Research Profile

TYPE 1 & TYPE 2

An Air Of Healing

Sometimes the glamorous life isn't all it's cracked up to be at least according to Wende Reenstra, PhD. When Reenstra graduated from college with a degree in economics, she landed a job in the fashion industry in New York City. The glitz of Seventh Avenue and the hustle and bustle of the country's biggest metropolis might thrill a lot of college grads just starting out in life, but for Reenstra, the excitement just wasn't there. "It wasn't enough for me" It wasn't stimulating" she says." "I was bored."

Wende Reenstra, PhD, hopes to show how hyperbaric oxygen, which is often used to treat "the bends" in divers, can help heal wounds in people with diabetes.

To expand her horizons she volunteered to work at a dermatology lab. The rest. as they say, is history. Two advanced college degrees later, Reenstra is working with colleagues at Boston University School of Medicine under a grant from the American Diabetes Association. Her mission is to determine the role oxygen plays in wound-healing in people with diabetes and to shed light on how a controversial treatment may help wounds heal faster.

Wende Reenstra, **PhD**

Occupation
Research Associate, Boston University School of Medicine

Professional Focus
The role of oxygen in diabetic wound-healing

Outside Interests
Scuba diving, sailing, photography

Research Funding
ADA Research Award

Ouch!

It doesn't take much to create a wound: a slip of the wrist with a razor, a misplaced step on something sharp, even the constant rubbing of the inside of your shoe against your foot. But there's more to a wound than a bit of bleeding and pain. There's a whole chain of events that goes with it.

Say you get a papercut. Right away, blood vessels under the surface of your skin constrict to stanch the flow of blood. This changes the oxygen levels in the blood near the wound site, which activates platelets near the wound. The platelets release enzymes called growth factors. Growth factors, in turn, attract cells necessary for healing, bind to them, and signal them to start working.

Macrophages, vascular endothelial cells, and fibroblasts are among the cells that help heal wounds. Macrophages are white blood cells that help prevent infection by eating bacteria. Vascular endothelial cells line the blood vessel walls. Fibroblasts are "construction workers." They multiply at the wound site, then release substances that act as scaffolding for other cells to "walk on" to get to the surface of the wound and start repairs. Fibroblasts make some scaffolding while they are multiplying, but they increase their scaffolding output once they are well established at the site.

When the macrophages, vascular endothelial cells, and fibroblasts arrive at the scene of the accident. the change in oxygen in the blood prompts them to release receptors on their surfaces so that growth factors can bind to them and tell them what to do.

This is all well and good, except that, as previously noted, oxygen is reduced when blood vessels initially constrict at a wound site. Sensing less oxygen. the platelets send out distress signals to stimulate blood vessel growth and call for the fibroblasts to make more scaffolding.

But there's a vicious cycle at work. The cells need oxygen to put out receptors for growth factors, so if there is less oxygen, there are fewer receptors. Fewer receptors means the growth factors are less likely to hook up with the cells and signal them to get to work. To help counteract this, the fibroblasts call in reinforcements. It takes time for the fibroblasts to call for help, multiply, and lay down scaffolding, which is why it usually takes a few days for a scab to form over a wound.

So why don't you bleed uncontrollably right after you are cut? Don't forget that the blood vessels constrict. But then the endothelial cells come to the rescue. Endothelial cells don't need as much scaffolding or oxygen to begin their work, so they are able to start rebuilding the lining of the injured blood vessel while the fibroblasts are still multiplying and laying scaffolding for the other cells that help healing.

Diabetes can interfere with wound-healing, however. In people with diabetes. oxygen may already be lower at a wound site because of peripheral vascular disease. Peripheral vascular disease can damage blood vessels in your extremities and along the surface of your body. and disrupt blood to those sites. Lower blood flow means less oxygen in the affected areas. because blood carries oxygen.

Reenstra pauses to enjoy a sunset with with her husband, Jon Buras, MD, PhD.

When you combine the effects of peripheral vascular disease with the natural constriction of the blood vessels to stanch blood flow when you have a wound, it makes for slow healing. The less oxygen there is. the fewer growth factor receptors the cells will make, the less hook-up with growth factor there is, the longer it takes to get the cells working.

Reenstra has a few ideas about how to get around that. Basically, she wants to bring more oxygen into the blood and to the wound site. She figures that the more oxygen there is, the more receptors there will be, the more growth factors can hook up with the cells, and the more the cells can do what they are supposed to. "If you have a whole bunch of receptors sitting there on the surface of the cells and growth factor passes by, you have a good chance of grabbing it," she says.

Is Healing In The Air?

To watch how cells respond to varying concentrations of oxygen and to see how cells from people with diabetes respond compared with those of people who don't have diabetes, Reenstra works with fibroblasts obtained from about 35 people with type 2 and their siblings who do not have diabetes. "Fibroblasts are great," she says. "I don't have to hurt anyone or any animals. I can take a little piece of skin, then grow the fibroblasts in tissue cultures. They grow like weeds there. You can even freeze the cells to store them, and they'll still work later."

From the get-go, Reenstra noticed something about the fibroblasts. "The cells from the people with diabetes multiplied more slowly," she says. "Even in normal conditions, they don't have that many receptors. They multiply about half as fast." Why they multiply more slowly remains a mystery, for now.

The research team exposed the fibroblasts to varying concentrations of oxygen at different pressures. Normally, the concentration of oxygen in room air is about 20 percent, and cells in the blood are exposed to a slightly lower concentration. Reenstra exposed the cells to hyperbaric oxygen, which is 100 percent oxygen, at high pressure.

And?

"The fibroblasts from the people with diabetes grew faster. Almost as fast as their siblings' did," she says. "I'm looking at whether the increase is due to a higher number of receptors being expressed. I suspect it is, but I'm still confirming that part."

Reenstra notes that hyperbaric oxygen therapy is a controversial treatment for wound-healing. A person receiving hyperbaric oxygen therapy lies down in a pressurized chamber and breathes air that is 100 percent oxygen.

"People have used hyperbaric oxygen for years to treat wounds, but no one has been able to show how it works. And because [many doctors and scientists] don't know how it works, they look at it like voodoo medicine," she says. "There are a lot of studies showing that if you treat people with wounds with hyperbaric oxygen, you can save them from amputation. If I can figure out how and why it works, maybe more people will be inclined to use it."

If things turn out as Reenstra expects, she suggests a one-two punch with conventional treatment for wounds. "People have been putting solutions of growth factor directly into wounds. It works because the number of receptors is down, and by increasing the amount of growth factor present, you have a better chance of hitting those few receptors," she says. Her suggestion is to increase the number of growth factor receptors with hyperbaric oxygen therapy, then apply the growth factor.

The Stuff Of Life

Reenstra's interest in hyperbaric oxygen sprang from one of her favorite pastimes: scuba diving. Hyperbaric oxygen is used to treat divers who get "the bends," a potentially fatal condition that makes breathing difficult when a diver resurfaces too quickly.

Diving is a hobby she shares with her husband, Jon Buras, MD, PhD, who is the chief diving medical officer for the Massachusetts State Police. "He's doing research in hyperbaric oxygen, too, but for a different application," she says. "So we have a lot in common. There's a lot to talk about."

They'll have even more in common when Reenstra finishes her MD degree in May. She doesn't plan on treating patients directly, but rather to work as part of a team with physicians who do treat patients. "I can speak the same language," she says. "I can say, 'This is what we are finding in the lab, so maybe it can help you understand how you can treat your patients more effectively.'"

Not that she's unfamiliar with providing treatment for diabetes. One of her two cats has diabetes, and she gives him insulin injections twice a day.

Her caregiving responsibilities are about to increase, however. She's expecting her first child in April. "That's one reason I'm sticking to research," she says, referring to how she will have to juggle career and family once the baby comes. "By sticking to one thing, one facet of life will be simpler. We're going to be very busy. There will be a lot to do. But it's going to be fun."

-TERRI D' ARRIGO