'Cotton candy' that heals?

Borate glass nanofibers look promising.

by Peter Wray

(Credit: The American Ceramic Society)

In late summer of 2010, registered nurse Peggy Taylor suddenly saw some longed-for signs of healing in a nasty shin wound in one of her patients with diabetes. Just a few days before, Taylor had done to the patient something that she and no one else in the world had ever done in wound care before: She had filled the wound with a material that could have been mistaken for cotton, but was in fact specially processed borate glass fibers.

Taylor, a wound-care specialist for more than four years, had been used to dealing with wounds that healed at slow and nearly imperceptible rates. But when she and the patient – who also happened to be a nurse – noticed the edges of the large, deep, stubborn wound had finally started to slope inwards, they were the happiest they had been in a long time.

"That was the first sign of healing," she said in an interview in late March. "It began as a 50 millimeter by 30 millimeter wound that was 3 millimeters deep. That was the day she really began going down the road to healing. Now, after using the glass fiber treatments for week after week on the wound, it is essentially gone."

And when Taylor says "gone," she means something close to "vanished." Not normal scarring, certainly. "It's amazing. There is so little scar tissue there, if I didn't know the wound was there, I'd have no idea," she claims.

This doesn't appear to be a fluke. Taylor, a certified Wound, Ostomy and Continence Nurse on the staff of the Phelps County Regional Medical Center (Rolla, Mo.), says that seven other patients participating in trials being conducted by PCRMC have had similar results with the glass fiber treatment. She says, in total, 12 patients are in the trials and the four who still have wounds are making progress, too.

Venous stasis creates hard-to-heal wounds

The history of Taylor's patient's wound is typical for a diabetic. "It started out as a bruise on her shin," she says. "It was the kind of thing where the patient said, 'Ow. It really hurt a lot, but I am glad I didn't break my leg.' It took awhile before she or anyone else realized there was a more extensive and deep-tissue injury there. In fact, it was a deep hematoma that eventually opened. It looked like a big number '6' and if it weren't for the debris in the wound, I would have seen bone."

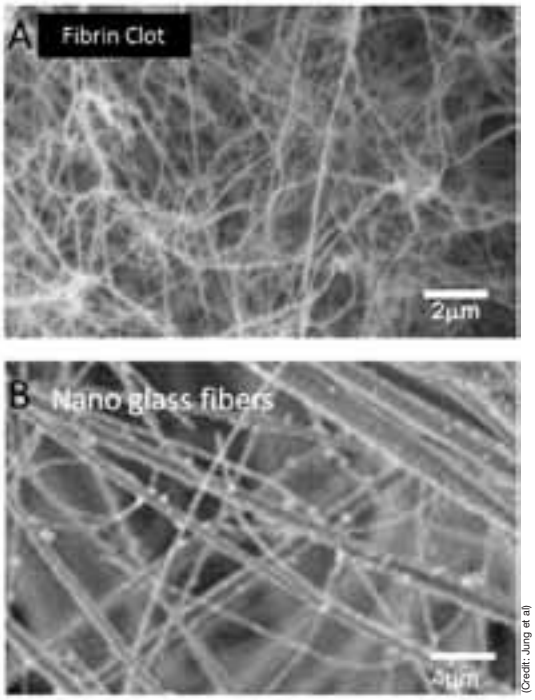
Taylor explains that diabetics and often the elderly develop troublesome and dangerous extremity wounds, called venous stasis ulcers. Aging diseases and diabetes wreak havoc on lower leg blood vessels. Blood and other fluids pool, and the vessels and their valves get damaged to the point where they don't function effectively.

And, unfortunately, that's only the beginning. If the fluid stays in the vessels, big differences in the pressure gradient between inside and outside the vessels form, and they start leaking fluid into other tissues. The fluid looks for a way outside the body and stretches skin tissue to form thin spots that can spontaneously crack and start weeping. A bump, even a small one, can accelerate the weeping process. A big bruise, such as the one her patient suffered, can trigger a large amount of weeping.

In these situations, the worst is yet to come, because the weeping fluids initiate the wound-forming stage. "This wound fluid is something of a cleaner," says Taylor. "It contains lots of enzymes. But, the fluid's enzymatic cleaning action eats away at the tissue at the surface of the wound. If the patient has a bandage or something over it, or even clothing, the fluid is held next to the skin and it starts to erode away the tissue. With the fluids from venous stasis, you get a wound that goes on and on because it won't quit weeping long enough for it to heal."

The wounds are annoying and painful, but a big danger arises because a hole in the skin is an invitation to bacteria and infection. When the elderly and diabetics don't have good circulation the chances of getting an infection in their lower extremities are enhanced. "You have bone that is close to the surface of the skin. The marrow in the bone produces your red blood cells, so suddenly you have a situation where an infection could become systemic" and potentially fatal, says Taylor.

Thus, nonhealing wounds and the infections that often accompany them are a big concern. And, to counter stagnant wounds and infections, limb amputation is often the only recourse. So, it's no wonder that patients with hard-to-heal wounds often seek out specialized wound-care treatments.



(Credit: Jung et al)

The initial stage of wound healing requires the formation of a fibrin clot. The top SEM image shows a fibrin clot composed of nanosized cross-linked fibrin fibers that initiate the healing process. The fibers shown below are made of the bioactive borate glass. The fiber diameter and overall microstructure is similar to the fibrin clot, and provides the wound with an artificial starting point.

Borate-based bioactive glasses

In 2010, Steve Jung, along with the father and son team of Delbert and Ted Day already knew a lot about bioactive glasses.

Del Day founded Mo-Sci Corp., a company that already made glass products for biological uses. Ted recently has taken over as CEO and president of the enterprise.

Jung, who looks to be in his late 20s, got to know the older Day, a renowned professor, at the Missouri University of Science and Technology. Jung earned his bachelor's and master's degrees in ceramic engineering at Missouri S&T and eventually a Ph.D. in materials science from the school.

Jung began working for Del Day in 2001, and in his Ph.D. work and collaborations with Day he became interested in bioactive glasses, especially borate glasses. "For decades, bioactive glasses have been known to bond well with hard and soft tissues," says Jung. "Much of this knowledge has been directed toward the regeneration of bone. But a lot of us also have been thinking about soft-tissue regeneration."

Jung acknowledges that most of the gains in bioactive glasses have been founded on silicate-based materials, but he says he was intrigued by some things he learned about borate glasses.

"An in-vitro study of lithium borate glasses showed it to have beneficial antibacterial effects against harmful bacteria, such as e.coli, salmonella and staph," says Jung. "Apparently the bacteria are killed as the lithium alkali is released into the immediate surrounding area of the glass, which creates a local spike in the pH."

Jung says he, Del Day and other collaborators compared the rates of how silicate-based and borate-based bioactive glasses reacted to body fluids. "In certain in-vitro experiments," he reports, "we determined that bioactive glasses containing boron as the glass former react to simulated body fluids up to five times faster than silicate glasses do."

Jung also says they were curious about a particular bioactive borate glass – 13-93B3 glass ($53B_2O_3$, 20CaO, $12K_2O$, $6Na_2O$, 5MgO, $4P_2O_5$(in weight percent)) – because of its calcium content. He notes, "Investigators

have reported that calcium is an important factor in the wound healing of skin and suspect that it is required for the migration of epidermal cells. It also may play an important role in the late stages of healing. Moreover, it appears that the presence of calcium in the immediate vicinity of an open wound helps the body to regulate wound-healing processes more effectively, particularly in open wounds."

Jung and Day thought about the general process of wound healing and how a beneficial scaffold might help. Medical studies have shown that the most effective treatment has been to cover the wound and allow the body to naturally support the delivery of growth factors or other required nutrients.

"Connective tissue has several progressive steps that must occur in order to properly heal a wound," explains Jung. "In the best-case scenario, initially, the wound will bleed, and in order to stop the bleeding, platelets in the blood are triggered to the wound site and stick to one another. Once the platelets have stopped the blood flow and a fibrin blood clot has formed, the blood clot releases growth factors and biological signals to recruit macrophages needed for inflammation. Typically, inflammation is confused with infection and inflamed tissue is considered to be bad. However, some inflammation is good, and even required to release growth factors that stimulate cell proliferation. These cells can then differentiate into tissues and eventually over the course of weeks to months will be remodeled and appear as if there was never a wound."

Jung and Day had an idea for a possible borate glass scaffold that might mimic the microstructure of a fibrin clot. They already knew how to create tiny glass fibers and they devised a way to make nanofibers (300 nanometers to 5 micrometers) from the 13-93B3 glass that produced a product that looked and felt like cotton.

(Credit: The American Ceramic Society; inset Jung and Taylor)

Peggy Taylor, an RN who specializes in wound care, examines photographs of healing wounds that she has treated with pads made of special borate-based glass nanofibers.

DermaFuse: The first in-vivo tests

Jung says the cottony nanofiber glass, recently given the name DermaFuse, seemed promising from the start. He rattles off, "It's dynamic and 'gives' or bounces back if compressed. It's flexible and could be easily placed on a wound. Its structure maximizes surface area and can control moisture levels. It's antibacterial and antifungal. It's biocompatible. And with DermaFuse's high level of calcium and its clot-promoting structure … it might speed healing."

"It was worth a try," he says.

For comparative in-vivo testing, Jung and Day took the obvious next step and tried the material out on rats. They placed pads of the DermaFuse material, with fibers up to 5 micrometers in diameter, onto 15-millimeter-diameter full-thickness skin wounds next to identical untreated wounds created on the rats. They measured the wounds periodically until the wounds were healed (three to four weeks) and found no significant difference in the wound-closure rate between the treated and untreated wounds.

Jung says they weren't deterred by the lack of difference in closure rates. In fact, he says they expected those results because "wound closure in rats is mostly caused by wound contraction and not epithelialazation. The important thing was that the wounds showed highly differentiated dermal, epidermal and subcutaneous tissues. … The differentiated tissue was a good indicator that the bioactive glass fibers were providing a positive environment for tissue regeneration. In fact, we found soft tissue and blood vessels present adjacent to many of the reacted fibers."

Armed with these results, they wondered how the glass fibers might work on human wounds.

Ted Day knew something about the situation diabetics faced with stagnant, nonhealing wounds. The younger Day had previously worked as a director of Pharmacy and Ancilliary Services divisions of PCRMC.

Day obtained a license from Missouri S&T, which retains patent rights (based on his father's and Jung's work at the university), for Mo-Sci to use the material, and then he began to discuss DermaFuse with some of the doctors in Rolla and the center's staff, including Peggy Taylor.

"Ted Day called me and said they might have a new material for wound care available and asked if I'd be interested in it," Taylor recalls. "He said they used the material in hard tissues, and were interested in how it would work with soft tissue regeneration. Well, I am a nurse and I do nothing

(Credit: The American Ceramic Society)

Steve Jung, left, and Mo-Sci CEO and president Ted Day. Jung's research contributed to the development of the DermaFuse material, and he now works for Mo-Sci.

without being directed, so I asked him to talk to some of the doctors and talk to the hospital board and see if they were interested. I suggested to him that if one of the doctors was interested, they should ask for me to assist them with it. Then I could be involved."

Ted Day did formally contact PCRMC officials and the institution's Internal Review Board. He showed them samples of the DermaFuse and presented the data on the biocompatibility and excellent quality of regenerated tissue in the rat model. Day says the IRB ultimately approved a small-scale human trial to treat nonhealing venous stasis ulcers in diabetic patients.

"The IRB agreed to selected possible participants based on protocol they established," Day says. "Their criteria essentially narrowed in on patients whose wound status made them likely candidates for amputation down the road. Each participant had to have at least one nonhealing venous stasis ulcer, and that wound had to have been treated with conventional dressings with no improvement for a minimum of two weeks prior to enrolling. The treatments – applying a pad of the DermaFuse one or two times per week – were to be done only by PCRMC staff supervised by doctors until the wounds resolved.

Dr. William Stoecker, a dermatologist who practices at PCRMC, agreed to do most of the supervisory work for the IRB. And, Ted Day suggested to Stoecker that Taylor might be interested in helping.

"So, Dr. Stoecker did ask for my assistance," says Taylor. "Both of us had our doubts, but we have a pretty open-minded culture and we use a lot of cutting-edge technology for a hospital of our size. But we also got really curious about how the bioactive glass material might work."

The IRB granted approval for the treatments in July 2010, and Stoecker and Taylor got their first patient – the one mentioned at the top of this story – a month later.

"We started with one patient," recounts Taylor. She was our only patient for several weeks. Number two was a patient who soon dropped out of the study. Then came number three, four, five and six."

Taylor confesses that her first patient helped a lot with recruiting other volunteers for the trial. The small-town atmosphere in Rolla also helped. "With her nursing background, our first patient had been exposed to medical research before. She and her husband were very eager to see things like this new study happen. Her husband is a golfer and country-clubber and she is a bridge-club lady, and they talked it up among their friends and at their church. Because of them, pretty soon we had a lot of hubbub about this in the community and more people inquiring about the study. It also helped that a lot of people know the Days in this area," says Taylor.

The nitty gritty of using 'DermaFuse'

Wound care is not for the squeamish. Taylor eventually began treating 12 patients as part of the study, and the wounds she saw ranged from around 1 centimeter by 1 centimeter with a depth of 0.1 centimeter (about the size of a small fingernail) to much larger ones. "We have three or four in our study where I could see bone, tendon, vessels and nerve strands covered by a thin layer of debris. That's because these wounds have gone on and on for so long," she says.

The DermaFuse glass material arrives for use sterilized and in a flat foil packet. Taylor starts by physically removing unwanted debris (debriding) and flushing the area. She needs to begin with a clean, moist wound bed. Often an antimicrobial solution is applied.

Then its time for the glass. Taylor describes her method saying, "Because it comes to me in a flat pack, it gets kind of squished, but it looks just like cotton candy. You can form it, you can pick it, you can make any kind of shape you need out of it. Sometimes I apply the material with tweezers. Sometimes I put it on my gloved hand."

If the wound has a cavity or tunneling, it gets a little trickier. "I will use tweezers to pack the material up into all of the recesses before filling the rest of the wound. I don't pack it hard, but just a little to get it into all of the crevices," she says.

Once the wound is covered in the material, she applies a secondary covering to hold the DermaFuse in place. This is often followed by some type of compression wrap. The patients then can go for two or three days before they need to be seen by Taylor again.

Daily dressing changes can be more detrimental than helpful. She says, "You risk disturbing that fragile tissue in the wound bed too often and not giving a chance to mature into healing

tissue. I like to use products that can stretch the changes out to every two or three days, or even five to seven days. I have found that with this glass material changing the dressing daily would be way too often."

After the first treatments with DermaFuse, Taylor says it appears the glass "reignites" a beneficial inflammatory process and she sees a lot of initial drainage. But her response with the DermaFuse patients takes a different path than normal wound care. "In the past, I have always wanted to first debride any yellow sloughy stuff that didn't look good. But, I have found with [DermaFuse] that I can leave that debris. And, removing it can be a trick. It feels like it makes its own little environment. It is almost like a tightly woven web of tissue and product, and it feels like some of the product is well-adhered. I try not to disturb it.

She says some of the remains from the DermaFuse look like wet sand that she can flush out of the wound bed. "But anything that is gripping and hanging on, I try to leave there because it looks like the beginning of the healing matrix. We don't know for sure what is going on, but I often will see good granulation tissue already forming in the area the next time I change the dressing."

What surprises Taylor is that the glass fibers disappear. "Eventually I don't see any remains of the product anymore. Does it dissolve? Does it become part of the tissue? We don't quite know what the whole story is there. But it is just such a neat thing to watch that process," she says beaming with a smile.

Wouldn't the wounds have healed anyway with her experienced TLC? She admits that they might have. But she says that the only way the wounds would have healed so fast is if the patients had used what is called a vacuum-assisted closure system.

A wound VAC system requires a nifty but expensive negative-pressure device that can be aggravating to use. In brief, it is like a little machine, which the patient has to carry around-the-clock, that vacuum packs the wound. The problem is that the VAC equipment may cost $1,000 a week, plus the patient has to drag around the machine with a battery pack that can rundown or even die out at inconvenient times.

Taylor thinks the DermaFuse might be a cheaper, easier way to accomplish the same results. "Don't get me wrong," she says. "I am a major fan of the wound VAC. But, as a nurse, if I can see that tissue healing at a similar rate, I am really happy to see some magic happen in that wound bed that would otherwise require very expensive treatments."

Jung says that among the eight healed wounds, they have been able to document wound closure rates of 0.3 to 0.8 millimeters per day, depending on wound orientation.

Where are the scars?

The apparent lack of scarring from DermaFuse-treated wounds pleases the patients but stuns Taylor. She says she normally expects to see a ropey, hard scar form. "Our patients are elderly and have a lot of skin discoloration and you would think you'd see a dramatic scarring. But, we have healed wounds that show nothing or negligible scarring," she says.

"Seriously," Taylor exclaims.

Taylor does have a theory. She says that after a wound heals, there is another transformation in the skin: the "remodeling phase." This remodeling phase can last up to two years during which the scars can be reduced, in part because the continuing healing process breaks down bonds that are replaced with better, stronger tissue. That is why people sometimes feel that a scar has faded several years after an injury. "But with the glass fibers," Taylor says, "when the wound heals, I immediately am seeing a skin appearance that I would expect to see way out in the future. So, it appears that there is something more efficient about the healing with the fiber."

What's next for DermaFuse? Ted Day and Steve Jung say that beyond working with other PCRMC patients, they will be working with the Center for Wound Healing and Tissue Regeneration, University of Illinois at Chicago, for expanded testing. Taylor was preparing to make a presentation about the trials at a wound care specialists' conference in Dallas, Texas, and Jung will be presenting information at ACerS's upcoming Glass & Optical Materials Division annual meeting in mid-May in Savannah, Ga.

Ted Day is obviously excited about the business prospects for DermaFuse. He says Mo-Sci hopes to supply the materials to one of the larger medical supply companies that are in a better position to guide DermaFuse through full-scale federal human-testing requirements and, if approved, market it to medical professionals.

Day remarks that DermaFuse doesn't fit the typical pattern of Mo-Sci products. "It is the first time a material has presented itself to us as having all these unexplored possibilities, rather than us looking for a material to fill a buyer's particular requirements," he says.

He says he would be extremely happy if DermaFuse turns out to be an inexpensive alternative to treatments, such as wound VAC systems. But, he and Jung say they would be even happier if some of the other applications they are contemplating pan out.

"Can you imagine what it would mean if we can use these borate glass fibers on burn patients," Jung asks. "I'd love to think the fibers could speed those wounds to heal and minimize the scarring."

Day thinks of disasters and traumas. "I'd love to see the day when soldiers can carry packets of this stuff, and just slap it on a battlefield injury. It might begin to protect and sterilize the wound, and it might never have to be removed."

But Taylor loves what she is seeing already. "Sometimes when I am dealing with wounds," she says, "I have to study photographs of the wound from previous visits and put them next to each other to see if anything is improving. But when my eyes alone can tell me, 'Wow – that's a nice big change in the wound since the last time I saw it,' and you don't have to refer back to the last six weeks of photographs to see if we've really been building tissue there – there's nothing better!" ■