Healing wounds

Closing the gap

By Elizabeth Devitt

The first time David Kaufman saw a hyperbaric chamber he thought it was the scariest thing he'd ever seen. Although the machine didn't look especially frightening — a clear-walled cylinder with enough room for a long bed and a view of a personal movie screen — it was the last stop in an eight-month effort to heal a stubborn foot wound. If this treatment didn't work, he might lose another toe. Or maybe even his whole foot. The chamber represented the only thing between him and amputation. That scared him a lot.

"It did take some getting used to," says Kaufman about the treatment chamber. "You're all alone once they slide you in and lock the door. Then your ears start to ring when the pressure changes and they add the oxygen."

(img/article-wound.jpg)

Illustration by Harry Campbell

Although the hyperbaric chamber treatment was designed to save deep-sea divers from a deadly condition called the bends, it can help landlubbers too. By running pure oxygen in the chamber — room air is mostly nitrogen and has only about 21 percent oxygen — more oxygen gets into the bloodstream and delivered to the rest of the body.

Getting old wounds to heal is a big problem. In the United States, about 6.5 million patients suffer from persistent wounds — from bedsores to burns. Experts anticipate those numbers will only rise as the three major demographic groups that suffer from non-healing wounds are also expected to grow: people who have diabetes, are obese or are over 65. More than $50 billion — at least 10 times the yearly budget for the World Health Organization — is estimated to be spent annually on managing wounds, according to an analysis of data from the U.S. Wound Registry. Most of the treatments, like the hyperbaric chamber, have been in use for decades.

"The problem with wound healing is that it's been a backwater of medicine — a lot of snake oil and poultices — with no evidence-based medicine," says Geoffrey Gurtner, MD, a professor of surgery at the Stanford School of Medicine. But that appears to be changing. Wound healing as a medical specialty and as a subject of medical research is coming of age. Ironically, the old-fangled hyperbaric chamber is part of the reason that change is coming.

Throughout the United States, wound-care centers are popping up, with about 1,500 of these treatment centers nationwide. Housing technology like hyperbaric chambers and a spectrum of

specialists — from surgeons to infectious disease experts — these centers give patients a place to get comprehensive care for wounds. Revenue more than tripled over three years for Healogics Inc., which operates 540 wound-care centers across the country: from $75.4 million in 2009 to $271.5 million by 2012. Bellevue, Wash.,-based Accelecare has opened about 25 new wound-care centers every year, going from zero to 120 since launching in 2008, says Thom Herrmann, senior vice president of business development. Still, there's room for more: Only about a third of U.S. hospitals have a physician-led wound-care center, according to Jeff Nelson, president of Healogics.

In September, Stanford plans to open its own wound-care center, including a hyperbaric chamber — in partnership with Healogics. Stanford physicians will provide care while the company provides business management expertise and services such as hyperbaric equipment, staffing and training. But unlike most wound-care centers, Stanford's will be a site not only for care but for research and training.

The front lines of wound care and research focus on diabetics like Kaufman because long-standing diabetic ulcers are the most common, most expensive and most notoriously difficult wounds to heal. "For many diabetic patients the medical clinic is a revolving door," says Ronald Dalman, MD, chief of Stanford's Division of Vascular Surgery.

The more doctors understand how skin heals — or doesn't — the better they'll be able to help people having trouble recovering from wounds, such as cancer patients getting radiation therapy or burn victims. If the hardest-to-heal wounds can be improved, then those benefits will trickle down to everyone else.

Skin repair keeps us whole

When the skin is injured — whether by accidental trauma, surgical intention or illness — the body usually ramps up to start healing immediately. A call to arms signals the start of an orderly process involving all sorts of cells that guide an influx of new blood vessels, tamp down infection, build the scaffolding for new skin growth and ultimately lay down a new barrier to the outside world.

If our skin is working, it's a multilayered shield that can mend any chink in our armor. But when the skin's healing ability goes awry, it can put the health of our whole body at risk. Unresolved wounds are a breach in the body's defense system: a painful portal for infections that can invade the rest of the body — sometimes with life-threatening consequences.

No one appreciates that fact better than Kaufman, who has dealt with diabetes for 20 years. When glucose stays too high in the bloodstream, it blocks skin cells' ability to repair themselves and weakens the white blood cells that fight off infections. That slow healing coupled with poor circulation and loss of a sensation in the lower legs — two other common problems with diabetes — can lead to the loss of toes, feet or even limbs. Diabetes is the reason behind most leg amputations in the United States, and foot ulcers are a big, red warning flag. These wounds presage more than three-quarters of diabetes-related amputations, according to the American Podiatric Medical Association.

Kaufman, 62, never had a problem with wounds until he suffered a stroke in 2009. Then he lost much of the movement on his right side. With less activity, ulcers started showing up on his left foot, prompting his podiatrist to refer him to a surgeon. "But the first surgeon wanted to take off all my toes right away," says Kaufman. He'd already lost one toe from a previous infection and the surgery was intended to save the rest of the foot. "I was only having trouble with my pinkie toe then. So that didn't sound like such a good idea." The next physician he met was Dalman, a man Kaufman credits with

keeping him on his feet.

New ways to heal needed

To stave off surgery for a toe amputation, Kaufman first underwent a successful procedure to improve blood flow to his foot. Then Dalman recommended a series of hyperbaric treatments — at a non-Stanford site, as Stanford had no such facility at that time. Using multiple approaches is often essential to manage complex wounds, says Dalman. The high-oxygen treatment was the last little push toward healing that Kaufman needed, but it isn't an option for everyone. With chamber pressures that hit more than twice the normal atmospheric pressure, patients with congestive heart failure or lung disease would fare worse than their wounds. Newer treatments have been developed, such as skin substitutes and using suction to improve circulation, but more is needed.

"It's like the early days of infectious disease where simple hand washing went a long way to prevent disease, but people still needed antibiotics. We're in the same place with wound healing with diabetics; we tell people to watch their feet so we can catch ulcers in the early stages, but they still get chronic wounds that need treatment," says Gurtner.

Spurred by the plight of burn patients with debilitating scars, Gurtner first took a surface approach to the problem of wounds: He wanted to help people heal without thick scars. After studying the problem with biomechanical engineers, Gurtner led a team that developed a "stress shield" to reduce surgical scars. Since tension drives the skin to lay down thicker tissue, they designed a device to keep tension from pulling on the wound's edges. Although the technique works well for some patients, such as those with surgical incisions, it didn't help the burn patients. But it was a step in the right direction.

'Why would the same DNA heal without a scar when you're in the womb and then heal with a scar for the whole rest of your life?'

To find new ways of preventing scars, Michael Longaker, MD, director of the Stanford Program in Regenerative Medicine, dug deeper under the skin for answers. His work is driven by one of the major mysteries of skin healing: In the womb, we can heal without scars — right up until the third trimester. "Why would the same DNA heal without a scar when you're in the womb and then heal with a scar for the whole rest of your life?" he asks.

That question focused his attention on stem cells — the cells that are blank slates until called to do a more specialized job, such as becoming a cell that makes up bones or heart muscle. Or scars.

"Maybe the rapid restoration of tissue — a scar — was an advantage if it kept you from bleeding to death or being eaten by a saber-toothed tiger," says Longaker. "But scar tissue isn't always good. If we can figure out how to knock down the cells that make scars but still recruit cells that make blood vessels, then we could have scarless healing."

It takes blood to heal

Blood vessels are the pipelines through which all sorts of growth factors show up and start rebuilding after a skin defect. But injuries can destroy blood vessels.

So Longaker, Gurtner and a group of their Stanford colleagues tried another approach to getting those growth factors where they were needed: stem cell sponges. These hydrogel matrices were made

to act just like the skin of a developing fetus. They look like a dry wafer, but can be rehydrated with a fluid containing stem cells, and then added to the wound.

Early test results show these hydrogels accelerate wound healing. Now, the researchers are figuring out the best source of cells: fat, bone marrow or other sources. In the next round of clinical trials, in which Gurtner hopes to start enrolling patients before the end of this year, the hydrogel matrices will be tested on diabetic foot ulcers.

But ultimately these stem cell sponges are intended to help heal any chronic wound. It could be the perfect personal bandage if Gurtner's team learns how to seed the hydrogel with whatever type of tissue needs regrowing. Skull wound? Add early bone cells. And some types of cells might be guided to become other types. In the right matrix, for instance, fat cells (which have the advantage of being relatively easily accessible) might be persuaded to become new cardiac cells.

It may sound like a far-fetched treatment plan but the underlying science is compelling enough for the Department of Defense to fund some of this research. "It only makes sense," says Gurtner. "More of our soldiers are coming home wounded. In World War II, three were wounded for every one lost in battle. In Afghanistan, 13 soldiers are wounded for every one killed."

Researchers around the country are trying other strategies to rebuild blood vessels. On the other side of the country, Robert Kirsner, MD, PhD, vice chair of dermatology and cutaneous surgery at the University of Miami Miller School of Medicine, is studying a spray that delivers blood vessel and other growth factors directly on the wound surface — sort of like spreading fertilizer to get a healthier lawn. With this foaming gel, a combination of keratinocytes from the top layer of skin and fibroblasts from the layer below it, early studies showed that patients with venous leg ulcers healed an average of three weeks faster than those treated by standard care.

"The stakes are high," says Kirsner. "For some of the chronic wounds we treat, if we fail to heal these ulcers then patients have close to 50 percent mortality in five years — that's worse than the rates for someone with breast cancer."

Outside help

It isn't just physicians who are taking up the challenge of helping wounds heal. Interdisciplinary teams of engineers, chemists and other specialists are also creating new technologies to help skin that can't readily heal itself.

At Vanderbilt University in Tennessee, Craig Duvall, PhD, an assistant professor of biomedical engineering, is taking an approach that could be called "the enemy of my enemy is a friend" technique. He collaborated with chemical engineers and a pathologist to develop a spongy scaffold filled with small molecules that order wound-area cells to shut down production of an enzyme that blocks blood vessel growth in chronic wounds.

In normal wound healing, a molecule called HIF1-alpha helps trigger the growth of blood vessels when there isn't enough oxygen getting to cells. But HIF1-alpha is thwarted in the oxygen-depleted tissue of chronic wounds by an enzyme called PHD2. With fewer blood vessels, the skin defect is left without a way to get the repair factors and cells that it needs to heal.

When Duvall injects the foamy scaffold onto wounds, a steady trickle of small interfering RNA molecules work their way into wound cells and stop PHD2 production, giving HIF1-alpha a chance

to go back to work and help blood vessels sprout again. “We stop the negative feedback loop that impedes wound healing,” says Duvall.

Someday, scientists might just print a new patch of tissue to heal those wounds. A Harvard University team led by materials engineer Jennifer Lewis, PhD, took the first step by printing a three-dimensional tissue scaffold — complete with blood vessels.

Lewis and her colleagues used a 3-D bioprinter, a hulking custom-built machine that resembles a 2-ton version of an old-fashioned laser printer. The printer uses four “inks” that progressively layer a silicone-based outer border, an inner matrix with two kinds of skin cells called fibroblasts, and an interwoven vascular network that can be lined with living cells, to create three-dimensional tissues.

“We’re nowhere near the goal of making fully functional living tissue,” says Lewis. “But these vascularized tissue constructs represent a foundational step.” As a materials scientist, Lewis says it was a grand challenge to apply her background to create living things. Although she’s creating a new kind of toolbox, she’s quick to point out that scientific advances like this take expertise “on both sides of the aisle.”

Prevention is the best medicine

Improved methods for healing wounds would be wonderful, but preventing them would be even better. Along with other Stanford scientists, Gurtner is working to stop diabetic ulcers from developing in the first place. His group is repurposing a drug called deferoxamine, or DFO, already approved by the Food and Drug Administration for treating diseases that cause a toxic overload of iron in the blood. When a DFO-treated bandage is applied to the at-risk skin on a diabetic’s foot, it improves the skin condition — making it thicker and maintaining blood vessel growth.

But more research trials are needed before these new treatments are prescribed for patients. “Ultimately, the answers will be found in the clinics,” says Gurtner. It will be easier to get those answers at Stanford’s new wound center.

“Patients are realizing that wound care is very specialized,” says Subhro Sen, MD, clinical assistant professor of plastic and reconstructive surgery and co-director of the new center. When people cut a finger, they head for an emergency room or their primary care doctors. But if treatment is needed for chronic wounds, patients end up seeing a number of different specialists. “Now we’ll be able to give focused, multidisciplinary care. Instead of making multiple appointments at separate locations to see surgeons, get tests and consult with other specialists, patients can get that care all under one roof.”

That’s something Kaufman says he would have appreciated when he was making three-hour round trips from his home in Dublin, Calif., to see Dalman and the other doctors on his team at Stanford, plus twice-weekly journeys for hyperbaric oxygen therapy even farther afield. And while he’s happy that Stanford’s getting a wound treatment center, he’s hoping not to visit anytime soon. Wound-free for almost two years, Kaufman would rather spend his time taking long trips with his wife — like the round-the-world journey he was recently able to make, taking in the sights on his own two feet.

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A look at the deep friendship that formed between Stanford surgeon Leo Eloesser and painter Frida Kahlo.

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A common phobia's odd pathophysiology (http://sm.stanford.edu/archive/stanmed/2013spring/article6.html)

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