Jack and Adele Burns

Saving Limbs, Saving Lives

Multidisciplinary care and translational research advance diabetic wound healing

Boston accountant Jack Burns, 66, values his mobility and independence. But a series of foot ulcers and infections over the last 20 years—a complication of diabetes—have provided an ongoing challenge. Most recently, Mr. Burns developed Charcot foot, a serious condition in which the arch collapses as bones become unstable. By August 2014, this led to an infected ulcer on the sole of his foot.

Foot ulcers are common, affecting 15 percent of patients with diabetes at some point in their lives. Charcot foot, which involves both peripheral neuropathy and inflammation, is particularly tough to treat. As the condition progresses, bones become infected, and amputation of a foot or lower limb may be necessary.

"The traditional cornerstones of treatment for a diabetic foot ulcer involve debridement of necrotic tissue around the wound, applying a cast or some other orthotic device to take pressure off the foot, and treatment to fight infection," says Mr. Burns' podiatrist, Barry Rosenblum, DPM. For a year and a half, Dr. Rosenblum tried one intervention after another, seeking to avoid amputation. "When a wound won't heal, there's got to be a reason," says Dr. Rosenblum. "It was time to bring in a larger team."

A coordinated, flexible approach

BIDMC is a world leader in diabetic limb preservation thanks to a longstanding collaboration by three divisions in the Department of Surgery: Podiatry; Plastic and Reconstructive Surgery; and Vascular and Endovascular Surgery. This comprehensive approach has improved outcomes. Nationally, the success rate for diabetic limb preservation surgery is about 60 percent at 5 years. At BIDMC, the success rate has recently been closer to 85 percent.

"What makes us unique is our multidisciplinary collaboration," says John Giurini, DPM, Chief of Podiatry. "This enables us to do a comprehensive evaluation, develop a treatment plan, review a patient's progress, and change course as necessary." That expertise and flexibility is vital, as Mr. Burns' story demonstrates.

Dr. Rosenblum first consulted with Allen Hamdan, MD, Vascular and Endovascular Surgery. Diabetes damages blood vessels throughout the body, impairing the ability of infection-fighting cells to reach the site of an injury. Under the leadership of Marc Schermerhorn, MD, Chief of Vascular and Endovascular Surgery, BIDMC has emerged as an international leader in minimally invasive revascularization techniques to aid people with diabetes. Dr. Hamdan inserted a stent in Mr. Burns' left leg to increase the flow of blood to his foot.

Dr. Rosenblum next reached out to Matthew Iorio, MD, Plastic and Reconstructive Surgery, who has expertise in microsurgery, hand and foot reconstruction, and limb preservation techniques. "Our goal in limb preservation is to maintain function and patient independence," says Dr. Iorio. "It's not preservation at any cost, but what is best for the patient? How can we maintain a functional, pain-free limb safely?"

"Most patients with diabetes have significant comorbidities, such as heart or kidney disease, and the team takes that into consideration when planning treatment," says Bernard Lee, MD, MBA, MPH, FACS, Chief of Plastic and Reconstructive Surgery.

As it happens, Mr. Burns had already undergone a kidney transplant at BIDMC, which could complicate his recovery from limb preservation surgery. His diabetes raised risk of infection. Two other members were added to the team: Martha Pavlakis, MD, Nephrology, who was Mr. Burns' transplant doctor, and Simi Padival, MD, Infectious Disease, who has treated Mr. Burns for years. Both provided critical know-how.

"It was a real coordinated effort," Mr. Burns says. "Everyone was brought in from the beginning. I knew I was in good hands."

Operating in stages

"One of our major concerns is preventing a resurgence of infection after an operation." says Dr. Iorio. "We operate in stages, so that we can make sure we have a clean margin of healthy tissue before closing the wound."

First Dr. Rosenblum debrided Mr. Burns' wound to remove diseased tissue. Four days later, after pathology results indicated that the wound and bones were free of infection, Dr. Iorio performed an anterolateral thigh flap. He transplanted a section of skin and blood vessels from Mr. Burns' thigh to his foot, to cover the wound and enable it to heal. Mr. Burns then underwent a second operation to improve circulation to his foot.

"I went home on April 15," says Mr. Burns. "From then until Labor day, I could not put weight on my foot." He used a knee walker to get around and keep pressure off his foot as it healed.

Today he is able to walk on his own. He wears an orthotic leg brace and shoe to redistribute weight and take pressure off his foot. "The ulcer is completely healed," Mr. Burns says. "I've had no complications, no infection. I couldn't be happier." He and his wife Adele have two daughters, Michelle and Janine, and just welcomed their fourth grandchild into the world. "The baby was born at BIDMC," says Mr. Burns. "It's a great hospital."

Jack Burns discusses his recovery with podiatrist Barry Rosenblum, DPM, at a follow-up visit.

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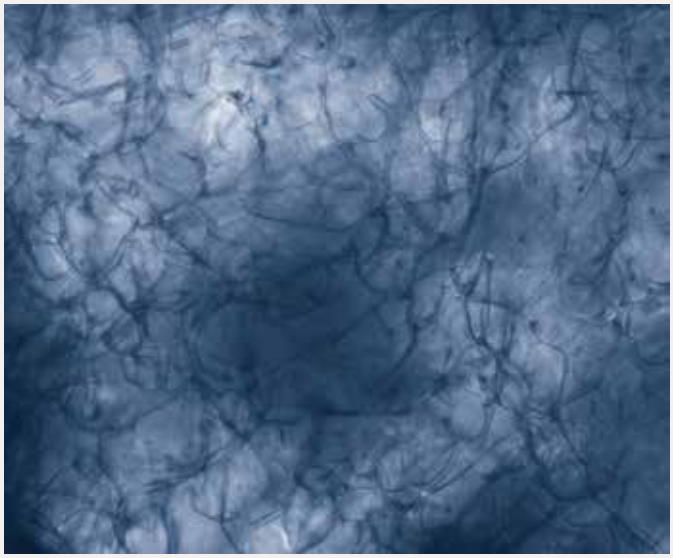
On the horizon: tissue regeneration

Aristidis Veves, MD, DSc, Director of the Rongxiang Xu, MD, Center for Regenerative Therapeutics, is leading the effort to find new options for saving limbs—ideally by coaxing the body to heal foot ulcers on its own. He is collaborating in this quest with two research colleagues from Vascular and Endovascular Surgery: Frank LoGerfo, MD, and Leena Pradhan-Nabzdyk, PhD.

Wound healing is complex and dynamic. Normally it involves three coordinated and overlapping phases: acute inflammation; cell proliferation and tissue regeneration; and tissue remodeling.

Drs. Veves, LoGerfo, and Pradhan-Nabzdyk have published a series of ground-breaking studies over the past few years which found that many people with diabetes have systemic chronic inflammation—similar to what is found in people with metabolic syndrome and cardiovascular disease—even before they develop a foot ulcer. This low-grade inflammation impedes the normal process of healing. In essence, the healing process gets "stuck," and cannot progress to the tissue rebuilding/remodeling phases.



A microscopic view of an alginate hydrogel bandage, one of the biomaterials now under development to improve wound care. (Image courtesy of Ting-Yu Shih, Harvard University.)

The team wants to find a way to convert chronic inflammation into acute inflammation—thereby kick-starting the normal healing process. To do so, they are investigating multiple agents simultaneously: neuropeptides, growth factors, and other molecules.

"We're looking at Substance P and Neuropeptide Y because they affect the functioning of both nerves and blood vessels," says Dr. Pradhan-Nabzdyk. "We know that neuropathy and vascular disease both contribute to problems in healing."

For instance, in one study, they found that substance P could improve wound healing in mice with diabetes. In another animal study, they found that an asthma medication, disodium cromoglycate (DSCG) helped stabilize mast cells, a type of immune cell, and can also enhance healing.

Dr. Veves and Lijun Sun, PhD, Director of the Center for Drug Discovery and Translational Research at BIDMC, have collaborated to develop a mast cell stabilizer suitable for topical use. Experiments in animal models show that it is just as effective as injected DCSG. With funding, the next step will be phase 1 and 2 studies in people.

Drug delivery systems are always a challenge in wound healing. The team is also collaborating with David Mooney, PhD, of the Wyss Institute for Biologically Inspired Engineering, to develop extended-release bandages made of alginate, a polysaccharide obtained from algae, and other biomaterials. "The healing process evolves over time," says Dr. Pradhan-Nabzdyk, "so an extended release delivery system is essential."

"This is truly translational research," Dr. Veves says. "We start with observations in patients with diabetes, we go back to the laboratory and come up with new options, and then we test them in animal models of the disease. Our ultimate goal is to find ways to intervene early to restore the normal healing process in people."

The support of the National Rongxiang Xu Foundation has been enormously helpful. "The Xu family's visionary support of this research is making regenerative therapy for diabetes a real possibility," Dr. Veves says.