

Parasites and Allergy

From IgE to Th1/Th2 and Beyond

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"Allergy – a disease of civilization."

Sir William Osler, 1894

When I began my career in immunology in the laboratory of Professor Abraham Osler (no relation to Sir William, the first Professor of Medicine at the Johns Hopkins School of Medicine) at the JHU in Baltimore some years ago, the initial focus of my research was IgE, basophils, and mast cells in human allergy (1,2). Later, in my own laboratory in the School of Hygiene and Public Health, we, as did many others, explored the biology of these subjects using helminth infections, for example, *Nippostrongylus brasiliensis* and *Dirofilaria immitis*, in mice and rats as an experimental model (3–7). Knowing of my work with parasites, my departmental colleague Professor Ernest Schiller invited me to collaborate with him in his research on human onchocercosis. This led me to Guatemala with him and his students and, subsequently, to Cameroon with my own project on onchocercosis (8–10). Two things about this disease were of interest to me: first, the extremely high serum levels of IgE (11) and, second, the allergic-like reactions that occurred

when infected individuals were treated with dithiocarbamazine, a reaction that was thought to be related to histamine release from the infected individual's mast cells. Meanwhile, human allergy still held my interest (12,13).

After certain events changed my life in the mid-1980s, I wound up in the Laboratoire de Parasitologie Experimentale at the Institut Pasteur, where malaria immunology was the principal research topic. After a year there and then five years in the immunology section of a pharmaceutical company, I returned to my initial interest, human allergy, with a position in the Centre d'Allergologie in Paris.

During all these years, I remained intrigued by the connection between parasitic infections and human allergy. My attention had been drawn to, among others, papers by Ellen Jarrett in the 1970s and early 1980s. The excellent review by Jarrett and Miller (14) summarized quite well what was known about IgE in helminth infections at that time. It was recognized that helminth infections are unique in stimulat-

ing the production of large amounts of IgE, both parasite-specific and nonspecific, and that IgE antibody and mast cells could play an important part in immunity to helminth parasites. Furthermore, in developed countries where standards of hygiene had led to a lower prevalence of helminth infections, serum IgE levels were very low, except in people with allergic diseases.

Epidemiological and immunological studies reported over the past two decades have demonstrated the complex interactions between allergy and helminth infections. Beginning in the 1970s, the work of Neil Lynch (whom, by the way, I had met when I was on sabbatical leave in Paris) and colleagues in Venezuela had revealed the lower prevalence of allergic diseases in helminth-infected tropical populations (15). This led to the hypothesis that parasites evade the immune response by stimulating excess production of polyclonal, clinically irrelevant IgE, which saturates of IgE receptors on mast cells, blocking access to parasite-specific IgE and thus suppressing allergic reactions. At the time, I was interested in the same question (16). As immunologists have since demonstrated, using animal models as well as data from the study of infected and/or allergic humans, the IgE-blocking hypothesis appears to be obsolete; the situation is much more complex than that.

An important turning point was the proposal put forward by Mosmann and colleagues in 1986 (17) that murine CD4⁺ T cells could be assigned to two different subsets, based on distinct, nonoverlapping cytokine secretion patterns in response to stimulation with specific antigens: Th1 cells secrete interleukin-2 (IL-2) and interferon- γ (IFN- γ) and Th2 cells secrete IL-4, IL-5, IL-9, IL-10, and IL-13. It was subsequently found that Th1 cells mediated delayed hypersensitivity and were associated with immune responses to bacteria and viruses and with autoimmune diseases, whereas responses of the Th2 type were associated with allergic diseases and immune responses to helminths.

This is where the so-called “hygiene hypothesis”—first postulated in 1989 by Strachan (18) to explain the increase in allergic disease prevalence that has been observed over the last two to three decades—enters the scene. The hygiene hypothesis stated that reduced exposure to microbes that are more common on farms and in less developed countries is responsible for the increased prevalence of allergic diseases. This was subsequently related to an hypothesized balance between Th1 cells and Th2 cells. Now, however, the hygiene hypothesis and the Th1/Th2 balance, which assumes that the exclusive production of either Th1 or Th2 cytokines could predictably and reproducibly dictate the outcome—immunity or allergic disease—of exposure to infectious agents and allergens or satisfactorily explain the pathogenesis of a variety of autoimmune diseases, are being seriously contested by a number of investigators (19–22). Concerning autoimmune diseases, Gor et al. (23) point to the inability of the Th1–Th2 paradigm to account for effects seen in animal models of human autoimmune diseases. Another example is seen in a large population-based study by Sheikh et al. (24), which recently found no evidence of an inverse relationship between Th1-mediated atopy and Th2-mediated autoimmune disorders, which they took to mean that the Th1–Th2 paradigm is an oversimplification.

Conferences on “Parasites and Allergy” were presented at several recent allergy congresses in Paris. As a topic editor of *Clinical Reviews in Allergy and Immunology*, I took this as my signal to organize a number of reviews on the same subject, with the broad aim to make more allergists aware of the important advances in parasite immunology and to bring them up to date on what is unfolding on the relationship between parasitic infections and allergy. Twelve outstanding specialists on this topic have written up-to-date reviews that will appear in two issues of this journal.

When the reader has finished reading these review articles, he or she should have a better perspective on the complexity of the relationship between allergic diseases and immunity to helminths and allergy. To quote Yazdanbakhsh et al. (22), I want this group of papers "... to focus on insights that may present an alternative immunological framework for the hygiene hypothesis and have important implications for future research and therapeutics."

Leading off, Cooper provides a general review of the potential role of geohelminth (or intestinal helminth) infections, the most prevalent of human helminth infections, in the development of atopy. He is especially interested in the effects of geohelminth infection on the postnatal development of allergen-specific T-cell responses in the context of varying intrauterine and postnatal exposures to geohelminth antigens. Next, Yazdanbakhsh and Matricardi review epidemiological and immunological evidence for and against the hygiene hypothesis and consider the contribution of parasites to the hygiene hypothesis. They propose that regulatory networks stimulated by persistent pathogens could suppress allergic reactivity.

The Caprons analyze, in the context of the high prevalence in many parts of the world of chronic helminth infections and the negative association between helminth infections and allergic diseases, the common mechanisms involved, including the dual function of IgE and the existence of regulatory networks. They propose that the mucosal component of the immune response to helminths is essential for the understanding of these regulatory networks, which at the gut level involves a Th3 T-cell subset that preferentially produces transforming growth factor- β (TGF- β), IL-10, and help for IgA production, similar to that which occurs in the oral-tolerance phenomenon.

In 1997, Allen and Maizels (19) suggested that it was far more important to address the role of individual cytokines during the immune

response, rather than using the Th1/Th2 descriptors, because not all cytokines within a particular subset mediate identical functions. Now, Wilson and Maizels bring us up to date on their thinking about parasites, allergy, and autoimmunity. They point out, as do the other contributors, that the resulting pathology in parasitic infections is a function of the immune response—essentially Th2 and T_{reg} in nature—to a slowly accumulating parasite burden. From their point of view, the immunological environment created by helminth infections can have a major impact on concurrent responses to third-party antigens, whether from other pathogens, allergens, or autoantigens. They propose that disordered immunoregulation, rather than a Th1/Th2 imbalance, is a more accurate description of the consequences of parasite infections.

Grencis and Bancroft concentrate on one major aspect of the host immune response to intestinal nematode infection, which is the role of the Th2 type cytokine IL-13 that is produced predominately by Th2 cells, although dendritic cells (DCs), mast cells, and natural killer (NK) cells have also been found to produce it. The reasons for their interest in this cytokine are twofold: (1) data over the last 5–10 yr has demonstrated a major role for it in the host protective immune response to gastrointestinal (GI)-dwelling nematodes; and (2) this cytokine has been shown to play a major role in allergic disease, asthma in particular. They take this to suggest that the inadvertent deployment of IL-13 in a worm-free environment has had major implications in terms of allergic disease.

The molecular basis for the allergenicity of parasites remains to be fully understood. Nematode parasites almost invariably promote an allergic phenotype bias in the immune response of the host, and by using the human hookworm parasite *Necator americanus* as an example, Franco et al. propose that in the course of its life cycle, this parasite becomes innately allergenic through the secretion of a molecular array designed to promote tissue migration

and homing, feeding, and survival against immunological attack. Subsequent immunological and physiological events seemingly protect the host from both the allergic sequelae of exposure to environmental allergens and, moreover, from the parasite itself.

As an added note, I was struck by the fact that a Medline search for papers on "parasites and allergy" listed many references dealing with allergy to mites—mites being identified as parasites. In that context, Yazdanbakhsh et al. speculated that chronic helminth infections might result in IgE responses that are cross-reactive with house dust mite. Hence, sensitization to parasites may induce clinically irrelevant cross-reactions to mites.

Finally, I would like to thank all the authors for their excellent contributions to this issue. It should generate much interest among allergists, immunologists, and parasitologists.

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