The POWER *of* HEALING

DERMATOLOGISTS BREAK NEW GROUND IN THE TREATMENT OF WOUNDS AND SCARS

BY **JAN BOWERS,** CONTRIBUTING WRITER

Never has the need for effective approaches to treating skin wounds and scars been greater. "We now have a 98 percent survival rate for our wounded warriors and our civilians who are burn and trauma patients," said Jill Waibel, MD, medical director of the Miami Dermatology and Laser Institute as well as clinical voluntary professor at the University of Miami. "It used to be that many of those patients would die. But just in the past 10 years, we've been encountering injuries that we had never encountered before." At the same time, an aging U.S. population is driving up the incidence and burden of chronic non-healing wounds; a fact sheet from the Association for the Advancement of Wound Care (**https://aawconline.org/wp-content/uploads/2015/10/Fact-sheet-1-final_May-2014.pdf**) points out that 4.8 million Americans have a skin wound or ulcer — more than those living with breast, colon, or lung cancer and leukemia combined — and chronic wounds cost $12 billion annually in direct and indirect costs.

Dermatologists have stepped up their role as wound care experts by advancing research and utilizing new tools to support the healing process.

- New devices for skin grafting are reducing damage at the donor site, while new research points to the importance of grafted hair follicles in stimulating the wound-healing response.
- Ablative fractional lasers are being used to treat old and new scars, to prevent scar tissue from forming, and to kick-start the healing process in chronic wounds.
- Cell- and tissue-based products (CTBs) promote tissue regeneration and wound closure in wounds where the healing process has stalled. >>

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Skin grafts

Two novel and very different approaches to skin grafting, both developed at the Wellman Center for Photomedicine at Massachusetts General Hospital, are proving effective at stimulating healing while minimizing pain and scarring at the donor site.

A device for epidermal micrografting, marketed as the CelluTome Epidermal Harvesting System (Acelity), uses suction and heat to create an array of micrografts, or blisters, in the epidermis. After a film dressing is placed on the micrografts, the physician swaps out the suction head for a disposable component containing a cutting blade, harvests the micrografts, and places the graft on the recipient site. "CelluTome is used now routinely in wound care centers," said the inventor of the technology, R. Rox Anderson, MD, professor of dermatology at Harvard Medical School and director of the Wellman Center. "I started using it for vitiligo, but the company took it to the chronic wound market. It's now being used for diabetic ulcers, some burn wounds, and pressure sores. For some conditions, such as segmental vitiligo, this treatment is probably a cure. Another important application is in treatment of blistering diseases such as epidermolysis bullosa."

Dr. Anderson's work with epidermal grafting prompted him to reflect on an alternative strategy for grafting; ideally, one that would utilize the full thickness of the skin, replete with hair follicles and sweat glands. Armed with a grant from the Department of Defense, he pursued the concept of "skin copying," or recreating live skin, with minimal damage to the donor site. Considering that needle sticks heal with no scar, Dr. Anderson's team developed a device with an array of more than 300 tiny needles that enter the skin simultaneously and remove full-thickness columns of skin. "We harvest a lot of skin in a hurry," Dr. Anderson noted. "In about 10 seconds, the device will harvest a 10-square-centimeter area, and you can do this over and over. So if I have a 100-square-centimeter wound, I could graft that in an operation that doesn't last more than five to 10 minutes." While traditional graft methods can create large second wounds at the donor site, the area from which the needles have harvested "is red for a while, but a few months later you can't even find it."

Each needle contains a wire that works like a piston to eject the column of skin into the wound bed. "It spits them out and scatters them on the wound," Dr. Anderson explained. "What was surprising to me was that the skin columns don't have to be right side up. If you throw them into a well-prepared wound bed, the columns reorient themselves; the dermis and epidermis figure that out and go about making real skin, a process that takes several weeks." Clinical testing is still in progress, but Dr. Anderson said the device is showing promise in the treatment of surgical wounds, and added that wound centers testing a prototype have reported "pretty good" results with chronic wounds. A study of its effectiveness in treating burns in children will be launched at the Boston Shriners Hospital, and the strategy is in the early stages of testing on radiation therapy burns at Mass General. The technology is being commercialized by SevenOaks Biosystems under the trademark ART™ (Autologous Regeneration of Tissue); Dr. Anderson said he expects it to be available to clinicians this summer.

The concept that autologous skin grafts act as pharmacologic agents to aid wound healing isn't new, but researchers are constantly seeking to optimize that function. "The latest is the idea that from certain locations, the graft may be a better pharmacologic agent, and one of the best may the hair-bearing areas, for a variety of reasons," said Robert S. Kirsner, MD, PhD, chair of dermatology at the University of Miami Miller School of Medicine, director of the University of Miami Hospital Wound Center, and chief of dermatology at the University of Miami Hospital. In a recent case study published in *Wounds* (2016;28(4):109-11), Dr. Kirsner's group described a side-by-side comparison of punch grafts of hair-bearing vs. nonhair-bearing skin in the treatment of a venous leg ulcer, measuring 59.3 square centimeters, in a 60-year-old man. A third area served as a control and received no grafts. After 6 weeks, the total wound size had decreased by 73 percent, with the greatest improvement seen in the area receiving the hair-bearing grafts, where the wound size decreased by 91 percent.

"It may be that the hair follicle has a superior drug delivery system; it may be better at sending out growth factors, cytokines, and other agents that help the wound heal," said Dr. Kirsner. "Our data was recently confirmed by a Spanish group publishing in the *Journal of the American Academy of Dermatology* [2016;75:1007-14]. The idea here, in the long run, is that if we can understand that some skin is better than other skin, we can begin to study the differences in those two locations and maybe eventually, we won't even have to use skin but we can use things the skin produces to stimulate healing."

The punch graft technique, epidermal grafting, and the needle harvesting graft all fall into the category of "low-risk" skin grafting technologies that are coming to fruition, Dr. Kirsner asserted. "These techniques and tools make skin grafting a lot easier and more practical for the average dermatologist. They also broaden the applications for grafting, because if it doesn't work the first time, you haven't spent thousands of dollars and created a donor site that takes a long time to heal."

Fractional lasers

The fractional laser — another product of Dr. Anderson's work at the Wellman Center — has become a mainstay of cosmetic dermatology, particularly in the area of facial rejuvenation. In addition, "we have found that the laser is amazing for scars. It heals the scar to almost normal skin," said Dr. Waibel.

Drs. Anderson and Waibel are two of eight experts in the treatment of traumatic scars who came together over a two-day period in 2012 to hash out a consensus on the evidence supporting laser treatment as scar therapy and develop a laser scar treatment algorithm. "A group of us had been working with wounded warriors for seven years, and lecturing military doctors, and people kept asking us, 'How do you do this?'" noted Dr. Waibel. "We realized we really needed to write an extensive paper to show what we've learned." The resulting consensus statement, which emphasizes the ablative fractional laser, was published in *JAMA Dermatology* (2014:150(2):187-93). While citing the need for prospective studies of specific scar types, the authors maintain that "early clinical results suggest that traumatic scars of virtually any origin will respond to ablative fractional laser therapy."

Another powerful motivation to gather the experts together, Dr. Waibel said, was the lack of reimbursement for treating scars with lasers. "It's maddening that we have a laser that can help a child who is burned head to toe in a fire, and the parents' insurance won't cover it. The active military personnel get their treatment covered in a military hospital, but once you're a veteran you don't have access to it. We are treating the wounded warriors pro bono right now and many still don't have access." Obtaining a reimbursement code requires a wealth of supporting evidence, including randomized controlled trials; Dr. Waibel said the consensus paper can serve as a "gourmet cookbook" that "leads you down the path" of greater utilization and further research. "The fractional ablative lasers are safe to treat scars, however before a dermatologist uses this laser there needs to be an understanding of scars, and laser-tissue interaction is recommended."

A recent development in Dr. Waibel's approach is beginning laser treatment earlier. "When I first started doing this, the reconstructive and burn surgeons told me to wait 12 months after an injury before treating the scar with a laser," she said. "They wait 12 months to do surgery. We don't recommend treating if there is an infection, or an erosion. But once the epithelium has covered the burn, it's safe to start lasering. I just finished a two-year clinical trial with acute burn patients, and I've been doing this in clinic for about five years. We can really change the course of that scar." Treating burn and trauma scars with lasers is happening around the world. Dr. Waibel expressed the hope that residents and young dermatologists will join the research effort because "we really do need to contribute to the science and to the understanding. We say we're physicians, not magicians, but this is the closest we can come to waving a magic wand to help these patients."

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The fractional laser's ability to stimulate tissue healing through thermolysis prompted another dermatologist to try it on a small group of elderly patients with posttraumatic wounds that were slow to heal. Tania J. Phillips, MD, professor of dermatology at the Boston University School of Medicine, treated three patients with the ablative fractional laser; two had lower-extremity ulcers resulting from Mohs surgery, and one had suffered a degloving injury to her foot in a car accident. "We did find that with one treatment of the CO2 fractionated laser, that it did seem to jump-start the healing process," said Dr. Phillips. "They healed pretty rapidly after that." Her theory as to why the laser seems to work centers on the differences between acute and chronic wounds. "We think, basically, the laser creates an acute injury that fools the chronic wound. In acute wounds, there are enzymes that speed the healing process; in chronic wounds, there are enzymes that actually degrade some of the proteins that are trying to heal the wound. And in acute wounds, the cells replicate; in chronic wounds, the cells behave like elderly, senescent cells."

Skin substitutes

The array of materials manufactured and/or processed to serve as wound coverings that promote healing are now collectively referred to as "cell- and tissue-based products, or CBTs" according to Dr. Kirsner. "That's an all-encompassing term for cellular products, engineered products, matrices," he said. "Usage has been driven by reimbursement, and for the past couple of years there's been favorable reimbursement for amniotic and placental membranes. That's the latest trend in wound healing from a skin substitute standpoint. Most of the studies that have been done for these tissue-based products have been in diabetic foot ulcers."

CBTs can be cellular or acellular products, and can be sourced from animals, humans, plants, synthetic materials, or a composite, explained another prominent wound care expert. Gary Sibbald, MD, professor of medicine and public health at the University of Toronto, said the cellular products, so called because they contain living cells, have a brief shelf life. Once placed on a wound "the cells probably die over three or four weeks, but during that time they may be able to produce enough growth factors to promote wound healing and get people over a hump." Acellular products provide a matrix into which a patient's own cells can migrate; they undergo processing that removes all living cells and leaves the extracellular matrix intact. Cellular products are more costly than acellular, and carry a higher risk of infection, Dr. Sibbald said.

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Comparing the effectiveness of the two types of products is problematic, Dr. Sibbald said, because they are likely used in different clinical scenarios. "Probably the cellular is more appropriate when you are at the very end of the healing process and you're stalled, whereas an acellular matrix might set down the dermal tissue for cells to migrate in, then build a better dermal base for the healing process. So you may very well look at the acellular product earlier on."

CBTs are appropriate for "stalled but healable wounds," such as diabetic foot ulcers, Dr. Sibbald said. "A healable wound means you have enough blood supply, and you've corrected the cause." He noted that they should be considered part of a toolkit that also includes lasers, skin grafts, electrical stimulation, ultrasound, and "active dressings" — wound dressings that contain or release growth factors. Before these advanced therapies are used, however, proper preparation of the wound bed is essential, Dr. Sibbald insisted. "That's making sure there isn't secondary infection, either in the surface compartment or in the deep and surrounding tissue; performing debridement; and achieving moisture balance." In addition, "you have to address the cause, or it's all for naught. Finally, you have to look at patient concerns like activities of everyday living, do they have a support system, can they get to appointments, can they feed themselves. A common saying is that you have to look at the whole patient and not just the hole in the patient." ***dw***