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Session Summary

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Prof. R. Pabst (Hannover, Germany) opened this session with a provocative and extensive discussion on how data on lymphocyte subsets in peripheral blood of HIV patients may be misleading with regard to the immunobiology and immunopathology of target organs such as the intestinal mucosa. He focussed on the fact that lymphocytes are highly motile cells which continuously recirculate between peripheral blood and various parts of the organized secondary lymphoid tissues, including Peyer's patches. Although considerable knowledge has recently accumulated with regard to mechanisms directing the migration of lymphocytes in terms of complementary adhesion molecules expressed on the circulating immune cells and on the endothelial cells of the microvasculature, the complexity of lymphocyte recirculation is becoming more and more overwhelming.

It is important to be aware of the fact that only approximately 2% of all lymphocytes are present in the blood, so the composition of this circulating fraction cannot be expected to truly reflect the subsets present in peripheral lymphoid organs. Also, the individual's age has an important impact on the subset composition, and so have genetics, stress and gender. Thus, the conventional markers used for naive (CD45-RA+) and memory (CD45-RO+) T lymphocytes change remarkably from infancy to adulthood; early on the thymus generates a large pool of naive cells whereas later on peripheral T-cell proliferation expands more and more the memory pool. An additional important variable is the relationship between lymphocyte proliferation and apoptosis, and HIV infection exerts a strong impact by speeding up apoptosis.

The traditional counts of CD4– peripheral blood lymphocytes and the CD4:CD8 ratios as parameters for evaluation of HIV infection, are necessarily only suggestive of what is going on in peripheral lymphoid tissues. Also, it would have been more reliable to perform such measurements on defined subsets, particularly on samples of separated CD45-RO+ circulating cells that might be a better indicator of peripheral lymphocyte activity. Notably, the Berlin group has shown that there is a much more rapid decrease of CD4+ T cells in the gut lamina propria than in peripheral blood in the initial phase of HIV infection. However, knowledge to this end with regard to the organized structures of the gut-associated lymphoid tissue (GALT) such as Peyer's patches, is at present rather scarce. The kinetics of the CD4+ cells might be quite different in these inductive sites compared with what has been observed in effector sites such as lamina propria. We have a long way to go before we know in detail the effects of HIV infection on the distribution and function of various lymphocyte subsets.

The next speaker was Prof G. Pantaleo (Lausanne, Switzerland) who discussed lymphoid compartments in HIV infection. He pointed out that it is important to be aware of the fact that HIV can occur in various forms in peripheral blood: as free virions, as a productive infection of CD4+ lymphocytes and monocytes/macrophages; as a latent infection of similar cells; and as infection of circulating dendritic cells. It is unclear which form is most important for dissemination of the virus throughout the body. In the early phase of HIV infection, viremia exists up to 20 days, while replication of the virus can be seen up to 25–30 days. However, virtually nothing is known about the distribution of HIV in secondary lymphoid tissues during this phase. Data suggest that a substantial virus load can be trapped in the germinal centers of lymphoid

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follicles in immune complexes that are bound to the follicular dendritic cells via complement receptors. This reservoir of virus particles can give rise to productive infection in lymphocytes as well as macrophages. Such productive infection will after variable time periods produce destruction of the lymphoid follicles. After months with a moderate viremia, the patient goes into an advanced stage of HIV infection with abundant viremia. It follows from the kinetics of the infection that treatment efficacy should be best at a relatively early stage when many cells with productive HIV infection are around.

Prof. R. Kurth (Langen, Germany) thereafter discussed regulation of HIV replication by cytokines, which is an exciting new area of virus research. For many years it has been known that some biological factor(s) released from CD8+ T cells can inhibit HIV replication. Several scientists have invested much effort to identify these inhibitory substances; but despite continued attempts at isolation, their precise nature has remained elusive. Therefore, it was a remarkable breakthrough when Prof. Robert C. Gallo's group in 1995 identified them to belong to the C-C or β family of chemokines, particularly including RANTES, MIP-1α and MIP-1β which exert chemoattractant effects on monocytes and lymphocytes in addition to several other cell types. Interestingly, subsequent studies have shown that certain receptors for such cytokines, particularly CCR2, CCR3 and CCR5, act as coreceptors with CD4 for HIV. Apparently, CCR3 can bind T-cell-tropic HIV, whereas CCR5 binds macrophage-tropic HIV. Blocking of these receptors inhibits completely the infection, whereas antibodies against the three mentioned chemokines can block the HIV-suppressive activity generated by CD8+ T cells. In 1996, Prof. Kurth reported a similar inhibitory effect of IL-16. This cytokine was originally described in 1992 as a T-cell-specific chemoattractant and therefore named lymphocyte chemoattractant factor (LCF). IL-16 has been shown to exert immunomodulatory and proinflammatory effects that induce cell-cycle changes and cytokine secretion by CD4+ T cells. Interestingly, it has definitely been shown that IL-16 binds to the CD4 molecule but at some distance from the binding site for gp120 from HIV. The first identified cellular source of IL-16 was CD8+ T cells, and it was subsequently demonstrated that these cells contain constitutively synthesized and stored protein in a bioactive form. IL-16 is released from CD8+ T cells in response to antigen, mitogen, histamine or serotonin, but the mechanism of secretion is unknown. Subsequent studies have shown that also other cell types can produce IL-16. The CD4-binding domain of IL-16 has been identified in its precursor protein. It has been suggested that this cytokine can induce signal transduction, but the precise way in which it inhibits HIV replication is unknown. Nevertheless, IL-16 clearly belongs to the family of CD8+ T-cell-derived HIV-suppressive factors. It is clinically important that such antiviral activity is positively correlated with the health of HIV-infected patients, being particularly high during the asymptomatic stages of infection. It is notable in this context that the African green monkey, which is naturally infected with SIV but never develops simian AIDS, possesses high immunodeficiency virus-suppressing cytokine activity. Altogether there is hope that synthetic agents that can bind to the receptors for such chemokines in the future may have a great therapeutic potential by blocking HIV infection. The suppressive mechanism of IL-16 is noncytolytic (i.e., it does not involve destruction of infected host cells); therefore, one consequence might be the establishment of latency, with the possible implication of prolonged virus infection without killing the host. In this context it is interesting that the IL-16 genes of humans differ from those of African green monkeys in only 16 of their 390 coding nucleotides. However, a combination of several defense factors are most likely required for control of immunodeficiency virus infection.

The last speaker in this session was Dr. T. Schneider (Homburg/Saar, Germany) who discussed secretory immunity in HIV infection. Dr. Schneider and his colleagues have established a short-term culture system for intestinal biopsies of HIV-infected patients to measure production of various Ig classes as well as antibody to HIV antigen and other infectious agents such as CMV and cryptosporidium. The data are compared with results obtained on serum and saliva from the same patients. They have also established a Western blotting method to identify the antibody specificities of the locally produced IgG and IgA. Of particular interest is the observed dominating intestinal production of IgG antibodies which might become involved in complement-activating immune complexes in the mucosa, thereby contributing to the intestinal immunopathology of HIV and secondary virus infections.

Dr. Schneider moreover presented evidence that the local IgA response to HIV and CMV is reduced in HIV-infected patients, and this relative immunodeficiency might promote virus infections of the gut. It was furthermore suggested that the pIg receptor-mediated transport mechanism for secretory IgA might deteriorate in AIDS, thus contributing to a high mucosal virus load in late stages of the disease. This is a controversial field, and more work is clearly needed to fully understand the status of mucosal immunity in HIV-infected patients. It is an

important clinical question because intestinal immunity is most likely of crucial importance in primary mucosal HIV infection of homosexual men and also in the secondary gut infections of AIDS patients.

Three abstracts for poster presentations were submitted to this session. Dr. M. Baier (Langen, Germany) from Prof. Kurth's group reported on molecular cloning, sequence, expression, and processing of the IL-16 precursor. Evidence was presented to suggest that the naturally secreted bioactive form of IL-16 is a small fragment derived from cleavage of the pro-IL-16 polypeptide produced by CD8+ cells. Dr. T. Zippel (Berlin, Germany) from Prof. E.O. Riecken's group presented a poster on the lack of CMV-specific IgA production in intestinal biopsies in HIV-positive patients with or without CMV enteritis. They found that local production of specific antibodies occurred mainly in the IgG class, and this might promote inflammation of the mucosa by complement activation. The weak intestinal CMV-specific IgA response was suggested to be insufficient to clear this virus from the gastrointestinal tract.

Finally, Dr. D.E. Nilssen (Oslo, Norway) from Prof. P. Brandtzaeg's laboratory reported an immunohistochemical study of duodenal IgA-, IgM-, and IgG1-producing cells which were found to be increased in the duodenal mucosa of patients with advanced AIDS. The results suggested that the local immune system is activated with preferential expansion of these three classes of B cells. It was concluded that the local B-cell system is surprisingly intact even in advanced AIDS and might elicit a polyclonal response against opportunistic and commensal luminal microorganisms, although the antigen specificities were not analyzed in this study. Altogether, the session constituted an excellent and exciting starter of the symposium; it documented that much general progress has been made in this field, but that our knowledge about the impact of HIV infection on peripheral lymphoid tissues and on the mucosal immune system in particular remains scanty.