

KEY QUESTIONS POSED BY ROUND TABLE PARTICIPANTS

1. *How much of the immunodeficiency in HIV infected patients may be attributed to cellular autoimmunity or humoral autoimmunity or both directed toward the T and/or B lymphocytes?*
2. *Do HIV-1 or HIV-2 have definable components that are immunosuppressive, immunostimulatory?*
3. *How do defective retroviruses produce so much immunodeficiency? Do intact or defective retroviruses generate host responses separate from immunoresponses which are immunosuppressive?*
4. *To what extent are changes in the bone marrow responsible for development of immune deficiency in AIDS?*
5. *How long does it take, after the initial infection, for histopathological changes to be recognizable in the various components of the lymphomyeloid complex?*
6. *Does HIV have a specific tropism for any of the cells in the bone marrow?*
7. *Does HIV infection compromise the migratory capacity of lymphocytes?*
8. *Is the life-span of CD₄⁺ lymphocytes altered early in immunodeficiency states, even before blood levels fall?*
9. *What is the relationship between loss of immunological functions such as antigen and mitogen reactivity or depressed delayed hypersensitivity, and the migratory capacity of lymphocytes?*
10. *Where are the mechanisms involved in the conversion from latent infection to immune disorders?*
11. *How does genetic variability of HIV relate to the pathophysiology of the disease.*
12. *What is the role of HIV regulatory gene products in neoplastic disorders observed among AIDS patients.*
13. *What is the link between immunodeficiency (or immune dysfunction) and angiogenesis, what is the nature of immune system-endothelial interactions in HIV infection, and can these processes be manipulated to the patient's advantage?*
14. *What is the mechanism of lymphatic obstruction in Kaposi sarcoma (KS) and AIDS-KS and is it reversible?*
15. *Does occult retroviral infection underlie or complicate some poorly understood lymphologic and angiogenic syndromes?*
16. *How important is defective antigen presentation in the evolution of immunodeficiency in AIDS? Does it precede T-helper cell drop out? What is its cause, and can it be reversed with accompanying improvement of T-helper cell numbers?*
17. *Why does follicular hyperplasia develop?*
18. *What is the role, if any, of cytotoxic cells in the pathogenesis of lymph nodal changes?*
19. *What kind of interactions exist between follicles and extrafollicular parenchyma?*
20. *What is the pathogenesis of the hypergammaglobulinemia and the related B cell activation in patients with AIDS.*
21. *Are autoantibodies to T cells involved in the immunodeficiency of AIDS?*
22. *What about the functional abnormalities of antigen-presenting cells in AIDS?*
23. *What are the host factors that affect the infection?*
24. *What role does the genetic background of the infected individual play in disease progression?*
25. *What role does viral heterogeneity*

play in generating interfering or defective pathogenic viral variants?

26. *What are the major immunologic compensatory mechanisms that occur in HIV infections?*
27. *What is the real significance of CD₄⁺ cell number? Are there other parameters (laboratory and/or clinical) either alone, or in combination with CD₄⁺ number, that are better predictors of risk of progression?*
28. *What are the implications of questions 26 and 27 for development of effective therapies for this disease?*
29. *Does the anchoring fiber endothelium complex of anchorage contain mechanically-receptors?*
30. *Does the shape of the lymphatic endothelial cell influence its response to cytokines?*
31. *Is transformation of the lymphatic endothelium via viruses the factor leading to its abnormal anchorage and abnormal response to cytokines?*

BRIEF VIEWPOINT BY PANELISTS:

Robert Good: My perspective is that AIDS, in the early states, must be associated with molecular immunosuppression attributable to a component or to components of the HIV₁ or HIV₂ retrovirus. Similarly, the polyclonal B cell activation is also due to a component or components of the HIV retrovirus. Later, destruction of T-cells via syncytia formation or destruction of T-4 cells during virus replication may be responsible. This action of the lenti retroviruses thus can be related to the pathogenesis in the transforming retroviruses of cats, mice and other animals.

Joseph M. Yoffey: In one way or another, whether in the early or late stages of the infection, the whole of the lymphomyeloid complex, including the bone marrow, must become involved. Should there be any free virus particles in blood or lymph, there appears to be every likelihood of the reticuloendothelial system playing a part in their removal. AIDS is predominantly a disease of the lymphomyeloid complex, with a variable involvement of lymphatic and vascular endothelium.

John Hay: It is puzzling why large numbers of lymphocytes disappear but that a very small proportion of them are actually infected with virus. Are there host-derived factors in viral diseases which depress the functional (including migratory) capacity of lymphocytes? Recombinant cytokines are potential candidates as mediators but it is not clear if the most relevant lymphocyte traffic regulating molecules have yet been identified.

Francoise Barré-Sinoussi: The possible consequences of infection of stem cell or progenitor T cell by HIV might explain, at least partially, the pathogenesis of AIDS. Such consequences could be: 1) massive replication of HIV in the cells as soon as they differentiate towards CD₄⁺ cells, followed by their disappearance; 2) down regulation of cellular genes involved in the differentiation pathway; 3) expression of cellular gene products, such as regulatory molecules playing an important role in the immune response and/or in the development of malignancies.

Marlys Witte: As advanced in 1987, we propose that the AIDS-KS complex represents one of a constellation of congenital and acquired "lymphologic syndromes" arising from the four basic elements of the lymphatic system--lymphatic vessels, tissue fluid or lymph, lymphocytes, and lymphoid aggregates, which also happens to form the battleground of the host response. Indeed, from what is already known, HIV is distinctly *lymphotropic*. Not only does this retrovirus seek out, infect, and destroy T-helper *lymphocytes*, the predominant circulating cell in *lymph*, but it also invades and passes from host to host through a variety of tissue fluids (i.e., *lymph*), producing a local response that interferes with the free movement of tissue fluid, macromolecules, and migrating cells (i.e., *lymphostasis*), occasionally accompanied by overt *lymphedema*. The virus initially excites then finally exhausts *lymph nodes* and other *lymphoid aggregates* in a process marked by intense neovascularization and vascular transformation, scarring, and obliteration, and in late stages by aggressive *lymphocyte* derived malignancies (lymphomas) and *lymphatic*-derived (KS) neoplasms.

Terence Ryan: I believe that Kaposi sarcoma is a significant, but not inevitable consequence of AIDS and that to understand it one needs a more general, biological viewpoint than that presented by most immunologists. My perspective is that the most signifi-

cant development in the understanding of the biology of endothelium is that it contains mechanico-receptors and that the response of cells containing mechanico-receptors to cytokine depends almost entirely on mechanical factors in the environment. Since the lymphatic endothelium is perhaps the most responsive of endothelia to mechanical forces, ignoring the mechanico-receptor function and cell shape may lead to misinterpretation of what is actually going on. Perhaps the single most important point is that the cell which has the shape of the attenuated lymphatic endothelium responds quite differently to cytokines from a cell that is rounded.

Paul Racz and Klara Tenner-Racz: The germinal center (GC) serves as one of the major reservoirs of HIV. Virus replication involving lymphocytes, follicular dendritic cells, and macrophages occurs here. The cellular diversity of GC offers HIV an opportunity to infect target cells of different origin. Quite possibly a genomic shift may occur at the transmission of the virus to a novel target cell. Thus, GC may be one of the anatomic sites where HIV acquires the ability to develop into a variant with preferential cell tropism.

Toshikazu Shirai: Several autoantibodies to lymphocytes are at least partly related to the immunological abnormalities in some patients with AIDS. Our work has focused on the effects of lymphocyte subsets of two monoclonal antibodies to each T cell subset and B cells established from autoimmune NZB mice.

John Sninsky: HIV infection represents a dynamic equilibrium of transcriptionally active and dormant infected cells, different

infected cell types, and "quasispecies" genomes. Superimposed on this complexity is the genetically restricted presentation of viral protein epitopes to the immune system and the resulting effect of the generated antibodies on cell-cell fusion and virus particle mediated infection. This complex process eventually results in a depletion of at least the T4 helper cells, and the ensuing raft of opportunistic infections that earmark AIDS. The viral and host factors that play a role in the development of immunodeficiency remain undefined. The stage of the viral life cycle, the nature of the interfering substance, and extent of perturbation, will undoubtedly contribute critically to the timing, severity and type of disease manifestations.

Arthur Gottlieb: Although considerable information about the human immunodeficiency virus has been developed in recent years, relatively little is known about the pathogenic mechanisms that take place following infection with HIV. Knowledge of the full natural history of this infection and the morbidity/mortality pattern is still emerging and may not be fully recognized for a decade. While the number of CD₄+ cells diminishes progressively over time and is generally predictive of progression, there is little information about the relative predictive risk of particular levels of CD₄+ cells in patients who are anergic to recall antigens, as compared with those that are immunologically responsive. It is my view that compensatory mechanisms occur in HIV infected patients, by which cells with T-helper function lacking the CD₄+ epitope, emerge and that this permits preservation of immunologic responsiveness for a period of time.