

Infection versus immunity: What's the balance?

William T. Shearer, MD, PhD *Houston, Tex*

This issue of the Journal is devoted to the theme of infection and immunity and to attempts to describe the balance of host forces that protect against those infectious forces that would invade. For most of our lives we remain unaware of the moment-by-moment interplay of host resistance factors and infectious agents. Yet as described in the articles herein, a natural sequence of clonal expansion of microbes develops in human beings born with faulty immunity or in those whose immunity is temporarily overwhelmed by infection. There are 3 intersecting concepts drawn out for us in this month's Journal—immunodeficiency, infection, and cancer—that meet in a common point in certain individuals, like the zero point of 3-dimensional axes. Most infections of humankind are attributed to being the result of chance, exposure, and dose of infectious agent. Compelling arguments are now being made, however, that at least in the case of the more severe forms of these infections, invading organisms have taken advantage of a hidden chink in the armament of presumed normal immunity. With special patients who need immunosuppressive treatments, there is often a manifestation of chronic infection and even the appearance of cancer. This issue of the Journal clarifies some of those mysterious mechanisms of immunity that enable the preservation of life.

In the lead *Current Reviews* article, Tosi summarizes the rapidly expanding field of innate immunity that, though lacking immune memory and clonal expansion of lymphocytes, probably protects against more infections than does adaptive immunity.¹ At epithelial skin surfaces, antimicrobial peptides disrupt the cell membranes of pathogens and prevent numerous skin infections.² Atopic eczema is a clinical example of deficiency in

β -defensins that leads to repeated staphylococcal infections in eczematous patches of affected skin.³ Mononuclear phagocytes and other cells contain Toll-like receptors that react with bacterial products, such as endotoxin and DNA sequences, and become active secretors of cytokines that regulate subsequent inflammatory responses.⁴ Children with deficiencies of the Toll-like receptor signaling pathway involving the IL-1 receptor-associated kinase (IRAK) are subject to infections with pyogenic bacteria.⁵ Numerous cytokines are involved in immune reactions, both protecting the host from infections and contributing to the complications of infections. In the latter category, perhaps IL-1 and TNF- α are best known for their pathologic role in gram-negative bacterial toxin-induced shock.⁶ Chemokines and their receptors are active in numerous immunologic reactions to infections, but none are more visible than the CCR5 and CXCR4 chemokine receptors that induce cognate receptor binding of the HIV-1 glycoprotein 120 and facilitate entry of the HIV-1 virion into target cells.⁷ The value of natural killer (NK) cells assumes more importance as we understand the primal role that they serve in host protection against viral infection and the development of cancer.⁸ Responding in an antigen-independent manner, NK cells bind and lyse virus-infected host and cancer cells by perforin formation or apoptosis induction. Complement⁹ and neutrophil-invaded immunity¹⁰ round out the repertoire of innate immunity, each contributing to that immediate response to infection that is so important prior to the engagement of the slower acquired immune responses. The illustration on the cover of this issue demonstrates how neutrophils police the vascular endothelium and, within seconds of detecting chemoattractants created by infections in the tissues, squeeze through intercellular spaces in pursuit of pathogens.¹¹ On arrival at the site of infections, neutrophils engulf and kill microbes through the formation of superoxide. No prior memory of these pathogens is necessary for this bacteriocidal function of neutrophils.

Thorley-Lawson¹² writes in the *Molecular Mechanisms* article on how the Epstein-Barr virus (EBV) takes up long-term residence in almost all human beings and occasionally produces lymphomas. Virtually all individuals with EBV lymphomas are either immunosuppressed (eg, transplant patients) or lack components of immunity on a congenital basis (eg, X-linked immunoproliferative disease).¹³ EBV remains in a latent state in resting memory B cells that do not express EBV proteins on their cell

From the Department of Pediatrics, Baylor College of Medicine, and the Department of Allergy and Immunology, Texas Children's Hospital.

Supported by the National Institutes of Health grants AI27551, AI36211, HD41983, RR0188, HD079533, HL72705, HD078522, contract 202PICL05; the Pediatric Research and Education Fund, Baylor College of Medicine; and the David Fund, Pediatrics AIDS Fund, and Immunology Research Fund, Texas Children's Hospital.

Received for publication May 31, 2005; accepted for publication June 1, 2005. Available online July 15, 2005.

Reprint requests: William T. Shearer, MD, PhD, Department of Pediatrics, Section of Allergy and Immunology, Baylor College of Medicine, 6621 Fannin St (MC-FC330.01), Houston, TX 77030. E-mail: wtsheare@TexasChildrensHospital.org.

J Allergy Clin Immunol 2005;116:263-6.
0091-6749/\$30.00

© 2005 American Academy of Allergy, Asthma and Immunology
doi:10.1016/j.jaci.2005.06.001

surface.¹⁴ Thus, these EBV-containing B cells remain invisible to cytotoxic T cells. EBV is thought to play a role not only in lymphomas but also in Hodgkin's disease, Burkitt's lymphoma, and nasopharyngeal carcinoma. Thorley-Lawson acknowledges that these cells may just carry EBV rather than being the result of EBV-initiated transformation events. He also questions why more EBV-driven tumors are not seen in human populations, even those immunosuppressed individuals. The answer seems to reside in the propensity of EBV-infected B cells to stop replicating under the influence of 2 viral genes—latent membrane protein (LMP) 1 and LMP2—and enter the latent resting memory cell condition.¹⁵ Circumstances that disrupt the immune system change this resting memory cell condition and favor tumor development. Thus, when human beings are given immunosuppressive drugs or have received therapeutic irradiation, immune forces are disrupted and the EBV B cell enters the replicating cell cycle. Unless killed by cytotoxic T cells, which respond to the newly expressed EBV cell surface antigens, these activated EBV cells could form oligoclonal tumor cells. These observations hold importance for immunologically normal human beings exposed to occupational or environmental conditions that cause immunosuppression, such as radiation in spaceflight.¹⁶

Mehandru and colleagues¹⁷ contribute a *Perspectives/Update* article to this issue that details the rapidly unfolding discoveries of the crucial role of gastrointestinal lymphatic tissue in acute HIV-1 infection. In the face of relatively stable peripheral blood CD4⁺ T (helper) cell concentrations in acute HIV-1 infection, there is a massive kill-off of tissue CD4⁺ T cells, particularly those of the gastrointestinal tract.^{18–20} Moreover, these gastrointestinal CD4⁺ T cells are of the memory phenotype and express the CCR5 chemokine receptor that attract the monocytotropic HIV-1 viral strains, as demonstrated in the simian model of HIV-1 infection.^{21,22} The emerging model of pathogenesis of acute HIV-1 infection suggests that the large pool of memory CD4⁺ T cells in mucosal surfaces becomes preferentially infected and stimulates repetitive rounds of viral replication and CD4⁺ T cell killing. Mehandru proposes that these discoveries will revamp the way clinicians decide when to intercede with anti-retroviral agents (ie, immediate versus deferred therapy), rekindle the debate of using immunomodulators to reduce the waves of inflammation and viral replication (eg, cyclosporine therapy during acute infection), accelerate the use of protective strategies for the gastrointestinal mucosal surfaces (eg, microbicides and CCR5 blockers), and redirect vaccine strategies to mucosal surfaces.

In the *Advances in Asthma, Allergy, and Immunology Series 2005: Basic and Clinical Immunology* article in this issue, Chinen and Shearer mention several noteworthy, recent publications dealing with the interplay between immunity and infection.²³ The importance of the HLA allele recognition system in viral infection is seen in human beings with certain HLA-B alleles with HIV-1 infection. HIV-1-infected individuals with HLA-B57 and HLA-B*5801 select for variants with a specific

mutation in the Gag epitope of HIV-1, but when this mutant viral strain is transmitted to another individual with different HLA alleles, this epitope reverts to the wild type.²⁴ In HIV-1 discordant couples, the risk of HIV-1 transmission is 2-fold higher (independent of HIV-1 viral load) if the couples share one or both HLA-B alleles.²⁵ In perinatal HIV-1 transmission, HLA-B*4901 and B*5301, alleles that inhibit mother-to-infant HIV-1 transmission (despite high HIV-1 viral load), differ from otherwise identical HLA-B*5001 and B*3501 alleles by 5 amino acids encoding the ligand for the killer inhibitory receptor (KIR) 3DL1 for NK cells.²⁶ The molecular basis for these 3 observations suggests strongly that recognition molecules on immune cells govern subsequent viral mutation and viral elimination through cytotoxic T cells and NK cells. Also summarized in the *Advances* article are the discoveries that mast cells participate in host defense via recognition of Toll-like receptors and viruses²⁷ and secretion of cytokines that recruit effector cell.²⁸ Articles in the area of primary immunodeficiency and infectious diseases are also cited, perhaps none more important than the identification of risks of malignancy when retroviral vectors are used to insert gene constructs in stem cells bone marrow derived in severe combined immunodeficiency.²⁹ In this instance, the retroviral vector has the potential to insert into the human genome in the promotor region of oncogenes and to trigger the development of T-cell leukemia.³⁰ Related to these observations in primary immunodeficiency is the *Images in Allergy and Immunology* article that pictures the case of a child who developed severe mosquito bite hypersensitivity, ulcerating skin lesions, enlarged and draining adjacent lymph nodes, and marked hepatosplenomegaly.³¹ Studies reveal that this child developed proliferation of EBV-containing NK cells similar, if not identical, to that seen in the few reported cases of chronic active EBV infection of NK cells that result in NK cell leukemia and lymphoma.³² It is possible that this child is an example of the atypical immunodeficiency that presents with a more common and less marked clinical phenotype that ultimately might be resolved by detection of causal genes, as proposed by Casanova³³ and reviewed by Bonilla and Geha³⁴ in an editorial in this issue.

In addition to the interaction of viruses with immunodeficiency, there is strong evidence for a pathogenic role for viruses in allergic diseases. For example, rhinoviruses cause more than 50% of upper respiratory infections and are thought to be responsible for the induction of acute exacerbations of asthma in the lower airway. Friedlander and Busse³⁵ review this evidence in this issue, and find that respiratory viruses are associated with approximately 80% of children and 50% of adults with wheezing episodes and that infection of the upper and lower respiratory mucosal surfaces induces increased airway hyperresponsiveness. This concept of rhinovirus induction of asthma includes (1) the attachment of the intercellular adhesion molecule 1 (ICAM-1) to the viral capsid molecules³⁶ and (2) the stimulation of proinflammatory cytokines IL-6, IL-8, IL-16, and RANTES chemokine.³⁷ The net result of

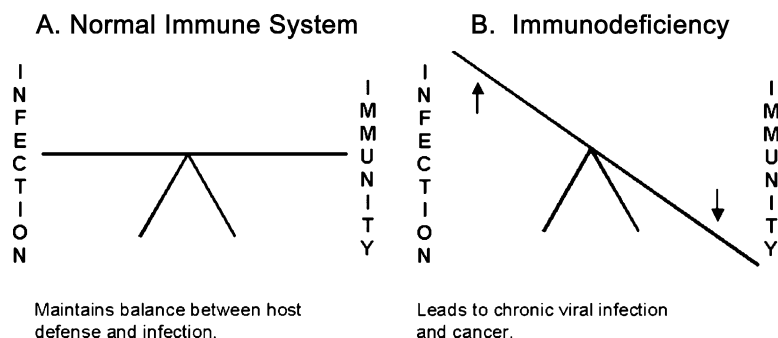


FIG 1. Balance between immunity and infection. **A**, Normal immune system. **B**, Immunodeficiency.

upregulation of these mediators is an influx of eosinophils, monocytes, T cells, macrophages, and neutrophils into respiratory tissue.³⁸ As a result of this increased inflammation of the airways, angiogenic growth factors might induce tissue remodeling of respiratory mucosa and could cause a permanent change in lower airway architecture and increased difficulties for treatment programs.

All in all, the theme of this month's Journal seems to have been substantially illustrated by the contributions of talented experts in immunity and infection. These inter-related concepts can be considered the 2 sides of a coin. Perhaps a better analogy is that of a teeter-totter: when the sitting board is horizontal, there is a balance between immunity and infection (Fig 1). When immunity is down, infections rise and immunity must be strengthened to gain balance, with the result that the inflammation of immunity often overshoots and infection drops. However, evidence is being gathered to strongly suggest that when this balance is upset, as is the case with immunodeficiency diseases, certain viruses are able to escape strong immune response and hide in a latent condition. When individuals who harbor latent viruses, such as patients receiving immunosuppressive drugs or therapeutic radiation, encounter an additional force, the latent virus is forced into its life cycle that yields outgrowths of clones of virus-containing transformed cells. More understanding of these balancing forces of immunity and infection is necessary so that we, as clinician-investigators, can intervene with the sometimes threatening consequences of imbalances in the forces of the immune system and infection.

I thank Carolyn Jackson and Ruth Herrera for assistance with the preparation of this manuscript.

REFERENCES

1. Tosi M. Innate immune responses to infection. *J Allergy Clin Immunol* 2005;116:241-9.
2. Ganz T. Defensins: antimicrobial peptides of innate immunity. *Nat Rev Immunol* 2003;3:710-20.
3. Ong PY, Ohtake T, Brandt C, Strickland I, Boguniewicz M, Ganz T, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med* 2002;347:1151-60.
4. Zarembek KA, Godowski PJ. Tissue expression of human Toll-like receptors and differential regulation of Toll-like receptor mRNAs in leukocytes in response to microbes, their products, and cytokines. *J Immunol* 2002;168:554-61.
5. Picard C, Puel A, Bonnet M, Ku CL, Bustamante J, Yang K, et al. Pyogenic bacterial infections in humans with IRAK-4 deficiency. *Science* 2003;299:2076-9.
6. Oppenheim JJ, Feldman M. Introduction to the role of cytokines in innate host defense and adaptive immunity. In: Oppenheim JJ, Feldman M, Durum SK, Hirano T, Vilcek J, Nicola N, editors. *The cytokine reference*. San Diego: Academic Press; 2001. p. 3-20.
7. Glass WG, Rosenberg HF, Murphy PM. Chemokine regulation of inflammation during acute viral infection. *J Allergy Clin Immunol* 2003;111:467-73.
8. Smyth MJ, Cretney E, Kelly JM, Westwood JA, Street SE, Yagita H, et al. Activation of NK cell cytotoxicity. *Mol Immunol* 2005;42:501-10.
9. Berger M, Frank MM. The serum complement system. In: Stiehm ER, Ochs HD, Winkelstein JA, editors. *Immunologic disorders in infants and children*. 5th ed. Philadelphia: Elsevier Saunders; 2004. p. 20-62.
10. Tosi MF. Immunologic and phagocytic responses to infection. In: Feigin RD, Cherry JD, Demmler GJ, Kaplan S, editors. *Textbook of pediatric infectious diseases*. 5th ed. New York: WB Saunders; 2004. p. 652-84.
11. Seo SM, McIntire LV, Smith CW. Effects of IL-8, Gro-alpha, and LTB(4) on the adhesive kinetics of LFA-1 and Mac-1 on human neutrophils. *Am J Physiol Cell Physiol* 2001;281:C1568-78.
12. Thorley-Lawson DA. EBV the prototypical human tumor virus—just how bad is it? *J Allergy Clin Immunol* 2005;116:251-61.
13. Shearer WT, Ritz J, Finegold MJ, Guerra IC, Rosenblatt HM, Lewis DE, et al. Epstein-Barr virus-associated B-cell proliferations of diverse clonal origins after bone marrow transplantation in a 12-year-old patient with severe combined immunodeficiency. *N Engl J Med* 1985;312:1151-9.
14. Hochberg D, Middeldorp JM, Catalina M, Sullivan JL, Luzuriaga K, Thorley-Lawson DA. Demonstration of the Burkitt's lymphoma Epstein-Barr virus phenotype in dividing latently infected memory cells in vivo. *Proc Natl Acad Sci* 2004;101:239-44.
15. Hochberg DR, Thorley-Lawson DA. Quantitative detection of viral gene expression in populations of Epstein-Barr virus-infected cells in vivo. *Methods Mol Biol* 2005;292:39-56.
16. Shearer WT, Zhang S, Reuben RM, Lee B, Butel JS. Effects of radiation and latent virus on immune responses in a space flight model. *J Allergy Clin Immunol* 2005;115:1297-303.
17. Mehandru S, Tenner-Racz K, Racz P, Markowitz M. The gastrointestinal tract is critical to the pathogenesis of acute HIV-1 infection. *J Allergy Clin Immunol* 2005;116:419-22.
18. Guadalupe M, Reay E, Sankaran S, Prindiville T, Flamm J, McNeil A, et al. Severe CD4+ T-cell depletion in gut lymphoid tissue during primary human immunodeficiency virus type 1 infection and substantial delay in restoration following highly active antiretroviral therapy. *J Virol* 2003;77:11708-17.
19. Mehandru S, Poles MA, Tenner-Racz K, Horowitz A, Hurley A, Hogan C, et al. Primary HIV-1 infection is associated with preferential depletion of CD4+ T lymphocytes from effector sites in the gastrointestinal tract. *J Exp Med* 2004;200:761-70.
20. Brenchley JM, Schacker TW, Ruff LE, Price DA, Taylor JH, Beilman GJ, et al. CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. *J Exp Med* 2004;200:749-59.

21. Mattapallil JJ, Douek DC, Hill B, Nishimura Y, Martin M, Roederer M. Massive infection and loss of memory CD4+ T cells in multiple tissues during acute SIV infection. *Nature* 2005;434:1093-7.
22. Li Q, Duan L, Estes JD, Ma ZM, Rourke T, Wang Y, et al. Peak SIV replication in resting memory CD4+ T cells depletes gut lamina propria CD4+ T cells. *Nature* 2005;434:1148-52.
23. Chinen J, Shearer WT. Advances in asthma, allergy, and immunology series 2005: basic and clinical immunology. *J Allergy Clin Immunol* 2005;116:411-8.
24. Leslie AJ, Pfaffertott KJ, Chetty P, Draenert R, Addo MM, Feeney M, et al. HIV evolution: CTL escape mutation and reversion after transmission. *Nat Med* 2004;10:282-9.
25. Dorak MT, Tang J, Penman-Aguilar A, Westfall AO, Zulu I, Lobashevsky ES, et al. Transmission of HIV-1 and HLA-B allele-sharing within serodiscordant heterosexual Zambian couples. *Lancet* 2004;363:2137-9.
26. Winchester R, Pitt J, Charurat M, Magder LS, Goring HH, Landay A, et al. Mother-to-child transmission of HIV-1: strong association with certain maternal HLA-B alleles independent of viral load implicates innate immune mechanisms. *J Acquir Immune Defic Syndr* 2004;36:659-70.
27. Kulka M, Alexopoulou L, Flavell RA, Metcalfe DD. Activation of mast cells by double-stranded RNA: evidence for activation through Toll-like receptor 3. *J Allergy Clin Immunol* 2004;114:174-82.
28. Marshall JS, Jawdat DM. Mast cells in innate immunity. *J Allergy Clin Immunol* 2004;114:21-7.
29. Chinen J, Puck JM. Successes and risks of gene therapy in primary immunodeficiencies. *J Allergy Clin Immunol* 2004;113:595-603.
30. Cavazzana-Calvo M, Lagresle C, Hacein-Bey-Abina S, Fischer A. Gene therapy for severe combined immunodeficiency. *Annu Rev Med* 2005;56:585-602.
31. Pacheco SE, Gottschalk SM, Gresik MV, Dishop MK, Okmura T, McCormick TG. Chronic active Epstein-Barr virus (CAEBV) infection of NK cells presenting a severe skin reaction to mosquito bites. *J Allergy Clin Immunol* 2005;116:470-2.
32. Tokura Y, Ishihara S, Tagawa S, Seo N, Ohshima K, Takigawa M. Hypersensitivity to mosquito bites as the primary clinical manifestation of a juvenile type of Epstein-Barr virus-associated natural killer cell leukemia/lymphoma. *J Am Acad Dermatol* 2001;45:569-78.
33. Casanova JL, Fieschi C, Bustamante J, Reichenbach J, Remus N, von Bermuth H, et al. From "idiopathic" infectious diseases to "atypical" primary immunodeficiencies. *J Allergy Clin Immunol* 2005;116:426-30.
34. Bonilla S, Geha RS. Are *you* immunodeficient? *J Allergy Clin Immunol* 2005;116:423-5.
35. Friedlander G, Busse WW. The role of rhinovirus in asthma exacerbations. *J Allergy Clin Immunol* 2005;116:267-73.
36. Yamaya M, Sasaki H. Rhinovirus and asthma. *Viral Immunol* 2003;16:99-109.
37. Papadopoulos NG, Bates PJ, Bardin PG, Papi A, Leir SH, Fraenkel DJ, et al. Rhinoviruses infect the lower airways. *J Infect Dis* 2000;181:1875-84.
38. Gern JE. Rhinovirus respiratory infections and asthma. *Am J Med* 2002;112:19S-27S.