ing the November 1995 assault on Jaffna. Cease-fires have been declared in Sudan for both polio and dracunculiasis eradication, expanding health truces beyond immunization.

Days of tranquillity permit warring parties to disengage and provide a glimpse of peace, but also give both sides a common goal to serve as a starting point for future negotiations. The resolution of conflict with incorporation of the rebels into the national army in El Salvador and, recently, in the Philippines provides evidence that days of tranquillity can be the first of many steps toward a lasting peace. Polio eradication activities must be conducted amidst current and future conflicts around the world. We are confident that there will be more truces and polio will be eradicated. The challenge for science is to continue the development of tasks and tools that can serve as instruments of peace.

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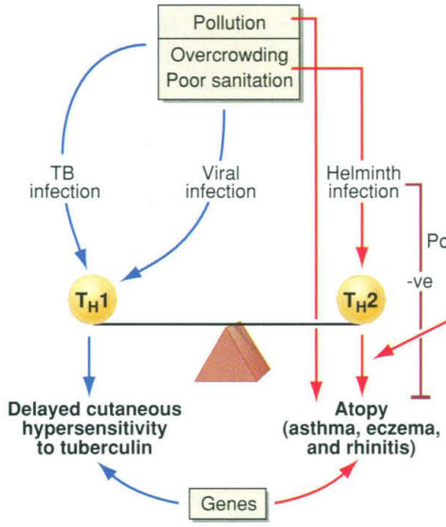
IMMUNOLOGY

Asthma: An Epidemic in the Absence of Infection?

William O. C. M. Cookson and Miriam F. Moffatt

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.



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.

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*).

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 infection 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 upregulate 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.

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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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SIGNAL TRANSDUCTION

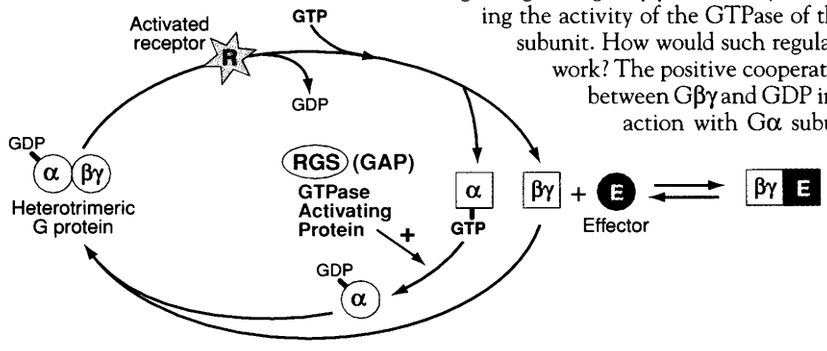
There Are GAPS and There Are GAPS

Ravi Iyengar

Although their main function is to regulate other proteins, guanine nucleotide–binding proteins (G proteins) are also guanosine triphosphatases (GTPases), cleaving guanosine triphosphate (GTP) to form guanosine diphosphate (GDP). Because of this activity, they oscillate between GTP- and GDP-bound states, and thus regulate diverse processes such as protein synthesis, cytoskeleton assembly, vesicle transport, and signal transduction. The superfamily comprises both small monomeric and large multimeric G proteins, but for all members, the release of bound GDP and the binding of GTP are highly regulated processes (*1*). The GTPase activity of small G proteins, such as EF-Tu and Ras, is stimulated by associated proteins called GAPs (GTPase activating proteins) (*2*). But GAPs for most large G proteins had not been described until recent work identified members of the regulators of G protein–signaling (RGS) family as GAPs for this subfamily.

The large heterotrimeric G proteins involved in signal transduction have α subunits, which are related to small G proteins, and βγ subunits that exist as a single complex. Both Gα and Gβγ can independently transmit signals (*3*). Signal termination for both Gα and Gβγ subunits likely occurs through GTP hydrolysis. How the GTPase terminates signaling through Gα subunits is easily understood given the observation that GDP-Gα subunits have much lower affinities for effectors than do GTP-Gα complexes (*4*). But how signaling through Gβγ is terminated has not been as clear. A report in *Cell* by Gilman and co-workers (*5*) and two others in *Nature* (*6*) identifying two members of the RGS family, GAIP and RGS4, as GAPs for members of the $G\alpha_i$ family and other recent papers shed light on this issue.

Members of the RGS family have been identified in yeast, *Caenorhabditis elegans*, and mammals (*7*). Sst2p in yeast and EGL-10 in *C. elegans*, homologs of RGS, suppress signal transmission by acting on the G protein–α subunit (*8*). Mammalian RGS can substitute for yeast Sst2p in regulating pheromone signaling (*9*), which is transmitted through Gβγ subunits (*10*). Taken together, these data suggest that RGS can regulate signaling through Gβγ subunits by modulating the activity of the GTPase of the α subunit. How would such regulation work? The positive cooperativity between Gβγ and GDP interaction with Gα subunits



A four-component heterotrimeric G protein–signaling system. The resting G protein is an αβγ heterotrimer with GDP bound to it. Activated receptor promotes the release of GDP, the binding of GTP, and dissociation of GTP-Gα from the Gβγ complex. GTP-Gα and Gβγ can now interact with their effectors and propagate the signal. RGS stimulates (+) the GTPase activity of the Gα subunit, resulting in the accumulation of GDP-Gα, which re-forms the stable heterotrimer. Free Gβγ leads to dissociation of Gβγ from effector, thus terminating signal propagation. R, receptor; E, effector; αβγ, the heterotrimeric G protein; and RGS (GAP), stimulator of the GTPase of the Gα subunit.

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