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Parasites, Allergy, and Asthma

Asthma is generally more common in developed than developing countries, and within developing countries, it tends to be rare in rural relative to urban populations (1). This indicates either that environmental factors associated with urbanization and affluence cause asthma or that aspects of a rural subsistence lifestyle prevent it. Given the clinical significance of the asthma epidemic in developed countries in recent decades, it is of obvious importance to investigate the factors responsible.

It was first suggested that intestinal parasite infections may be involved, possibly by blockade of allergen-specific IgE binding on mast cells by the high levels of IgE produced in response to the parasite (2), in the early 1970s. Epidemiologic interest in parasite effects persisted into the 1980s but appears to have diminished after a 1985 review concluded that the data “neither refute nor support the theory that parasite infection protects against asthma” (3). Recently however, the parasite hypothesis has again begun to attract attention (4–9), and in this issue of *AJRCCM* (pp. 313–317) Cooper and colleagues (10) report cross-sectional evidence that parasites protect against allergic sensitization and exercise-induced wheeze, but not other allergic symptoms, in children in Ecuador. Their findings on allergic sensitization are essentially similar to those reported in a subgroup of the same population in another article (11), which also presents data on total and specific IgE, but not symptoms. It is unfortunate that all of these data, if available for all of the participants in the present study, were not presented in a single report.

Several of the recent studies provide evidence of protection by parasites against allergic sensitization. In Gabonese children, *Schistosoma* infection is associated with a reduced risk of skin sensitization to house dust mite (6), an effect apparently mediated by interleukin-10 rather than IgE blockade (6, 12). Reduced allergic sensitization in the presence of helminth infection is also reported in adults from The Gambia (4), whereas a Venezuelan study has demonstrated that parasite eradication increases allergic skin sensitization and allergen-specific IgE

levels in children (13). These findings are all therefore consistent with those of Cooper and colleagues (10, 11).

In relation to wheeze or asthma, however, the data are less clear. The Gabon study did not present data on symptoms (6), but a study from Brazil suggests that asthma may be less severe in children infected with *Schistosoma* (7). Physician-diagnosed asthma has also been reported to be less common in Taiwanese children infected with pinworm (data on allergic sensitization not presented) (9), again suggesting a protective effect. In the Gambian study, however, neither helminth infection nor allergic sensitization was related to wheeze (4), whereas a study from China has reported an increased risk of childhood asthma as well as allergic sensitization in association with *Ascaris* infection (14). In Venezuela, eradication of parasites in children with asthma appears to have caused improvement, rather than deterioration, in asthma severity (15). These data are clearly much less indicative of protection against asthma, and the study from Ecuador is equivocal in this respect: parasite infections were associated with reduced risks of symptoms of asthma, rhinitis, and eczema, but significantly so only for exercise-induced wheeze (10).

Our own findings in Ethiopia are different again from many of these studies. We have shown a strong and intensity-related reduction in the risk of wheeze with parasite infection in independent studies of adults (5) and young children (8), but an increased risk of sensitization to *Dermatophagoides pteronyssinus* in rural adults infected with parasites, with dissociation from an increased risk of wheeze in the presence of higher-intensity parasite infection (5). In young children, allergic sensitization was unrelated to parasite infections or wheeze (8).

Why do these inconsistencies arise? Aside from false positive and negative findings, one obvious possibility is that some cross-sectional associations are due to confounding by exposure to endotoxin, hepatitis A, allergens, or any of the other factors linked to the etiology of asthma. Hepatitis A infection and Der p1 exposure did not confound our results

in adults in Ethiopia (5), but much larger studies than are currently available are necessary to fully resolve these issues. A second explanation is that allergic individuals are less likely to become infected with parasites, itself an attractive explanation for the evolutionary persistence of a common trait with little other obvious survival advantage. A further possibility is that some of these effects are parasite species-specific and that the confusion in the literature arises in part from confounding by infection with more than one parasite. Our studies, and those from the Gabon, are consistent to the extent that they demonstrate effects arising from parasites with a systemic phase in their life cycle (5, 6), in our case particularly hookworm (5). Systemic phase parasites such as the hookworm have developed defense mechanisms to allow them to survive the powerful immune responses mounted against them by the host (16), many of which are also likely to have antiallergic activity. Not all of the available data support this idea, however, and few studies, including this latest (10), have estimated independent effects for individual parasite species.

Those seeking a simple answer may find the inconsistencies irreconcilable and conclude that this line of investigation is going nowhere. The risk of this is, however, to miss seeing the wood for the trees because many of the effects described in these studies are strong and therefore likely to reflect important etiologic influences. The studies also contain other messages that should not be ignored. Given that allergic sensitization is a strong risk factor for asthma in most developed countries, the consistent lack of association in many of these tropical populations certainly merits further investigation. If valid, the inverse relationships reported in the studies cited also have important implications for current thinking on the role of T-lymphocyte immune polarization in the pathogenesis of allergic disease. Given that eradication of parasite infection is a universal public health goal, it is also important that any potential adverse effects of this policy are properly defined. The article by Cooper and colleagues (10) is a welcome contribution because it provides further evidence that something relevant lies in these associations. The challenge is to understand and apply them to practical benefit.

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Cellular Alchemy

Alchemy, the art of transmuting base metals into gold, has been contrary to accepted belief for some time. Only a few years ago, the concept of blood cells transmuting into lung cells would have been no less heretical because it was widely accepted that the human lung had a limited capacity to grow and regenerate. In this issue of *AJRCCM* (pp. 318–322), Suratt and coworkers (1) challenge this maxim by providing further evidence in support of the capacity of hematopoietic stem cells to replenish lung cells. The authors examined lung biopsies after male-to-female stem cell bone marrow transplantation in three subjects and three control subjects. Their approach was immunohistochemical staining of the cells for cytokeratin to identify epithelial cells, platelet endothelial cell adhesion molecule to identify endothelial cells, and fluo-

rescent *in situ* hybridization analysis to identify male cells. The results demonstrate that 2.5 to 8.0% of lung epithelial cells and 37.5 to 42.3% of lung endothelial cells were male, indicating the lung contained cells derived from the transplanted stem cells forming a chimera.

The cellular source of multipotential stem cells may differ in the lung, depending on their location within the bronchopulmonary tree. In the proximal airways (trachea and bronchi), the basal cells appear to be the major source of proliferative cells. Further down in the terminal and respiratory bronchioles, Clara cells increase their proliferative rate in response to injury (2). The type II pneumocyte appears to be the stem cell in the alveoli and is able to generate daughter cells that can differentiate into type I pneumocytes. Studies by Krause and