

Editorial

Immunity, morbidity and immunoepidemiology in parasite infections

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Experimental immunity is advancing our knowledge of all aspects of immunobiology at an ever-accelerating rate and the value of its application to immunoparasitology cannot be overstated. Animal models allow host-parasite immunology studies to be carried out in targeted gene knockout hosts, in standardized environments, with controlled manipulation of the infecting parasite. Longitudinal infection studies, which could be unethical in man, can follow the development of immunity or immunomorbidity in the mouse, with all host tissues available at any point for detailed examination using the whole range of immunology, molecular biology, cell biology and postgenomic techniques. This contrasts with the techniques and biological samples that are available to the field immunologist or immunoepidemiologist who is directly concerned with parasitic infections in the living, naturally infected host.

Immunoepidemiology is not an exact or well-defined discipline. The term first came into common use in relation to studies on human parasite, often helminth, infections (1). This was perhaps because, in order to understand the immunobiology of human parasite infections, we need an understanding not only of the immunological processes but also of how these responses interact with the many complex ecological, genetic and behavioural host and parasite factors that also influence who gets infected, with which parasites and what is the clinical outcome of these infections within host populations. Understanding these interactions is of crucial importance if we are to make progress in developing vaccines against many of the intractable parasitic diseases that afflict man.

In endemic areas, many of the major disease causing parasitic infections affect the majority of the human population for a large proportion of their lives, and the same parasite can cause a wide spectrum of disease syndromes, of differing

severity, in different individuals. Classical epidemiology combined with clinical studies and parasitology tells us how parasite infections and their associated morbidity are influenced by host age and sex, and duration and intensity of infections. Epidemiology can also be combined with host and parasite genetic studies and with analysis of environmental variables, vector biology, nutrition or cultural factors influencing human exposure to infection and susceptibility to disease. Such complexities make it difficult to directly extrapolate immunological findings from experimental animal models, *in vitro* studies, or small-scale or hospital-based human studies directly to the population level. Immunological data on populations exposed to infection in disease endemic areas, and combining it via epidemiological style analysis with data generated by other scientific disciplines, is necessary to bridge the gap between the cutting edge discoveries of basic immunology and what happens when human populations are exposed parasite infection in the real and very complex world.

Many metazoan and protozoan parasites are precisely adapted to their hosts, parasite and host having coevolved in intimate partnership. Animal models, if they exist for a particular human parasite, cannot be expected to provide the definitive analysis of all aspects of the immunological interactions between parasite and the natural host as this key coevolutionary component of the relationship will be absent. Many of these parasites are able to persist in the host for many years and even use their host's immune system to their advantage. Thus, for example, not only do schistosomes have a comprehensive range of immune manipulation and evasion mechanisms that allow them to live in the human blood stream for years, but they use the host's immune response to facilitate the passage of their eggs from the blood to the outside world (2). Such long-term intimate host-parasite relationships are not easy to reproduce experimentally. Helminths such as schistosomes take longer to reach sexual maturity than mice, making it impossible to have a good murine model of the many changes in the host-parasite relationship that occur in chronically infected children around

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Accepted for publication: 21 February 2005

the time of puberty (3). The combination of good immunological, epidemiological and clinical data on naturally infected populations is needed to test whether or not mechanisms detailed in experimental models have significant roles in infection and disease. However, descriptive data are also needed to direct experimental immunologists' attention to the immunological issues that are important to human disease.

This Special Immunoepidemiology Issue of *Parasite Immunology* brings together up to date reviews of some important human parasitic infections, with the aim of illustrating the recent advances and present limitations in our knowledge of the immunobiology of human parasite infection and disease. However, it is significant that while reviewing human-parasite immunological interactions, all these articles are continuously cross-referencing from human response to animal model and back again. This reflects the fact that immunoepidemiology is a crucial bridging activity needed to link experimental immunoparasitology and basic immunology to human parasitic infection and disease.

Intestinal nematodes cause a breathtaking number of infections in the world, both in human populations and in domestic animals, despite the fact that simple safe effective drug treatments are available for their treatment. The combined prevalence of the human intestinal nematode worms *Ascaris lumbricoides*, *Trichuris trichiura* and the hookworms in the world population is estimated to be some 3800 million infections (4). Despite this we still know little of the host-parasite immunological interactions that allow these parasites to so successfully establish chronic infections and cause reinfections in such a high proportion of the world population. However, recent immunoepidemiological studies have suggested that *A. lumbricoides* and *T. trichiura* may be controlled by human Th2-mediated immune responses, although the two parasites may differ in the degree to which they can to evade some of these responses to establish new infections after treatment. Bradley and Jackson's article provides a comparative review of human immunological interactions with *Ascaris* and *Trichuris* using the detailed immunological data from experimental animal models to supplement the necessarily more restricted data from human studies. They also consider the potential immunological implications of 'de-worming' the world population in relation to other infectious diseases and associated immunopathology. To complete the picture of man's immunological relationship with his most common intestinal worm species, the article by Quinnell *et al.* provides a review of recent immunoepidemiological studies on hookworm infections and the use of mathematical modelling to provide evidence that human populations in endemic areas do develop protective immunity. Although, as is true for all human parasite infections, more immunoepidemiology studies are badly needed, antilarval IL-5 and IgE responses may be associated with protection, and Th2 hook-

worm responses such as these may be involved in immunological interactions with other diseases.

From these articles it will be clear that parasite immunologists have long been aware of the close similarities between the human immune responses to parasitic worm infections and environmental allergens. Indeed, it is likely that the evolution of IgE, eosinophils, mast cells and basophils and their associated regulating cytokines was due to the selective pressure to control worm infections rather than through a perverse need to suffer allergy. However, the apparent rarity of allergic diseases and autoimmune diseases in populations living in developing countries where worm infections still have high prevalence has also suggested to some a causal relationship between the decline in helminth infections and the increase in these immunological diseases in the developed world. Experimental models have shown that helminth infections or helminth antigen injections can prevent autoimmune disease in models such as Type I diabetes in NOD mice, experimental autoimmune encephalomyelitis, Graves thyroiditis and collagen-induced arthritis (5) as well as modulate disease in allergy models such as murine anaphylaxis (6). The advent of the T helper 1 and T helper 2 paradigm suggested that counter regulation between IFN γ and IL-4 might account for the down-regulation of Th1 mediated autoimmune diseases by Th2 inducing worm infections. However, the modulation of Th2 allergy by Th2 inducing helminth infections has pointed to the importance of mediators such as TGF β and IL-10, which are now known to down-regulated both Th1 and Th2 responses. Notwithstanding the data from the experimental animal models (reviewed in 7), the strongest evidence for a causal link between exposure to parasitic worms and suppression of immunological diseases comes from studies showing an effect of antiworm chemotherapy on atopy or the risk of asthma. The article by Cooper critically reviews the immunoepidemiological evidence for a causal link between geohelminth infections and reduced risk of allergy and suggests that more evidence is needed, particularly from studies that focus on antihelminth interventions at the time when children are first exposed to infections.

The resurgence of human African trypanosomiasis, combined with the possible development of parasite drug resistance, is a worrying situation for a vector-borne infection commonly considered to be invariably fatal if left untreated. However, the article by Sternberg considers reports, from large-scale human surveys, that infections can be found with varying levels severity or even in asymptomatic carrier states. These observations are discussed in relation to immunological and genetic data that are predominantly derived from cattle studies and experimental models. However, variations in patterns of human inflammatory responses and disease appear to be consistent with a relationship between inadequate control of inflammatory mechanisms and morbidity,

and underlines the pressing need for further detailed immunoepidemiological studies on immunoregulatory responses. Compared with human trypanosomiasis, much effort over many years has been focused on the interactions between *Plasmodium* species, their mosquito vectors and the clinico-epidemiology of human malaria. This has revealed many complex but important patterns of infection and morbidity in which the role of the host immune response is implicated, but still not clear. Infants and pregnant women are the groups within most malaria endemic areas that are most susceptible to severe morbidity and mortality. Can we rationally design vaccines to protect these groups against malaria if we do not know which immune responses prevent human infections, and whether these responses also protect against or exacerbate different forms of severe morbidity, or even if the responses that protect nonpregnant adults are also effective in early childhood or pregnancy? Hviid's article reviews recent immunoepidemiological studies that shed light on the clinico-epidemiological puzzle in which young women in endemic areas who have protective immunity against clinical *P. falciparum* infection suddenly become susceptible to clinical disease during their first few pregnancies, and are then protected again during later pregnancies. Immunoepidemiological data combined with a growing understanding of the relationship between protective IgG responses against blood stage parasite variant surface antigens on infected erythrocytes and the expression by the parasite of new variant antigens, is providing potentially important insights into severe pregnancy-associated *falciparum* malaria.

Parasite infections may modulate human vaccine responses (8) and it has been reported that maternal filariasis or schistosomiasis during pregnancy can suppress the subsequent IFN γ responses of children to BCG vaccination (9). Immunological interactions between coinfecting parasites is an area of developing interest that is reflected in a number of articles in this Special Issue. Many of the major human parasitic diseases are coendemic in developing countries where the resident populations are also exposed to a wide range of viral, bacterial and other infections. Thus, other coinfecting organisms will accompany most human parasite infections. Yet, 40 years after the classic studies of Buck (10) pointed out the potential effects of polyparasitism on human health, most human or animal model studies are firmly focused on single parasite infection. We have a growing understanding of how innate immune mechanisms recognize different classes of pathogen and up-regulate appropriate adaptive responses; the importance of down-regulatory mediators such as IL-10, TGF β and of regulatory T cells; and the cross regulation between Th1 and Th2 responses to intercellular and helminth pathogens, respectively. This knowledge of innate, regulatory and counter regulatory mechanisms provides testable theoretic frameworks for studies of immunological inter-

actions between coinfecting pathogens. Animal models of immunological interactions in coinfection are becoming fashionable (11–15) and immunoepidemiological studies are now also examining this issue (16). Apart from the catastrophic immunosuppressive effects of HIV-AIDS, subtle, but important, coinfection effects are likely to be occurring in man. The article by Carvalho and da Fonseca Porto considers the interactions between two infections that are wide spread but unusually asymptomatic, human T cell lymphotropic virus type 1 (HTLV-1) and *Strongyloides stercoralis*. It appears that *S. stercoralis* patients coinfecting with HTLV-1 have modified antiparasite immune responses, with increased IFN γ and decreased Th2 responses. This is associated with increased prevalence of *S. stercoralis* infection, reduced efficacy of treatment, and greater risk of disseminated strongyloidiasis. In the last review of this Special Issue, Booth and Dunne demonstrate that where microgeographical differences occur in the distributions of coendemic parasite infections, or of exposure to different infections, Geographical Information System (GIS) data can be used to analysis interactions between infections in relation to morbidity. This is illustrated by reference to studies on the effects of high exposure to malaria on the hepatosplenomegaly in *Schistosoma mansoni* infected Kenyan schoolchildren.

Although the measurement of immunological parameters in medium to large scale human studies is still limited to a restricted range of biological samples (peripheral blood, urine, stools, etc.), and repeat blood sampling for longitudinal studies is practically and ethically problematic, technical advances in assay, computing, and analytical methodologies are opening up many new possibilities for immunoepidemiology. The application of DNA microarray techniques, and the testing for multiple cytokines or other immunologically active molecules using microbeads and ultra-small scale technologies is allowing many more immunological parameters to be measured on smaller samples. No longer is 10 mL of blood required to test half a dozen cytokine responses on purified PBMC *in vitro*. Soon, many immunological, physiological, biochemical, genetic and other markers will be testable simultaneously on finger prick blood samples. Analytic techniques will have to change and new, nonclassical, statistical methods, – perhaps similar to those being developed for postgenomic DNA microarray analysis – will have to be introduced to cope with data mining and the need to validate associations derived from multivariate testing of large study cohorts. Given the numbers of potential variables involved in determining specific immunological or epidemiological outcomes, large multicentre studies, conducted and analysed according to shared protocols, are now needed to confirm or refute findings from smaller studies. Furthermore, to understand and combat the major human parasitic diseases a holistic approach to human studies needs to be developed, so

that data from ecological studies, parasitology, vector biology, classical epidemiology, anthropology, clinical studies, and immunoepidemiology, can be combined. Such developments will ensure that human immunological studies will provide crucial data on parasite infections, but remain practically and intellectually challenging.

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