Book Reviews
463

of the field at present is provided. The theme of cytokine involvement in intestinal function is carried through two other chapters in disparate areas of interest. One describes the role of cytokines in the IgA response, to which much of the mucosal response is dedicated. N. Lycke presents a conceptually pleasing and logically formatted discussion of the formation of PP and the link between PP and IgA responses. The role of cytokines in the IgA response is also a well-developed focus. The other cytokine-related chapter is aimed at immunity to intestinal helminths. The immune response to these infections represents one of the few examples in vivo where there is a clear indication that the type of T cell response makes a difference. Thus, Th1-type responses are associated with susceptibility to infection while Th2-type responses result in clearance of the parasite. Perhaps surprisingly, this chapter was the only one that dealt with infectious disease in any detail. While some of the other chapters touched on aspects of this area, in a book focused on mucosal T cells, the inclusion of more material on actual immunity to bacteria and viruses would provide a more complete picture of the raison d'etre for the mucosal immune system. Nevertheless, *Mucosal T Cells* will provide the aficionado with useful background material, and although some chapters may beguile the uninitiated, several are worthwhile reading for beginners in the field.

For those interested in a comprehensive treatment of mucosal immunity, the newly published *Mucosal Immunology*, edited by Ogra, Mestecky, Lamm, Strober, Bienenstock, and McGhee will be an excellent resource. Formerly titled *The Handbook of Mucosal Immunology*, this volume has grown exponentially along with the field, weighing in at 1628 pp., and can now be compared with the stalwart general immunology text *Fundamental Immunology*, edited by W. Paul. Since the latter provides only a cursory look at mucosal immunity, the two books together give a much-needed inclusive view of the immune system. *Mucosal Immunology* covers a great deal of ground, from the detailed structure of the mucosal immune system to delivery systems for vaccines. Given the rapid growth in the field over the past years, it is difficult to imagine that the pace will continue. If it does, this tome may necessarily grow to two volumes!

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The Cost of Immune-Mediated "Collateral Damage" in the Nervous System

In Defense of the Brain: Current Concepts in the Immunopathogenesis and Clinical Aspects of CNS Infections
Edited by Phillip K. Peterson, M.D. and Jack S. Remington, M.D.
Oxford: Blackwell Science (1997). 355 pp. $95.00

Immunological and Infectious Diseases of the Peripheral Nerves
Edited by N. Latov, John H. J. Wokke, and John J. Kelly, Jr.
New York: Cambridge University Press (1998). 435 pp. $145.00

Metaphors derived from military life are helpful in understanding how the immune system functions. The term collateral damage is most often used to describe damage from aerial bombardment to structures and individuals near the intended target of a bomb. There is sometimes political motivation to minimize collateral damage, as evidenced during the recent Operation Desert Fox. In contrast, in order exert maximal military, economic, and pyschological impact, the aim is to maximize collateral damage, as any student of World War II would know. The human nervous system, particularly the central nervous system, is extremely limited in its ability to regenerate after injury. For this reason, the immune system and the nervous system have evolved, and sometimes even coevolved with the microbial world, to elaborate intricate mechanisms to protect the brain and its connections to the outside world, even when under microbial attack.

Mature brain cells are terminally differentiated and are not normally replaced after death. Other organs are comprised of cell types that have the capacity to divide, and this makes them far less vulnerable to immune-mediated damage. For example, when liver cells are killed by an immune attack against a virus, they can be replaced, unlike brain cells, which cannot. Two recent books, Peterson and Remington's *In Defense of the Brain,* and Latov, Wokke, and Kelly's *Immunological and Infectious Diseases of the Peripheral Nerves,* provide some pertinent examples of the perils of collateral damage to the brain and what is done to avoid it.

Rabies would represent the utter failure to protect the brain from collateral damage. Hillary Koprowski, perhaps the sage on the subject of confrontations between the brain and the immune system, dating back to his influential work in the early 1950s to produce a polio vaccine, and Bernhard Dietzschold describe the ravages of rabies: "...even the Sanskrit word *rabhas* from which rabies originates evokes fear since it means 'to do violence.'" (*In Defense of the Brain*, p. 239). In rabies infection, experimental studies show that the virus itself shuts off critical neuronal genes, including genes encoding neurotransmitters and neuropeptides, and even suppresses transcription of housekeeping genes, provoking

a crisis leading to a breakdown in neuronal function. The immune system reacts vigorously and intensifies the crisis killing the damaged neurons via cell-mediated and humoral mechanisms. Death invariably follows in all cases, unless hyperimmunization with rabies vaccine allows neutralization of the virus, before it hijacks neuronal genes, and elicits a massive and self-defeating immune response.

Viral persistence is perhaps the ultimate compromise where mutual benefit is derived for the host/hostess, whose brain survives, and the virus, which lives on in neurons, ready to reproduce in the future. Two chapters in *In Defense of the Brain*—"Herpes Simplex Infections of the Nervous System" by Richard Whitley and Ann Arvin and "Viral Persistence in the Central Nervous System" by Glenn Rall and Michael Oldstone—describe some of the mechanisms underlying viral persistence. Both viral genes and neuronal genes are involved in the development of persistence. The virus itself must be noncytopathic, and it must not provoke the immune system. In this way the virus may persist without killing the brain of its host/hostess.

One of the strategies that has evolved from the neuron to permit viral persistence and avoid deadly collateral damage from the immune system is that it is very inefficient at expressing class I and class II molecules of the major histocompatibility complex, at least in a constitutive manner. This is somewhat ironic since at least three prime components of the myelin sheath, myelin-associated glycoprotein (MAG), protein zero (P0), and myelin/oligodendrocyte glycoprotein (MOG), are themselves members of the immunoglobulin supergene family, a family including MHC, immunoglobulin, and the T cell receptor. One key molecule, Thy-1, shared by T cells and neurons, is also a member of the immunoglobulin supergene family. MOG, one of the myelin gene products that has membership in the family of immunoglobulin supergene molecules, is actually encoded within the MHC and shares a high degree of homology with bovine butyrophilins and B-G antigens located within the chicken major histocompatibility complex.

Oldstone and Rall describe various other mechanisms whereby neuronal genes encode molecules that attenuate viral transcription. Neuronal genes are, in turn, influenced by viral persistence. In some cases persistent viruses impair neurotransmitter synthesis, and nerve growth factor production. This has led to some stunning speculations that certain neurologic and psychiatric diseases may be triggered by persistent viruses that alter critical neuronal functioning. Schizophrenia and multiple sclerosis are yet two prominent diseases, where at least some investigators have considered a role for persistent viruses, resident either in neurons (leading to schizophrenia), or oligodendroglial cells (leading to multiple sclerosis).

Viral persistence can be abrogated many decades later. Shingles are caused by reactivation of the herpes varicella zoster virus, sometimes 60 or 70 years after a childhood bout with chickenpox. One wonders if the current recommendation to alter the natural infection with chickenpox in childhood, and prevent it with a chickenpox vaccine, might produce an unwanted change in the natural history of this usually benign childhood disease. Might those children who do not have natural exposure to chickenpox then be more susceptible to zoster later in life?

Finally, leprosy is another example of the delicate balance between microbes and the nervous system, in this case the peripheral nerves. Individuals who are susceptible to infection with *Mycobacterium leprae*, develop, in some cases, tuberculoid leprosy, caused by a vigorous Th1 type response to *M. leprae*, with production of IL-2 and interferon-γ. The skin, innervated by nerves that are afflicted with a vigorous delayed type hypersensitivity response to the microbe, becomes insensitive to pain and to heat. However, often there is some spontaneous recovery as the immune system attacks the *M. leprae*. In lepromatous leprosy the patient is unable to mount a Th1 response to the microbe, and the response is largely of a Th2 nature, with production of IL-4, IL-5, IL-10, and IL-13. It is likely that immunoregulatory sequences in the DNA encoding *M. leprae* polarize the immune response either towards the Th1 or Th2 phenotype, depending on genes in the host or hostess. Some evidence exists that certain class II HLA types influence whether Th1 or Th2 immunoregulatory sequences in *M. leprae* predominate. The Th2 responses allow huge numbers of the mycobacteria to proliferate in the nerve sheath, in the absence of a cellular immune reaction. Widespread sensory loss occurs. Due to anesthesia, trauma occurs unnoticed, with subsequent damage to fingers, and ulcerations throughout the skin. The appearance of such lepers is frightening to the uninformed.

These two books are an excellent place to educate oneself in the fascinating interplay between the microbial world, the immune system, and the brain. At institutions where microbiologists and immunologists work in separate departments and often in separate worlds, appreciation of these interactions might foster some spectacular collaborations. Add to this, the nervous system as the site of confrontation between microbe and the immune system, and one has a rich area for investigation, with a stunning array of real diseases to understand and to remedy. Understanding how collateral damage is minimized during immune confrontations with microbes in the brain will unlock many mysteries in neurobiology, microbiology, and immunology.

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