



THE “NOW WHAT?” FIELD OF MEDICINE

REHAB DOCS PLY THE
BIOLOGIC UNDERPINNINGS OF
INJURY AND RECOVERY
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Cane resting on her one good leg, Kimmy Perilloux rolls up her long-sleeved T-shirt. The exterior of her arm still looks strong, but signs of diabetes line the inner arm: There is a thick bandage on the biceps, toward the armpit, where she received her insulin injection earlier that morning. Three off-white furrows appear near the wrist, where a surgeon inserted fistulas for dialysis treatment.

Physician Michael Boninger asks Perilloux to extend her arms and turn her palms up. He presses down on them gently. “My arm hurts,” because of the fistulas, she explains. Boninger stops.

Boninger had begun the exam by reviewing Perilloux’s medical history, a particularly long one for a 46-year-old. Diagnosed with



PULLING BACK THE HANDS OF TIME
In the Department of Physical Medicine and Rehabilitation, faculty are researching better ways to deal with, slow, or reverse the decline of the body.

juvenile diabetes at age 13, she has sickle cell trait, renal failure, heart problems, peripheral neuropathy. Oh, and one other thing, she says. “I’m an above-knee amputee.”

“Jeez, ya done yet?” Boninger says, in his Midwestern accent. (He’s from Cleveland.) Perilloux hasn’t lost her sense of humor, though, and laughs along with the doctor.

She then lists her medications—drugs for her heart, kidneys, and stomach. Plus aspirin, anti-histamines, and an anti-itch pill, as needed, to avoid creating a lesion that would jeopardize a limb. But there’s one more scrip she needs from Boninger.

It’s for a wheelchair. Perilloux has been falling down a lot lately—her prosthesis feels awkward, especially after dialysis, and walking on it wears her out. Sometimes she doesn’t extend the leg enough, and she falls. She hasn’t been hurt too badly yet, but Boninger doesn’t want to chance it. An injury on the foot or lower leg could jeopardize her remaining leg.

She’s come to the right place. Boninger, University of Pittsburgh professor and chair of physical medicine and rehabilitation (PM&R), is something of a wheelchair evangelist. His mission—to give the imperfect and impaired body increased function. For someone like Perilloux, a wheelchair means freedom. Instead of looking out her apartment window getting depressed, she could simply take a city bus to a friend’s house.

Boninger is a physiatrist, a specialist in rehabilitation medicine. While other disciplines focus on the root causes of illness and injury, physiatrists occupy a special and growing place in the medical arts—making the best of impaired bodies like Perilloux’s, where no real “cure” yet exists. He has authored pioneering studies in repetitive stress injuries for wheelchair users. “In physical medicine, the only outcome we look at is function,” says Boninger. “Are we getting less pain and more function?”

As chair of Pitt’s department, Boninger is at the helm of a research juggernaut that now ranks number one in National Institutes of Health (NIH) funding for departments of its kind. The rehab docs in PM&R are researching better ways to deal with, slow, or reverse the inevitable destruction of the body—whether destroyed through disease, bullets, stress, trauma, or time. They study the molecular mechanisms behind recovery, new technologies, and biologic therapies that could restore tissue and increase function.

After watching Perilloux struggle down the hallway with a cane, keeling awkwardly over her prosthesis, Boninger takes a step back.

“She’s a walking billboard for everything we

do here,” he says. “We’ve saved her life with dialysis; but the question now is, what do you do next to restore some type of function in her life?”

It’s the question the rehab docs in PM&R all must ask. When the disease or the injury becomes less a question of “if” and more a question of “how much,” what do you do? What can you do? This is the gray area, between sickness and health, where rehab docs live. This is “Now what?” medicine.

A SIDE EFFECT OF MODERN MEDICINE

Boninger is a trim, buoyant man who rises at 5 a.m. and gets on his elliptical trainer, where he catches up on doctoral student papers and outgoing grant proposals from his faculty.

He received a bachelor’s degree in engineering from Ohio State University, then got hooked on rehab medicine during third-year rotations in medical school.

“You have long-term contact with patients—you’re not dealing with emergencies,” he says of his chosen field. “And,” he continues, “patients get better. It’s about them getting better.”

“I had a kid who came into the hospital; [he] was riding his bicycle and was hit by a car. Had a brain injury and really came into the hospital completely impaired. We did a lot of therapy with this kid, and he walked out a month later, ready to go to school.”

Boninger came to Pitt in 1993, to what was essentially a clinical division.

“We had zero NIH dollars, and we were a division of orthopaedic surgery,” Boninger says. In 2000, the dean of the medical school and senior vice chancellor for the health sciences, Arthur S. Levine, made PM&R a department of its own. Now the department’s 36 faculty brim with grants from the NIH, the Department of Defense, and other big-league funders.

Boninger also directs the Institute for Rehabilitation Research, which has a brand-new home at UPMC Mercy for patients recovering from stroke and severe, acute injuries to the spine and brain.

In many ways, the rise of Pitt’s department corresponds with growth in rehab medicine as a whole. The field was born after World War II, with the return of thousands of wounded soldiers who would have died from their wounds in the prepenicillin era.

Like most medical disciplines, the field was guided more by practice and craft wis-

dom—using methods that seemed to work in the past—than by any kind of mechanistic understanding of human biology. If electrical stimulation or exercise seemed to work, then most patients got those treatments, regardless of whether doctors knew for which patients they worked best.

This began to change in the 1990s, when the NIH opened a center for study in the field and availed researchers of more research funds.

“Sure we know things like exercise are good for you, but we don’t know why they work,” says Leighton Chan, chief of the rehabilitation medicine department at the National Institutes of Health Clinical Center in Bethesda, Md. But to improve upon these therapies, he says, “You need to know the biological basis for why these things work.”

Among those who took advantage of this new landscape was Boninger, who studied secondary injury in wheelchair users. After years of pounding on wheel rims, patients develop severe problems in their shoulders and wrists.

“If you can imagine, it’s like taking someone with paraplegia and giving him tetraplegia,” Boninger says.

After conducting epidemiological studies of wheelchair-born impairments, he put his engineering degree to use and, working with a team, developed an ergonomic push-rim that makes gripping and stopping easier. He has also designed a hand-cycle exercise machine that is synced with a video game. (Boninger holds patents on both technologies, which are marketed by a company his brothers own.) The game makes the exercises more interesting for patients in rehab and allows those who can’t use their legs to get the benefits of cardiovascular exercise.

Interest in rehab research has grown, too, partly because of modern medicine’s many successes, says John Whyte, director of Moss Rehabilitation Research Institute in Philadelphia.

“Medicine that eliminates acute infectious diseases that kill people young also allows them to wear out their joints, rupture their discs, or develop Alzheimer’s disease,” Whyte says. “There’s nothing in the trends to suggest modern medicine will reduce the need for rehab. Rather, it will increase the need.”

FINDING THE ORIGIN OF PAIN

Gwen Sowa asks the tall man in baggy shorts to stand up. Ed James is a former tennis pro, current tennis coach, and walking



sports injury. James, 49, has torn his rotator cuff and labrum and strained his patellar tendon. He's had a grade-3 ankle sprain, a torn tendon in his wrist, and a torn groin. (The last injury happened when he mistakenly fell into a split. "This was change-my-life pain," he says of the groin tear. "I'm talking, I'm driving a car, I hit a pothole, and I have to pull off the road and be in tears for 5 minutes.")

"Stand on one foot," Sowa instructs him, demonstrating the *Karate Kid* stance for him. James wobbles

on his right leg. Sowa checks his hip alignment, which seems fine, before she tells him it's okay to place his foot down again.

James is here because of chronic muscle pain in his hip and spasms in his neck, which he's had since an 8-year-old hit him in the eye with a tennis ball last year. His wobbly performance on one leg tells Sowa that his hip abductor (the outside of the thigh) is weak. This is curious, she notes, because he uses it all the time.

For the hip, Sowa writes a scrip for his physical therapist to put James through dynamic balancing exercises and to use an anti-inflammatory patch in the area. For his neck, she sends him to a massage therapist.

These therapies will probably reduce the inflammation responsible for James' pain, but Sowa, Pitt assistant professor of physical medicine and rehabilitation, thinks there's a better way to treat patients like him. She's researching the molecular pathways that lead to inflammation in pursuit of biomarkers that could spell out more precisely what's causing these problems and, more importantly, whether the solutions she's given him are working.

Among those who could benefit from such a test would be the large numbers of Americans who suffer from lower-back pain. Lower-back pain, a by-product of a sedentary lifestyle, will afflict about 9 in 10 Americans at some point in their lives. Estimates put the health care cost of lower-back pain at around \$32 billion

per year, making it the most expensive nonlife-threatening condition. But for the enormity and ubiquity of the problem, we still know relatively little about the mechanisms that cause it or remedy it. Exercise is good for the back, of course, but how much, and what kind? The question of dosage in exercise is very much unresolved, according to Anthony Delitto, professor and chair of physical therapy in Pitt's School of Health and Rehabilitation Sciences.

"We're flying blind as far as dose is concerned," says Delitto, who has studied the enormous health costs lower-back pain incurs. "We want to be a little more enlightened about dose. We could be underdosing, for all we know. At the same time, we have a patient sitting in a chair in front of us, and [she wants] to be treated."

Delitto is collaborating with Sowa on biological research into the role exercise plays in reducing inflammation.

Sowa, who has a PhD in biochemistry and an MD, takes cultured intervertebral disc cells and gives them a "workout." In a specially designed chamber, she applies stretch and compression forces that mimic exercise. At certain levels of exercise, the cells produce lower levels of inflammatory molecules. Above a certain threshold, the exercise appears to be damaging—the inflammatory molecules increase. Experiments in rats have produced similar results. (She wagers that exercise could be a better anti-inflammatory than ibuprofen, but has yet to do a head-to-head comparison.) Sowa hopes her research will lead to a biomarker that can give real-time updates of a treatment's efficacy.

A biomarker would be helpful for James, the former tennis pro who had a hard time standing on one leg.

And a biomarker assay would give Sowa a real-time read on the exercises she's prescribed for him. Do they reduce the seroprevalence of inflammatory markers, like interleukin-1 and nitric oxide? What about molecules that reduce inflammation? A test for TIMPs, a group of protease inhibitors that limit the inflammatory cascade, could provide a glimpse into how James' stretching and balancing exercises are working on the molecular level.

MRI and other imaging technologies offer little insight into the molecular pathways Sowa is interested in, especially in the short term.

"The biomarkers potentially could show up in minutes; you could do the exercise regimen, sample the blood, and immediately know, 'Did you do the right thing, or not?'"

GETTING STEM CELLS TO ACT THEIR AGE

Since stem cells were discovered in the 1960s, researchers have held out hope that they could be used to boost recovery within the deteriorating body. Despite the high hopes, success with stem cell therapies has been elusive. When transplanted into a new body, stem cells from older people tend to die off quickly, form scar tissue, and fail to divide rapidly enough to make a difference.

But what if these cells were sent to the gym? That's more or less a question being asked by Fabrisia Ambrosio, a PhD assistant professor of physical medicine and rehabilitation, physical therapy, and orthopaedic surgery. Ambrosio and her collaborators at Pitt explore the possibility that electrical stimulation and exercise—two standard physical therapy interventions—can help improve the performance of transplanted adult stem cells.

Ambrosio says that even when an adult stem cell from a younger donor is injected into the body of an older person, the grafted cells tend to behave like the cells in their new environment.

It's as if these young cells are like children sent to live in a nursing home, she notes.

They take a look at the '50s furniture, the Perry Como records, and black-and-white television. Before long, they start wearing track suits and queuing up for the *Early Bird* special.

"I'm trying to refurbish their environment, put in modern contemporary furniture, so even the old, resident stem cells can say, 'I need to spruce up my place here,'" says Ambrosio.

With "e-stim" and exercise, transplanted stem cells in mice reproduce more quickly and don't die or form scar tissue as quickly as those in a control group.

Both of these therapies increase blood supply to the affected area. Ambrosio thinks this could be a factor in improving the vitality of grafted stem cells. "I think that exposing the stem cells to either nutrients they need or growth factors they need—or even contact to stem cells in other locations—[is what's] allowing them to behave better."

Ambrosio has also found that stem cells in older patients might be made to "act younger" through such methods.

This could have serious implications for older patients, like those who've suffered a fall, which can often set off a cascade of additional health problems. "Our idea is if you can give [patients] a little bit of a jump start by injecting their own stem cells, then can you speed up the healing process and get them back faster to doing the things they were able to do before."

THE MYSTERIES OF THE INJURED BRAIN

The most common type of traumatic brain injury occurs in a car crash. The brain stem and neck act as a fulcrum, accelerating the frontal lobes into an impact with a hard surface—a windshield, a dashboard. Patients lose memory of the crash. As they recover, they go through a stage called “agitation,” during which they are edgy, angry, unsure of why they’re in a rehab ward. Sometimes, they get violent.

“You’ve got to be able to duck quick,” says Amy Wagner, also of the Department of Physical Medicine and Rehabilitation. Wagner, an MD, studies the neurobiology of the injured brain.

Critical care docs often prescribe anticonvulsants and antipsychotic meds to curb some of the behavioral effects seen in agitation. That’s probably a good thing. But Wagner has found that different physicians prescribe these meds for different lengths of time. Some prescribe them longer than indications would warrant. So she studied the effect that long-term dosage has on brain injury patients and found that longer dosage times can hurt the brain’s long-term recovery.

She’s also looking at how variations in the dopamine transporter gene affect a patient’s recovery. Dopaminergic stimulants—like the popular drug Ritalin, indicated for ADHD—help brain injury patients wake up, improve attention and motor processing speed, and increase their levels of arousal. Wagner wants to better understand the relationship between dopamine, the genes that regulate dopamine’s movement through the brain, and the structures in the brain that dopamine and its stimulants target. Her next project will look at whether gender and hormones play a role in modulating dopamine transmission after brain injury.

As with most research about the brain, Wagner’s subject is shrouded in mystery. Thousands of genes and molecules are involved in neurotransmission—she’s chosen a few that seem likely to play a part in recovery.

Wagner knows the damage brain injury can wreak on a patient’s life. While rounding on rehab wards, she sees people who, in an instant, have lost their fundamental purchase on reality. She sees a lot of hardship, yet little could be more interesting to her than trying to understand and fix something as complicated as the injured brain.

“The fun part and challenge in brain injury is that everybody’s brain injury is different,” Wagner says. “We don’t really know everything about the normal state of the brain, and we certainly don’t know much about the injured brain.”

HOW TO MAKE YOUR ARM MOVE WHEN YOU DON’T ACTUALLY HAVE ONE

The stereo speakers in the room hiss with static, and a clutch of guys in lab coats and paper booties do the scientific equivalent of a sound check before a rock show.

“Is that all L6 or all L7?” asks Douglas Weber, Pitt assistant professor of physical medicine and rehabilitation as well as bioengineering, to a roomful of grad students and postdocs huddled around a bank of humongous computer monitors.

“That’s all L6,” says one of his PhD students, James Hokanson, referring to the purple waveform on his screen. The wave is based on an electric impulse being recorded near the L6 dorsal root ganglion of a cat in the middle of the room.

Weber holds one of the cat’s rear paws in his hand. As he strokes the fur, a crackling, popping, Geiger-counter-like sound peals across the speakers (which are, by the way, “classic Bose 301s” that Weber’s had since he was an undergrad). Waves splutter in the many tiles on Hokanson’s screen. The sound is the cat’s nervous system, firing off a report from skin cell to brain: “Something’s touching my fur.” The electrodes in the cat intercept the signal and carry it to the speakers and computer.

Weber is trying to map the neural network involved in proprioception—the body’s understanding of where its different parts are in relationship to one another. His focus is neural prosthetics—the cybernetic science that could one day help an amputee move a robotic arm just by thinking.

To do that, neuroengineers like Weber must map how the limbs report to the brain sensations like how heavy an object is and whether it’s hot or smooth.

Each of the 90 electrodes implanted in the cat can listen in on two or three neurons. Weber points to a messy waveform on one of the screens. Hokanson hits a few keystrokes and the scribbles change color—from one big scribble of white to two distinct waves—one short and red, the other longer and yellow. These represent the electrochemical banter of two neurons in the leg, caught on tape by a 10-micron-thick platinum electrode.

Weber is one of several Pitt researchers working on basic research underlying neural prosthetics—that group notably includes Andrew Schwartz, professor of neurobiology (who was Weber’s PhD adviser at Arizona State University). Monkeys in Schwartz’s lab are able

to move an artificial limb—just by thinking.

Wei Wang, an MD/PhD assistant professor of physical medicine and rehabilitation, has partnered with Weber to map the motor cortex of the brain. They’d like to be able to wire the cortex to a prosthetic arm. When the brain “thinks” a movement, the arm would get the signal, and move.

As a preliminary step, Wang and Weber are studying the brains of young patients with epilepsy. In these children, the seizures are severe enough that surgery to remove the problematic part of the brain is recommended. To do this, a neurosurgeon implants cortical electrodes (via craniotomy) to determine what functions the patients may lose if the section is removed. Wang and Weber are piggybacking on this procedure by inserting their own microelectrode arrays and putting patient volunteers through a series of basic tests.

On his laptop, Weber keeps a video of one of these tests in which a 12-year-old girl plays a primitive video game (actually, an early version of *Super Mario Bros.*) without using her hands. When she “tells” him to, Mario jumps, hits a cauldron, and *Ping!*, the cauldron turns into a coin.

It’s basic stuff—the girl controls only one degree of freedom (down and up; a researcher controls the character’s lateral movement on the screen). But Wang and Weber say they are getting closer to determining what parts of the brain control which motor functions.

They aren’t able to record individual neuronal signals, but they might not need to in order to work a robotic arm. If each neuron is the equivalent of a fan in a stadium, the electrodes can pick up a cheer from a single section. Because of redundancies in the brain, eavesdropping on a cheering section may be just as good, if not better, than listening to each individual fan.

“When you’re moving your hand, you’ll see all these neurons around a given part of the brain get excited,” Wang says.

The field holds promise that, soon, a robotic arm could be manipulated from the brain.

But when? “We’re at that difficult point in the development where it’s like, ‘Okay, are we really ready to start doing this work in patients?’” Weber says. “At some point we need to decide, ‘Okay, we know enough about the signal processing; we know enough about how the signals change over time. We’re ready to do this.’” ■

To protect privacy, patients’ names were changed in this story.