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EVOLUTIONARY CAUSES AND CONSEQUENCES OF IMMUNOPATHOLOGY

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■ **Abstract** Immune responses can cause severe disease, despite the role immunity plays in defending against parasitism. Indeed, immunopathology is a remarkably common cause of disease and has strong impacts upon both host and parasite fitness. Why has immune-mediated disease not been eliminated by natural selection? What constraints might immunopathology impose upon the evolution of resistance? In this review, we explore two major mechanistic causes of immunopathology in mammals and consider how such disease may have influenced immune system design. We then propose hypotheses that could explain the failure of natural selection to eliminate immunopathology. Finally, we suggest how the evolution of strategies for parasite virulence and host resistance may be shaped by this "double-edged sword" of immunity. Future work may reveal whether immunopathology constrains the evolution of resistance in all host taxa.

1. INTRODUCTION

Inappropriate immune responses can have profound fitness effects. Most obviously, failure to control parasite proliferation may be detrimental to host fitness. But immune responses also damage hosts if responses are too strong, involve the wrong parasite-killing mechanism, or are elicited by the wrong antigens, including those on the host's own cells (leading to autoimmunity) or on innocuous substances such as food (leading to allergy). Such immune-mediated diseases are termed immunopathology.

On the face of it, immunopathology conflicts with Darwinism: Organisms should not self-harm. Evolutionary biologists spent much of the past century analyzing—and for the most part explaining—other traits that appeared maladaptive. But unlike altruism and the peacock's tail, immunopathology causes human disease. Immunopathology is thus a surprising omission from evolutionary biology to date, given the humanitarian importance as well as intellectual appeal of understanding apparently maladaptive immune responses.

In this review, we start by explaining the causes of two common classes of immunopathology: Type 1 and Type 2. We then argue that, although immunopathology probably helped to shape the immune system, the failure of natural selection to eliminate immune-mediated disease demands evolutionary explanation. Finally, we contend that several areas of evolutionary research could be reshaped by a full appreciation of immunopathology. For example, immunopathology can increase the costs of both parasite virulence and host defense, thereby altering selection on these traits and leading to different evolutionary optima from those predicted under the assumption that immunopathology does not occur (e.g., Figure 1*a* and 1*b*; the theory behind this is discussed in more detail in Sections 4.1 and 4.2).

1.1. Severe Infectious Disease Usually Involves Immunopathology

During infection, immunopathology can be difficult to distinguish from more direct effects of parasites, but the distinction is real. Consider 10 tropical diseases accorded high priority by the World Health Organization (WHO). These diseases, the most deadly of which are tuberculosis and malaria, account for billions of infections and nearly 3 million deaths per year. They also have profound sublethal effects (WHO 2004). Critically, all 10 are at least partly immunopathological (Table 1), and hosts with the most severe symptoms do not necessarily harbor the most parasites.

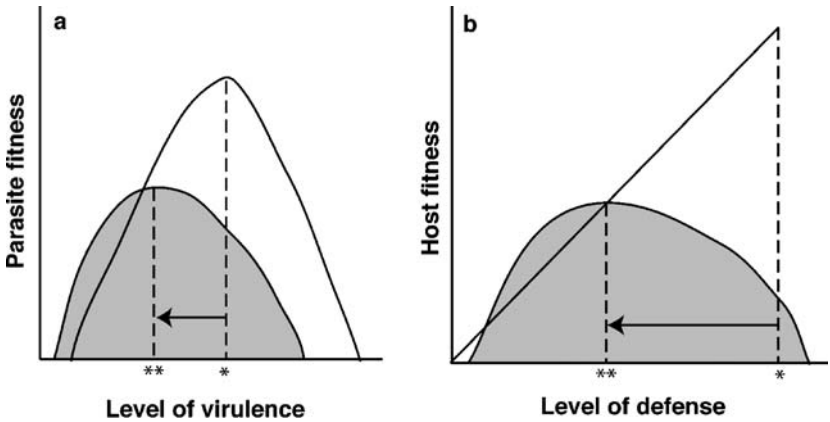

Figure 1 Optimal strategies for parasite virulence (*a*) and host defense (*b*) may be altered by immunopathology. For example, (*a*) if immunopathology increases virulence without increasing transmission—e.g., by killing the host—we predict selection for decreased parasite virulence (**) compared to that predicted under an assumption of no immunopathology (*), and (*b*) if high investment in defense is associated with immunopathology, we predict lower optimal levels of defense (**) than those predicted in the absence of immunopathology (*). In both diagrams, the gray curve represents the fitness function in the case of immunopathology.

In tuberculosis, for example, the immune response that clears bacteria also recruits fluid and cells into the air spaces of the lung (Bekker et al. 2000). Similarly, the immunological molecules that control malaria replication exacerbate disease (Akanmori et al. 2000); in mice, 10% of malarial anemia is explained by immunological exuberance rather than parasite-mediated destruction of red blood cells (Graham et al. 2005). Beyond the WHO top 10, immunopathology is manifest in common diseases of tropical and temperate residents alike. For example, influenza induces much more immunological activity than is necessary to clear the virus, and it is the excess that does most of the damage to the lung (Hussell et al. 2001, Xu et al. 2004). Immunopathology may also have delayed fitness consequences, reducing lifespan in people prone to strong immune responses (Finch & Crimmins 2004). It is said that Chagas disease (#7 in Table 1) long debilitated and eventually killed Charles Darwin (Adler 1997), so infection-induced immunopathology may have even claimed one of evolutionary biology's finest minds.

This dual effect of the immune system—fighting infection while causing immunopathology—is driven by two broad classes of mechanisms, cytotoxicity and tissue remodelling. Both are required for resolution of the diverse infections encountered over a lifetime, but each causes disease if immoderate. Cytotoxic immune responses, for example, can spiral out of control to kill host as well as parasite cells (Pfeffer 2003). Tissue remodelling is essential if the immune system is to sequester parasites or their eggs, but excessive deposition of collagen and subsequent hardening cause organs to become blocked, stiffened and, ultimately, dysfunctional (Wynn 2004). As we explain below, beyond some threshold, the parasite-controlling function of the immune system ends and host tissue damage begins.

1.2. Humans and Mice as Model Systems

Throughout this review, we focus upon humans and mice. These are the most intensively studied hosts, so they are the best-characterized models for the biological phenomenon of misdirected defense. We do expect that our general arguments will apply to other mammals, other vertebrates, invertebrates, and maybe even to plants. Such extrapolation is, however, not immediately possible: We are unaware of any attempt to determine the importance of immunopathology in infectious disease severity in "natural" mammalian-parasite interactions, let alone in nonmammalian systems. When data like those in Table 1 become available for diseases that afflict animals other than ourselves and our domesticated or laboratory mammals, it may become apparent that immunopathology is actually rare in nature.

Could the bulk of immunopathology in human populations and laboratory mice be a consequence of novel environments or novel parasites? For people, the novelty may include the plethora of parasites acquired after human populations became dense enough to sustain their transmission. Studies of wild animals could determine whether novel conditions are necessary for immunopathology, and we look forward to such work. In the meantime, we note that a selective factor can be important even if few affected individuals are observed. For instance, risk of injury has

TABLE 1 Estimated fitness effects of immunopathology in 10 tropical diseases accorded high priority by the WHO

Disease[a]	Infectious agent	People infected[b](Source)	Deaths in 2002[c]	Age at greatest risk(Source)	Is there evidence that severe cases are immunopathological?(Source)
Tuberculosis	*Mycobacterium tuberculosis*	1,900,000,000(Dye et al.1999)	1,566,000	20–30 years(Daniel et al. 2004)	Yes, faulty responses prolong disease(Hirsch et al. 1996) and lung damage is independent of bacterial load(Ehlers et al. 2001)
Malaria	*Plasmodium* species	300,000,000(WHO 2004)	1,272,000	<5 years(Snow et al. 1999)	Yes, unregulated immune responses increase disease severity(Akanmori et al. 2000, Dodoo et al. 2002, Li et al. 2003, Omer et al. 2003)
Leishmaniasis	*Leishmania* species	12,000,000(WHO 2000)	51,000	<20 years(Saran et al. 1989)	Yes, immune responses increase the size of skin lesions(Louzir et al. 1998) and damage the liver(Satoskar et al. 2000)
Sleeping sickness	*Trypanosoma brucei*	300,000(WHO 2000)	48,000	>20 years(Abaru 1985)	Yes, unregulated responses(Magez et al. 2004) damage the central nervous system(Hunter & Kennedy 1992, Maclean et al. 2004)
Dengue	Dengue viruses	50,000,000(WHO 2000)	19,000	<15 years(Gubler 1998)	Yes, secondary responses cause hemorrhagic fever(Mongkolsapaya et al. 2003) and 11% of liver damage(Libraty et al. 2002)
Schistosomiasis	*Schistosoma* species	200,000,000(WHO 2004)	15,000	>20 years(Booth et al. 2004)	Yes, liver and urinary tract damage are immune-mediated(Booth et al. 2004, Hesse et al. 2004, Hoffmann et al. 2002, Wamachi et al. 2004)
Chagas disease	*Trypanosoma cruzi*	16,000,000(Moncayo 1992)	14,000	>20 years(Jorge et al. 2003)	Yes, damage to heart muscle is due to inflammation(Andrade 1999, Holscher et al. 2000) not parasite load(Soares et al. 2001)
Leprosy	*Mycobacterium leprae*	750,000(Sasaki et al. 2001)	6000	20–35 years(Scollard 1993)	Yes, inappropriate immune responses damage nerve cells(Khanolkar–Young et al. 1995, Spierings et al. 2001)
Lymphatic filariasis	*Wuchereria* & *Brugia* species	120,000,000(Michael & Bundy 1997)	0	>40 years(Leang et al. 2004)	Yes, elephantiasis is associated with immunological hyper-responsiveness(Sartono et al. 1997)
Onchocerciasis	*Onchocerca volvulus*	17,000,000(WHO 1995)	0	>20 years(Murdoch et al. 2002)	Yes, corneal opacity and skin damage are immune-mediated(Hall & Pearlman 1999, Stewart et al. 1999)

[a]We investigated 10 diseases prioritized by the Special Program for Tropical Disease Research, a global research partnership convened by the World Health Organization (WHO) (http://www.who.int/tdr/index.html). The diseases are high priority because they affect millions of people and yet receive only scant dollars and scientific attention. We obtained the annual mortality attributable to each infection and the age group most affected by severe disease. Then we evaluated the field and laboratory evidence that immunopathology has a role in severe cases. We were specifically interested in whether disease symptoms were in excess of those attributable to within-host parasite density. Immunopathology was implicated in severe cases of all 10 diseases.

[b]Estimated number of people infected at any given time. The lower limits of the WHO's estimated range of number of cases is shown.

[c]Mortality data are based upon the World Health Report (WHO 2004), which often underestimates cause-specific mortality rates (cf. van der Werf et al. 2003). This table is thus conservative in its estimates of mortality. Furthermore, for reasons of space, we have omitted quantitative estimates of sublethal fitness effects of these diseases, though such estimates are available (WHO 2004).

undoubtedly posed significant selective pressures on avian flight, yet birds with crash injuries are extremely rare (Cuthill & Guilford 1990). To determine the selective pressure imposed by immunopathology in nature, it may be necessary to provoke hyper-responsiveness experimentally in wild animals. It is our contention that such experiments will confirm that, as in people and mice, immunopathology has severe fitness effects. Moreover, as we discuss below, many aspects of the highly orchestrated vertebrate immune system can be understood as adaptations to reduce immunopathology. Unless these are highly atypical, immunopathology must have had a major role in the evolution of immunity in general. From what we know of human diseases (e.g., Table 1), immunopathology can bring selective pressures upon hosts that rival selection due to parasitism itself.

2. MECHANISTIC AND EVOLUTIONARY CAUSES OF IMMUNOPATHOLOGY

Immunopathology is prevalent, but how might it constrain the evolution of resistance, and why has it not been eliminated by natural selection? Two major classes of parasites, microparasites (mostly intracellular) and macroparasites (mostly extracellular), are matched by two major types of immunity (Abbas et al. 1996): Type 1 responses are mainly cytotoxic and are essential to killing microparasites, whereas Type 2 responses enable tissue remodelling to combat macroparasites. Cytokines are the molecules that enable these Type 1 versus Type 2 antiparasitic (effector) mechanisms. Here, we focus upon tumor necrosis factor alpha (TNF-α) and interleukin 13 (IL-13), which characteristically function in these two different types of response. For both cytokines, the context and quantity in which they are produced determine their protective efficacy. A constrained ability of the immune system to regulate these cytokines may be the prime evolutionary explanation of immunopathology.

2.1. Control of Microparasites Versus Type 1 Immunopathology: TNF-α

TNF-α is at once the most protective and most pathological of cytokines. It is critical to the induction of nearly all immune responses (Pfeffer 2003) and, along with other Type 1 cytokines, is important for control of microparasites. To kill these parasites as well as tumors (hence its name, tumor necrosis factor), TNF-α has a broad array of functions, including recruitment of cells to the site of infection, activation of phagocytic cells to release toxic chemicals, and even direct killing of target cells (Tracey & Cerami 1994). Such powerful antiparasitic activities, if not moderated or properly directed, result in severe host tissue damage.

The deadliest example of a TNF-α response gone wrong is that of septic shock. In this case, TNF-α is released in enormous quantities into the bloodstream following escape of bacteria from the gut into the blood (i.e., sepsis). The TNF-α

alters blood vessel walls to allow blood fluid, clotting factors, and cells to enter the tissues, as would be appropriate if TNF-α were released in a localized site of infection. Systemic release, however, causes shock—decreased blood volume and multiorgan failure. Mice deficient in TNF-α readily survive a level of sepsis that would kill a normal mouse but succumb to minor bacterial infections (Pfeffer et al. 1993). Such hosts avoid immunopathology but fail to control parasite replication.

TNF-α's dual role is also well documented in malaria (Akanmori et al. 2000, Dodoo et al. 2002, Li et al. 2003, Omer et al. 2003). TNF-α does protect against disease by killing infected red blood cells (RBCs). Yet TNF-α is associated with changes to blood vessels of the brain, which can lead to coma and death during cerebral malaria (Hunt & Grau 2003). In milder malaria, too, as parasites rupture out of the RBCs, the host responds with bursts of TNF-α that lead to fever and malaise. Hosts must therefore balance the need to kill parasites against the dangers of excess Type 1 cytokine. We have found quantitative evidence in support of this balanced optimum in mice with malaria: The least anemic were those who made Type 1 responses of intermediate magnitude (Figure 2, based upon data in Graham et al. 2005). Among the other WHO top 10, TNF-α also has dual roles in sleeping sickness (Maclean et al. 2004), Chagas (Holscher et al. 2000), and leprosy (Khanolkar-Young et al. 1995). TNF-α can even be purely pathological, as in autoimmunity (Pfeffer 2003).

Variation in TNF-α responsiveness—and, more generally, the magnitude of infection-induced inflammatory responses (Terry et al. 2000, van de Vosse et al. 2004)—has a polymorphic genetic basis. Though the effects of TNF-α promoter polymorphism are tied up with the major histocompatibility complex (MHC) in terms of chromosomal location, TNF-α polymorphisms affect disease outcome even when its effects are dissected from those of MHC (Daser et al. 1996). Genetic heterogeneity for TNF-α expression has particularly been shown to influence the likelihood of severe anemia and cerebral symptoms during malaria (Bayley et al. 2004). We thus have reason to expect that heterogeneity in the expression of TNF-α-mediated pathology is heritable and can evolve. In Section 3.3 below, we consider why natural selection might not have eliminated immunopathological expression of TNF-α.

2.2. Coping with Macroparasites Versus Type 2 Immunopathology: IL-13

Very different cytokines are involved in the Type 2 response elicited by large, extracellular macroparasites, such as the worms that infect over a third of the world's population (Chan 1997). Along with other Type 2 cytokines, IL-13 is stereotypically induced by helminths, despite the vastly different physiologies and life histories of, for example, nematodes versus trematodes. IL-13 helps to expel worms from the intestines (Finkelman et al. 2004) and destroy tissue-dwelling worms such as filarial nematodes (Maizels et al. 2004). But IL-13, like TNF-α, can cause disease when its quantities are not modulated.

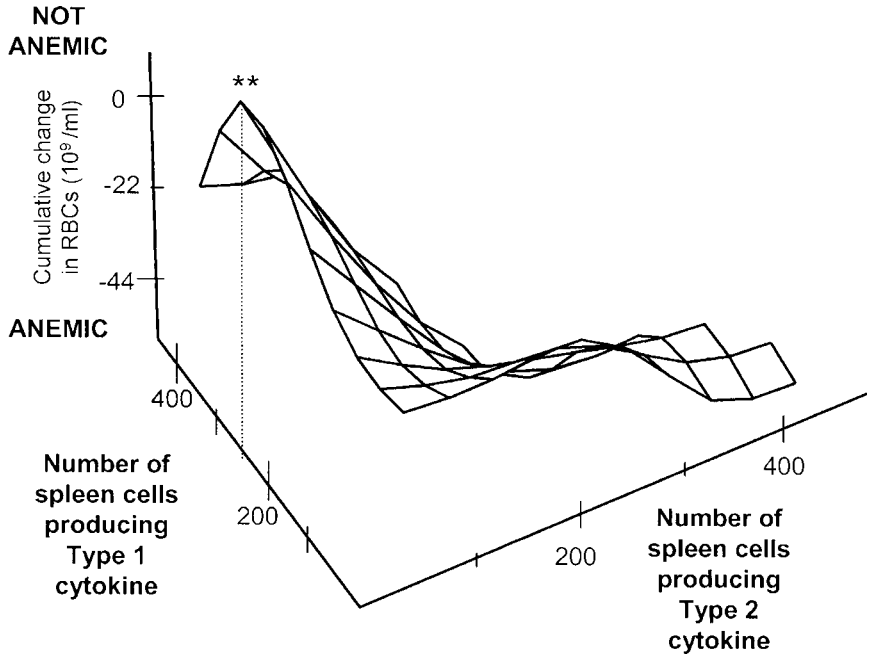

Figure 2 The optimal immune response to malaria balances parasite killing against immunopathology. During studies of malaria-filaria coinfection (Graham et al. 2005), we were able to identify quantitatively the immune response that minimized the severity of malarial symptoms. We used this system because concomitant filarial infection extends the range of immune responses that laboratory mice mount against malaria. We found that the healthiest (here, least anemic) mice were those that made Type 1 immune responses of intermediate magnitude. The observed optimum—i.e., the immune response that minimized cumulative loss of red blood cell (RBC) density—is indicated by ** (whole-model $P < 0.005$, with significant linear and quadratic functions of Type 1 cytokine).

The importance of getting the right IL-13 balance is illustrated by the tissue remodelling induced by schistosomiasis (#6 in Table 1). Schistosomes live in blood vessels and release thousands of eggs per day. A large proportion of these become lodged in host tissues, particularly the liver. Eggs release tissue-damaging toxins, and the immune system protects the liver by encapsulating the egg in an orderly arrangement of cells and molecules called a granuloma (Hoffmann et al. 2002). IL-13 is essential for the creation of this granuloma, providing the framework for extracellular matrix deposition and onward structural strengthening via collagen deposition (Wynn 2004). As tissue remodelling proceeds, more and more collagen is recruited. Here, immoderate IL-13 can cause fibrosis, filling liver tissue with so much collagen that it can no longer perform blood purification. It is this fibrotic

immune response that leads to host death (Hoffmann et al. 2002). IL-13 can also go wrong in the absence of infection: It is becoming increasingly apparent that IL-13-mediated fibrosis is responsible for severe diseases such as asthma, where the immune system is trying, unsuccessfully, to contain foreign objects (Wills-Karp 2004). To avoid immunopathology, production of IL-13 must be tightly regulated in organs such as the lung or liver.

The IL-13 gene, like the TNF-α gene, is highly polymorphic in people around the world (Tarazona-Santos & Tishkoff 2005). Functionally, IL-13 polymorphisms help to control predisposition to at least 2 of the WHO top 10: severe versus mild schistosomiasis (Dessein et al. 2004) and onchocerciasis of the skin (Hoerauf et al. 2002). Overall, Type 1 versus Type 2 cytokine bias is also genetically controlled and is predictive of how well a host fights different infections (Mitchison et al. 2000). Again, the genetic raw material for evolutionary change appears to be present. Indeed, we suggest below that the risk of immunopathology may have shaped immune responsiveness.

3. CONSEQUENCES OF IMMUNOPATHOLOGY FOR EVOLUTION OF THE IMMUNE SYSTEM

The fact that some of the most potent antiparasitic molecules have profound destructive power has probably helped to shape regulatory pathways in the evolution of mammalian immunity. Several design features of the immune system are indicative of the importance of avoiding immunopathology. We present these here and then move on to assess hypotheses to explain why evolution has not succeeded in fully eliminating immunopathology.

3.1. Evolution of Type 2 Effector Responses to Minimize Immunopathology

The evolutionary reasons for a Type 1 response, as outlined above, are readily apparent: Without it, we die from overwhelming microparasitic infection. The reasons for the evolution of the Type 2 response are less obvious. Yet IL-13 and other Type 2 cytokines have multifaceted roles suggestive of strong selection pressures posed by immunopathology.

It may seem, from the foregoing discussion of IL-13, that the reason we need a Type 2 response is to fight worms. However, Type 1 responses (e.g., macrophages activated by cytokines such as TNF-α) are also capable of destroying worms (Rodriguez-Sosa et al. 2004, Thomas et al. 1997). We propose that Type 1 responses are not normally used this way because of the immunopathology that goes with large-scale TNF-α-like responses. The benefits of controlling rampantly proliferating microparasites must outweigh the costs of self-harm. But macroparasites are not immediately threatening—worms tend to induce lower case fatality rates than do microparasitic infections (WHO 2004), and even mice totally deficient in

adaptive immunity survive worm infections, albeit at much higher parasite burdens (Urban et al. 1995). Thus, better-targeted control is possible, and the Type 2 response may have evolved as a safer alternative to the damaging Type 1 response. Importantly, cytokine cross-regulation ensures that strong Type 2 responses inhibit Type 1 responses (Abbas et al. 1996). The central theme in the evolution of Type 2 immunity to macroparasites may thus have been avoidance of Type 1 immunopathology.

There is a further means by which IL-13 minimizes the fitness effects of worm infection. Worms cause wounds, due to their size, motility, and necessity to eat host tissue. For example, feeding by common intestinal parasites such as hookworms induces wounds with strong fitness effects: Beyond the dangers of internal bleeding, unhealed worm bites in the intestinal wall might lead to gut leakage and, ultimately, sepsis. More generally, many intestinal worms have stages that migrate through the lung, which means that billions of people worldwide (Chan 1997) harbor lung-migrating parasites. Lung damage induced by migrating worms is appropriately repaired (McNeil et al. 2002), and it is becoming clear that IL-13 helps to direct such healing (Wynn 2004). Which activities of IL-13 arose first is open to question, but the evidence suggests that Type 2 cytokines function as much to prevent pathology as to kill macroparasites.

3.2. Moderation in All Things: A Major Role for Adaptive Immunity

Cytokines that, in excess, lead to immunopathology are produced during both innate and adaptive immune responses. Beyond the mutual inhibition between Type 1 and Type 2 cytokines (Abbas et al. 1996) that can minimize immunopathology, critical additional control is provided by regulatory T cells of the adaptive immune system. These immunomodulatory cells dampen responses that are too damaging to self-tissue (Mills 2004) by producing cytokines, particularly transforming growth factor beta (TGF-β) and interleukin 10 (IL-10), that inactivate effector cells—e.g., by switching off the production of toxic molecules by phagocytes (Mills 2004). Regulatory T cells can also increase the activation threshold at which Type 1 or Type 2 cytokines are produced (Abbas et al. 2004), thereby preventing immunopathological levels of activation from being achieved at all.

Important roles for regulatory T cells have been demonstrated for many of the WHO top 10, including malaria (Hisaeda et al. 2004), leishmaniasis (Sacks & Anderson 2004), schistosomiasis (Hesse et al. 2004), filariasis (Taylor et al. 2005), and onchocerchiasis (Satoguina et al. 2002). The critical importance of modulatory adaptive immunity is especially well illustrated in malaria, where regulatory T cells, IL-10, and TGF-β are required for host survival (Hisaeda et al. 2004, Li et al. 2003, Omer et al. 2003). Without these modulators, hosts die of malarial immunopathology, as outlined in Section 2.1 above. T regulatory cells also protect against other forms of immunopathology, including Type 1 autoimmune attack of the central nervous system in multiple sclerosis (Viglietta et al. 2004) and Type 2

allergic responses to airborne particles in asthma (Maizels et al. 2004). Indeed, in human populations, genetic polymorphisms in both IL-10 (Moore et al. 2001) and TGF-β (Gentile et al. 2003) are associated with differential predisposition to infectious, autoimmune, and allergic diseases. Immunopathology may have imposed strong selection pressure for the immune system to use these pathways to eliminate cells that are causing harm to self, even well after selection against self-reactivity in the thymus early in development.

It is tempting to speculate that the adaptive immune system may have evolved expressly to use antigen-specific receptors to focus and direct the response only where needed and to control the production of potentially destructive cytokines such as TNF-α and IL-13. The greatest defense against the fitness effects of infection may indeed be moderation (Figure 3).

3.3. Why Has Evolution Not Eliminated Immunopathology?

Despite these antipathology design features of the immune system, immunopathology still dramatically reduces the fitness of people and mice (Table 1). Why has selection not eliminated such self-harm? Below, we outline several explanatory hypotheses; these are not mutually exclusive but instead may combine to cause immunopathology to persist. The relevant explanation will almost certainly vary from system to system. Importantly, we should be able to detect which explanation holds.

First, immunopathology may be retained by a balance between costs and benefits of fighting parasites. Frank (2002) suggested that polymorphism at antigen recognition loci might be maintained by processes beyond mutation-selection balance. Such processes probably maintain polymorphism at cytokine loci as well. For example, occasionally excessive TNF-α or IL-13 responses may be unavoidable consequences of useful parasite-killing or tissue-remodelling mechanisms. Natural selection may favor high responsiveness as the default option immediately following infection, to ensure control of parasites despite the risk of immunopathology. Such decision rules should themselves select for mechanisms to moderate responses (e.g., regulatory T cells) and focus them on known threats (e.g., memory responses). Frank (2002) called for mathematical analysis to clarify the necessary conditions for stable polymorphism between high- and low-response tendencies. We second that call, adding that consideration of response efficacy (via Type 1, Type 2, and modulatory cytokines), plus empirical work to quantify costs and benefits, are also critical to that analysis.

Second, immunopathology may result from the constrained ability of the immune system to achieve optima. The design flaws may consist in poor modulatory control, signaling delays, or other mechanisms. For example, hosts are unable to simultaneously mount the two mutually antagonistic types of response. Some immunopathology may thus be a consequence of the Type 1–2 cross-regulation intrinsic to immune functioning, a proposition that has generated testable hypotheses about coinfection (Graham 2002). Still, invoking such trade-offs to explain immunopathology just shifts the problem back a level. What makes the regulatory

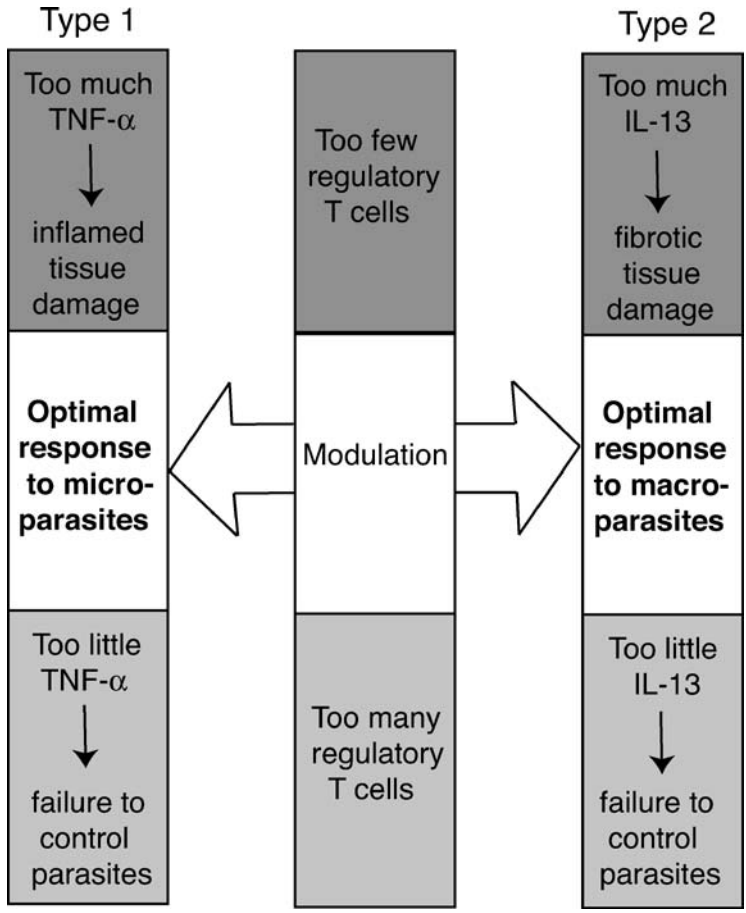

Figure 3 To control the negative fitness effects of infection, the magnitude of Type 1 responses to microparasites and Type 2 responses to macroparasites must be controlled. For example, TNF-α hypo- and hyper-responsiveness against microparasites are equally detrimental to host fitness, and the optimal region in the left-hand bar may correspond to the optimal antimalaria response identified in Figure 2 (e.g., 200–300 spleen cells producing Type 1 cytokines). T regulatory cells are critical to achieving such optima. For a mechanistic view, see figure 5 of Mills (2004).

mechanisms insufficient? Why are signals indicating self-harm so slow to arrive? The implication is that more precise immunological control is more expensive than immunopathology. Just how these engineering costs arise remains to be determined.

Third, immunopathology may be expressed mostly in cases where selection has not had time to act. It may be that novel parasites or environments experienced by modern humans, for instance, impose substantial selection on genetic

determinants of immunopathology, but there has not been sufficient time to make the response to this selection detectable. Further, parasites, by virtue of shorter generation times, may have a coevolutionary grace period during which host responses are suboptimal (Behnke et al. 1992).

Fourth, lateness of onset could result in reduced selection against immunopathology. As with other diseases of senescence, selection against late-life immunopathological disease may be weak, whether infection is current (Table 1) or summed over a lifetime (Finch & Crimmins 2004). This hypothesis can be rejected, however, for early-onset immunopathologies.

Finally, selection on parasite genotypes may be an evolutionary cause of immunopathology—for example, when immune evasion or immunopathology itself is good for parasite transmission (explored in Section 4.1, below). A positive association between immunopathology and transmission might favor parasite genotypes that manipulate host immunity. Such manipulations are common among helminths (Maizels et al. 2004), protozoa (Sacks & Sher 2002), and viruses (Tortorella et al. 2000), and immunomodulatory products of parasites are genetically polymorphic in at least some species (Behnke et al. 1992, Britton et al. 1995, Yatsuda et al. 2001). It is critical, for both biomedical and evolutionary studies, to determine whether parasites or hosts benefit most from modulated immune responses and, relatedly, whether hosts are being manipulated into immunopathology.

The development of evolutionary explanations of other apparently maladaptive traits has proven highly productive, expanding evolutionary theory while revealing new properties about the traits in question. Evolutionary explanations of immunopathology may well do the same, revealing insight into the evolution of complex systems while successfully predicting the occurrence and severity of immunopathology, as well as the clinical and evolutionary consequences of medical interventions designed to alleviate it. With such studies, the interests of global health management and evolutionary biology would converge.

4. CONSEQUENCES OF IMMUNOPATHOLOGY FOR EVOLUTIONARY RESEARCH

We propose that at least three research areas in host-parasite evolutionary biology would benefit from a focused inclusion of immunopathology: the evolution of virulence, the evolution of resistance, and the evolution of immunogenetic polymorphism (e.g., in the MHC). Other research areas might likewise benefit, but we are most familiar with the aims and methods of these three. We argue that they are also representative of active research in host-parasite evolutionary biology—the combined literature on just the evolution of virulence and ecological immunology accounts for about one third of the host-parasite evolution literature (on all host taxa) searchable by Pub Med and Web of Science. We end this section by addressing empirical obstacles that all research areas must overcome to incorporate immunopathology.

4.1. Evolution of Parasite Virulence

Immunopathology can alter the costs and benefits of parasite virulence. Virulence in evolutionary terms is defined as the negative impact of infection upon host fitness. As such, virulence encompasses damage due to direct effects of parasites as well as damage due to infection-induced immunopathology. The two sources of virulence can be difficult to distinguish in practice, but they may have very different evolutionary implications.

Parasite strategies for host exploitation are predicted to evolve toward greater virulence when high replication rates and high virulence are associated with high transmission rates (Frank 1996). If immunity acts solely to reduce parasite replication, then selection is predicted to increase parasite virulence (Gandon et al. 2001). The underlying assumption that virulence and transmission are positively correlated has strong empirical support, at least in some disease systems (Mackinnon & Read 2004). But when virulence is determined independently of parasite density—for example, if immunopathology decouples transmission and virulence—then the costs and benefits of virulence are likely to be altered (Lipsitch & Moxon 1997).

Parasites might benefit from immunopathology if it is accompanied by increased transmission. In tuberculosis, for example, there is good evidence that immunopathological necrosis of the lung enhances transmission (Ehlers et al. 2001, Kaushal et al. 2002). Similarly, tissue remodelling around schistosome eggs facilitates their passage into the environment to complete the life cycle (Doenhoff 1998). Immunopathology is also associated with increased transmission of dengue (Gagnon et al. 1999, Mongkolsapaya et al. 2003) and chronicity of leishmaniasis (Sacks & Anderson 2004). Immunopathology thus seems to aid transmission of at least 4 of the WHO top 10. In these cases, the assumed positive relationship between virulence and transmission would be upheld even at the immunopathological extreme of the spectrum, and the qualitative (if not quantitative) predictions of basic theory may hold.

It is equally possible, however, that immunopathology is bad for parasite fitness, increasing virulence without increasing transmission. In this scenario, immunopathology increases the cost/benefit ratio of parasite virulence. This would qualitatively alter the predicted trajectory of the evolution of virulence (illustrated in Figure 1*a*), possibly selecting for decreased virulence via decreased replication or immunogenicity. For at least 3 of the WHO top 10, inducing severe immunopathology appears to bring no benefit to the parasite. Lymphatic filariasis, for example, is most virulent (i.e., causes elephantiasis) when nontransmissible (Behnke et al. 1992, Sartono et al. 1997). Severe cases of sleeping sickness are associated with inflammatory reactions to parasites in the central nervous system (Hunter & Kennedy 1992), and it may be excess TNF-α that breaches the blood-brain barrier (Maclean et al. 2004). Can this migration possibly facilitate transmission to the tsetse fly? In malaria, cytokines that, if unchecked, cause severe disease (Akanmori et al. 2000, Dodoo et al. 2002) can also block parasite transmission (Karunaweera et al. 1992). As these examples demonstrate, the effects of

immunopathology upon virulence-transmission relationships may not conform to the positive correlation assumed in basic theory.

Several theoretical studies support the idea that pathological immune responses can alter the evolution of virulence. The important acknowledgment that virulence is a coevolutionary issue (beginning with van Baalen 1998) led to the insight that the evolutionary trajectory of virulence strongly depends on whether hosts develop resistance at all, and whether resistance is qualitative (i.e., each host is either susceptible or resistant) or quantitative (Gandon & Michalakis 2000, Gandon et al. 2002). Costs of immunological up-regulation further alter the evolution of virulence (Alizon & van Baalen 2005, Day & Burns 2003, Restif & Koella 2003), but only by distinguishing between direct and indirect effects of parasites were Alizon & van Baalen (2005) able to consider closely the role of immunopathology. Their provocative results lend formal support to the intuitive arguments above: The relative amount of damage that immune responses do to hosts versus to parasites determines the evolutionarily stable level of virulence (Alizon & van Baalen 2005).

A theoretical study to explore how immunopathology impacts the evolution of virulence might usefully add host heterogeneity. Baseline immunopathology (accounting for the proportion of mild disease that is due to immune hyper-reactivity) would be complemented by additional immunopathology experienced only by a proportion of hosts (accounting for the excess immunopathology that kills, as in each of the WHO top 10; Table 1). Such a model could assess whether there is a threshold proportion of damage due to immunopathology above which immune responses rather than parasites dominate dynamics. It might also predict the influence of mild versus severe immunopathology on the evolution of virulence. Better still, its parameters would be measurable and, thus, the model testable. It is our contention that in both theoretical and empirical work on the evolution of virulence, a role for immunopathology should at least be assessed before it is omitted from study.

4.2. Evolution of Resistance

Immunopathology is arguably the highest cost of immune defense. As such, it should be considered in studies of ecological (Sheldon & Verhulst 1996) or evolutionary (Lochmiller & Deerenberg 2000) immunology. To life history theorists, immunity, like foraging behavior or territorial defense, is just another trait whose costs and benefits are traded off against other fitness determinants (e.g., frequency with which nestlings are fed) (Sheldon & Verhulst 1996). Most work in ecological immunology focuses on whether costs of immunity can explain heterogeneity among hosts in their level of defense (reviewed by Schmid-Hempel 2003). Essentially, if immunity were cheap, then all hosts would be predicted to respond vigorously to infection. If, on the other hand, immunity were expensive, then hosts with differing budgets at their disposal and differing allocation priorities would differ in their investment in defense. In the costly defense scenario, immunoheterogeneity is unsurprising.

Several studies have indeed demonstrated fitness costs of immune defense (Ilmonen et al. 2000, Råberg & Stjernman 2003), but physiological costs have proven more difficult to detect (Lochmiller & Deerenberg 2000). Part of the problem may be that only energetic physiological costs have received substantial attention in this literature. In an explicit test of the energetic costs of immunity that showed lower basal metabolic rates in mice with higher adaptive immunity, Råberg et al. (2002) concluded that the evolution of immunity was probably not constrained by energy. Some studies do concede that another probable physiological cost of the immune system is immunopathology—Schmid-Hempel (2003) even proposed that "self-reactivity" is greatly underrated in ecological immunology—but very few measure how benefits of defense trade off against immunopathological costs. Studies investigating the optimal strength of response that balances the benefits of parasite killing against risks of immunopathology (e.g., Borghans et al. 1999, Råberg et al. 1998, Segel & Bar-Or 1999, Wu et al. 1996) are generally conducted outside of ecological immunology.

Most studies instead assume that greater numbers of immunological cells or molecules confer greater fitness [e.g., Nunn et al. (2000), with reservations registered by ourselves (Read & Allen 2000)]. Although there is empirical support for the notion that more is better (Biozzi et al. 1984, Luster et al. 1993), there is also substantial evidence to the contrary (Table 1; Figure 2). Exuberant immune responses can lead to complete parasite clearance and yet host death via immune-mediated organ damage, not energetic collapse.

Inclusion of immunopathological costs in ecological immunology models might predict relatively low optimal levels of defense (illustrated in Figure 1*b*). Still, arguments about condition-dependent costs of defense [e.g., a lower cost and thus higher optimal magnitude of response in high-quality individuals (Getty 1998)] as well as context-dependent costs (e.g., increasing benefit of immunity with increased exposure to infection) can apply to immunopathology. For example, the cost of defense may be energetic for nutritionally stressed individuals, whereas high-quality individuals with lots to invest in immunity may be more prone to immunopathological costs. This idea should be testable in many systems.

Theoretical studies confirm that immunopathology should receive greater attention in this field. For example, the efficacy of immune responses is a key determinant of the optimal level of investment (van Boven & Weissing 2004). More compellingly, theory that explicitly sets out to minimize the sum of parasite-induced and immunopathological damage can help to explain circumstances when the immune system should choose one response (e.g., TNF-α) over another (e.g., IL-13) (Shudo & Iwasa 2001) and lends formal support to the idea (in Section 3.1, above) that Type 2 immunity exists primarily to prevent immunopathology. Theory even predicts when immunomodulation should begin: just after parasite replication plateaus (Shudo & Iwasa 2004). These predictions should be testable, as should the further prediction that immunomodulation requires serial overshooting (Shudo & Iwasa 2004). In future, costs of resistance would ideally be broken

into energetic and immunopathological parts. The extent to which covariance of the two determines evolutionary predictions would be of great interest.

Intriguingly, mathematical models that account for immunopathology predict incomplete clearance of parasites as the optimal way for a host to spend its resources (Medley 2002, Shudo & Iwasa 2004), according with empirical and verbal models (Behnke et al. 1992). Essentially, the costs of immunopathology can come to outweigh the benefits of parasite clearance. If subsequent research shows that the tolerable parasite burden is quantitatively predictable, then evolutionary biology will have contributed enormously to biomedicine. It may be possible to predict, for instance, the worm burden that is worth expelling despite the risk of immunopathology. This threshold is likely to vary across host species, sex, and condition, as well as parasite species—a rich area for experimental and field tests. Only by incorporating immunopathology can ecological immunology make such a contribution.

4.3. Evolution of Antigen Recognition Polymorphism

Perfect recognition of parasite antigens does not preclude immunopathology. Explicitly genetic theories of defense that are based upon recognition of parasites by the immune system aim to interpret immunoheterogeneity (Hedrick 2002)—to explain high diversity of MHC alleles, for example, via heterozygote and/or rare allele advantage (Apanius et al. 1997, Borghans et al. 2004, McClelland et al. 2003). Such approaches have unmasked selection pressures on genes that encode parasite-recognizing proteins (Frank 2002, Schmid-Hempel 2003). For instance, a parabolic relationship between parasite load and the number of stickleback MHC alleles has provided evidence of balancing selection and suggests that there are limits to the benefits of MHC allelic diversity (Wegner et al. 2003).

However, heterogeneity in the ability of hosts to recognize parasites does not always explain the distribution of disease (Hill 1998). The immune system must not only recognize parasite antigens but it must also choose the appropriate number and type of parasite-killing mechanisms (i.e., modulated Type 1 versus Type 2 responses; Figure 3). Defined antigens elicit differentially protective immune responses in mice with matched recognition capabilities, and similar processes operate in human hosts (Frank 2002). The recognition and effector steps of an immune response are therefore equally important: Mounting the wrong type or magnitude of response, even against the right antigen, can be very detrimental to host fitness (Graham 2002). Even in cases where MHC explains a good deal of variance in fitness, incorporating immune effector function may do still more.

Indeed, data from biomedical genetics studies support the notion that cytokines can rival or surpass the importance of MHC genotype in determining the outcome of infection (Behnke et al. 1992, Hill 1998, Mitchison et al. 2000). For the WHO top 10 (Table 1), allelic variants at MHC loci help to explain susceptibility to tuberculosis, malaria, dengue, and leprosy (Hill 1998). Inclusion of cytokine polymorphism further explains susceptibility to those diseases and adds leishmaniasis

and schistosomiasis (Hill 1998) as well as onchocerciasis (Hoerauf et al. 2002) to the list. Such synergy between recognition and cytokine profiles explains the outcome of many other infectious diseases (Daser et al. 1996). For example, MHC Class II promoter polymorphism affects the type of effector mechanisms preferentially enabled by a host; this has led to the intriguing suggestion that beyond recognition capability, heterozygote advantage may consist in flexibility or fine-tuning of parasite killing (Mitchison et al. 2000).

Recognition processes thus combine with effector mechanisms to determine whether hosts clear infection entirely, control parasite replication yet permit transmission, and/or generate immunopathology. These outcomes have different evolutionary implications and merit further study (Frank 2002). Integration of the influences of the efficacy and specificity of responses is certainly an important step toward a "unified defense theory" (Jokela et al. 2000), but evolutionary studies as yet largely omit investigation of immune response efficacy. With this review of how cytokines determine protection versus pathology and thus alter evolutionary trajectories, we hope to equip all sides for theoretical and empirical progress.

4.4. Empiricism

To optimize empirical studies of the evolutionary causes and consequences of immunopathology, the main innovation needed is quantification of immune-mediated disease. This is not trivial: There is unlikely to be one measure applicable to all host-parasite interactions. Direct measurements would ideally be made—for example, the diameter of immunopathological lesions of the liver or lung (Doenhoff 1998) or the number of T cells targeting uninfected host cells (Gagnon et al. 1999). Such measurements may be system-specific and technically difficult to obtain, but just a single, well-chosen marker of immunity (such as titer of a key cytokine) would be an important advance, if the immunology were analyzed alongside parasite density as predictors of host and/or parasite fitness. When carefully chosen (Read & Allen 2000), even nonspecific measures are remarkably good at predicting resistance to infection (Biozzi et al. 1984, Luster et al. 1993). Similarly, rough estimates of success at killing parasites are better than ignoring immune efficacy.

An immediately promising experimental direction would be to take advantage of the reagents and methods available to dissect immune responses in mice and farm animals. Heterogeneity among hosts (observable even among laboratory mice) makes it possible to statistically disentangle fitness effects of high parasite density versus excess cytokine production (Figure 2) (Graham et al. 2005). It is also possible to examine the fitness consequences of artificial selection for high versus low levels of immunological activity in agricultural systems (e.g., the work of Magnusson et al. 1999). Such data could reveal the true shape of the net benefit curve for defense (thereby verifying or falsifying Figure 1*b*). Is the assumption of more-is-better largely correct? Studies of model animals should also help to define immunological measures that reliably predict fitness and provide guidance for choosing measures in nonmodel systems.

We hope that the experiments would be paralleled by analogous field studies in human and wild animal populations. Already, genetic and epidemiological studies of immunopathology are performed in human populations (Akanmori et al. 2000, Booth et al. 2004, Dessein et al. 2004, Dodoo et al. 2002, Maclean et al. 2004); analogous studies in wild mammals, especially rodents, are feasible. Moreover, human studies could generate much valuable data for evolutionary ecologists if measures of disease transmission were included. In wild animal populations where individual host fitness and life histories are well characterized—e.g., in mammals (Clutton-Brock & Pemberton 2004) or birds (Sheldon et al. 2003)—measurement of immunogenetic polymorphisms or cytokine levels [e.g., TNF-α in birds (Erf 2004)] would lead to substantial advances. With proper design, vaccination studies even make it possible to detect directional versus stabilizing selection on immune responsiveness in natural populations (Råberg & Stjernman 2003). The possibilities for improving current empirical practice to better understand evolutionary immunopathology appear substantial.

5. OUTLOOK

Only via concerted evolutionary and mechanistic study will we come to understand causation sufficiently well to predict the occurrence of immunopathology and its impact upon host and parasite evolution. Given the wide range of infections that induce immunopathology, understanding self-harm is essential to elucidating how natural selection acts on host and parasite genotypes in their major arena of interaction, the immune system.

Evolutionary analysis of immunopathology should open up new avenues of research. Not least is a systematic analysis of how medical interventions might alter the contribution of the host to the severity of infectious disease. For example, might vaccination increase immune efficiency by minimizing immunopathology—shortening the relatively damaging innate phase of a response and/or shortening the entire response via precisely targeted parasite killing? Or might vaccination instead boost immune responsiveness to more pathology-prone heights (Alizon & van Baalen 2005)? The evolutionary implications of these ecological effects of immunopathology could readily be explored (e.g., Gandon et al. 2001). A cost-benefit analysis of immunity might also quantitatively inform the rational treatment of fevers, which are often immunopathological. Finally, as we have reviewed elsewhere (Graham 2002), coinfections prevalent in natural populations may impose conflicting selection pressures on immune responsiveness. Do medical treatments that minimize the prevalence of coinfection predictably alter the odds of immunopathology? Short of clinical trials, we currently have no way of knowing the effects of, for example, antihelminthics on malarial disease burdens.

Our arguments about immunopathology may also apply to diseases of non-vertebrate hosts. Invertebrates share many immunological traits with vertebrates, making use of similar parasite-killing mechanisms—for example, an earthworm

homologue of TNF-α can kill protozoa (Olivares Fontt et al. 2002), and there is evidence that the snail hosts of schistosomes, like the human hosts, use fibrosis to fight worms (Zhang & Loker 2004). Given these similarities, plus the progress and promise of research in ecological immunology of invertebrates (Rolff & Siva-Jothy 2003), we may soon understand how evolutionary immunopathology operates in invertebrate as well as vertebrate taxa. As with vertebrates (Read & Allen 2000), the relationship between, for example, hemocyte number and immune efficacy is not necessarily linear. Fitness could be reduced at both the low end, where individuals are undefended against parasitism, and at the high end, where individuals experience immunopathology. Indeed, fruit flies (Brandt et al. 2004) and beetles (B. Sadd & M.T. Siva-Jothy, manuscript submitted) appear prone to immune-mediated disease. If generalizations about immunopathology extend to invertebrates and beyond, deeper understanding of the costs and benefits of defense will begin to emerge.

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