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Perspectives

Asthma--An Epidemic in the Absence of Infection?

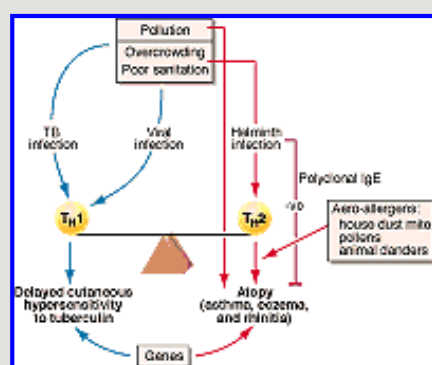
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Asthma is a chronic and debilitating disease, causing swollen and inflamed airways that are prone to constrict suddenly and violently. Asthmatics have attacks of shortness of breath and wheezing that can be life-threatening or even fatal. The prevalence of asthma in Westernized societies has risen steadily this century, doubling in the last 20 years (1). Asthma now affects one child in seven in Great Britain, and in the United States it causes one-third of pediatric emergency-room visits. Asthma is familial, and genome-wide searches by our group and others have shown that many genetic loci predispose to the disease (2). It is unlikely, however, that the genetic makeup of stable populations can change significantly within one century, so the probable cause of the epidemic must lie in the environment. In this issue of *Science*, Shirakawa and his colleagues (p. 77) present evidence for a novel environmental cause of asthma (3).

Asthmatic airway inflammation is initiated by immunoglobulin E (IgE)-mediated allergy ("atopy") to airborne proteins ("allergens"). For asthmatics, the most important source of allergens is the house dust mite. These mites thrive in warm, moist conditions and are ubiquitous in human bedding. There is a dose-response relation between exposure to mite antigens and asthma, and a plausible but unproven case can be made for increasing levels of mite in modern heated homes (1). In Japan, asthma has increased just as the population has moved away from the traditional bare and well-ventilated house to Western-style buildings. In Arizona, however, the dry heat means that mite allergy is rare, yet asthma is as common in Tucson as elsewhere in the United States. This suggests that the innate ability to become allergic can readily find alternative antigens.

Air pollution may aggravate existing asthma but is not responsible for the asthma epidemic (1). Comparisons have been made between the prevalence of asthma and allergy in highly polluted Leipzig in East Germany and clean Munich in the West (4). Surprisingly, the prevalence of asthma and skin tests to common allergens was lower in the East. Similar comparisons between Sweden and polluted Poland show the same phenomenon (5). The German investigators also found that the prevalence of asthma was lower in the youngest children of large families than in children high in the birth order (6).



An advantage of infection. Atopy (asthma and other allergic

diseases) is reciprocally related to immunity to tuberculosis (as measured by delayed cutaneous hypersensitivity to tuberculin) (3). If an individual has predominantly T_H2 T cells, the T_H2 phenotype interacts with environmental allergens to produce atopic disease. Infections may alter the balance between T_H1 and T_H2 phenotypes. The clean living conditions of Western society, by reducing the incidence of infection, may tip the balance toward the T_H2 phenotype and predispose to asthma.

These results suggest that asthma prevalence has increased because of something lacking in the modern environment, rather than through the positive actions of some toxic factor. Respiratory and other infections are much more common in polluted and crowded Eastern block countries than in the West, and younger children get more infections from their siblings than single or older children. Childhood infections may, therefore, paradoxically protect against asthma. The study by Shirakawa *et al.* on children in Japan focuses on tuberculosis as a key in-fecton influencing asthma prevalence (3).

Inflammation is modulated by helper T (T_H) lymphocytes. T lymphocytes may be classified into T_H1 and T_H2 types, according to the pattern of their cytokine production (7). T_H1 cells secrete interferon- γ (IFN- γ), interleukin-2 (IL-2), and lymphotoxin, whereas T_H2 cells secrete IL-4, IL-5, IL-6, IL-10, and IL-13. T_H1 cells enhance cellular immune responses, and T_H2 cells favor the humoral response. Although the T_H1/T_H2 classification is an oversimplification, cells exhibiting the T_H2 phenotype up-regulate IgE production and are prominent in the pathogenesis of airway inflammation and asthma.

As in other modern societies, infection with *Mycobacterium tuberculosis* (Mtb) has declined steadily in Japan during this century. This is in part due to a comprehensive program of inoculation with attenuated bovine tuberculosis vaccine bacillus Calmette-Guérin (BCG), which is administered at 3 months of age. Children are tested for delayed hypersensitivity to tuberculin (DHT) at 6 and 7 years of age and are re-inoculated with BCG if the skin test is negative. Final skin testing is carried out on all children when they are 12. Shirakawa *et al.* studied 867 children after the age of 12 and showed a clear negative relation between DHT responses and two parameters--the presence of asthma and the serum IgE concentration. Children with positive DHT responses to tuberculin had serum cytokine concentrations suggestive of predominant T_H1 responses, in contrast to the T_H2 profiles seen in children with negative DHTs.

These results are an important extension of observations in the 1960s and 1970s that there is a reciprocal relation between inflammatory and humoral responses to vaccination regimes (7, 8). This reciprocal relation has also been attributed to preferential activation of T_H1 or T_H2 subsets of T cells and is consistent with the genetic predisposition to T_H1 or T_H2 responses of different strains of mice.

Central to the relevance of the results is the hypothesis that the immune system can be manipulated to manifest a persistent T_H1 or T_H2 response. If this is the case, vaccination to induce T_H1 responses may be effective against asthma and other allergic disorders (9). In mice, overwhelming *Schistosoma mansoni* infection induces T_H2 responses. The infection concomitantly down-regulates the T_H1 response to other antigens and delays the clearance of vaccinia virus (10). However, in humans with filariasis, who show T_H2 -biased cytokine profiles, the ability to respond to Mtb proteins is not lost (11). Children with eczema, another atopic condition, occasionally undergo spontaneous remission after severe bacterial or viral infections (12), although usually temporarily. Both of these observations suggest that alterations in the T_H2/T_H1 balance may become important only in the presence of continued overwhelming infection.

Also confusing the T_H1/T_H2 theory of asthma are the findings that helminth and other parasite infection may protect against allergic diseases, despite up-regulation of T_H2 responses. This type of infestation is invoked to explain the low prevalence of asthma in rural Africa and the Venezuelan slums (13, 14). Helminth infection produces high levels of polyclonal IgE that, possibly by saturating the number of binding sites for IgE on mast and other effector cells of allergy, prevent activation of these cells by the relatively trivial exposures to allergens.

Thus, the results of Shirakawa *et al.* invite the speculation that the decline in childhood tuberculosis infection in Japan is causal in the recent asthma epidemic. However, the incidence of other infections may also be declining, so the case for tuberculosis requires further study. Nevertheless, the new results emphasize the complexity of the environmental contribution to asthma and remind us that identification of the relevant factors may ultimately resolve this epidemic.

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