# VASCULAR IMPLANTS' NEW WAVE

BETHESDA, Md.—One may not naturally associate implantable medical devices—such as artificial hearts—with biotechnology, or even biology. And vascular grafts typically consist of inert synthetic materials: in the past, Dacron, and now GoreTex (polytetrafluoroethylene). But this is changing. According to Frederick J. Schoen (Brigham and Women's Hospital, Boston, MA), speaking at the International Biotechnology Conference on Applications to Medical Devices and Perspectives for Future Development held here in March, "the direction of biomaterials development is going from very inert materials that have an absolutely passive relationship with the organism in which they are implanted to materials that have well-controlled active interactions with their host."

Especially for vascular grafts, the trend is towards developing "organoids:" implantable units that consist of a scaffolding (be it GoreTex fibers or collagen) seeded with cells—perhaps genetically engineered to secrete growth hormones—that will proliferate and essentially reconstitute the living tissue for which the graft serves as a substitute.

Why bother? Because biomaterials used in implantable medical devices often cause complications. According to Schoen, thrombosis or thromboembolism is the main complication of cardiovascular devices. As well, devices can cause problems with infection, defective healing, degeneration of the materials, and local tissue interactions. And for cardiovascular bypass surgery, there is a constant problem: according to Allan D. Callow (New England Medical Center, Boston, MA), no matter how delicate the surgical manipulations or how inert the implant, the mere act of insertion and the presence of the implant elicits a continuing reaction to injury by the arterial wall. In its most serious manifestation, this response ultimately results in severe proliferative overgrowth, which in turn can cause secondary thrombosis and occlusion. Adds Alexander W. Clowes (University of Washington, Seattle), hyperplasia of arterial smooth muscle is a major factor in the development of intimal thickening and the failure of vascular reconstructions.

Biotechnological means may aid in solving this problem. "The goal is to find devices that elicit the least degree of biological reaction...[to] identify the cellular and humoral elements that are the product and players in the repair/proliferative response and the ways and means to modulate these many factors," says Callow. In the artificial environment of a graft, adds Clowes, "the rules of [vascular] wall-building go on, even though we provided a synthetic scaffolding." The endothelium is on top, the smooth muscle cells are underneath, as well as "whatever else forms an adventitia." But if there are no platelets—traditionally considered the source of various growth factors—then what drives the process of intimal thickening?

In an attempt to understand the factors behind hyperplasia, Clowes has looked at growth factors and their effects on endothelial cell and smooth muscle cell proliferation. Using a baboon model of intimal hyperplasia in synthetic (GoreTex) arterial grafts, Clowes and his colleagues have shown that perfusates of such grafts, obtained *ex vivo*, contain growth-promoting activity—largely platelet-derived growth factor (PDGF).

Thus, intimal hyperplasia is largely a matter of smooth muscle proliferation. The problem is how to control it. Seeding grafts with endothelial cells might work (the spontaneous regeneration of the endothelium seems to be associated with the cessation of growth); so might direct pharmacological intervention (heparin, calcium channel blockers, and angiotensin converting enzyme inhibitors have all been shown effective in controlling injury-induced smooth muscle cell growth). But perhaps the most alluring way is by local pharmacological intervention—a.k.a. gene therapy. The gene introduced into the endothelial cells might code for a protein that inhibits cell growth, for instance a modified PDGF receptor that lacks activity but still binds PDGF. There would be local expression of the inhibitor, which might affect cells regionally without any systemic effect.

This is the type of approach that W. French Anderson (National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD) has taken. In the vascular implant model being developed in his lab, the implant is a "holding system for cells secreting protein...It consists of scaffolding plus cells plus growth factor plus a biomaterial such as collagen." Anderson's group has developed a GoreTex implant "which the body seems to accept as a 'neo-organ'...It also induces a blood supply and a nerve supply."

—**Jennifer Van Brunt**