

# Sticking it to stubborn wounds

Delivering growth hormone key in new treatment being tested here

By Abram Katz, Register Science Editor (New Haven Register)



The body usually heals wounds all by itself, building a scaffold of proteins and then growing cells to replace the ones lost.

People with diabetes cannot always count on natural restoration. The nature of the disease damages nerves and blood vessels, leading to stubborn ulcers on the lower, load-bearing, extremities.

About 20 million Americans have type I or type II diabetes. The conditions are marked by either an inability to make insulin or an acquired resistance to the hormone. The number of Americans with the disease is expected to double by 2030.

Insulin is made in the pancreas and normally moves glucose from the bloodstream into cells, where the sugar can be metabolized.

Unusually high levels of glucose can affect nerves, resulting in diabetic neuropathy. There are several types of neuropathy. The most common kind is peripheral neuropathy, which causes numbness, tingling and pain in the extremities, and especially the legs and feet.

Pressure from shoes and other objects is not felt, which can lead to sores. Poor blood circulation and other factors can transform a sore into an ulcer that is extremely difficult to heal.

"With bunions or hammer-toe, they cannot feel their feet rubbing against the shoe. People step on needles, glass, pencils, toothpicks," said Dr. Peter A.

Blume, assistant clinical professor of orthopedics at the Yale School of Medicine. Normally, a person impaled on a toothpick would immediately stop and remove it. People with diabetic neuropathy might walk on it for several hours. The result could be a nonhealing wound.

When damage becomes too severe, limbs are amputated. About 100,000 lower limbs of people with diabetes are amputated every year in the United States, and the number is sure to grow.

Current methods to encourage healing include repeated removal of dead or dying skin, placing the patient in a hyperbaric oxygen chamber, and administering antibiotics.

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Conventional treatment can take months. But a novel way of harnessing the cells surrounding ulcers holds the promise of healing these wounds in several weeks. The method also seems to reduce repeat injuries at the same spot.

Blume is among a group of researchers at 25 medical centers testing the new way to close these troublesome lesions. The treatment is called Excellerate and is made by the Tissue Repair Co., a subsidiary of Cardium Therapeutics of San Diego, Calif.

Essentially, the system uses viruses to insert growth genes into skin cells. The Tissue Repair Co. calls this biotechnology "gene-activated matrix," or GAM.

Blume said GAM employs the platelet-derived growth factor gene, or PDGF. PDGF is inserted into adenoviruses in a gel, or matrix.

When the gel is applied to the wound, skin cells migrate through the matrix and encounter the adenoviruses, which insert their genes, including the PDGF stowaway.

Platelet-derived growth factor interacts with the body's immune system, spurring production of skin cells. More specifically, PDGF stimulates formation of blood vessels, a process called angiogenesis, Blume said.

The process helps heal the wound by increasing blood flow, recruiting repair cells and growing new skin.

This is necessary because cells surrounding a wound eventually become senescent, or old, if the lesion does not heal, Blume said. Senescent cells do not divide or interact with other cells, hindering healing. These relatively inert cells also do not clear enzymes that interfere with cell replacement.

Another treatment, debriding wounds — that is removing dead cells — stimulates the immune system into recognizing the wound again, and allowing healing to proceed. Thus, periodic scraping out of the ulcer gradually makes the wound smaller.

Hyperbaric treatment works by saturating the wound and surrounding tissues with oxygen. This also compensates for compromised circulation.

Excellerate is different because it takes control of the skin cells at a genetic level

and makes them grow.

In practice, the engineered adenoviruses are immobilized in a synthetic material. Cells that naturally propel themselves pass through the thicket of viruses, picking up the growth hormone.

In an earlier study of patients with diabetic foot ulcers that did not heal, researchers found that Excellerate is safe and appears to be well tolerated. Twelve patients completed the treatment protocol. Of that number, 80 percent experienced complete closure of previously nonhealing wounds.

The current study is a phase II trial involving 215 patients. It will be randomized and double-blind. If that study shows good results, a larger phase III study would follow. Then, if approved by the U.S. Food and Drug Administration, Excellerate would be put into clinical use.

Mary Gugliotti, 70, of Waterbury is among the patients in the current study. She has had foot ulcers and other wounds for 16 years. One of the wounds has been open for two years despite skin grafts, special pressure-relieving boots, and moisture therapy, Blume said. She sees Blume at his private practice at Affiliated Foot and Ankle Surgeons, in New Haven, periodically for wound debridement.

"I don't get discouraged," she said.

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