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INSIDE LAB INVEST

INFLAMMATORY REACTIONS INVOLVE MORE THAN BLOOD VESSELS: The heavy emphasis in recent years on angiogenesis and all of the ways that endothelial cells respond to injury leaves one with the impression that inflammation begins and ends with the cells that line blood vessels, small and large. Not so, point out **Witko-Sarsat and colleagues** in this issue (*Lab Invest* 2000;80:617–653), in their far reaching analysis of how neutrophils function during inflammatory reactions. They begin with a topical review of leukocyte adhesion and migration, and provide many insightful descriptions of this complex process that are often overlooked by reviewers. Topics of this extremely thorough presentation range from phagocytosis, cytokine actions, apoptosis, and different disease processes that involve neutrophils. No one who teaches leukocyte patho-biology to students, at any level, should pass this up.

ENDOTHELIUM AS A TARGET OF LEPROSY: Leprosy is an infectious disease caused by the organism *Mycobacterium leprae.* Much recent focus on this disease has centered on the host immune response, which can vary between two polarized extremes ranging from IFN-γ-dependent granulomatous reactions (tuberculoid type) to antibody-rich, cell-poor reactions (lepromatous type). This focus on the host response has diverted attention from the infectious properties of the microbe. In the current issue of the journal (*Lab Invest* 2000;80:663–670), **David Scollard** reminds us that infection with *M. leprae* primarily involves vascular endothelial cells, and that the proclivity of *M. leprae* to damage nerves may relate to infection of endothelium in epineural blood vessels rather than infection of the peripheral nerves themselves. With this as a starting point, Scollard shows that cultured human umbilical vein endothelial cells, the most widely used in vitro system for studying endothelial function, can be targets of *M. leprae* infection. This simple model may be used to investigate the pathogenesis of tissue injury independent of this immune response.

MICROWAVE VIRTUES EXTENDED The ability to demonstrate antigenic determinants in tissue sections has been greatly enhanced by microwaving the sections before incubation with the antibody. This method of antigen retrieval has now been tested as an enhancer for fluorescence in situ hybridization (FISH). **Kitayama, Igarashi, and Sugimura** have devised a protocol that greatly improves the results of FISH on routinely processed paraffin embedded tissue sections (*Lab Invest* 2000;80:779–781). The effectiveness of the method defined by the group at Hamamatsu University reportedly resides in the use of intermittent radiation to facilitate the hybridization reaction. Ninety-three percent of lymphocytes that have been fixed for 2 weeks yielded normal diploid signals when the new protocol was used. Intermittent irradiation for 1 hour allowed for detection of clear hybridization signals in cancerous tissues that had been fixed for up to 4 hours in buffered formalin. Although the reason for the improved results is not understood, enhancement of intermolecular movement and binding efficiency are likely mechanisms. With the increased availability of probes and knowledge about important loci that are deleted in early stages of neoplasia or during tumor progression, it should be possible to analyze the topography of these events in tissue sections. Clearly, methodology that rends accessible routinely processed and stored tissue blocks can provide invaluable data. By studying large number of cases, perhaps with the help of tissue micro-array technology, complex patterns of microdeletion will be able to be correlated to the natural history, epidemiology, and outcome of specific cases. Presumably this knowledge will contribute to early detection of tumors. Lets indeed hope that intermittent cooking yields the best FISH.

NONIMMUNE FACTORS IN MURINE TYPE I DIABETES: Type I (sometimes called juvenile) diabetes is an autoimmune disease. The process typically begins with inflammation around the pancreatic islets (peri-insulitis), proceeds with development of autoantibodies to islet cell-specific antigens, and culminates in T-cell–mediated destruction of insulin-producing (as well as other) islet cell populations (insulitis). The peri-insulitis stage may be the setting in which autoreactive B and T cells emerge. A widely used animal model for this disease is the nonobese

diabetic (NOD) mouse, which develops a genetically programmed sequence of autoimmunity that includes peri-insulitis, appearance of autoantibodies to islet cell antigens, and insulitis. Some of the genes contributing to autoimmune diabetes in the NOD mouse can be mapped to regulators of the immune system (eg, to specific alleles of Class II major histocompatibility complex molecules) but others are not so obviously related to the immune system. In the current issue of the journal (*Lab Invest* 2000;80:769–777), **Rosmalen and colleagues** seek to examine some of the cellular events that may be controlled by these other "nonimmune" genes. It has previously been noted that two events ordinarily precede peri-insulitis and autoantibody production, namely islet hypertrophy and peri-insular accumulation of dendritic cells, the major antigen presenting cell type involved in the activation of naive T cells. These events could be interpreted as setting the stage for a breakdown in self-tolerance by overproducing islet antigen and recruiting the single cell type best able to sensitize T cells to these tissue-specific antigens. However, it had not been possible to exclude that one or both of these events is actually a consequence of autoimmunity (not yet detectable) rather than a cause. Rosmalen and colleagues take advantage of the severe combined immunodeficiency (*scid*) mutation, which largely ablates the development of T and B cells, to ask whether autoimmune lymphocytes are necessary for islet enlargement or for dendritic cell recruitment. They find that when the *scid* mutation is homozygous in NOD mice, islets still enlarge and dendritic cells still accumulate, albeit at a less impressive level. Thus these events can occur in the absence of autoimmune lymphocytes, solving the chicken versus egg problem. Interestingly, insulin treatment is known to suppress islet enlargement. The next piece in the puzzle might be to see if insulin treatment also blocks dendritic cell recruitment. In any event, the NOD/SCID mice (or even more complete ablation of the adaptive immune system by using a RAG gene knockout instead of the *scid* mutation) should prove useful in dissecting further the interplay between immune and nonimmune factors in autoimmune diabetes.