

Helminth Infections and Allergic Diseases

From the Th2 Paradigm to Regulatory Networks

André Capron, David Dombrowicz, and Monique Capron*

Inserm U547, IFR 17, Institut Pasteur de Lille, France

Abstract

Both helminth infections and allergic diseases are characterized by a Th2 response. The former mostly affects developing countries while the latter is steadily increasing in westernized countries, since most parasitic diseases have been eradicated. However, besides the cytokine pattern, both pathologies display striking similarities regarding the cell types involved in the process, the mucosal component of the inflammatory reaction and the immunoglobulin isotypes produced, IgE and IgA.

Recent advances also suggest that allergic pathologies and some other inflammatory diseases arise from a similar dysfunction of the regulatory mechanisms, existing within the immune system. Such a dysregulation leads to a rupture of tolerance towards allergen. Chronic and moderate helminth infections might be beneficial to the induction of various regulatory mechanisms, involving specific regulatory cell populations (dendritic cells and lymphocytes), inhibitory receptors, blocking antibodies and two prominent cytokines: IL-10 and TGF- β , which would decrease the incidence of allergic diseases. This mechanism could provide a new vision of the so-called "hygiene hypothesis".

Index Entries:

Helminth parasites; allergy; regulation; mucosal; tolerance.

It is noteworthy that since the early days of basic studies on immediate-type hypersensitivity and on immune responses to helminths, emphasis was given, in both pathological situ-

ations, to the existence of so-called reaginic antibodies, which were identified half a century later as IgE.

Stemming from the Casoni's reaction in hydatid disease, there is a recurring association of helminth infections with remarkably high IgE production, which is likewise seen in allergic diseases. The immunological links between

*Author to whom all correspondence and reprint requests should be addressed. E-mail: monique.capron@pasteur-lille.fr

helminth infections and allergic states have grown stronger over the past decade, as our ability to study the cellular and molecular components of both types of immune responses has progressed.

In this review, in the context of the high prevalence of helminth infections worldwide, we intend to analyze the common mechanisms involved, the dual function of IgE, and the existence of regulatory networks leading to the apparent paradox of a lower prevalence of allergic diseases in helminth-infected populations.

A Wormy World and the Th2 Paradigm

It is not commonly realized that two-thirds of the human beings on this planet (3.5 billion) are infected by helminths; these infections are also highly prevalent in domesticated animals (1). Each of the intestinal helminths (ascaris, hookworm, and whipworm) infects 1 billion people, and the tissue helminths (such as schistosomes, filarial worms, and tapeworms) infect altogether half a billion individuals (2).

Three major features of helminth infections need to be underlined:

1. Most of these worms are long-lived parasites: they are responsible for chronic infection, and chronicity is a key parameter in the tuning of the immune response to them.
2. Although pathological manifestations can be observed in half a billion cases of helminth infection (notably, in the case of the tissue helminths), direct mortality is low but morbidity is high and has a very important effect on Disability Adjusted Life Years.
3. Helminths can be found in a great variety of internal niches, from the gut to blood vessels, from skin to various internal tissues.

Particular emphasis should be given here to the generally underscored existence of a sig-

nificant mucosal component of the antiparasite immune response. For example, adult schistosomal worms, which are intravascular parasites, are the source of millions of eggs that deposit over many years in the mucosa of the gut and urinary bladder, inducing a strong specific IgA response that has only recently been identified (3–6).

The Th2 Paradigm

Before the discovery of IgE in 1968, the pioneering observation of Ogilvie et al. (7) on schistosomiasis had pointed towards a prominent feature of the immune response against helminths. The demonstration of elevated levels of IgE in helminth-infected individuals and the subsequent demonstration of the protective role of IgE in experimental animals and in humans gave substance to the concept of a particular profile of immune response against helminths (8–10).

The conceptual revolution brought about by Mossman and his colleagues—dividing T helper (Th) cells into two populations with contrasting and cross-regulating cytokine profiles—gave a definitive and substantial framework to the now-accepted dogma that Th2 responses are a unique characteristic of helminth infections (11,12).

The current paradigm for the immune mechanism in helminth infection is based on a powerful and selective Th2 response, expressed through IgE antibodies, eosinophilia, and mast cell proliferation. High levels of total and specific IgE are observed, and elevated expression of interleukin-4 (IL-4), IL-13, and IL-5 are found in infected humans (13).

Although the Th2 preferential polarization is antigen-specific, it can eventually convert the immune response to bystander antigens from a Th1 to a Th2 profile.

Later in this review, we will discuss some of the facets of host-parasite signaling pathways that may account for such a striking polarization, as well as its regulation by the

parasites themselves. Although common denominators related to host receptors may eventually be identified, it is likely that the diversity of sites occupied by helminths may involve diverse immune mechanisms, as has been shown for the various life stages of schistosomes (14).

Again, what appears to be a striking and unique feature of the immune response against helminths is the prolonged—5–15 yr—Th2 response that results from the long parasite life-span, and this represents a permanent challenge to the host's immune system.

The IgE Paradox

Shortly after the identification of IgE as the fifth class of human immunoglobulin (Ig), it was reported that elevated IgE concentrations (7), including specific IgE (9), were a hallmark of helminth infections.

The demonstration that IgE could be an essential humoral component of antibody-dependent, cell-mediated killing of schistosome larvae in rats, primates, and humans led to the discovery of the unsuspected role of IgE in defense mechanisms against metazoan parasites (15,16).

Together with the discovery of low- and high-affinity receptors on inflammatory cells, macrophages, eosinophils, and platelets, passive transfer experiments provided the first experimental evidence that IgE antibodies could be an essential component of protective immunity (17).

These findings in experimental and human schistosome infections pointed to the key role of anaphylactic antibodies (IgG subclasses and IgE) in the defense against worms and led to a re-evaluation of the general biological significance of "anaphylactic" antibody responses, hitherto considered only in the context of allergy.

We postulated that this polarized response could have an evolutionary significance and might represent a primary mechanism of defense against parasites (15–17). Indeed, the

late appearance of IgE in phylogeny, the complex immunological network controlling its production, as well as the high rate of evolution of the ϵ chain, suggest that nature provided for the continuous existence of this peculiar Ig class.

If so, then a major biological function of anaphylactic antibodies might well be to represent an essential evolutionary component of the complex response to parasites. Clinically significant allergic responses to environmental allergens may thus reflect an inappropriate activation of the immunological circuits and effector pathways that were initially aimed at helminths and conferred resistance to these infections (17). These concepts were entirely consistent with the major conceptual revolution that was brought about at the same time by the new Th1-Th2 paradigm, including the polarization of cross-regulating cytokine profiles (11).

On the other hand, following our initial demonstration in rats, a number of epidemiological studies in various endemic areas provided strong evidence that IgE may be one of the keys to protective immunity against schistosome infection in humans (18).

A brief comment should be made here regarding long-standing discrepancies between mice and rats, arising from the absence in mice of IgE-dependent effector mechanisms. It is now well-established that, in contrast to humans and rats, mouse eosinophils do not express the high-affinity or the low-affinity receptor for IgE, Fc ϵ RI, and Fc ϵ RII, respectively (19). Likewise, murine macrophages do not express Fc ϵ RI, whereas human monocytes and rat macrophages do (20). Moreover, major structural differences are observed between human and mouse CD23⁺ B cells, whereas soluble CD23 affects IgE production in an opposite manner in man and in mice. Thus, in many respects the mouse model appears rather inappropriate for the study of IgE-dependent immune responses in the context of parasitic infections and allergic reactions. This comment

can also be extended to some IgA-dependent mechanisms. Indeed, mice do not even possess the gene encoding CD89, the high-affinity IgA receptor, which is likely to be involved in human eosinophil-mediated ADCC reactions.

In sum, there is now a broad consensus that IgE antibodies, and more generally the various components of the Th2 response, are major effectors of protective immunity against helminths. Rather than being regarded as merely a marker, the IgE response to parasitic infection should be seen as the result of a complex Th2-dependent regulatory circuit, with precise evolutionary significance, leading to basic mechanisms of defense against infections characterized by their chronicity and limited clinical expression of inflammatory or allergic processes.

The IgE paradox, stemming from the apparently dual function of the antibodies produced in parasitic infections and allergic diseases, raises some important issues that are at the heart of our understanding of the regulation of immune responses in parasitic infections and allergic diseases.

Immune Responses to Helminths and Allergens

In contrast to the spectacular widespread increase in the prevalence of allergic diseases (21), especially in industrialized countries, evidence of reduced prevalence of allergic diseases in developing countries has been accumulating for many years (22).

It is noteworthy that, similar to allergic states, e.g., asthma, the overall prevalence of autoimmune diseases and chronic inflammatory bowel diseases has increased dramatically in industrialized countries during the last decade, where, at the same time, extended improvement of hygiene, intensive practice of vaccination, and the use of antibiotics and antihelminth drugs have resulted in a spectacular decrease of infectious and parasitic diseases, notably in children (23–25). In this

context, illustrating the influence of environmental factors on disease profiles in human populations, the so-called “hygiene hypothesis” (26) has been seen during the last 10 yr as a kind of unified framework, where reduced exposure and decline in viral and bacterial infections during childhood were regarded as the key explanation for the observed increase of allergic diseases.

The framework of this hypothesis has been reinforced by the overall concept that a balance between Th1 and Th2 immune responses is pivotal and that reduced exposure to microbial agents during early childhood leads to a weak stimulation of Th1 cells, resulting in overexpansion of the Th2 cell population and a predisposition to allergy (23–25).

Although very attractive, the immunological basis of this “hygiene hypothesis” does not account for the observed escalation of autoimmune disorders and inflammatory bowel diseases, which are characterized by Th1 responses, and the existence of an overlapping negative association between helminth infections and allergic diseases, in spite of the proverbial and strong Th2 profile that characterizes the latter conditions (27).

Although some allergic disorders can be observed during the acute phase of certain helminth infections, there is now convincing evidence from many parts of the world that populations heavily infected with helminths are rarely affected by allergic diseases (28,29).

The most remarkable features of this situation are:

1. A consistent inverse relation between helminth infections and atopic diseases;
2. A striking discrepancy between the high levels of IgE seropositivity and the low level of skin reactivity or clinical scores to allergens;
3. A reduced Prausnitz-Kustzner response; and
4. The importance of worm burden and chronicity of infection.

Light infections are associated with high skin reactivity and heavy infections with the absence of atopy. It is clear from a number of studies that, paradoxically, helminth infections, typically associated with Th2 polarization, protect against allergy. Several hypotheses have been proposed to account for this helminth-associated protection from allergy.

The Virtue of Regulation

It should be reemphasized that, conversely to most pathogenic organisms, worms are long-lived, thus being responsible for chronic infections that are dominated by a permanent and complex tuning of immune responses. In addition, in the case of heteroxenic parasites, the various stages of the life cycle may induce distinct and opposite profiles of cytokine expression. In the case of schistosomes, for instance, the invading stage of the infective larvae is marked by a strong Th1 response, whereas the production of eggs by adult worms is accompanied by a spectacular shift to a Th2 profile (14).

In such a context, it is to be expected that a single regulatory mechanism can hardly account for the complex picture occurring in these infections, where there is permanent cross-talk involving the parasite and multiple host factors. There is now growing evidence for a common mechanism for decreasing inflammatory reactions, thereby providing a means of escape that is essential for parasite survival.

The Concept of Blocking Antibodies

The concept of blocking antibodies was elaborated some 60 yr ago in the context of allergen "desensitization" (immunotherapy), which involves immunization with increasing doses of allergen in allergic patients (30).

Recent work has established that high IgG4 antibody titers are associated with decreased atopy (31), indicating that this subclass of antibody might be associated with downregulation

of allergic reactions via its function as blocking antibody.

In helminth infections, among the various mechanisms regulating protective immunity, we showed, initially in rats, that isotype regulation plays an important role (32). Evidence was obtained in this experimental model that the expression of immunity could result from a balance between effector and blocking antibodies (33). In humans, high levels of both IgE and IgG4 are also produced during helminth infections. Preliminary evidence indicated that in humans there is a significant correlation between susceptibility to re-infection by *S. mansoni* and increased production of IgG4 antibody to the vaccine candidate Sm28 GST and its defined B-cell epitopes (34). In subsequent studies, IgG4 was consistently associated with susceptibility to re-infection (35), and it was concluded that the clinical expression of immunity in schistosomiasis was more closely related to the IgE/IgG4 balance than to the absolute level of each of these isotypes. Opposing effects of IgE and IgG4 were not dissociated in the analysis, indicating that these isotypes were probably antagonizing each other. Although IgG4 might inhibit IgE-mediated reactions, evidence that IgG4 can compete strongly with IgE for binding to antigens provides another acceptable explanation. Although both IgE and IgG4 responses initially depend on IL-4 and IL-13 produced by Th2 cells (36), it has been shown recently that the production of IgG4 antibodies is regulated, in an antigen-specific context, by IL-10 and interferon- γ (IFN- γ) produced by Th0 cells (37). This supports the view that these isotypes can be dissociated, despite their reported dependence on IL-4, which would justify the name "alternative Th2 response," recently given to IgG4 antibody production (31). The putative role of IL-10 in preferentially driving an IgG4 response should be put in the broader context of the general properties of this pleiotropic cytokine. Recent observations have indeed supported the view that IL-10 is a key player in antiinflammatory networks (38).

Inhibitory Receptors and Regulation of Antiparasite Immunity

Because the humoral immune response triggered by parasites is, in essence, polyclonal and involves the production of IgG as well as IgA and IgE, it seems obvious that FcγR receptors might also be part of the immune defense against helminths. Among these receptors, we would like to single out FcγRIIb/CD32b, the only inhibitory receptor among FcRs for its potential role in regulating the immune response, and maintaining it within the appropriate intensity range so as to be effective against the parasite but not overtly detrimental to the host.

FcγRIIb is a single-chain receptor bearing an Immunoreceptor Tyrosine Inhibitory Motif, whose activation by IgG immune complexes can negatively regulate B-cell and effector-cell function. Receptor cross-linking on B cells triggers antigen-specific apoptosis, while co-aggregation of FcγRIIb with B cell receptor (BCR) terminates BCR-induced signaling and regulates antibody-driven affinity maturation and ultimately Ig production. Likewise, cytotoxicity or phagocytosis by effector cells such as macrophages/monocytes can also be modulated by co-aggregation of FcγRIIb and activation of FcγR (FcγRIII/CD16 or FcγRI/CD64) by IgG-IC as well as by co-aggregation with other FcRs, such as FcαRI/CD89 and FcεRI (39,40). In the latter case, immune complexes contain parasite-specific IgG of different isotypes. It is tempting to speculate that the regulatory process induced by parasite antigens would also have a more general effect on the host's responsiveness to other antigens (e.g., allergens, autoantigens, etc.) and would thus block or at least increase the minimal threshold required for the induction of pathologic inflammation.

The Antiinflammatory Network and the So-Called Counter-Regulation Hypothesis

For some time now, the negative association between helminth infections and allergy has, in the context of the hygiene hypothesis, been interpreted as the result of strong stimulation of Th2 responses, leading to a Th1 vs Th2 imbalance (41). More recently, emphasis has been given to the existence of a strong regulatory network in response to high and prolonged exposure to pathogens (23–25, 42).

It has been known for a long time that chronic parasitic (in particular, helminth) infections are associated with T-cell hypo-responsiveness, reduced cytokine production, and more recently, the production of down-regulatory molecules such as IL-10 and TGF-β (43–47).

It is of interest to note that IL-10 provides a mirror image of the regulatory role of this molecule in helminth infections and allergy (48,49). High levels of IL-10 are seen in individuals infected with filarial worms or with schistosomes, whereas, conversely, allergic individuals express lower levels of IL-10 (50). Successful allergen immunotherapy is associated with a marked increase in IL-10 production (37). Recent data on urinary schistosomiasis and atopy in Gabon convincingly support the view that parasite-induced IL-10 lowers the risk of skin reactivity to mite allergens (51).

On the basis of observations showing that IL-10 produced in chronic schistosomiasis is central to suppressing atopy in African children, it has been proposed that the induction by helminths of a robust antiinflammatory regulatory network offers a unifying explanation for the observed inverse relationship between parasite infections and allergic disorders (23).

Extending this concept, a counter-regulation hypothesis, based on the key homeostatic role of IL-10 in the control of inflammatory processes, has been proposed (25). Although very

attractive, and consistent with clinical epidemiology of *Schistosoma* infections, IL-10 can hardly be regarded as the single factor responsible for antiinflammatory reactions observed in chronic helminth infections. This highly pleiotropic molecule can act at multiple stages of the immune response, from antigen presentation by antigen-presenting cells (APC) to regulation of mast cell degranulation. It is therefore difficult to assign to it a particular mechanism for the precise function of this cytokine. In fact, the recent identification of regulatory T-cell populations that are characterized by a particular profile of cytokines, including IL-10 and TGF- β , requires careful consideration in the context of helminth infections (52).

Following preliminary observations in lymphatic filariasis showing that the presence of suppressive cytokines (IL-10 and TGF- β) is associated with little evidence of clinical disease (44), additional studies support the view that CD4⁺CD25⁺, Tr1, or possibly Th3 T-cell subsets could be involved in the suppression of ongoing inflammation in infected individuals.

In generalized onchocerciasis, *Onchocerca*-specific downregulation is associated with high IL-10 and/or TGF- β production, and T-cell hypo-responsiveness is reversed by the addition of anti-IL-10 and anti-TGF- β antibodies, suggesting the participation of regulatory T-cell subsets (46). Concomitantly, in individuals chronically infected with *Schistosoma haematobium*, we found a high production of IL-10 and TGF- β associated with a high specific IgA response (47), which is compatible with the Th3 response that is part of the immune mechanism of oral tolerance (53,54).

In the framework of our study, two additional observations deserve consideration (50): first, the specific IgA response and the production of TGF- β and IL-10 were found to be significantly higher in females than in males. Second, this gender-dependent regulation was associated in females with weak production of

Th1-related cytokines (e.g., IFN- γ) and pro-inflammatory cytokines (e.g., tumor necrosis factor- α [TNF- α]), the absence of antigen-induced proliferation and evidence for a specific cell death process engaged in a gender-dependent manner (47). Our observations are consistent with other recent studies demonstrating that in schistosome infection, sex- and age-related hormonal factors influence susceptibility to infection, and antibody production (55–58). Confirming our results in rodents, we have shown for the first time in humans a gender-dependent regulatory response profile, which strongly favors a tolerance mechanism (59,60).

A Wormy World of Tolerance

Although various facets of the immune response to helminths have been widely explored, little attention has been paid to its mucosal component and in particular to the immune functions of IgA antibodies and their participation in regulatory processes with a Th3 profile.

After the initial demonstration in rats that IgA antibodies were associated with protective immunity to schistosomes (3), we demonstrated a significant association between IgA antibodies to the candidate vaccine Sm28 GST and the age-dependent decrease in egg excretion in humans (4,5). Our suggestion of a potentially protective role of IgA antibodies in human schistosomiasis is supported by the results of several convergent investigations. In particular, confirming initial observations made in Kenya, studies in Senegal have shown a significant association between the IgA response to protective antigen and the development of acquired immunity (4,47). A detailed analysis of the populations under study revealed the gender-dependent specific IgA response to the candidate vaccine that resulted in a level of antibodies four times higher in females than in males (47).

It is now well-established that TGF- β and IL-10 cooperate to induce IgA secretion by human B cells (61). TGF- β produced by Th3 cells is now recognized as a major help factor for IgA production (54).

Very little is known regarding the antiinflammatory role of IgA antibodies and, in particular, of secretory IgA (sIgA) at the mucosal level. Recent studies have however indicated that nonallergic children tend to have higher levels of sIgA and that the levels of sIgA are higher in sensitized infants with no allergic symptoms than in sensitized children with symptoms (62). Furthermore, high levels of sIgA seem to protect sensitized children from developing allergic symptoms during the first 2 yr of life, supporting the idea of a possible protective role of sIgA against the development of allergy (62). It has also been shown that specific IgA prevents increased airway responsiveness and lung eosinophilia in a mouse model of asthma, pointing further to the role of IgA in the regulation of allergic reactions (63,64).

Eosinophils themselves can produce significant amounts of IL-10 and other immunomodulatory cytokines (65–67), and we have recently shown that IgE or secretory IgA complexes are very potent inducers of IL-10 release (65,66). In contrast, sIgA immune complexes are able to inhibit significantly the CD28-mediated release of IL-2 and IFN- γ (65). These results suggest that sIgA at the mucosal level might be part of the various cross-regulatory signals modulating inflammatory reactions and it could be relevant to the so-called “oral tolerance” phenomenon.

In light of these observations and comments, we propose that the mucosal component of the immune response to helminths is essential for the understanding of the regulatory network, leading to the confirmed negative association between helminth infection and allergic, inflammatory, and autoimmune diseases. In this context, at the gut level the Th3 subset is preferentially producing TGF- β ,

IL-10, and help for IgA production, and it plays an essential role in the oral-tolerance phenomenon. Although no definitive evidence is available, the Tr1 subset appears to produce IL-10 preferentially and it does not appear to be involved in IgA helper function. Some evidence favoring this view comes from the recent demonstration that human CD25⁺ CD4⁺ T suppressor cell clones produce TGF- β but not IL-10 and are distinct from Tr1 cells (68).

Finally, in our view, the concept that the regulatory network developed in chronic helminth infections is related to “mucosal” tolerance is supported by our other observations, similar to other situations recently described (69), of the clear existence of a specific cell-death process that leads to the deletion of Th1 and Th2 cells and to the appearance of a Th3 phenotype. These specific regulatory processes would promote IgA production, which is found in chronic infectious diseases in humans.

Concluding Remarks

There is now accumulating and convincing evidence that chronic helminth infections induce a complex response network that downregulates the inflammatory reaction. In the light of our own contributions, we have deliberately focused our comments on human infections. But it is fair to say that numerous contributions that are entirely consistent with our view have also been made using animal models.

Among the most important factors concerning this regulation, IL-10 has been recently shown to be a key player in antiinflammatory reactions, but in the context of helminth infections, no precise information has been given on the status of TGF- β and IgA responses. These factors, in addition to IL-10, characterize a particular population of regulatory T cells described as Th3, which are the basis of mucosal tolerance.

During the course of our investigations of an anti-schistosomiasis vaccine, we have been

able to identify a strong IgA response to the protective antigen and its major epitopes in humans chronically infected with schistosomes (*Schistosoma mansoni* and *Schistosoma haematobium*). Later, we showed that this specific IgA production is associated with elevated TGF- β and IL-10, giving the immune response a Th3 profile. It was moreover shown that the appearance of this profile is accompanied by a strong apoptotic process in Th1 and Th2 cells, both phenomena being more prominent in females than in males (50).

We think that these observations, which complement other recent reports, are consistent with the view that in helminth infections the mucosal component, which has been largely underestimated, must be considered as essential for the understanding of the induction of a regulatory process that resembles mucosal tolerance. This tolerance mechanism, which is entirely compatible with the long-duration helminth infections, could provide a basis for a new vision of the so-called "hygiene hypothesis." The tolerance that leads to downregulation of inflammatory, allergic, and autoimmune diseases, like that occurring in chronic helminth infections, appears to be the beneficial consequence of a "wormy world."

In this context, we would argue that the eradication of pinworms, whipworms, ascaris, and so forth in industrialized countries, where they were highly prevalent 40 yr ago, through the systematic administration of antihelminth drugs, may have been one of the contributing factors to the increased incidence and prevalence of allergic and autoimmune diseases.

For those of us who have spent their life developing new and efficient tools to reduce the incidence of helminth infection and limit the burden of parasitic diseases on public health, there are obviously some important lessons to be drawn from this whole collection of new information.

References

1. Maizels, R.M., Holland, M.J., Falcone, F.H., et al. (1999), *Immunol. Rev.* **171**, 125–147.
2. Crompton, D.W.T. (1998), *Parasitol. Today* **4**, 162–169.
3. Grezel, D., Capron, M., Grzych, J.M., et al. (1993), *Eur. J. Immunol.* **23**, 454–460.
4. Grzych, J.M., Grezel, D., Xu, C.B., et al. (1993), *J. Immunol.* **150**, 527–535.
5. Capron, A., Dombrowicz, D., and Capron, M. (1999), *Microbes Infect.* **1**, 485–490.
6. Capron, A., Riveau, G.J., Bartley, P.B., and McManus, D.P. (2002), *Curr. Drug Targets Immune Endocr. Metabol. Disord.* **2**, 281–290.
7. Ogilvie, B.M., Smithers, S.R., and Terry, R.J. (1966), *Nature* **209**, 1221–1223.
8. Johansson, S.G.O., Bennich, H.H., and Berg, T. (1971), *Prog. Allergy* **1**, 157.
9. Dessaint, J.P., Bout, D., Wattre, P., and Capron, A. (1975), *Immunology* **29**, 813–823.
10. Jarrett, E.E. and Miller, H.R. (1982), *Prog. Allergy* **31**, 178–233.
11. Mossman, T.R., Chemvinski, H., Bond, M.W., et al. (1986), *J. Immunol.* **136**, 2348–2357.
12. Pearce, E.J. and Sher, A. (1991), *Exp. Parasitol.* **73**, 110–116.
13. Sher, A. and Coffman, R.L. (1992), *Annu. Rev. Immunol.* **10**, 385–409.
14. Pearce, E.J. and MacDonald, A.S. (2002), *Nat. Rev. Immunol.* **2**, 499–511.
15. Capron, A., Dessaint, J.P., Capron, M., and Bazin, H. (1975), *Nature* **253**, 474–475.
16. Capron, A., Dessaint, J.P., Capron, M., et al. (1987), *Science* **238**, 1065–1072.
17. Capron, M. and Capron, A. (1994), *Science* **264**, 1876–1877.
18. Hagan, P., Blumenthal, U.J., Dunn, D., et al. (1991), *Nature* **349**, 243–245.
19. de Andres, B., Rakasz, E., Hagen, M., et al. (1997), *Blood* **89**, 3826–3936.
20. Dombrowicz, D., Quatannens, B., Papin, J.P., et al. (2000), *J. Immunol.* **165**, 1266–1271.
21. Sears, M.R. (1997), *Lancet* **350**, 1015–1020.
22. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee (1998), *Lancet* **351**, 1225–1232.
23. Yazdanbakhsh, M., Kremsner, P.G., and van Ree, R. (2002), *Science* **296**, 490–494.
24. Bach, J.F. (2002), *N. Engl. J. Med.* **347**, 911–920.
25. Wills-Karp, M., Santeliz, J., and Karp, C.L. (2001), *Nat. Rev. Immunol.* **1**, 69–75.
26. Strachan, D.P. (1989), *Br. Med. J.* **299**, 1259–1260.
27. Masters, S. and Barrett-Connor, E. (1985), *Epidemiol. Rev.* **7**, 49–58.
28. Godfrey, R.C. (1975), *Clin. Allergy* **5**, 201–207.
29. Lynch, N.R., Hagel, I., Perez, M., et al. (1993), *J. Allergy Clin. Immunol.* **92**, 404–411.
30. Loveless, M.H. (1943), *J. Immunol.* **47**, 165–180.

31. Platts-Mills, T., Vaughan, J., Squillace, S., et al. (2001), *Lancet* **357**, 752–756.
32. Grzych, J.M., Capron, M., Dissous, C., and Capron, A. (1984), *J. Immunol.* **133**, 998–1004.
33. Khalife, J., Capron, M., Capron, A., et al. (1986), *J. Exp. Med.* **164**, 1626–1640.
34. Auriault, C., Gras-Masse, H., Pierce, R.J., et al. (1990), *J. Clin. Microbiol.* **28**, 1918–1924.
35. Demeure, C.E., Rihet, P., Abel, L., et al. (1993), *J. Infect. Dis.* **168**, 1000–1008.
36. Gascan, H., Gauchat, J.F., Aversa, G., et al. (1991), *J. Immunol.* **147**, 8–13.
37. Akdis, C.A., Blesken, T., Akdis, M., et al. (1998), *J. Clin. Invest.* **102**, 98–106.
38. Pretolani, M. and Goldman, M. (1997), *Immunol. Today* **18**, 277–280.
39. Ravetch, J.V. and Bolland, S. (2001), *Annu. Rev. Immunol.* **19**, 275–290.
40. Takai, T. (2002), *Nat. Rev. Immunol.* **2**, 580–592.
41. Umetsu, D.T., McIntire, J.J., Akbari, O., et al. (2002), *Nat. Immunol.* **3**, 715–720.
42. Matricardi, P.M. and Bonini, S. (2000), *Clin. Exp. Allergy* **30**, 1506–1510.
43. Mahanty, S. and Nutman, T.B. (1995), *Parasite Immunol.* **17**, 385–392.
44. Levings, M.K., Bacchetta, R., Schulz, U., and Roncarolo, M.G. (2002), *Int. Arch. Allergy Immunol.* **129**, 263–276.
45. King, C.L., Mahanty, S., Kumaraswami, V., et al. (1993), *J. Clin. Invest.* **92**, 1667–1673.
46. Doetze, A., Satoguina, J., Burchard, G., et al. (2000), *Int. Immunol.* **12**, 623–630.
47. Remoue, F., To Van, D., Schacht, A.M., et al. (2001), *Clin. Exp. Immunol.* **124**, 62–68.
48. Mocellin, S., Panelli, M.C., Wang, E., et al. (2003), *Trends Immunol.* **24**, 36–43.
49. Levings, M.K., Bacchetta, R., Schulz, U., and Roncarolo, M.G. (2002), *Int. Arch. Allergy Immunol.* **129**, 263–276.
50. Borish, L., Aarons, A., Rumbyrt, J., et al. (1996), *J. Allergy Clin. Immunol.* **97**, 1288–1296.
51. van den Biggelaar, A.H., van Ree, R., Rodrigues, L.C., et al. (2000), *Lancet* **356**, 1723–1727.
52. Bach, J.F. (2003), *Nat. Rev. Immunol.* **3**, 189–198.
53. Weiner, H.L. (2001), *Microbes Infect.* **3**, 947–954.
54. Weiner, H.L. (2001), *Immunolog. Rev.* **182**, 207–214.
55. Bundy, D.A.P. (1988), *Immunol. Today* **4**, 186–189.
56. Fulford, A.J.C., Webster, M., Ouma, J.H., et al. (1998), *Parasitol. Today* **14**, 23–26.
57. Remoue, F., Rogerie, F., Gallissot, M.C., et al. (2000), *J. Infect. Dis.* **181**, 1855–1859.
58. Remoue, F., Mani, J.C., Pugniere, M., et al. (2002), *Infect. Immun.* **70**, 601–605.
59. Eloi-Santos, S., Olsen, N.J., Correa-Oliveira, R., and Colley, D.G. (1992), *Exp. Parasitol.* **75**, 168–175.
60. Nakazawa, M., Fantappie, M.R., Freeman, G.L., Jr., et al. (1997), *Exp. Parasitol.* **85**, 233–240.
61. Defrance, T., Vanbervliet, B., Briere, F., et al. (1992), *J. Exp. Med.* **175**, 671–682.
62. Bottcher, M.F., Haggstrom, P., Bjorksten, B., and Jenmalm, M.C. (2002), *Clin. Exp. Allergy* **32**, 1293–1298.
63. Schwarze, J., Cieslewicz, G., Joetham, A., et al. (1998), *Am. J. Respir. Crit. Care Med.* **158**, 519–525.
64. Schneider, A.M., Li, F., Zhang, X., and Gordon, J.R. (2001), *Cell Immunol.* **212**, 101–109.
65. Woerly, G., Roger, N., Loiseau, S., et al. (1999), *J. Exp. Med.* **190**, 487–495.
66. Kayaba, H., Dombrowicz, D., Woerly, G., et al. (2001), *J. Immunol.* **167**, 995–1003.
67. Dombrowicz, D. and Capron, M. (2001), *Curr. Opin. Immunol.* **13**, 716–720.
68. Levings, M.K., Sangregorio, R., Sartirana, C., et al. (2002), *J. Exp. Med.* **196**, 1335–1346.
69. Akbari, O., Stock, P., DeKruyff, R.H., and Umetsu, D.T. (2003), *Int. Arch. Allergy Immunol.* **130**, 108–118.