“Fewer than three out of 10 people who suffer severe vision impairment even leave their homes.”

A NEW CENTER FOCUSES ON RESTORING VISION

BY CHUCK STARESINIC

AN INVISIBLE PROBLEM

On the door to Lieutenant Ivan Castro's room at National Naval Medical Center in Bethesda, Md., Major General Gale Pollock found a handmade sign that read, "Use Vision Precautions." (In other words, as you enter this room, don't assume the soldier inside can see you or anything else.) As an army nurse, it was Pollock's job to check on the wounded soldiers in the naval hospital. Never mind that she was a major general and chief of the U.S. Army Nurse Corps. She was an army nurse.

"He didn't track me when I came into the room," Pollock recalls. "So I put my hand on him when I got there, so he'd know where I was."

How are you doing?

Crappy.

What's going on?

I'm blind.

Castro didn't say a word about his other injuries, which were extensive. A mortar blast had killed two army snipers standing next to him on a rooftop in Iraq. The force of the explosion broke Castro's arm and left the bone protruding. It broke his nose,

PHOTOGRAPHY | STEPH HOOTON/PICTOGRAM STUDIO

collapsed his lungs, and blew off part of his trigger finger. His protective eyewear was driven into his face. One eye was destroyed. The other was patched over in hopes that stateside specialists could salvage some of his vision. But when a physician in Bethesda finally removed the patch and shone a flashlight into the remaining eye, Castro mistakenly thought the bandage was still on.

I'm blind, he told Pollock.

"He was like a deflated balloon," she would later say. "All the life spirit had drained out of him."

She probed for a way to reach him, asking him what he liked about being in the army. Bull's-eye. He started to come to life as he told Ranger stories to this two-star general. Being a U.S. Army Ranger clearly meant everything to him.

What happened next may illustrate a critical difference between being a nurse and being an army nurse. Pollock decided to, in her own words, "piss him off."

I think you're lying to me lieutenant, she said.

Pollock felt Castro tense beneath her hand, but she plowed ahead: You can't be a Ranger, because Rangers aren't quitters. And if you are a Ranger, you better stop telling people. You are an embarrassment to anyone who ever was, is, or will be a Ranger. You are a quitter.

Castro rolled up on one elbow and yelled: I told you I'm blind!

Pollock yelled right back: And I told you you're a quitter! I've got other blind service members in the military. So what the hell is your problem? You are a quitter.

Just a few years earlier, Gale Pollock admittedly did not have much of a handle on the extent of vision problems among service members and veterans. Then, she learned that 10–13 percent of all the combat injuries in Iraq and Afghanistan involve the eyes. As she dug deeper, the extent of the problem began to emerge. It has only grown larger as the wars have dragged on.

"We have just over 100 now in the military who have had one or both eyes enucleated," Pollock says. "We have over 1,000 who are legally blind."

Pollock and her staff then began to ask what there was to offer these folks, soldiers and civilians alike. She was not impressed with the answers.

"Fewer than three out of 10 people who suffer severe vision impairment even leave their homes. That's why it's an invisible issue in America, because they are not out there. We don't see people struggling. We don't realize how many there are who are struggling. We occasionally see someone with a white cane or a guide dog, and we think, 'Look how well they are getting along!' And we falsely assign that positive to the entire community of vision impaired. But it's a continuum, and the people you see out there are the risk takers and the 'Don't you tell me I can't do that' kind of person. … At the other end you have people who are so chronically depressed that they are suicidal. Then you have the bulk of them in the middle.

"My role as a nurse," says Pollock, "is to raise people to their highest level of functioning, regardless of their injury or disability." She started talking with the blind and injured, she says, telling them, "Hi. I'm your new big sister, and I'm going to find a way for you to have a higher quality of life."

She traveled to different research centers and talked with clinicians focused on the eye. Along the way, she met Joel Schuman, professor and chair of the Department of Ophthalmology in the University of Pittsburgh School of Medicine, and Alan Russell, a Pitt University Professor of Surgery and director of the Pitt/UPMC McGowan Institute for Regenerative Medicine. Russell and Schuman were taken with her single-minded attention to getting science out of the lab and into the clinic, where it could help people struggling with their vision today.

One of the first things Pollock would learn about Pitt was that a collaborative culture permeated the place. When she met Schuman, an expert in glaucoma, he was deep in conversation with Russell, who might not have known much about eyes at that point, but knew a great deal about the body's inherent ability to heal and regenerate tissue.

These scientists, Pollock realized, were not just talking about correcting damaged vision with better lenses, implants, or transplants. They were talking about a fundamentally different approach—coaxing the body into growing new corneal tissue to replace scar tissue, for example, or getting a severed optic nerve to reconnect on its own. Both of these are tissues that, once damaged, do not heal in any meaningful way. These scientists believed they could change that.

As Russell puts it, regenerative medicine is about "accelerating the pace at which the body heals itself into a clinically relevant time scale. Instead of ameliorating symptoms, we will regenerate lost function of the body."

Louis J. Fox is a guy who knows how to both work hard and enjoy the rewards that hard work brings. Or, put another way, he's a guy who doesn't know how to sit still.

"I'm a type A personality by genetics," he says.

Until 1999, Fox made a living as a senior executive at Gerald Metals, in Stamford, Conn. He ran its global precious metals trading and financing group. He often worked 12–14 hours a day. For fun, he piloted his own plane.

He "retired" in 1999. Fox's idea of a retirement activity involved starting a gold commodities trading company. (More on that later.)

At the beginning of 2000, just as this happy, successful commodities trader entered what was expected to be a blissful, relaxing, and productive phase of life, Fox noticed that the vision in his right eye was a little off. Something wasn't quite right when he closed his left eye and tried to read the traffic signs. He found an eye doctor who told him his vision was 20/25 in that eye. For a guy who'd recently been 20/20 or better in both eyes, this wasn't good.

For the most part, the human eye is a nonvascular organ, meaning its various parts do not contain blood vessels. The exception is the retina, which makes up the entire back wall of the globe that is the eye. More than half of the inner surface area of this globe is the retina, which is suffused with a network of blood vessels. The central retinal artery delivers oxygen-rich blood to this network through a single entry point in the back of the eye. Once depleted of its oxygen, blood leaves the eye via the central retinal vein. In Fox's right eye, a blockage occurred in this vein, and the blood began to back up in the eye. The central part of the retina, which corresponds to the center of one's field of view, was beginning to swell and bleed. The retinal tissue was becoming damaged.

"We don't realize how many there are who are struggling."

When Fox asked his doctor what could be done, he was told, "Not much." It could heal itself, but it might not.

Fortunately, Fox still had excellent vision in his left eye. He applied for and received a waiver from the Federal Aviation Administration to fly as a pilot with monovision. Three years after his right retinal vein occluded, he woke up one morning and noticed something wasn't quite right about his left eye. Fox was among the 6–14 percent of people with central retinal vein occlusion who experience it in both eyes, leaving him unable to drive a car, let alone pilot an airplane.

One day, his wife, Dorothy Fox, called him into the room to catch a segment of the CBS television show *Sunday Morning*. It was all about vision restoration at the University of Pittsburgh, where he received his undergraduate degree in 1964. Being a Pitt grad, Fox went ahead and called the University and soon found himself in touch with Russell and Schuman.

On a subsequent visit to the Pitt campus and the McGowan Institute for Regenerative Medicine, Fox was bowled over.

"You have to understand, the world I come from—the commodity world—is a very different-thinking kind of world," he says. "It's dynamic. In the world of commodities, every day is different. It's never the same, and you can't get stuck in old ways of thinking. Well, you can, and people do, but the real successes are because it's so dynamic and people see that. That mentality seemed to pervade the whole Pitt/UPMC/McGowan medical community. And it was both refreshing and exciting."

Fox was in a good position to recognize this sort of thinking. When he "retired," he and some partners started buying a lot of gold-mining properties with the intention of drilling them and developing gold reserves. "We weren't going to mine the properties," Fox says. "We were going to hold the properties and develop the reserves with the view that we thought gold was going to go up significantly higher. We were more right than we ever thought, because in 2000, gold was around $200 an ounce. Today, it's about $950 an ounce and looking like its going higher."

In 2009, Fox announced a $3 million commitment to what is now the Louis J. Fox Center for Vision Restoration of UPMC and the University of Pittsburgh, a collaborative effort of the UPMC Eye Center and McGowan. UPMC has pledged to match all such philanthropic donations to the center.

As of 2008, the Fox Center is under the leadership of executive director Gale Pollock, now retired from the army.

LEFT: Ivan Castro crosses the Boston Marathon finish line with a guide on his left. BELOW: After the race with his wife, Evelyn Galvis, and Gale Pollock (middle).

FINISH LINE PHOTOS COURTESY I. CASTRO AND G. POLLOCK

"If a mammalian fetus loses a limb in the first trimester, it regrows it," says Russell. "But this ability is lost as we age. A child who loses a fingertip in the first six months of life regrows it. By age 5, they do not." McGowan Institute researchers are finding ways to kick-start these dormant abilities of tissue regeneration. And what they are doing seems to apply to every organ system in the body.

The Louis J. Fox Center for Vision Restoration applies this same sort of thinking to the eye. The work of Stephen Badylak, Pitt professor of surgery and director of tissue engineering at the McGowan Institute, is a perfect example. Badylak's lab constructs scaffolds around which the body regenerates new tissue—a lost fingertip, for example. They start with an extracellular matrix derived from pig bladders that are essentially washed of all cells, leaving connective tissue that comprised the structure of the organ. The body seems to recognize biochemical signals from the matrix as a summons to populate the scaffold with cells and generate new tissue. The scaffolds are eventually absorbed, leaving no trace. Recently, Badylak's lab began to ask whether they could convince the body to repair a severed optic nerve.

"You can have a perfectly functional eyeball, but if you don't have the nerves to convey those signals back to the brain, you don't have vision. We don't have the skills to repair a severed optic nerve," says Badylak, but he adds that the body probably does. He says it's too early to say exactly how his lab needs to shape or apply the matrix to accomplish this. He also doesn't know if it will be necessary to seed the matrix with neuronal cells or stem cells from the patient, but he's optimistic it will work.

"Imagine the optic nerve as a telephone wire with loads of cables running through each wire. We would form a sleeve around the severed ends of the optic nerve that would contain not only the guidance cues to say the severed nerve should grow in this direction, but also cues that would promote actual cell division and elongation of the dendritic processes and the axonal processes. I think, frankly, that it will be a tube-shaped sleeve that is going to get our best first results." He says the questions then become: *Do we need to add a cell component? Do we need to fill the sleeve with a gel form of the matrix to help promote this?*

As with the optic nerve, doctors have few options when it comes to repairing damaged corneas right now. This clear covering that permits light to enter the eye is a fascinating tissue. The outermost layer consists of cells that regularly slough off and regenerate. Superficial scratches and wounds to this layer leave no permanent scars. But the innermost layer is a different story. The cells and proteins that make up this layer are rigidly structured to be both strong and transparent. An injury or infection that damages this innermost layer will lead to the growth of scar tissue that lacks the proper structure and is not transparent.

Roughly 10 million people on the planet have cloudy corneas that they can't see through properly. To date, the only cure is corneal transplantation, a procedure that is very common and highly successful in this country. As a nonvascularized organ, the cornea is immune-privileged, meaning it does

not cause rejection. However, many parts of the world are not equipped for corneal transplants, and many peoples have cultural taboos about donating or receiving organs.

Jim Funderburgh is a PhD cell biologist and a Pitt associate professor of ophthalmology who has explored the cornea since the mid-'70s.

"I've always been what is known as a 'grind and find' biochemist," he says with a laugh. "I've spent my whole career taking tissues apart and looking at the molecules and seeing how they fit together and how they work."

Recent discoveries have Funderburgh looking to get his lab's discoveries on the fast track to the clinic. He and his colleagues were the first to discover, isolate, and culture stem cells from the innermost layer of the cornea. (A Japanese lab published a similar description around the same time, and these may prove to be the same cell type.) They found that these cells, even after many rounds of expansion in the lab, continue to produce the biochemical components of the cornea's structure, including a protein called lumican, which is key to the proper structure and transparency of the cornea. What would happen, Funderburgh asked, if these cells were injected into a damaged cornea?

Their experiment was a cautious first step—they injected human corneal stem cells into mice that cannot produce lumican and therefore have cloudy corneas.

The results were kind of shocking, Funderburgh says. The stem cells apparently had the ability to completely reconstruct the tissue. "There wasn't any inflammation. There wasn't anything obvious going on—it was just that the mouse corneas got clear. They took this matrix, which was improperly put together, and which we always thought was like cement, and they turned cloudy corneas clear. And when we went back to look at the collagen structure, it had changed also, so it was kind of shocking. We had to do it a few times to make sure we were really right. It was a very exciting possibility that just by injecting these cells we could maybe take care of corneal scars without having to do a transplant."

With his interest in stem cells, Funderburgh has long been associated with the McGowan Institute, but the new Fox Center for Vision Restoration brings more attention and more resources to bear for moving discoveries like his to the clinic. With Pollock's enthusiastic support, he's exploring how to culture these cells in such a way that the FDA will approve them for use in a clinical trial.

"Gale Pollock," he says, "is the kind of person who walks into your office and says, 'Okay, when are you going to help my soldiers?' She has seen it. She has seen the effects of corneal and ocular injuries and blindness, and she knows what a devastating thing it is. She can really bring it home to you that it's not just piddling in the lab. There are people that need this."

"This device is not going to give you vision. But it makes a huge difference."

At a press conference in May 2009 announcing the $3 million commitment from Louis Fox, retired Marine Corporal Mike Jernigan demonstrated a futuristic, experimental device called the BrainPort.

Like Castro, the U.S. Army Ranger blinded in battle, Jernigan was blinded in an explosion in Iraq. A pair of artillery shells had killed one of his fellow Marines and wounded three others. Of the survivors, he was the worst off. The front of his head caved in. Traumatic brain injury only begins to describe his case. His forehead was gone, and 45 percent of his brain crushed. Somehow, thanks to a Kevlar helmet, Jernigan says, there was no penetrating brain injury. He says that he had 30 major surgeries in 12 months and "flatlined" during three of them. He lost both eyes.

But at the press conference in Pittsburgh, Jernigan, sporting a pair of black wraparound sunglasses, placed a small plastic device (an IOD, for intra-oral device) on his tongue. Electrical cables connected the IOD to the sunglasses, which have a tiny, unobtrusive camera mounted on the bridge. Jernigan, who has no eyeballs, sat before a black felt screen with white shapes. As the camera picked up the images, data were transmitted to the IOD, which contains a grid of tiny electrodes in contact with Jernigan's tongue.

"It feels like putting a 9-volt battery on your tongue," says Jernigan. Pollock describes the feeling as "like champagne bubbles."

The BrainPort is being developed at the University of Wisconsin and field tested here at Pitt, among other places. The information conveyed from the camera to the tongue makes its way to the user's visual cortex. Before the wowed audience at the press conference, Jernigan correctly described the shapes and directional arrows placed on the screen in front of him.

In the coming year, researchers at the Fox Center for Vision Restoration hope several dozen people who have lost their vision will test the latest version of the BrainPort.

"This device is not going to give you vision," says Jernigan. "But it makes a huge difference. It might not be vision, but it's not total darkness, either. A device like this can give a person like myself a lot of hope and a lot of excitement about where this technology can go."

To all appearances, Jernigan does not have trouble venturing out of his house. He is a political science major enrolled at the University of South Florida. He uses a guide dog to get around. (Although he has a BrainPort at home, he doesn't use it much—testimony to the refinement required before the device will help a large number of people in daily life.)

And Ivan Castro, whom Gale Pollock reached out to in his Bethesda hospital bed by directly challenging him, has remained in the army, been promoted to captain, and met the challenges of his postinjury life head on.

"I think he did six marathons last year," says Pollock. "I saw him finish the Boston Marathon. He and some of his colleagues I am absolutely focused on helping now. We are going to demonstrate to the world that life does not stop if you've lost your sight."

To convey the plight of those with lost vision, Pollock often describes a wide spectrum of activity, with Jernigan and Castro occupying the "go-getter" end and a more reclusive majority taking up the rest. But Jernigan is quick to counter that the spectrum may not be as wide as it first appears.

"When I first came home, I was scared to leave my apartment," he says. "I was scared to walk past the sidewalk and get into the parking lot, because I was afraid I'd get hit by a car. And that's the type of stuff you deal with. I had a tight family and a lot of support, and I went to counseling. If it wasn't for that, I don't know what would have happened. And that's what a lot of people don't understand. Everyone looks at me as the person who can't be stopped and doesn't let anything get in [his] way, but nobody realizes that I'm three steps away from being reclusive. That's just how it is." ■