Sv, with the implication that this may obscure evidence for a threshold dose below which there is no excess cancer risk. These allegations are not correct.

Of the 86,572 subjects with individual dose estimates, 38,316 received doses in the range from 0.005 to 0.20 Sv, and a comparable sample of 36,549 received essentially zero doses of less than 0.005 Sv. Thus, about 85% of the cohort received doses in the range of direct interest for radiation protection, whereas only 2.6% of the cohort received doses of more than 1 Sv.

We stress that the RERF study is not just a high-dose study. There is a lack of focus on low-dose risks for solid cancers because the dose response is very linear, and important issues involving age at exposure and time since exposure should be addressed using all the data.

Modern analyses of these data, including those carried out by committees of the United Nations (*1*) and of the National Research Council (*2*), are not based on comparisons of broad dose categories.

The data for solid cancers, including tumor registry incidence data as well as cancer mortality data, are inconsistent with the notion of a threshold for radiation effects. However, epidemiological studies have inherent limitations in assessing such issues, and it is important to also consider basic radiobiology results.

Donald A. Pierce
Dale L. Preston
Radiation Effects Research Foundation, 5-2 Hijiyama Park, Hiroshima 732, Japan

References

1. *Sources and Effects of Ionizing Radiation* (U. N. Scientific Committee on Effects of Atomic Radiation, United Nations, New York, 1994).
2. National Research Council, *Health Effects of Exposure to Low Levels of Ionizing Radiation, BEIR V* (National Academy Press, Washington, DC, 1990).

■

Safety of Hepatitis B Vaccine

The editorial by Gerald R. Fink describing the development of yeast recombinant technology at the National Science Foundation (1 Mar., p. 1213) was enlightening. However, readers may be left with the misconception that persons who receive plasma-derived hepatitis B vaccines risk "infection with other blood-borne viruses carried by the vaccine." There is no evidence that plasma-derived hepatitis B vaccines have ever posed an increased risk of infection with blood-borne pathogens. The decision to use any vaccine should be based on three criteria: safety, efficacy, and cost. All available data indicate that plasma-derived hepatitis B vaccine is as safe and efficacious as recombinant vaccines, while costing considerably less.

Currently, all plasma-derived hepatitis B vaccines undergo inactivation procedures (formalin treatment alone or in combination with heat treatment) that eliminate the risk of infection with blood-borne pathogens (*1*). Furthermore, epidemiologic studies and national surveillance of vaccine-related adverse events in the United States and other countries have demonstrated no association with infections transmitted by blood in children and adults who received plasma-derived hepatitis B vaccine (*2–4*). Studies of hepatitis B vaccine have shown that the antibodies produced after administration of plasma-derived vaccine or recombinant vaccine are alike in terms of their ability to elicit protective determinants and that the efficacies of plasma-derived and recombinant vaccines are comparable (*2*, *5*, *6*). Although the cost of recombinant vaccine continues to decline, it still is more expensive than plasma-derived vaccine. Factors that contribute to the higher cost include start-up expenses associated with recombinant technology and patents that protect the products.

Primary hepatocellular carcinoma and

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.

Howard A. Fields
Francis J. Mahoney
Harold S. Margolis
Hepatitis Branch,
Division of Viral and Rickettsial Diseases,
National Center for Infectious Diseases,
Centers for Disease Control and Prevention,
Atlanta, GA 30333, USA

References

1. "Requirements for hepatitis B vaccine prepared from plasma" (Technical Report Series No. 858, World Health Organization, Annex 3, 1994).
2. K. R. Stratton, C. J. Howe, R. B. Johnston, Jr., Eds., *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality* (National Academy Press, Washington, DC, 1994).
3. D. P. Francis *et al.*, *J. Am. Med. Assoc.* **256**, 869 (1986).
4. Advisory Committee on Immunization Practices, *Morbid. Mortal. Week. Rep.* **40** (no. RR-13), 10 (1991).
5. P. Hauser, P. Voet, E. Simoen, *Postgrad. Med. J.* **63** (suppl. 2), 83 (1987).
6. F. E. Andre and A. J. Zucherman, *J. Med. Virol.* **44**, 144 (1994).
7. M. Kane, *Vaccine* **13**, S47 (1995).

■

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-