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PANEL DISCUSSION: PATHOPHYSIOLOGY AND IMMUNOLOGY

DR. M. WITTE: We have 25 more minutes to talk about pathophysiology and differences between the blood and lymphatic circulation.
DR. RYAN: I'd like to ask Dr. Morris what he thinks the high endothelium is doing if not having to do with lymphatic traffic? Has he found a function for it?
DR. MORRIS: All I can say is that it seems quite obvious that lymphocyte migration is focused on high endothelial venules in rodents. But, I've always wondered whether it isn't because the cells are having great difficulty getting out of those vessels rather than their egress being facilitated. In fact, if you see a railway station with a lot of people congregating around the entrance to the station it's because they can't get in very easily. It may well be in the case of the sheep you never see this focus of cell migration or the high endothelial venules associated with it in the nodes because the cells can get out very quickly. Cell migration in sheep nodes occurs quite diffusely through the node through low endothelium, and of course, it occurs in rodents with low endothelium such as athymic mice. I just don't believe experiments have been done which demonstrate conclusively that the selectivity of lymphocyte migration is located in the interaction between lymphocytes and high endothelial venules. Perhaps it is in rodents, but it's certainly not in sheep. The fact that you can find these vessels so early in areas where there's clearly no lymphocyte migration taking place militates against that proposition. It's not an adaptive modification of the endothelial structure relating to lymphocyte traffic as has been held for long times.
DR. RYAN: Hasn't it been suggested that high endothelial vessels in the skin were associated with arteriovenous shunts? Do you think there's any question of shunting going on? Have any studies been done where these high endothelial vessels really are in relationship to the arteries and the veins? Are they shunt systems in any way?
DR. MORRIS: Well, Dr. Sherfel in our lab has done a lot of work, for instance, on the permeability of these structures in Peyer's patches and in lymph nodes. She's demonstrated that they are in fact much more permeable vessels that other venules. One of her early contentions was that the high endothelum represented a mechanism whereby you could minimize the extravasation of material during the passage of cells across the endothelial wall. But beyond that, I haven't really got any comment to make. It's just that I believe it's dangerous to assume that the specificity of migration is implicit in those vessels. I would open up that question by suggesting that specific migration and non-specific migration occurs quite unassociated with the structural elements known as high endothelial venules. Could I ask a question of Dr. Olszewski? You made the comment that these large cells in peripheral lymph are Langerhans cells. Could you tell me why you believe that's so and what are your criteria for asserting that these large cells in peripheral lymph are in fact Langerhans cells? The reason I ask is that those cells are characteristic of peripheral lymph no matter where you collect it. The same cells are present in peripheral lymph from the liver, thyroid, ovary, intestine, and all organs studied. Yet, as far as I know, there's never been any description of the presence of Langerhans cells, say in the ovary or the liver.
DR. OLSZEWSKI: The criteria for identifying Langerhans cells, first of all, are in the electron microscopy, the specific granules. I am familiar only with the human Langerhans cells. Besides the histochemistry and the membrane characteristics, the most important feature is the OKT6 receptor, which is the most specific marker for these cells.
DR. MORRIS: Well, all of these cells are strongly Ia^+ no matter where you collect them from.
DR. OLSZEWSKI: The other point is that they can be collected only from the prenodal lymph. They practically never pass through the lymph node. I am a bit amazed to hear that you say they can also be found in peripheral lymph from the thyroid gland.
DR. MORRIS: Absolutely. They're the feature of peripheral lymph no matter where you collect it.
DR. OLSZEWSKI: In sheep, not in man.
DR. MORRIS: Not in man?
DR. OLSZEWSKI: Even in the thoracic duct in man, it is very difficult to find any Langerhans cells.
DR. MORRIS: You don't find them in the thoracic duct of sheep either. That's the point. These cells don't transgress the node, but they are the typical peripheral lymph constituent in all the animals that I've looked at which doesn't include man.

DR. OLSZEWSKI: We may agree on that point that they are very common in the peripheral lymph but I have not heard about any organs or tissues except skin and gut where they can be collected in large numbers. There is another point. There might some other macrophages because Langerhans are practically not macrophages according to the classical criteria. They don't phagocytose anything and they are non-adherent cells. But there might be some others which are adherent and might be mistakenly called Langerhans cells. But my experience is limited only to this. Also, in addition to the problem of high endothelial venules, there's approximately 10% of recirculating lymphocytes which do not migrate through the lymphoid but rather through the non-lymphoid tissue. We have never been able to demonstrate high endothelium in the venules, for example in the skin, although we've been looking very carefully for this feature. So, we usually find lymphocytes close to the blood capillary but without associated high endothelium.

DR. M. WITTE: In granulomatous and other inflammatory disease, you do see high endothelium in the skin.

DR. OHKUMA: Concerning the topic of Langerhans cells. It is known that the Langerhans cell originate from the bone marrow so it should have migrated through the bloodstream. Maybe Olszewski's result is merely due to less probability of finding it. Another thing, if you culture the Langerhans cells, the granules typically under the microscope tend to disappear. So this granule is not a criteria to decide whether it is a Langerhans cell or not.

DR. OLSZEWSKI: May I only add to what you just said that these cells migrate with blood; the precursors in bone marrow are precursors of Langerhans cells. They certainly migrate with blood because there's no other way to reach the skin or any other organ. But no cells of that shape or function have so far been described and found by others in the peripheral blood. There have been some, a very small percentage, this is 0.12% of cells which resemble Langerhans cells found in the peripheral blood but they were defined by their very high antigen-, alloantigen-presenting activity, and a shape which did not fit to the normal blood monocytes, but that's all. Nobody has really carried out labeling, especially with the OKT6 antibody, to prove that these cells are found in blood.

DR. CASLEY-SMITH: I wonder if I could be nasty about cell culture. As I understand it, the average lifetime of an endothelial cell in the body is about 10 years, give or take a year or two. God knows what the average lifetime of the cells in endothelial culture are but they're centainly dividing rapidly so they're switched into quite a different mode. Now we know that granulation tissue has many peculiarities not exhibited by the adult tissue. So I'm saying you have to be terribly careful. If you find lots of actin, for example, what does that mean? During wound healing, the cells have got to rummage around and fight and get out there and do things.

DR. M. WITTE: I think Miles Johnston and I can tell you at least about lymphatic endothelial cells in culture. We talk in terms of months and years for these cells, and the particular cell line we showed you was started in 1984. These cells sometimes go into a quiescent stage. They're sitting in a confluent monolayer. They're not dying; they're just sitting there waiting for something. Sometimes that something is fibroblast growth factor and sometimes it isn't. When you pay attention to them sometimes you can get them to grow, but they also have very long lifespans, at least very long times between their generations.