

Editorial

Birds or zebras?

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In this issue of *Allergy*, Curtis et al. (1) report the results of indoor pigeon allergen sampling in dust and air in order to establish allergen contamination data of outdoor animals. They found high indoor levels of pigeon allergens in the vicinity of outdoor pigeon nests, but also in houses and hospitals that did not have pigeons in the immediate surroundings. Their study was undertaken following questions on indoor exposure by pigeon sensitive patients and an occupational physician. Because of the high allergenicity of pigeon allergens, they reasoned that even a low exposure to wild pigeon allergens may cause respiratory disease, especially 'hypersensitivity pneumonitis' (2–7). One could seriously wonder why such an effort should be undertaken. Should we really consider pigeon allergens as a cause of substantial morbidity? Are allergy or allergic alveolitis due to wild pigeons diseases that are under-reported, misclassified, easy to miss, sometimes hard to prove, but nevertheless often seriously disabling and potentially fatal (8), or are they 'zebras' (9)? With respect to diagnostics, the current study has several implications, and raises new questions.

Extrinsic allergic alveolitis, hypersensitivity pneumonitis, or allergic alveolitis (AA) which is the recently recommended term (10) owing to the fact that organic material was recognized as a separate disease almost 300 years ago (11). More than 40 specific etiologic agents, including animal proteins, bacteria, fungi, insect proteins, chemicals, and drugs, have been identified since the 1960s (8, 12). Owing to effective preventive measures in occupational medicine, AA nowadays mainly occurs as a result of domestic exposures, and bird allergens constitute the majority of the causative agents (8). The estimated prevalence of AA among pigeon breeders varies between 1 and 10%, depending on the definition used (13, 14). AA has also been

described in pigeon breeder's offspring (15–22), but the prevalence of AA or allergy owing to wild pigeons in the general population is unknown. City pigeons have been able to adapt and survive efficiently in the larger metropolitan areas in the West: it is estimated that pigeon populations equal roughly 2% of the size of the human population of large cities (Bundes Arbeitsgruppe, Stadttauben, Germany, personal communication), and are mainly concentrated in the inner city areas. Pigeon allergens may cause more respiratory disease than is generally assumed for several reasons. The current study suggests that pigeon allergens can be present in sufficiently high concentrations in public buildings to cause AA or allergy to pigeon allergens. There is no doubt that the prevalence of allergy and asthma in the Western world is increasing (23). Hence, allergens may induce allergy and/or asthma more easily than a few decades ago. Typical inner city allergens from cockroach and mice have been implicated to play a role in the worldwide increase of prevalence of asthma and allergy (24–26), and pigeon allergens may act likewise in causing allergy, asthma, AA, or both (27). Traditionally, pigeon breeder's lung has been described in adults keeping pigeons and, occasionally, in their offspring. It is never considered in patients who do not keep birds themselves. However, in the last 2 years four case reports appeared on AA owing to wild city pigeons (2–5), and the presence of AA in a teacher of the pigeon-infested high school reported by Curtis et al. (1) may be regarded as the fifth one. It seems highly unlikely that AA as a result of wild pigeons would be limited to these cases: we may be looking at the tip of an iceberg. As allergen avoidance does not really apply or cannot be realized for wild pigeons, it seems to be of most importance that general physicians and (pediatric) pulmonologists realize that AA owing to pigeons may

mimick allergic asthma and that its symptoms may improve with asthma treatment, especially when allergens are avoided during hospital admissions and systemic steroids are administered, but that it can eventually progress to disabling or even fatal end-stage lung disease. A truly effective approach consists of early recognition and control of exposure. Recovery depends on the duration of the illness (time to diagnosis) and the exposure to the insulting agent, the age of the patient, and the immunological response of that patient (8).

The clinical, radiological and pathological presentation of AA may be categorized as acute, subacute or chronic (8). AA is mainly the result of an immune response including IgG antibodies, complement and sensitized lymphocytes. Allergens reaching the alveoli elicit a combined (T cell) cellular and a humoral reaction. The resulting inflammatory response involves lung infiltrates of interstitial and alveolar mononuclear cells (mainly T cells and macrophages) (28). This is reflected in a diffuse interstitial granulomatous lung disease, in which Th1 lymphocytes play an important role (8). Progressive compression and blockage of bronchioli (*bronchiolitis obliterans*), and eventually pulmonary fibrosis may occur. The AA was reviewed recently (8, 14). These destructive processes are associated with aspecific symptoms such as acute illness with fever, dyspnea and malaise that improves quickly following antigen elimination, or as an insidious process mimicking severe asthma, with general discomfort, coughing, shortness of breath, weight loss, and behavioral changes (15–17, 20, 22). The subsequent loss of lung function is typically reflected by restrictive and diffusion defects with hypoxemia, especially after exercise. Occasionally, small airways disease causes obstruction (8, 14).

In typical cases, a known exposure, characteristic interstitial lung disease with serologic confirmation of IgG antibody to the offending antigen suffice for diagnosis (8). However, the study by Curtis et al. (1) indicates that even careful questioning of the patient with respect to the relevant outdoor allergens is of little value because the patient can be unaware of exposure to pigeon allergens. Furthermore, the traditional additional diagnostic tests such as routine chest x-ray, lung biopsies or serological investigations all have their limitations.

Standard chest x-ray may show milliary nodules and reticulations in most lung fields (predominantly in the lower lung zones), and patchy infiltrates and hilar adenopathy may be present. However, these findings are not specific, and severe disabling AA may be associated with a normal chest x-ray (29). In AA, only up to 80% of standard chest x-rays may be abnormal (30), and radiographic changes are probably best evaluated by means of high-resolution computed tomography (31).

There is no consensus on the indication to carry out a

lung biopsy in suspected AA cases in general. According to some (19, 32) the diagnostic yield of lung biopsies is worthwhile, whereas others disagree (33, 34). The choice to proceed to lung biopsy has to be made based on the individual case probably.

For common indoor allergens like house dust mite, cat and cockroach, tests are now commercially available, which allow quantitative measurements of these allergens in house dust (35). For a number of common indoor and occupational allergens, threshold levels have been established above which there is an increased risk of allergic asthma (36, 37). Exposure to pigeon antigens is commonly verified by measuring 'precipitating antibodies' by the double immunodiffusion technique. However, this technique is not very sensitive, unsuitable to monitor effectiveness of avoidance measures (38), and is not very specific as a marker of disease as many asymptomatic bird breeders have elevated antibody levels (12). Furthermore, individuals may develop specific antibodies against only one type of pigeon allergens, such as feathers, serum or intestinal mucins and not necessarily against all (3).

The paper by Curtis et al. (1) is the first one to show that pigeon antigens can be quantified in indoor environments, that substantial levels of wild pigeon antigen can be detected in buildings that carry nesting sites, and that it is even present in detectable levels in homes and hospitals that have no pigeon nests in their direct vicinity at all. They collected fresh dropping samples from pigeons for preparation of extracts to be used in antiserum production and ELISA development. The difficulty in working with pigeon droppings related to the standardization and the stability of the preparation has been recognized (39). Pigeon serum may be a more stable antigen, because of less contamination by micro-organisms (40). Reynoud et al. did not find precipitins against pigeon fecal antigens in sera from patients without precipitins against antigens from bird sera, suggesting that testing for pigeon serum antigens has comparable sensitivity (40). IgG antibodies from patients with pigeon breeder's disease cross-react strongly with the sera of other avian species, and also with proteins in hen's egg yolk and egg white (41). In this study, the allergen content of dust samples was expressed as inhibitory activity/gram dust. The main argument against the use of inhibitory activity/gram dust is that allergen exposure may be better quantified by activity per square meter (42).

We can conclude that allergy and AA owing to wild pigeons is a diagnosis with unknown prevalence in the general population, perhaps underreported, hard to prove, and easily misclassified. At the same time, AA is a disorder that may lead to disabling and a potentially fatal lung disease, which is a rare condition indeed. Symptoms may mimick those of allergic asthma, and even respond to asthma treatment. The only way to estimate sensitivity or AA owing to city pigeon allergens

in the general population is to address this in future epidemiological studies. The study by Curtis et al. (1) strongly suggests that the anecdotal evidence for the development of AA as a result of wild city pigeons (2–5) can be explained by high indoor concentrations of allergens to these outdoor birds, and that it can be present in ‘clean’ homes and public buildings. In the

case of nonresolving chest disease, symptoms of allergic asthma not or only marginally responding to adequate treatment, or ‘atypical asthma’ without good recovery, we suggest to consider unusual allergens, and to look out of the patient’s windows for animals. If they fly and have two legs, they’re no zebras.

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