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Powell, examining a patient who has lost a toe to diabetes, is working on a gene therapy that may help prevent amputations.

HGF may be an alternative to amputation

Don't go barefoot. Don't smoke. Take care trimming your toenails. When prevention tips like these fail, or go unheeded, people with advanced diabetes can face a harsh reality: amputation of their feet or legs.

Diabetes can damage nerves and blood vessels and lead to tissue damage and tissue death, especially in the legs and feet. As a result, if even small wounds go unnoticed and untreated, they can turn into dangerous infections. Sometimes the only treatment for the condition, called critical limb ischemia (CLI), is amputation.

Leg: "These patients have no options left," says Richard Powell, M.D., a DMS vascular surgeon and researcher. "Their quality of life is like a stage-IV cancer patient. They're miserable. Their leg is constantly hurting them. The only way to treat them medically is to give them so much Percocet that it makes them almost unconscious."

Powell and several colleagues are leading three gene-therapy and two stem-cell-therapy trials that they hope may provide alternatives to amputation for patients with CLI. The most promising option involves injecting into a patient's leg muscle a gene that codes for a protein called hepatocyte growth factor (HGF). Once inside the muscle cells, the gene starts pumping out HGF—which in turn promotes the growth of new blood vessels. If the leg and foot can be stimulated to grow new, healthy blood vessels, more blood will reach them and ailing tissue may have a chance to heal.

If the leg and foot can grow new vessels, ailing tissue may heal.

Trial: So far, the treatment has worked splendidly—in rabbits and other animals. It also worked very well in humans in a highly controlled trial in Japan, where the company developing the HGF treatment is located. In that trial, the therapy was so effective at healing patients' leg and foot ulcers that the study was stopped early so participants who were getting a placebo could be given HGF.

In the U.S. trial, however, led by Powell and funded by the Japanese Company, AnGes, the results were not as clear-cut. The treatment "was safe and well tolerated," Powell and his collaborators wrote in the journal *Circulation*. But "there was no difference between groups in secondary end points, including . . . pain relief, wound healing, or major amputation."

Powell suspects the Japanese trial produced such promising results because it set narrower entry criteria for participants and because the participants were hospitalized for the duration of the trial. In the U.S. study, patients had a wide variety of ulcers and were treated at 20 different centers. Because of the variables in the U.S. study, says Powell, "it wasn't a surprise" that the therapy didn't improve outcomes.

Hurdle: But just proving that HGF therapy is safe was a significant hurdle. Any gene therapy that promotes blood-vessel growth has the potential to promote tumors, at least in theory, and so far HGF seems to be avoiding that unwanted side effect.

Powell recently presented the results of the U.S. trial to the Food and Drug Administration (FDA). "You want to get an idea of what the FDA is willing to accept for endpoints and patient population and things like that," he explains. AnGes will soon submit a proposal to the FDA for an 800-patient, multinational, Phase III trial, to start in 2009. Phase III trials are aimed at determining how effective a drug is and are usually very expensive. Powell says a ballpark figure for this one is about $20 million.

Although Powell receives about $10,000 a year in consulting fees from AnGes, he is quick to point out that he holds no stock in the company. He and other DMS faculty have been working with AnGes for several years. Powell says the firm "needs a group of people who can understand the basic science well enough to be able to go to the NIH [National Institutes of Health] and talk about it, . . . but at the same time . . . be able to understand how to set up the clinical trial[s]. . . . It's hard to find that sort of breadth, and that's what we have."

Cost: He admits that if HGF gene therapy becomes commercially available, it is likely to be very expensive. But "if you amputate [a patient's] leg," he points out, "they are going to go to a nursing home. And unless they die within a few weeks, the nursing home stay is going to be super-expensive. . . . If they are already at home, trying to keep them at home [is optimal]. The best way to keep them at home is to keep their leg on. So if you can keep their leg on with a medication [instead of amputating it], it might actually turn out to be pretty cost beneficial."

In addition, when you regularly see diabetic patients who face having a limb removed, it's only human to want to find a better way to help them. JENNIFER DURGIN