result of these changes the activated cell is stimulated to divide, thus expanding the population of cells with the desired specificity for antigen.

The new ability to study T-cell receptor function may also help to clarify the role of the thymus gland in T-cell development. Newly formed T cells enter the thymus and there acquire the surface molecules characteristic of T cells in general and of the various subgroups. Several participants in the Pacific Grove meeting reported that formation of the antigen receptor at least begins during the cells' sojourn in the gland. They found that the gene rearrangements needed to join the V, D, and J segments of the β-chain gene occur in thymic T cells. "The rearrangement starts in the thymus," says Tak Mak of the Ontario Cancer Institute in Toronto. "This suggests an inductive role of the thymus on the gene." The α-chain gene apparently rearranges later, however.

One of the many mysteries of T-cell development relates to the requirement that the receptor recognize foreign antigen in conjunction with a histocompatibility molecule, which is essentially a marker that distinguishes "self" from "nonself." The T cell can be activated only by an antigen-presenting cell of the same histocompatibility type but it must not be triggered by the self-marking histocompatibility molecule alone because the result would be an immune attack on the body's own tissues. This implies that there is a way of eliminating, presumably in the thymus, any T cell with a receptor having a high affinity for the self marker. Ellis Reinherz of Harvard's Dana-Farber Cancer Institute has proposed a possible means of achieving this.

He and his colleagues have found that there are two distinct ways of activating T cells, one through the specific antigen receptor and the second through another surface molecule, which is found on almost all T cells and has been given the designation T11. Activation through T11, unlike that through the specific receptor, does not require antigen-presenting cells or interleukin-1, although triggering cells by either pathway induces the calcium ion influx and interleukin-2 production. The T11 pathway is regulated by the specific receptor. Occupation of the antigen receptor makes the cells refractory to activation through T11.

The T11 molecule may be the evolutionary ancestor of the specific receptor, Reinherz speculates. It appears on T-cell surfaces early in the thymic portion of development, before the receptor is formed, and may be important in stimulating expansion of the immature T-cell population. Antigen-specific receptors appear later. Reinherz suggests that if any of these receptors binds well to the self histocompatibility molecules in the thymus, the cells bearing them will be unable to divide because the thymus lacks interleukin-1, which is needed for activation by the receptor pathway. Moreover, they will also become refractory to activation through T11 and will effectively be removed from further action. "This may explain how you can select out T cells with high affinity for self," he says.—**JEAN L. MARX**

Virus-Heart Link Studied

Viruses can produce atherosclerosis in experimental animals and can cause human cells to accumulate cholesterol in tissue culture. Viruses also have been found in human arterial tissue removed during bypass surgery. On the basis of this information, some investigators are persuaded that viruses may be the underlying cause of heart disease in people.

The story of viruses and heart disease began about a decade ago with the discovery by Catherine Fabricant of Cornell University that a herpesvirus that infects cats causes lipids and cholesterol to accumulate in cultured cat kidney cells. "The idea that viruses could induce cholesterol crystals in cell culture made me hypothesize that similar viruses might do the same thing in human cells and might possibly cause atherosclerosis," she says.

Fabricant and her colleagues, including Julius Fabricant of Cornell and C. Richard Minick of New York Hospital–Cornell Medical Center, went on to show that the herpesvirus that causes Marek's disease in chickens causes atherosclerosis in those animals. The virus also alters lipid metabolism in cultured chicken arterial cells, causing an accumulation of cholesterol and cholesterol esters, Fabricant says. More recently, Fabricant found that cytomegalovirus, a human herpesvirus, causes human arterial cells to proliferate and accumulate cholesterol in culture.

For years, however, Fabricant's group worked nearly alone. "I've been considered a crackpot," she remarks, "but now I've gained a little more acceptance." Among the investigators who are looking at her work with renewed interest are Michael DeBakey, Joseph Melnick, and their associates at Baylor College of Medicine and Earl Benditt and his colleagues at the University of Washington School of Medicine.

For the past few years, the group at Baylor has been examining arterial tissue from bypass surgery patients for evidence of herpesviruses. Using electron microscopy, they found that about one-third of the more than 200 patients had cytomegalovirus in their diseased vessels.

Benditt, working with Thomas Barrett and James K. McDougall, also looked for herpesviruses in artery tissue using molecular probes of viral messenger RNA. With that technique he found herpes simplex viruses.

It is not entirely clear what these associations of herpesviruses with atherosclerotic plaques mean. Nearly everyone, at some time, is infected with at least one of the herpesviruses and there is no evidence that heart patients are any more likely to have had a herpes infection than anyone else. But herpesviruses are attractive as a cause of heart disease for several reasons. First, they cause cells to proliferate, "like micro tumors," as Melnick puts it. Then, there is the cell culture work showing that human cells accumulate cholesterol and lipids when they are infected.

In addition, the viruses remain latent in cells after a person has been infected, leaving open the possibility that they can take years to produce disease. Douglas Cines of the University of Pennsylvania, who is intrigued by the viral hypothesis, remarks, "Atherosclerosis begins in young people and develops over decades. Herpesviruses persist in cells in a latent state and are activated periodically. It is possible to imagine that from time to time the virus breaks out and does its thing."

But since herpesviruses are so ubiquitous, it is very difficult to go from an association of the viruses with atherosclerotic plaques to a demonstration that the viruses actually caused the plaques. Still, as Melnick remarks, "We are continuing to put a lot of effort in [to studies of the viral hypothesis]. If we thought it was a blind alley, we would stop."—**GINA KOLATA**