LETTERS

Stretching out

Whether recent reports about the human immune system explain earlier "anomalous results," "open new avenues of research," and suggest a new "paradigm"—or merely recapitulate "long-known" phenomena—is debated. (Right, a dendritic cell approaches a helper T cell to initiate an immune response.) And three writers describe an editorial by Philip H. Abelson as "moderate" and "rational," "interesting," and "crosswise," respectively.

Immunological Tolerance

In the 22 March issue, three papers on immunological tolerance (Reports, J. P. Ridge *et al.*, p. 1723; M. Sarzotti *et al.*, p. 1726; T. Forsthuber *et al.*, p. 1728) were featured, as well as a major comment on them in Research News (E. Pennisi, p. 1665). Because these papers purport to overthrow the major tenets of modern immunology, they have received even wider publicity over the news wires and in many daily newspapers.

While the research reported in these papers is competently done, and the results interesting, it is unclear how the inferences and conclusions drawn by the authors could have passed peer review. Nor is it clear why the authors' elaborations of these inferences should have been so uncritically reported in Research News.

It has been demonstrated for almost 30 years that there is nothing mystical about the fetal or neonatal period. The fetus of many species may express immunological competence to many different antigens at different stages of gestation and even beyond birth (*1*), and the mouse has long been known to slowly expand its immunological repertoire during the neonatal period (*2*).

We have known for almost 100 years that the mammal cannot distinguish between noxious and benign antigens; indeed, Paul Ehrlich's 1897 side-chain theory of antibody formation (a selectionist precursor of Burnet's Clonal Selection Theory) fell from favor precisely because of the demonstration that a host of nonpathogenic substances might induce an immune response. The concept of a "danger signal," with its implication of an evolutionary basis, is not viable.

We have known for well over 30 years that the balance between active immune response and tolerance induction (and maintenance) depends on a wide variety of factors, including the physical and chemical nature of the antigen, dose, timing, mode of access to the immune system, and so forth; we have long known also that the adult may be rendered tolerant under appropriate conditions (*3*).

The balance between tolerogenic and immunogenic dose, between B and T cell tolerance, between one and two signals, and the entire question of self-nonself has been debated widely since Burnet's original formulation. Burnet's initial theory has been modified substantially by later data; to raise it now as a straw man to be demolished is not reasonable. These questions are scarcely new.

Arthur M. Silverstein
Institute of the History of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA

References

1. J. Sterzl and A. M. Silverstein, *Adv. Immunol.* **6**, 337 (1967); J. B. Solomon, *Foetal and Neonatal Immunology* (North-Holland, Amsterdam, 1971).
2. N. H. Sigal and N. R. Klinman, *Adv. Immunol.* **26**, 255 (1978); N. R. Klinman and P. J. Linton, *ibid.* **42**, 1 (1988).
3. D. W. Dresser and N. A. Mitchison, *ibid.* **8**, 129 (1968); W. O. Weigle, *ibid.* **16**, 61 (1973).

Response: Neonatal tolerance has fascinated the immunologic community for 50 years, resulting in apparently conflicting publications that can be broadly divided into three groups which state that neonatal antigen exposure causes (i) clonal deletion, (ii) suppression, or (iii) an immune response (see Silverstein's letter). The prevalent view has been that the neonate is immune privileged.

The three reports in the 22 March issue may have resolved this controversy and demonstrate why neonatally induced immunity has been perceived either as clonal deletion or suppression. In our report (p. 1728), for

example, we showed that memory cells lose lymph node homing receptors and lose their ability to migrate to lymph nodes (figure 1 in the report). Hence, when lymph node responses are studied, as has been the case in the past, the lack of antigen reactive cells seemed to suggest that these cells were clonally deleted, which substantiated the clonal deletion model for neonatal tolerance. But, as we have shown, the memory cells were simply redistributed in the organism (figure 1 in the report). Furthermore, we have shown that neonatally induced T_H2 immunity results in apparent suppression when T_H1 immunity is measured (table 1 in the report). The previous data, which seemed to conflict, reflect a single mechanism: induction of T_H2 immunity.

Clearly, the currently favored clonal deletion model is insufficient to fully explain self-tolerance. Our reports have added two important aspects to this discussion. First is Matzinger's danger model, on which she comments below. Second, our findings substantiated the active T cell tolerance idea, showing that what was thought to be "suppressor cell"–mediated self-tolerance actually translates into T_H2 cell–mediated effects.

With regard to the "wide variety of factors" that can define outcome, there has not been a basic understanding of the rules that govern the outcome. This is where the impact of our studies lies. Matzinger and her colleagues showed that it is the type and activation state of the antigen-presenting cells that decide whether a response is engaged or tolerance results. Sarzotti and her co-workers determined how the dose of the virus affects response. Our own report showed that the adjuvants can reliably guide the response to the T_H1 or T_H2 directions.

I agree that "these questions are scarcely new," but for the first time there may be a satisfactory answer concerning the mechanism that underlies neonatal tolerance.

Paul V. Lehmann
Department of Pathology,
Case Western Reserve University,
Cleveland, OH 44106–4943, USA

Response: Roughly two millennia before Copernicus, Aristarchus proposed a heliocentric model to explain the motion of the planets. Why was it ignored? Thomas Kuhn's suggestion was that, at that time, there might have been no general dissatisfaction with the reigning paradigm (Earth at the center) and therefore no reason to abandon it (*1*). By the time Copernicus suggested his version, the motion of planets could no longer be easily explained by the view that the Earth was central, and the intellectual community was ready for a "new" idea. During that period of almost 20 centuries, there had been many findings that did not fit with the ruling paradigm, but most of them went unrecognized, examples of the "retrorecognition" phenomenon (*2*), whereby clear anomalies in a paradigm are recognized only after a new conceptual framework has been set forth to replace the defective one.

Roughly 100 years ago, as Silverstein points out, Ehrlich thought that the immune system's primary function was to detect and protect against noxious pathogens. It seems that this view was replaced by Burnet's self-nonself model because the latter was better able to explain two new phenomena, the ability to raise immune responses to nonnoxious substances (*3*) and the discovery of neonatal tolerance (*4*). Over the ensuing years, both of these findings were extensively examined and, in both cases, some clear anomalies appeared, many of which were ignored. For example, a variety of nonpathogenic substances can indeed induce immune responses, but, as Charles Janeway has emphasized, they almost never do in the absence of immunological adjuvants, which contain bacterial products (*5*). Thus, the mere presence of "foreignness" is

not enough. Some essence of pathogenicity is also required.

The picture with neonatal tolerance has also been clouded considerably since the original pioneering experiments. As Silverstein mentions, there have been scattered examples in which neonatal immunity rather than tolerance was seen. We referred to some of these in our paper and have since been made aware of others (6). Altogether, these studies showed that neonates were able to make many different kinds of responses. They cleared viruses, generated graft-versus-host disease, and made T_H1 and T_H2 responses; and a few experts in the field began to understand that neonatal tolerance was more complicated than had first been envisioned. Yet many immunologists were unaware of the complications, and recent textbooks continue to describe neonatal tolerance in terms of the immaturity of the neonatal T cells (7).

Why have the anomalous findings had so little impact?

Perhaps this was another case of retrorecognition. The findings simply didn't fit with a paradigm that had found its strongest early support in the original neonatal tolerance experiments, and there was no alternative model to fit them into. If youthful immune systems were able to respond to a variety of antigens, making a variety of responses, how could self be distinguished from nonself? Although some scientists attempted to deal with the problem by changing the temporal model to a spatial one (moving tolerance into the thymus, where the T cells, rather than the individual, are immature), these models could not easily account for tolerance to tissue-specific peripheral antigens, and no self-nonself model can account for new antigens that might appear throughout life.

Looking back, a historian of science might wonder what would have happened if Peter Medawar's group had gotten a different result. Although Burnet's Clonal Selection would certainly have prevailed as the modern operating model, what would have happened to self versus nonself? Perhaps Clonal Selection would have served as a mechanism to generate specific responses to dangerous pathogens and to allow for antigen-specific memory.

Our results, in combination with those of the other groups showing that neonatal mice can respond, open up the possibility of a new model based on clonal selection but not on self and nonself. Although the results, by themselves, do not disprove the self-nonself model (8), they do undermine one of its experimental underpinnings and are more easily placed in the context of the "danger" model (9), which suggests that the immune system is primarily concerned with detecting and protecting against "dangerous" pathogens and that tolerance is a continuous process regulated throughout life by each bodily tissue. We were pleased that Silverstein reminded us of Ehrlich's early views. We could be in far worse company.

Ephraim J. Fuchs*
John Paul Ridge
Polly Matzinger
Section on T Cell Tolerance and Memory (Ghost Lab), Laboratory of Cellular and Molecular Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA

*Present address: Johns Hopkins Oncology Center, Baltimore, MD 21287, USA.

References and Notes

1. T. S. Kuhn, *The Structure of Scientific Revolutions* (Univ. of Chicago Press, Chicago, IL, 1970).
2. A. Lightman and O. Gingerich, *Science* **255**, 690 (1992).
3. D. W. Dresser and N. A. Mitchison, *Adv. Immunol.* **8**, 129 (1968); W. O. Wiegle, *ibid.* **16**, 61 (1973).
4. R. E. Billingham, L. Brent, P. B. Medawar, *Nature* **172**, 603 (1953).

5. C. A. Janeway, *Cold Spring Harb. Symp. Quant. Biol.* **54**, 1 (1989).
6. J. G. Howard and D. Mitchie, *Transplant. Bull.* **29**, 1 (1962); J. Sterzl and A. M. Silverstein, *Adv. Immunol.* **6**, 337 (1967).
7. W. E. Paul, *Fundamental Immunology* (Raven, New York, ed. 3, 1993); C. A. Janeway and P. Travers, *ImmunoBiology* (Garland, New York, ed. 2, 1996); A. K. Abbas, A. H. Lichtman, J. S. Pober, *Cellular and Molecular Immunology* (Saunders, Philadelphia, PA, 1991).
8. This was better done by an earlier paper (*10*), in which we showed that unprimed adult female mice responded to the male antigen, H-Y, when it was presented by dendritic cells but became tolerant when it was presented by resting or activated B cells. The inevitable conclusion from this study was that their responses were dictated by the cell presenting the antigen rather than the "foreignness" of the antigen itself.
9. P. Matzinger, *Annu. Rev. Immunol.* **12**, 991 (1994).
10. E. J. Fuchs and P. Matzinger, *Science* **258**, 1156 (1992).

Response: Our report demonstrated that the susceptibility of newborn mice to a virus was not the consequence of a "slowly expanding immunological repertoire" but an example of immune deviation (*1*) driven by the relatively high dose of virus encountered by the neonatal immune system. The development of type 1 or type 2 responses is determined by the dose of virus inoculated in newborn mice and influences the development of protective immunity. Our report and those of Ridge *et al.* and Forsthuber *et al.* used non-"mystical" concepts and approaches (dose of antigen, type of APCs, adjuvants) known to the immunological community for a long time. However, in combination these approaches offered a simple and comprehensive explanation of immunological nonresponsiveness in newborn mice.

Marcella Sarzotti
Research Service,
Veterans Affairs Medical Center,
10 North Greene Street,
Baltimore, MD 21201, USA and
Department of Microbiology and Immunology,
University of Maryland School of Medicine,
Baltimore, MD 21201, USA
E-mail: msarzott@umabnet.ab.umd.edu

References

1. C. R. Parish, *Transplant Rev.* **13**, 35 (1972); P. A. Bretscher, G. Wei, J. N. Menon, H. Bielefeldt-Ohmann, *Science* **257**, 539 (1992).

The three reports on immunological tolerance provide intellectual support for the clinical observation (*1*) of down-regulation of cellular immune responses in patients receiving allogeneic blood transfusions. This is particularly well documented in organ transplantation, surgery, and cancer. Recent evidence from both animal and human studies suggests that the high doses of alloantigen involved in clinical transfusions induce a T_H2 immune response, and the expected down regulation of the T_H1 response (*2*, *3*). The trauma of surgery alone causes T_H2 responses, compatible with Matzinger's "danger" theory. Allogeneic transfusions also have been successfully used to treat two disease processes that likely represent overactive T_H1 immunity in adults—repetitive spontaneous abortion (*4*) and rheumatoid arthritis (*5*). These observations in humans support the point made by the authors that manipulation of immunity in adults may be more feasible than previously believed on theoretical grounds.

Neil Blumberg
Blood Bank/Transfusion Medicine,
University of Rochester Medical Center,
Rochester, NY 14642, USA
Joanna M. Heal
Department of Medicine,
University of Rochester Medical Center

References

1. N. Blumberg and J. M. Heal, *Transfusion* **35**, 879 (1995).
2. S. A. Kirkley *et al.*, *Lancet* **345**, 527 (1995).
3. G. F. Babcock and J. W. Alexander, *Transplantation* **61**, 465 (1996).
4. J. F. Mowbray *et al.*, *Lancet* i (no. 8435), 941 (1985).
5. J. B. Smith and J. G. Fort, *J. Rheumatol.* **23**, 220 (1996).