

February 24, 1998

## Injectable Heart Drug Grows Blood Vessels

By LAWRENCE K. ALTMAN

Doctors in Germany have developed an experimental drug that creates new blood vessels and increases the blood supply to the human heart within days after injection, they reported yesterday in an American medical journal.

It is the first time that a drug has led to growth of new coronary blood vessels by mimicking the way collateral vessels naturally develop in some people with blocked arteries. The drug, a protein known as a growth factor, is called F.G.F.-1 (for fibroblast growth factor). The doctors made it with genetic engineering techniques in their laboratory in Fulda, Germany.

F.G.F.-1 was injected into heart muscle near the grafts that surgeons made to create new channels around blocked coronary arteries during standard bypass operations at the Fulda Medical Center. For now, the drug could not replace bypass surgery, the German doctors said.

But they and American experts expressed hope in interviews that with more research, F.G.F.-1 or another drug might be injected directly in the heart without surgery. One idea is simply to inject the growth factor or a similar drug in an arm to find its way to the heart to grow bypasses without surgery. But these experts were divided in speculating whether that could ever be done.

Dr. Thomas-Joseph Stegmann, the head of the team, said the chief objective was to prove the concept that F.G.F.-1 could safely produce new blood vessels in the heart. Although other growth factors are now used safely in medical practice, some experts had warned of dangers with F.G.F.-1. One, Dr. Wolfgang Schaper of the Max Planck Institute in Bad Nauheim, Germany, wrote in 1993 that he doubted that the growth factor would have more than moderate benefit and said "its pronounced toxicity would preclude its use in human patients."

Among the fears were that F.G.F.-1 might worsen heart disease, produce excessive growth of vessels and cause tumors.

"Now we know it works," Dr. Stegmann said.

But because of the way the experiment was designed, the German team could not determine how much improvement was due to the drug and how much was due to the bypass operation, since both were performed at the same time.

In 1993 and early 1994, Dr. Stegmann's team performed bypass operations on 40 men and women 50 years and older who agreed to be divided into two equal groups by random choice. One group received active F.G.F.-1. As a scientific control, the second group received a version made inactive by heat treatment.

Beginning four days after injection, a network of tiny capillaries, the vessels that connect arteries and veins, grew outwardly like the spokes radiating in a bicycle wheel in all 20 F.G.F.-1 recipients. One type of test showed that the new vessels sprouted from existing blood vessels in the injected site, bypassed areas blocked by fatty deposits, and attached to the far end of the damaged artery. The process, angiogenesis, occurs naturally during pregnancy, wound healing and other conditions.

Three months after the injections, another test, X-rays known as angiograms in which a radio-opaque chemical is injected to outline the coronary arteries, showed that no new blockages had developed.

No serious unwanted effects from the growth factor were seen in the 20 recipients, and all are alive, the German team reported in *Circulation*, a journal published by the American Heart Association in Dallas.

F.G.F.-1 has not been patented, Dr. Stegmann said in a telephone interview. If the growth factor proves its mettle in further tests and comes to market, it will be expensive, like other genetically engineered drugs, Dr. Stegmann said. But he said there was no way to put a dollar value on such potential therapy.

F.G.F.-1 is one of several substances that doctors are testing to try to grow new heart vessels. The need for such a procedure is particularly great among patients who have blocked arteries that are not amenable to bypass because they are so narrowed that surgeons cannot sew a vein or artery into them to bypass the obstruction.

Among others seeking to grow new blood vessels in diseased hearts is a team headed by Dr. Jeffrey M. Isner of St. Elizabeth's Hospital in Boston. His team has used a different technique, known as gene therapy, to produce new blood vessels around blocked arteries in legs and is awaiting approval to use the same material (known as V.E.G.F. for vascular endothelial growth factor) in the heart.

At New York Hospital-Cornell Medical Center in New York, Dr. Wayne Isom's team recently started testing gene therapy along with bypass surgery.

In Germany, the patients' heart function improved as measured by a standard test known as the ejection fraction before and after the bypass and drug therapy. The test measures the amount of blood that the left ventricle, the heart's main pumping chamber, expels with each beat and indicates how well it is pumping. An ejection fraction from 60 percent to 75 percent is considered normal, although some doctors lower the limit to 50 percent.

In important details not included in the scientific paper, Dr. Stegmann said the fraction improved in both groups over the last three years. In the one that received F.G.F.-1, it rose to 63.8 percent from 50.3 percent. In the one that received the inactive substance, it rose to 59.4 from 51.5 percent. The statistical difference between the groups was marginally significant, Dr. Stegmann said.

Other experts said they found the findings encouraging, despite the study's small size and limitations.

"Proof of the concept that you can use a protein to create new blood vessels is an important milestone and step" toward developing such molecular therapies for heart patients, said Dr. Victor J. Dzau, who heads the department of medicine at the Brigham and Women's Hospital in Boston.

The German experiment is the latest in a decadeslong quest to find a way to grow new vessels in diseased hearts. In the 1930's, American surgeons sprinkled talc in the sac that surrounds the heart as an irritant to produce inflammation and indirectly improve blood supply to the heart. But the therapy was soon abandoned because it had limited benefit, in part because the inflammation could not be directed to a specific site and the death rate from surgery was high.

The quest has continued even after more recent advances like bypass operations and a technique known as angioplasty in which a balloon-tipped tube is inserted and then inflated to remove obstructions. The reason is that many patients do not benefit from such procedures.

In coronary bypass operations, surgeons use arteries and veins from elsewhere in the body to fashion new channels to restore blood flow around blockages in the coronary arteries to nourish the heart.

Dr. Stegmann said that the new findings grew out of research that Dr. Band Schumacher, a co-author who is a biochemist and a heart surgeon, started in 1991 during a visit to Dr. Tom Maciag's laboratory at the American Red Cross in Rockville, Md.

Dr. Schumacher prepared the F.G.F.-1 in cultures of E. coli bacteria, isolated and highly purified the protein, and then tested it in animals. He said his team learned to grow and purify the protein in large enough amounts when others had failed.

Dr. Stegmann said his team stopped after 20 patients because he wanted to wait for angiograms performed three years after injection of F.G.F.-1 before testing it in more patients. The angiograms are expected to be done later this year.

Then, if all is well, Dr. Stegmann said his team will take the next step: injecting the growth factor without surgery. Injection will probably be through cardiac catheterization, a technique in which a tube is inserted through a vessel in the leg or arm and then guided to the heart.