Now *in vivo*: Altering endothelial cells

Like the bed of a swiftly moving river, endothelial cells lining blood vessel walls maintain intimate contact with blood flowing throughout the body. Such proximity tantalizes researchers who seek cells they might genetically alter to deliver a steady flow of medication through the bloodstream or secrete chemicals to bust blood clots.

Investigators have already succeeded in inserting some types of genes into the DNA of cultured endothelial cells, causing the cells to secrete the gene's enzyme product *in vitro*. Now, for the first time, two independent research groups report successfully implanting genetically altered endothelial cells into the arteries of live animals. The cells, they say, produced the desired enzyme product.

The researchers chose an enzyme that is easily detectable but cannot treat disease. Nevertheless, they say their work takes a key step toward genetic therapy via the circulatory system. Moreover, suggests James M. Wilson of the University of Michigan Medical Center in Ann Arbor, some of their findings may lead to improved success with small-diameter vascular grafts – often required by diabetics who have damage to small blood vessels.

Wilson and his colleagues at Tufts University School of Medicine in Boston and The Whitehead Institute for Biomedical Research in Cambridge, Mass., used a retrovirus to insert a bacterial gene called *lacZ* into endothelial cells extracted from the blood vessels of seven dogs. They grew the genetically altered cells along the interior of Dacron tubes 4 millimeters in diameter, forming grafts to splice into the carotid arteries of the same dogs. Five weeks later, the researchers stained the cells to reveal beta-galactosidase, an enzyme produced by the *lacZ* gene. They describe their work in the June 16 SCIENCE.

According to W. French Anderson of the National Heart, Lung, and Blood Institute, physicians perform about 350,000 vascular grafts in the United States each year and about 100,000 of these fail, in part because small-diameter grafts tend to clog or collapse. If researchers could alter the endothelial cells in these grafts to produce vessel-dilating chemicals, the success rate might dramatically improve, Anderson suggests.

Wilson says one goal of his research is to lay the foundation for clinical trials of a genetically engineered graft. "We thought a lot about clinical applications in the design of our experiment," he says. But developing a drug-delivery system from endothelial cells may prove difficult even if the basic genetic manipulation is achieved, he adds. "You would need a lot of cells to make a lot of protein .... A [vessel-like] graft may not have enough surface cells; a radiator-like device to increase the surface area may be needed."

In a separate experiment described in the same issue of SCIENCE, Elizabeth G. Nabel and her colleagues at the University of Michigan Medical Center infused *lacZ*-containing endothelial cells into the leg arteries of nine pigs. Upon removing portions of the arteries two to four weeks after seeding them with the genetically altered cells, Nabel found evidence that the cells were producing the *lacZ* enzyme. She terms her nonsurgical technique "complementary" to that of Wilson and his colleagues. "It can be useful to work directly with an artery through the use of a catheter instead of requiring surgery," Nabel notes.

Both Wilson and Nabel say they have begun experiments to determine whether endothelial cells can produce the enzyme for more than a few weeks. And Wilson told SCIENCE NEWS he has recently engineered endothelial cells to produce two other major protein classes – membrane and secreting proteins – in addition to enzymes. Anderson says he and others have begun work on genetically engineering endothelial cells to produce tissue plasminogen activator, a compound that destroys blood clots.

– R. Cowen

Radioactive drugs ease bone-tumor pain

Radiation-emitting chemicals may provide relief for some cancer patients who suffer continuous, toothache-like pain from tumors that have infiltrated their bone. Two of these experimental treatments show impressive success rates and almost no harmful side effects in people whose breast and prostate cancers have spread to bone, researchers reported in St. Louis this week at a meeting of the Society of Nuclear Medicine.

Cancer patients whose malignancies have spread to bone often fail to respond to standard cancer therapies. Physicians usually try to limit tumor growth – and the pain that accompanies it – with external radiation, hormones or chemotherapy, but hormones and chemotherapy may provide no pain relief and external radiation is extremely toxic to normal tissue. Its side effects – which include bone marrow depression, vomiting, diarrhea and lung inflammation – are especially damaging in patients who harbor many small, dispersed bone tumors, says nuclear medicine physician Harry R. Maxon of the University of Cincinnati Medical Center.

Radioactive cancer drugs cause little or no harm to the patient because they can be given in small, intravenous doses, which the body concentrates near bone tumors, says Ralph G. Robinson at the University of Kansas Medical Center in Kansas City. Once at the tumor site, the drugs give off therapeutic beta-particle radiation that travels only a short distance and so does not affect tissue beyond the bone, he explains.

Robinson's team recently completed trials of radioactive strontium-89 – which chemically mimics calcium – on 28 prostate and four breast cancer patients. They found the injections relieved pain for two to three months in 85 percent of the patients, confirming results of European and Canadian studies and those from Robinson's initial studies in U.S. patients.

"We also found that optimum treatment dose is probably somewhat higher than that used in large numbers of patients in the past. We predict from [our new] results that we will achieve greater than a 90 percent response rate with [this] somewhat higher dose with very acceptable bone marrow toxicity," Robinson says. However, a yet-unpublished British study found no significantly better pain response with higher doses, says nuclear medicine specialist Alexander J. McEwan at the Cross Cancer Institute in Edmonton, Alberta. Strontium-89 has now entered a large-scale patient trial in 30 U.S. hospitals in its last phase before FDA approval, Robinson adds.

In the first human administrations of a radioactive compound called rhenium-186-hydroxyethylidene-diphosphonate, Maxon's team found it alleviated bone pain in 80 percent of 28 prostate and seven breast cancer patients. In addition, injections of the rhenium compound produced "very minimal" bone marrow toxicity and no evident toxicity to any other tissue. "So we hope it will be ready for much more widespread use in a couple of years," Maxon says. The rhenium compound concentrates in metabolically active bone because of its attached phosphonate, which bone absorbs, he explains.

Unlike strontium-89, rhenium-186 gives off imageable gamma-particle emissions in addition to beta particles, enabling scientists to monitor the compound's distribution and amount with ease, Maxon says. Rhenium-186 also has a shorter life in the body than strontium-89 and so theoretically could be given in higher doses, which may be more effective for patients with more advanced disease, McEwan says.

Researchers still don't know how the nuclear therapy works to relieve pain, but they believe it acts to shrink or slow the growth of the tumor at its interface with bone. These drugs do not provide a cure, however. The treatment, notes Robinson, "doesn't totally shrink the tumor to nothing and make it go away." *– I. Wickelgren*