Two approaches bolster heart-bypass outlook

Heart-bypass surgery is a modern marvel in which doctors steal a blood vessel from a healthy part of the body and use it to reroute blood around a blocked coronary artery.

If only it worked consistently. More than 360,000 such operations take place yearly in the United States. Within a decade, however, in about half the patients the grafted vessels thicken so as to dangerously impede flow. Patients then must endure clot-busting drugs, vessel-opening procedures via devices threaded to the heart, or more surgery.

Now, two studies suggest other ways that physicians and patients might keep the blood flowing. One line of research employs artificial DNA to discourage a patient's own genes from signaling growth that thickens the walls of the grafted vessels. The other study indicates that revving up blood concentrations of high-density lipoprotein—HDL, or good cholesterol—helps maintain clear bypass vessels.

Studying a type of surgery in which a vein is used to bypass a blocked leg artery, Victor J. Dzau and Michael J. Mann of Brigham and Women's Hospital in Boston use pieces of DNA to shut down destructive growth within the grafts. The artificial DNA interferes with activation of genes that trigger growth of an abnormal tissue layer in the graft. Physicians can monitor vessel grafts in legs with ultrasound, making them easier to assess than heart-bypass grafts.

Of 33 people who had this leg-artery bypass surgery, 17 received a vessel that had been soaked in a solution containing the artificial DNA. Sixteen others received vessels bathed in an inert substance. Roughly half the people in each group were high-risk patients with advanced vascular disease. Patients and their surgeons didn't know which patients received treated grafts.

Over the next year, 11 of the 16 patients receiving untreated vessels experienced blockages that occluded at least three-fourths of the blood flow in the graft. Only 5 of 17 patients getting the DNA-treated vessels had this much clogging, Mann says.

The study "represents the first scientifically collected evidence that patients with cardiovascular disease may actually derive benefit from a gene-based therapy," Mann says. He presented the work at the American Heart Association's 72nd Scientific Sessions in Atlanta this week.

"If this works in the legs, there's no reason why it shouldn't work for the heart," says Valentin M. Fuster, a cardiologist at Mount Sinai Medical Center in New York.

The clogging of the veins often used for bypass grafts occurs in part because they have thinner walls than arteries do, Dzau says. The vessels frequently respond to the arduous role of acting as arteries by adding abnormal tissue, sometimes leading to vascular disease, or atherosclerosis.

When the scientists observed snippets of the vein grafts in a laboratory dish, they found that about 90 percent of the vessel cells responded to the artificial DNA by switching off genes that induce abnormal cell production. Moreover, most of the vessels in these dishes and in animal studies strengthened after the treatment—appearing more like real arteries, Mann says.

In the other study, researchers at the Cleveland Clinic Foundation tracked 432 men who had undergone heart-bypass surgery in 1978 and 1979. Doctors had preserved blood samples at the time of surgery, and they checked the patients' cholesterol every 5 years. After 15 years, men with HDL concentrations that stayed higher than 35 milligrams per deciliter (mg/dl) accounted for three-fourths of the group. These men were 1 1/2 times as likely to have survived as were the participants whose HDL readings fell below that mark, says cardiologist JoAnne Micale Foody, who presented the findings.

In men, physicians consider HDL less than 35 mg/dl to be unhealthy. Exercise can boost HDL concentrations, and there's evidence that the B vitamin niacin and some anticholesterol drugs are also effective

While the precise mechanism at work in these patients is unclear, Foody says the gains may stem from HDL's role in clearing low-density lipoprotein, the so-called bad cholesterol, from the blood. Some studies also indicate that HDL is able to remove inflammatory immune cells that can lead to blood clots in arteries, Fuster says. —*N. Seppa*

HIV-like gene lies buried in human DNA

Scientists exploring the evolution of viruses can't dig into the ground for fossils. Instead, virologists can look inward to the genetic code within their own cells for signs of ancient infections.

As much as 1 percent of human DNA consists of genetic fossils of viruses that once inserted their genes into the genomes of human ancestors. While studying one such viral remnant, investigators have found that a virus that infected primates many millions of years ago used a protein with an uncanny resemblance to one employed by the modern killer HIV.

This unexpected finding may force scientists to rewrite their histories of the AIDS virus and similar viruses because they had considered the HIV protein, named Rev, a recent viral innovation, says Bryan R. Cullen of the Howard Hughes Medical Institute at Duke University Medical Center in Durham, N.C. He and his colleagues report their analysis of the Rev-like protein in the Nov. 9 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

Unlike most viral remnants, rendered inactive by the ravages of time, the one studied by Cullen's group retains several genes that can still make proteins, though they can't produce an infectious virus. Scientists believe that 30 million years ago the virus, which they call human endogenous retrovirus K (HERV-K), first infected the germ cells—sperm or eggs—of Old World monkeys whose descendants include the human species.

By entering the germline, the virus forever established itself in every cell of those monkeys' offspring. Such infections probably occurred a few dozen times over the next 25 million years, given that people have more than 50 different copies of HERV-K in their genome, says Cullen.

Generally considered harmless, HERV-K lies dormant in most cells. In a few tissues, including the placenta, the genes of the retrovirus produce proteins whose effect is not known. For unexplained reasons, certain tumor cells also exhibit high levels of HERV-K activity.

Several years ago, German researchers studying the genes of HERV-K suggested that one of them encodes a protein similar to the Rev used by the AIDS virus. Rev shuttles a copy of HIV's genetic material out of an infected cell's nucleus, a necessary step in the creation of new viral particles.

Because today only HIV and a few other infectious retroviruses have a Rev protein, scientists theorized that it's a recent development in viral evolution. Consequently, Cullen was initially skeptical that a retrovirus as old as HERV-K produces such a protein. His group, however, has now shown that the HERV-K protein, called c-orf, can indeed bind retroviral genes and ferry them out of the nucleus.

Scientists place HERV-K and HIV in different retroviral families. Cullen's finding suggests that an ancient ancestor of the HIV family picked up its Rev through a genetic swap with HERV-K or a related retrovirus.

Alternatively, notes John M. Coffin of Tufts University School of Medicine in Boston, both may have stolen the ancestral gene for Rev from cells they infected. "Studying [retrovirus remnants] has great potential for illuminating the evolution of all viruses, including HIV," he adds. —*J. Travis*