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# ROUND TABLE PARTICIPANTS

*Top row, left to right: A.A. Gottlieb, F. Barré-Sinoussi, M. Witte, T. Ryan, J. Ziegler*
*Bottom row, left to right: J. Diebold, P. Racz, K. Tenner-Racz, R. Dorfman, M. Dictor*

# PANEL DISCUSSION: THE FOUR COMPONENTS OF THE LYMPHATIC SYSTEM--LYMPH, LYMPH NODES, LYMPHOCYTES, AND LYMPHATICS

**DR. M. WITTE**: First discussion will focus on the four components of the lymphatic system—lymph, lymph nodes, lymphocytes, and lymphatics. We'll begin with the relationship of the virus with body fluids, whether cerebrospinal fluid or blood or lymph including the lymphocytes or other types of cells contained therein. The next segment of the discussion will concentrate on the lymph nodes or aggregates of lymphocytes and other immune cells and then the final discussion will be on lymphatics and specifically Kaposi's sarcoma. We will undoubtedly spill over into the other elements but the discussions naturally fall into these particular areas. Let's begin with questions of the speakers or comments about the presentations.

**DR. RACZ**: I have one remark on the first presentation. I support your concept. We performed an autopsy 3 or 4 weeks ago on a similar patient to the one you showed with very extensive lymphedema; following interferon therapy, part of the edema disappeared but the patient died of an opportunistic infection. Histology showed that on the left leg there was morphology like myxedema. All the lymphatics were markedly dilated. Around some lymphatics were giant cells and macrophages with hemosiderin. When we think treated Kaposi's sarcoma has disappeared, in reality it doesn't disappear, and one thing we find is these macrophages with hemosiderin. I would like to describe the histology of the lymph nodes which contained only a small rim of lymphoid tissue with extensive dilatation of the sinusoid, and in some sinusoids we saw the development of so-called vascular sinus transformation. So, this is another example of the picture you presented.

**DR. WITTE**: I wonder if we're seeing some new syndrome, whether it's only HIV-associated or perhaps a common pathogenesis associated with a number of different bacterial agents, viral agents, or maybe even congenital disturbances. Perhaps we might talk a little bit about that.

**DR. RACZ**: Our patient was documented to have HIV-infection and also had Kaposi's sarcoma.

**DR. DORFMAN**: Dr. Gottlieb, the impression I had from you was that in your experience, Kaposi's sarcoma is the prime tumor that occurs in patients with AIDS, but from my own experience and that reported by others, for some unexplained reason, lymphomas are occurring with increasing incidence whereas Kaposi's sarcoma is decreasing in patients with AIDS. I wonder if you haven't encountered that in your own experience.

**DR. GOTTLIEB**: Yes, I would agree with that. I was summarizing the experience as of a certain point in time. The disease keeps evolving, and we are learning much more about it as time goes on. It is true that one is seeing a higher frequency of lymphomas in comparison with Kaposi's and Kaposi's is declining. I don't have an explanation. Perhaps the other panelists might, although one thought that has been pre-

sented is that the education efforts, at least in the United States, may have contributed to this decline and that there may be some decreased multiplicity of infection in given patients. But I really don't think that as yet there's an explanation nor do I think that the whole scenario has been played out.

**DR. RACZ**: Dr. Gottlieb, have you seen also increased numbers of cases of monocytic leukemia?

**DR. GOTTLIEB**: Not in my own experience, but I should be careful to state that my experience is based on patients who are undergoing investigation with an experimental immunotherapeutic agent and so I don't speak for the constellation of symptoms that might be seen.

**DR. RYAN**: Could I come back to the point about the changing pattern of lymphoma and Kaposi's? I suppose everyone looks at the African story. There are parallels to some extent although we don't know whether there have been changes. There have been geographical variations with pockets of high incidence of lymphomas and other pockets where there's a high incidence of Kaposi's. I rather suspect that feature could give us a clue as to what's going on.

**DR. WITTE**: Regarding the route of infection, somehow we always talk about the blood route and transfusions and IV drug abusers but we don't talk about the route when that isn't the case, which is most of the time. I showed a slide that specifically delineates the lymphatic route of infection. Maybe everybody's presuming that it is lymphatic but I'm not aware of anyone saying it. When the organism enters via the genitalia or via the rectum, is it not coming into the lymphatics more likely and more primarily than breaking through and getting directly into the bloodstream? I would just like to ask the opinion of the panel on that point.

**DR. RACZ**: I think this is a very important question, and in the next minutes we will present evidence that this is true especially in the first phase of the infection. The lymphatics have a very important role in the spreading of the infection.

**DR. ZIEGLER**: This is reminiscent of the story with Epstein-Barr virus which at first drew everybody's attention to the bloodstream until it was determined that the virus gets in through the pharynx and probably is harbored in pharyngeal epithelial cells and only gets into B cells by accident causing the mononucleosis syndrome. Dr. Barre-Sinoussi, the hallmark of attachment of the virus has been to the CD4 molecule on the lymphocyte. What I've heard you say is that this is not an essential receptor for the virus, and I wonder if you could speculate on either other receptors or other ways in which the virus could infect cells.

**DR. BARRE-SINOUSSI**: I did not say that it's not essential. We've already seen today that the CD4 molecule is associated with the receptor for the virus. We still believe that CD4 is not the only molecule involved in recognition of the cells, and there is some evidence already that some cells do not express a high level of CD4 molecule and might be easily infected whereas some other cells expressing a low level of CD4 molecules are not infectable at all. So, we have evidence that some cells which don't express CD4 are infectable by the virus.

**DR. ZIEGLER**: What do you think of Dr. Witte's suggestion that the nature of the HIV infection is really through the mucosa? It might be picked up from there by trafficking macrophages in the mucosa and brought into the body in that manner.

**DR. BARRE-SINOUSSI**: Yes, I think that it's possible.

**DR. WITTE**: Geographically, it's attractive because what is hit first and foremost is the mesenteric system of lymph nodes, and the opportunistic infections are those that affect that system, particularly the mycobacterial infections. It seems like such a straightforward hypothesis, and could be demonstrated by culturing lymph from these areas.

**DR. DICTOR**: I would like to touch on the question of Kaposi's sarcoma's changing incidence and panorama. I will show a slide later this afternoon based on data from the CDC in their first 14,000 cases of reported Kaposi's in homosexual/bisexual males. In the first group of 1,000 cases, its frequency was about 46% and as of April last year, it was down to about 22% of AIDS cases. Part of that decline, of course, will be reporting artifact but I don't think it explains the whole picture. I'm glad that the clinicians here at the table also recognize that there's been a change in spectrum. The second facet of the question is, the last year I had a short discussion with one of the pathologists at the Armed Forces Institute of Pathology where they have apparently become interested in the Kaposi's question. They claim that in their discussions with African pathologists, the endemic African Kaposi's is being seen less and less. That's also what I gathered in separate discussions with a pathologist from Khartoum in the Sudan. The clinical spectrum of the disease is changing and if one takes a holistic view of Kaposi's sarcoma, which I do, it's very difficult to follow all these changes simply by changing one cofactor such as CMV. I have a hard time with CMV as a decisive cofactor on whether one develops Kaposi's, and I will be presenting later some other thoughts in perhaps another direction that one could consider.

**DR. DORFMAN**: Carrying along in that sense, based on our knowledge of the pathogenesis of lymphoma, it would seem that the Epstein-Barr virus might be the prime organism inducing lymphoma in AIDS patients. I think the genome has been identified, and all the lymphomas are B cell lymphomas. Conversely, if there is a virus that is inducing Kaposi's sarcoma, it's unlikely to be Epstein-Barr virus and may be something quite different if not HIV, some other organism that one really needs to look for in the pathogenesis of Kaposi's sarcoma.

**DR. WITTE**: Are you convinced that it's an organism necessarily?

**DR. DORFMAN**: I don't think anybody knows that.

**DR. BARRE-SINOUSSI**: It's difficult to believe that CMV is a cofactor in Kaposi's sarcoma because CMV infection among hemophiliacs is very common, and I haven't seen Kaposi's sarcoma in hemophiliacs with AIDS.

**DR. DICTOR**: The CDC as of April last year lists about 4 or 5 cases in which Kaposi's has been described in close to 200 hemophiliacs, and I agree with you completely. If one would compare two groups of AIDS patients who have similar exposure to viruses, it would perhaps be hemophiliacs and homosexual males as far as EBV, or especially hepatitis, parvovirus, CMV, and a host of other agents, and yet, there's a marked difference in their rate of Kaposi's sarcoma. To go back to your provocative comment as to whether it's induced by an organism, I think yes it is but the organism is being transmitted in a very differential fashion.

**DR. RYAN**: You as Chairman suggested that there was a general sort of lymphotropic or lymphologic syndrome of which AIDS is an example. Would you like to take any part out of AIDS which you would not find in your lymphotropic syndrome? I'm really thinking about the central nervous system. Do you think in any other syndromes you ever see a central nervous manifestation like you see in AIDS?

**DR. WITTE**: Are you talking clinically? Because there's no question that in some of the lymphedema syndromes, if the brain is involved and there is lymphatic obstruction or hypoplasia of the cervical draining lymphatics, you do get a clinical syndrome of "lymphogenic encephalopathy" described by Foldi. It has been described experimentally and clinically and resembles "pseudotumor cerebri" with a fairly characteristic pattern electroencephalographically. It can be reproduced experimentally by tying off the cervical lymphatics. Even though the brain presumably doesn't have lymphatics, it obviously has a tissue fluid drainage system. I don't think it matters whether you call something a lymphatic or a tissue fluid pocket or a pathway or whatever. Nonetheless, tissue fluid has to be drained someway or another. Could I ask a question? It seems strange to me that there have been no reports of HIV infection of endothelial cells *in vitro*. There have been demonstrations of blood vascular endothelium infection on tissue sections, and I would be surprised if blood and lymphatic vascular endothelium are not target cells or at least reservoirs for HIV as for other viruses.

**DR. BARRE-SINOUSSI**: It has been tried without any success.

**DR. RACZ**: We performed very carefully examinations for the major core proteins of the HIV. Using *in situ* hybridization, we have never seen infection of the endothelial cells. High endothelial venule cells sometime show positivity but this is a false positivity we can see also in the controls.

**DR. WITTE**: I thought that viral antigens have been localized in the blood capillaries of infected brain and presumably are not false positives.

**DR. RYAN**: Dr. Gottlieb, I was interested in your comment about thrombocytopenia being an early symptom or sign and it is unexplained. Again, my population of AIDS and my interest in Oxford is entirely in the hemophiliacs. I'm not aware of that kind of problem in the hemophiliac population and I wonder if anyone else has noticed it.

**DR. GOTTLIEB**: Thrombocytopenia is not necessarily an early sign but it is not infrequently seen, and it does appear to have an autoimmune aspect to it. Antibodies have been characterized raising questions of dysregulation or improper immune regulation rather than immune deficiency in these patients. That's another aspect of the immunopathogenic process that is difficult to understand but it is seen.