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cirrhosis resulting from chronic hepatitis B virus (HBV) infection kill more than 1 million persons annually (7). In 1992, the World Health Assembly recommended that infants be routinely vaccinated against hepatitis B in all countries with high endemic rates of chronic HBV infection. Unfortunately, the populations of many developing countries with high rates of chronic HBV infection do not benefit from hepatitis B vaccination because of the misperception that plasma-derived vaccine may be infectious and donors are not able to finance the higher cost of recombinant vaccine. Acknowledgment of the safety of plasma-derived hepatitis B vaccine would greatly facilitate the prevention of the high rate of death from HBV-related chronic liver disease in these countries.

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Immunology Taught by Darwin

We read with interest the recent article by Rolf M. Zinkernagel (12 Jan., p. 173) reexamining the idea that the function of the immune system is the recognition of the distinction between self and nonself. We applaud Zinkernagel for recognizing that any theory of immune system functioning must be based on the predicted outcome of the coevolution between parasites and their hosts. As evolutionary biologists, we find it refreshing to see immunologists attempt to shape their conceptual understanding of immunity using an evolutionary framework. One must, however, avoid erroneous group selection arguments.

Group selection arguments often suggest that various adaptations in organisms have evolved for the "good of the species." While many adaptations may indeed benefit the

species, the selective forces favoring such traits directly are usually extremely weak and easily swamped by individual-level effects. Hence such group-level benefits are best interpreted as by-products of the benefits that a particular adaptation accrues to individuals within a population (1). Only under conditions of extreme group isolation (the classical models of group selection) or high group relatedness (the models of kin selection) can group selection be effective in the production of adaptation (2).

Zinkernagel proposes that his conception of immunobiology "reflects the coevolutionary balance reached between the immune system and viruses to guarantee survival of both virus and host." However, the outcome of the parasite-host relationship represents a trade-off between transmission and virulence, and intermediate and even high levels of virulence can evolve, provided that transmission between hosts is not compromised (3).

Zinkernagel suggests that "By coevolutionary necessity, cytopathic viruses induce protective immunity efficiently, to avoid elimination of the essential host species [emphasis ours]." One need only consider the fate of a gene in a virus that causes its bearer to avoid elimination by the immune system to see that these viruses will be much more successful in future generations than their altruistic counterparts. Differences in the kinetics of responses to cytopathic viruses and noncytopathic viruses may have an evolutionary function, but the purpose proposed by Zinkernagel seems implausible.

By viewing natural selection acting primarily at the individual level, Zinkernagel does not offer a viable alternative to the idea that the immune system distinguishes self from nonself. Rather, he identifies means by which evolution may have economized effector functioning by localizing immune responses. We believe the recognition of nonself is essential to immune system functioning, as "nonself" is likely to have different genetic interests from those of the host; this conflict of interest is at the heart of host-parasite coevolution (4). The argument that the immune system distinguishes harmful from harmless (rather than self from nonself) erroneously assumes that virulence (or avirulence) is a fixed trait in parasite populations. Counting on the continued benevolence of another living organism, when increased rates of transmission may offer opportunities for increased virulence, is a precarious proposition, particularly as the density of the human population increases. The most reliable way for the immune system to defend against parasites and pathogens that may potentially shift their level of virulence is to have an effective means of distinguishing self from nonself (4).

The history of infectious disease demon-

strates that as population densities increased following the agricultural revolution, new diseases emerged (5). Today we are still facing emerging epidemics such as AIDS and the rise of drug-resistant pathogens. Group selection arguments cannot explain these phenomena.

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Response: McKean *et al.*'s point about epidemiology is well taken: in fact, an increase of population density most of the time increases the frequency, severity, and extent of disease, in balance with herd immunity. I agree that mutual overall balances between infectious agents and host populations are important and that immunity is only one part of this equilibrium. McKean *et al.* point out that I have used a group selection argument. However, I feel this is a misrepresentation of the general thrust of my paper, which is basically about the overall balance between infectious agents and the host, including the immune system. This balance is different for each virus or group of viruses. Therefore, McKean *et al.*'s arguments about "successful viruses" may be incomplete. Noncytopathic viruses such as LCMV and hepatitis B virus are successful, and so are some cytopathic viruses, but at "different costs" and by "different mechanisms."

I wanted to stress the importance of antigen localization of different effector functions because, particularly in skin and solid organs, there is no "local" immunity. The examples discussed in my paper, where T cells ignore self and foreign antigens or where T cells get exhausted by foreign antigens, show that the immune system does not fundamentally distinguish between self and nonself, although functionally the system is set up to not usually react against self.

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Corrections and Clarifications

In the article "New York courts seek 'neutral' experts," by Eliot Marshall (*News & Comment* 12 Apr., p. 189), a member of the scientific advisory panel was incorrectly identified as Fred Alan Wolf. He should have been identified as physicist Alan Wolf of the Cooper Union for the Advancement of Science and Art in New York.

Fritz Kleinhans' name was misspelled in the Author Index (p. 1891) for volume 271, January-March 1996 (29 Mar., p. 1887).

Letters to the Editor

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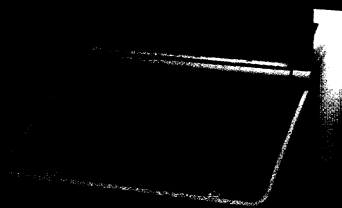
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