate response shortly returns to base line levels or can easily be reversed by the administration of bronchodilators. Several hours after exposure, whether or not the initial response has occurred, the sensitive patient will experience systemic and pulmonary symptoms similar to an acute attack (Fig. 4). Rales are heard at the lung bases; there is a rise in temperature with a concomitant leukocytosis and shift to the left. A further fall in pulmonary flow rates with a variable diffusion defect may also be observed. These "late" abnormalities are usually resistant to bronchodilators. The late reaction disappears spontaneously over the next 8 hours, and all other detectable abnormalities return to normal. The provocative reaction may be aborted by pretreatment with corticosteroids but is not affected by antihistamines.¹⁶ It has also been reported that the reaction can be uniformly prevented by pre- and postchallenge treatment with disodium chromoglycate,^{10, 20} although this has not been our own experience.

PATHOGENESIS

While the immunologic nature of pigeon breeders' disease is well accepted, there is not sufficient information indicating the exact mechanisms involved in the production of the signs and symptoms or the pathogenesis of the disease.

It is believed that IgE is involved in the immediate type of skin reaction and that it may play a role in the production of late-onset skin test.¹⁶ Perhaps IgE may play some role in the production of signs, symptoms, and histologic lesions by acting through the alternate complement fixation pathway or by releasing mediators such as platelet-aggregating factor through the interaction of antigens with sensitized basophils or mast cells.

Certainly the role of IgG in the pathogenesis of the disease cannot be over-

looked. The findings of precipitins in the serum, IgG in the skin biopsies, and the known property of IgG-antigen complex to induce granulomas are all important.²⁸ The usual IgG-antigen-induced lesions seen are vasculitis, and such lesions have not been seen in lung biopsies of patients with pigeon breeders' disease. Hemorrhagic vasculitis and alveolitis, however, have been seen in animal models in which antigen-antibody reactions have been induced in the lung.^{29, 30} Perhaps the short latent IgG with skin-sensitizing capacity, as described by Parrish,³¹ may prove to be important in the immunogenesis of these diseases.

Finally, the role of cellular immunity must be considered. The lung lesions resemble those of cellular hypersensitivity,^{7, 13, 14} and lymphokines have been detected from the leukocytes of individuals with pigeon breeders' disease.³² A tuberculin type skin reaction, however, has not been uniformly demonstrated in pigeon breeders' disease. This may be due to the depletion of the antigen by the immediate or late type of skin reaction or to the possibility that the antigens presently used are not appropriate to elicit the cellular reaction. In a few cases in which the dual skin response was suppressed by several local injections of antihistamine into the site of antigen injection, however, a tuberculin type reaction could be elicited.³³

The recent use of animal models has indicated that lesions resembling those of human pigeon breeders' disease may be demonstrated when antigen interacts with sensitized lymphocytes in the absence of detectable antibodies.²⁹ Further work, using more sophisticated measurements of the processes occurring during the patient's illness, and, most important, using animal models to define and elucidate the vagaries of the immune responses of the lung, will be necessary to clarify the problems of hypersensitivity pneumonitis.

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