

MILD

THROBBING

INTENSE

RADIATING

EXCRUCIATING

NAGGING

MODERATE

HEAVY

SHARP

DULL

TAUT

NUMB

SORE



EVIDENCE SUGGESTS DOCTORS WILL ONE DAY
BE ABLE TO END CHRONIC PAIN | BY JOE MIKSCH

IT'S NOT JUST IN YOUR HEAD

On Dec. 8, 2011, a Cleveland Browns defender rolls up on the leg of Pittsburgh Steelers quarterback Ben Roethlisberger. The weight of the assailant forces the quarterback's ankle to do things ankles shouldn't do. Yet Roethlisberger finishes the game and—with the exception of one missed start—finishes the season despite a clearly painful injury diagnosed as a high-ankle sprain.

As he limped around the pocket in those last few games, pain was telling Roethlisberger that perhaps he shouldn't be out there trying to run away from 300-pound men with bad intentions.

Pain was reminding Roethlisberger that he had an injury and saying that putting his 250-pounds of heft on that damaged ankle probably wasn't doing the joint much good. *Come on, man, this isn't helping you heal.* Through the offseason, though, Roethlisberger's ankle will get better, the pain will go away, and in 2013 the Steelers will dismantle their opponent in Super Bowl XLVII by a score of 118 to -45 and all will be right with the world.

Emily Dickinson said of pain, "It has no future but itself." But the shadows may be lifting. There's much to figure out still, yet the work of Pitt researchers offers new inroads, and new optimism, for treating seemingly intractable pain.

ILLUSTRATIONS | TIM GROEN

But sometimes pain is just pain. It doesn't help anything. (Not in any way that we know of. Oddly, in some cases—and we'll learn more about this later—an intolerance of pain may be associated with a resistance to the ravages of cancer.) It doesn't tell you to not let your body do certain things. It doesn't protect you from reinjury. And it may never stop. Ever. Chronic pain—the kind associated with cancer, arthritis, fibromyalgia, diabetes, postsurgical agony that continues after the wound has healed, and phantom pain, among other conditions—can ruin lives and is difficult, if not impossible in some cases, to treat.

What do you do when it seems there's nothing but pain? You've fallen into a pit of

A key that can open the lock of chronic pain has yet to be made. Still, we've been allowed a glimpse behind the door. The work going on in Pitt labs—and some optimism—makes it possible to imagine a world where gene therapy can help a pain-wracked body produce more of its natural painkillers, where doctors can predict who will respond to a certain treatment and who requires another approach, where stopping nerves from going haywire can put a bedridden sufferer back out on the golf course. Pitt researchers are working toward a world where chronic pain sufferers are not thought of as malingerers, and no one says, "There's nothing 'wrong.' It's just in your head."

the standpoint that it makes you half-aware of what's going on. It doesn't block pain, though, it just blocks the perception of pain." If that's not enough of a problem, Glorioso concludes, narcotic-related side effects—dulling of perception, constipation, the need to dose every few hours—can stop pain sufferers from taking narcotics. And a pain drug not taken is no pain drug at all.

Since 1999, Glorioso has been working to find a new way, a more precise way, to calm or even eliminate chronic pain. And it looks like he might be getting close. His work, conducted in concert with, among others, David Fink of the University of Michigan and Michael Gold, professor of anesthesiology at Pitt, has come

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depression, and you can barely hold the pill that's supposed to confer relief. You wake up crying because it hurts so much. Getting up and going to the bathroom is so excruciating that there are times you don't. You've become a hermit trapped by agony.

Poet Emily Dickinson had a pretty good grasp on chronic pain when she wrote, "It has no future but itself."

"It's been a longstanding argument in the field—some people believe that [chronic] pain is centrally driven [caused by malfunctions in the brain], and that flies in the face of all the evidence," says Gerald Gebhart, Pitt professor of anesthesiology, medicine, neurobiology, and pharmacology and chemical biology, as well as director of the University's Pittsburgh Center for Pain Research. "Basically, if you don't have peripheral input, you don't have pain. While it's true that pain is in the brain in the sense that you interpret peripheral events there, our progress has been on the afferent side, the pain fiber side. And we're identifying genes, mediators, and growth factors that contribute to pain. If you could identify two or three [such] things that are involved, you might be able to block pain selectively. That's the key for treating pain."

If these efforts are successful, the 25 percent of American adults who suffer from chronic pain will be grateful, as will the U.S. economy. The Institute of Medicine estimates that chronic pain costs us \$560 billion to \$635 billion annually in terms of lost productivity and health care costs.

One nearly foolproof way to treat pain—acute or chronic—is flooding the body with an opiate like morphine. The drug can even bring relief to most terminal cancer patients who are in extreme agony.

How sensible is that approach for people with arthritis, for example, or diabetes? There's really no practical treatment for their pain. Non-narcotic nonsteroidal anti-inflammatory drugs such as aspirin and ibuprofen can help, but not much, says Joseph Glorioso III, PhD professor of microbiology and molecular genetics in the University of Pittsburgh School of Medicine. "You give them narcotics, and they can become tolerant and/or addicted," or the narcotics can render a patient relatively pain-free but in a mental fog, he adds.

And, he continues, "The problem with any systemic [drug] application to treat pain is that it goes everywhere, and it affects the brain and so on. Morphine is not a very nice drug from

far enough that phase I and phase II clinical trials have ended successfully, and a phase III trial will begin soon.

In essence, Glorioso hopes to curtail pain by stuffing a herpes simplex virus (most of us carry the dormant virus anyway), engineered so it can't reproduce, with the gene for enkephalin, one of the body's self-made pain relievers. The virus, with its payload, is injected into the skin, and then the herpes virus does what herpes viruses do: It follows the nerves to the nuclei of the sensory nerves off the spinal cord. Then the gene product is released inside the spinal cord.

"Now the thing that's interesting about enkephalin is that it's a protein that's processed into small peptides that are just five amino acids long," Glorioso says. "And the peptides bind to a specific receptor. When they bind, they block the release of neurotransmitters, and so the pain signals are lost or inhibited. The beauty of it is that the receptors are only on the right neurons for silencing."

This gambit had proven successful in rats on numerous occasions. It was time to see whether it worked in people. A company called Diamyd Medical, of which Glorioso's a stakeholder (Glorioso will also earn royal-

ties from the gene-therapy technology under a University licensing agreement), conducted the trials, recruiting and treating 10 adults with intractable cancer-related pain. The results of the phase I trial, published in the *Annals of Neurology* in 2011, seem promising.

“Pain is usually measured on a self-reporting scale of 1-to-10,” Glorioso says. “One is nothing, and 10 is bad news. Well, these patients had scores of eight or nine that went to almost zero.

“So far, it has worked extremely well!”

Glorioso’s optimism is not dampened by the fact that the phase I trial was very small—some of the 10 patients succumbed to their cancer, as well. After all, he says, the trial was intended to test the safety of the treatment and the ability of patients to tolerate it. Yet it also showed a measurable, and significant, decrease in reported pain.

Phase II, using a similar patient population, is not only larger, but it is randomized, double-blind, and placebo-controlled. Phase I participants were also given morphine during the four-week trial. Phase II (which has ended, with results pending) assesses the efficacy of the gene therapy minus morphine. Thirty patients are enrolled.

“We’ve already found that gene therapy is longer-lasting and doesn’t induce tolerance like opiates do,” Glorioso says. “And we’ve found that it complements morphine, enhancing its effects so you can lower the dose substantially. In phase II, the real boon for patients is the possibility that we’ll be able to withdraw morphine completely.” To be able to do so, he says, would mean that patients would not only be relieved of their pain, they would not have to endure any of morphine’s unpleasant side effects.

“Joe’s stuff has been tested, and it’s quite interesting, and it works,” Gebhart says. “The results are being evaluated. They’ve found a way to increase enkephalin, an opioid made by the body. But there’s another side of the spectrum—finding the genetic differences, the genetic contributions that lead to chronic pain or total pain insensitivity. If you find out what [the issues are] genetically, you can find out what the underlying ion channel or molecule is.” Then scientists can imagine new treatments taking advantage of the body’s natural painkillers or those tailored to the individual, he says.

Pitt’s Inna Belfer, an MD/PhD associate professor of anesthesiology and human genetics, calls what Gebhart is referring to “the pain genome.” Thus far, more than 10 genes have been proven to play a role in human perception of pain and pain tolerance. More are being sought.

From Belfer’s perspective, to know the pain genome is to pave the way to pain relief, personalized-medicine-style. She offers an example: A genetic variation causes some women who have never experienced chronic pain to experience perpetual agony after giving birth. Small doses of pain medication provide relief for some. Others can’t get any relief, no matter how high the dose. Redheads feel pain more acutely. And a genetic variation shared by some breast cancer victims—recently pinpointed by Belfer and her colleagues—makes them almost untouchable to pain medications but four times as likely to survive. Finding a way to manipulate the responsible gene or genes is a distant but, to Belfer, attainable goal.

“All of this started with animal work in 1999,” says Belfer, who also directs the molecular epidemiology of pain program at Pittsburgh Center for Pain Research. “We found that, when you control very tightly for environmental factors, you see that 40 to 60 percent of variability [in how mice experience pain and respond to treatment] is genetic. We see something very similar in humans. Twin studies show that there is a very pronounced genetic contribution to variability in pain and analgesia. Not only are these genes statistically associated with pain modalities, we have functional data.”

The process of finding pain genes in humans begins with a suspicion (termed the “candidate gene approach”) or a genome-wide association study. The researcher takes one group of people with a certain trait—as in the aforementioned case of breast cancer victims who are extremely susceptible to pain but more likely to beat the disease—and a control group of similar women who have breast cancer but don’t exhibit a tendency to be resistant to pain-relief drugs.

Belfer suspected that the gene (OPRM1) that codes for a particular opioid receptor might play a role.

“It’s an obvious candidate in that [the receptor] binds to opioids,” she says.

It turned out that the women who tended to suffer pain more and survive longer were found to have a variation in OPRM1 not shared by the control group. (The variation is a single nucleotide polymorphism, or SNP, in which one form of a gene, called an allele, differs from the other form of that gene.)

The fact that this SNP (people say “snip”) relates to pain wasn’t much of a surprise (since it is an opioid receptor), but its association with cancer survival sure was.

“All we have now is a statistical association between this particular allele and survival, but the sample size was over 2,000, and we think it was a well-designed study. So this leads us to the conclusion that Mother Nature is doing something balanced,” Belfer says. “These women are poor responders to opiates throughout their lives, but when it comes to breast cancer, the same polymorphism makes them better survivors. This was absolutely unexpected.”

This kind of discovery, and this is a conclusion that applies to the pain genome project as a whole, Belfer says, will do two things: It will provide new drug targets for the treatment of pain, and it will predict outcomes for already-established treatments.

“We will know whether to give this patient opiates, or we will know that opiates don’t work,” she says. “We will know whether we should give a patient bigger doses of opiates or whether dosage is not a factor, and they simply won’t respond.”

As is often the case, though, it’s not as simple as all that. Identifying a pain gene is one thing. Understanding all the factors that influence the expression of such a gene is another, much more complex matter entirely.

In October, Belfer and colleagues at McGill University in Montreal and the University of Florida in Gainesville published a paper in *Nature Neuroscience* showing that the activation of the vasopressin receptor pathway (vasopressin is an antidiuretic hormone) can relieve inflammatory pain caused, in this study, by capsaicin, the stuff that makes hot peppers hot. Well it did so in some cases. Once in a while.

Mice lacking a certain gene (AVPR1A),

which encodes for the vasopressin receptor, bit and licked at their hind paws, which were irritated by capsaicin. Pain-resistant mice had significantly higher numbers of the receptors and didn't gnaw and lick. But something curious happened when Belfer et al. tried to replicate these findings in people. Subjects who were given a vasopressin-like drug on their first day of testing experienced no pain relief. Those who received the drug on the second day did.

So, why? Well, Belfer and her team theorized that because it's something new, an experience fraught with novelty and maybe a sense of anxiety, the first day of testing might be stressful for participants. Examining the data, the team found that stress activates the natural production of vasopressin. Administering it as a drug, it turns out, only works if the pathway hasn't already been activated by stress, explaining why those who received the vasopressin analog on day two, when they felt more comfortable, experienced pain relief.

(When the researchers looked back at their mouse data, they discovered that the mice that

Pathological changes to these pain sensors can cause sufferers of irritable bowel syndrome and pancreatitis—among other diseases—to continue to suffer after the underlying cause of their agony is treated. Davis wants to understand what causes this damage and how it can be reversed.

How he came to want to do so is a bit unusual.

"I started out as a developmental neuroscientist with a background in anatomy, physiology, and neurophysiology. And my wife [PhD Kathryn Albers, Pitt professor of medicine in the Division of Gastroenterology, Hepatology, and Nutrition] was two doors down. She's a molecular biologist, and back in the '90s, when transgenic technology was just taking off, she developed a transgenic mouse that overexpressed a developmentally important growth factor—nerve growth factor (NGF)—in the skin."

Neat-o, thought Davis—who is also a PhD professor of medicine in the Division of Gastroenterology, Hepatology, and Nutrition,

A pain drug not taken is no pain drug at all.

had been in the testing environment longer were the ones who responded best to the vasopressin drug. They'd fared much better than the newbies who were freaking out before becoming acclimated. The group can't yet be certain that stress is what skewed their results, but the correlation, Belfer says, is there.)

"And there are other factors, too. The interplay between genes and environment is really everything," Belfer says. She notes that a patient's anxiety level, sex, sleep patterns, and so on, all make a difference. "Finding the gene, understanding the molecular pathway—that's vital, of course. But we must not only identify and understand genetic factors, we must also identify and understand risk factors [for pain] that may be demographic, clinical, or psychosocial that influence genetic expression," she says.

What of the nerves themselves? They are, after all, responsible for sensing pain and telling the brain, *That hurts!* This is the bailiwick of Brian Davis, who, with Gebhart and others, is searching to understand and find ways to treat the primary reason for doctor visits in the United States: ongoing somatic and visceral pain (particular flavors of pain detected by specialized nerves in the skin and organs).

as well as a professor of neurobiology. But nerve growth factors weren't in his line of study, and he wasn't particularly interested in the model. "So I begrudgingly looked at [Albers' mice]—and they had this incredible phenotype where the sensory nervous system was really [ramped up]."

Suddenly Davis found Albers' mouse model interesting. And soon it became the genesis for a new line of scientific inquiry. "We had very disparate interests, but we came together because of this tool she made. I went from having a developmental lab to ... a pain lab."

NGF is vital. Without it and other growth factors, the nervous system doesn't develop. In adults, NGF modulates pain sensitivity and the development of pain fibers. That's helpful. But, when it's overactive, it can cause hypersensitivity to pain. (Hypersensitivity is one symptom that makes some people wonder whether a patient's pain is real or imagined.)

"In a lot of disease states like rheumatoid arthritis, inflammatory bowel disease, or cystitis, NGF goes up, and things get hypersensitive," Davis says.

But further study proved that NGF isn't the only player.

"As important as NGF is, there's actually another growth factor called artemin that's maybe more important, and, in fact, it may work synergistically with NGF to produce chronic pain states not only in the gut, but in the skin and musculature as well."

The Davis/Albers group has found that a population of sensory neurons has receptors for both NGF and artemin. These neurons also have certain channels that are known to play a role in inflammatory pain. That's part of the puzzle.

In 1997, when Michael Caterina (now a professor at Johns Hopkins University) was a postdoc in David Julius' lab at the University of California, San Francisco, he identified the receptor for capsaicin. At first scientists thought the receptor, called TRPV1, only sensed heat, but it turns out that TRPV1 is present in many pain-sensing neurons. Why is it so prevalent?

"It's actually probably more important for inflammatory pain than detecting heat," Davis explains. "Originally it was thought to be a thermal detector, but it turns out that you can use genetic engineering and get rid of it, and animals are still relatively normal in being able to detect heat—but they don't develop inflammatory pain."

Drilling down deeper, Davis and colleagues found that sensory neurons that express TRPV1 also express the receptors for NGF and artemin. A series of experiments then showed that if such sensory neurons are exposed to NGF and artemin alone, pain lasts for about four hours. If TRPV1 is thrown into the mix, pain lasts for six days.

Then add in TRPA1, which responds to mustard oil. When TRPA1 and TRPV1 exist in cells along with NGF and artemin receptors, Davis says, "You have this really evil population of sensory neurons that express TRPA1 and TRPV1—both of which, if you knock them out, decrease inflammatory pain—and these cells also express the receptors for the growth factors, which increase inflammation. It's like the perfect storm converging on one type of neuron." This perfect storm doesn't exist in all of us, just, it seems, those of us who experience this kind of ongoing nerve-related pain.

These growth factors are among those primarily responsible for wiring organs with nerves. In cases of visceral pain—such as colon, bladder, stomach, and pancreatic cancer—70 to 80 percent of the cells that innervate those organs express TRPV1 and

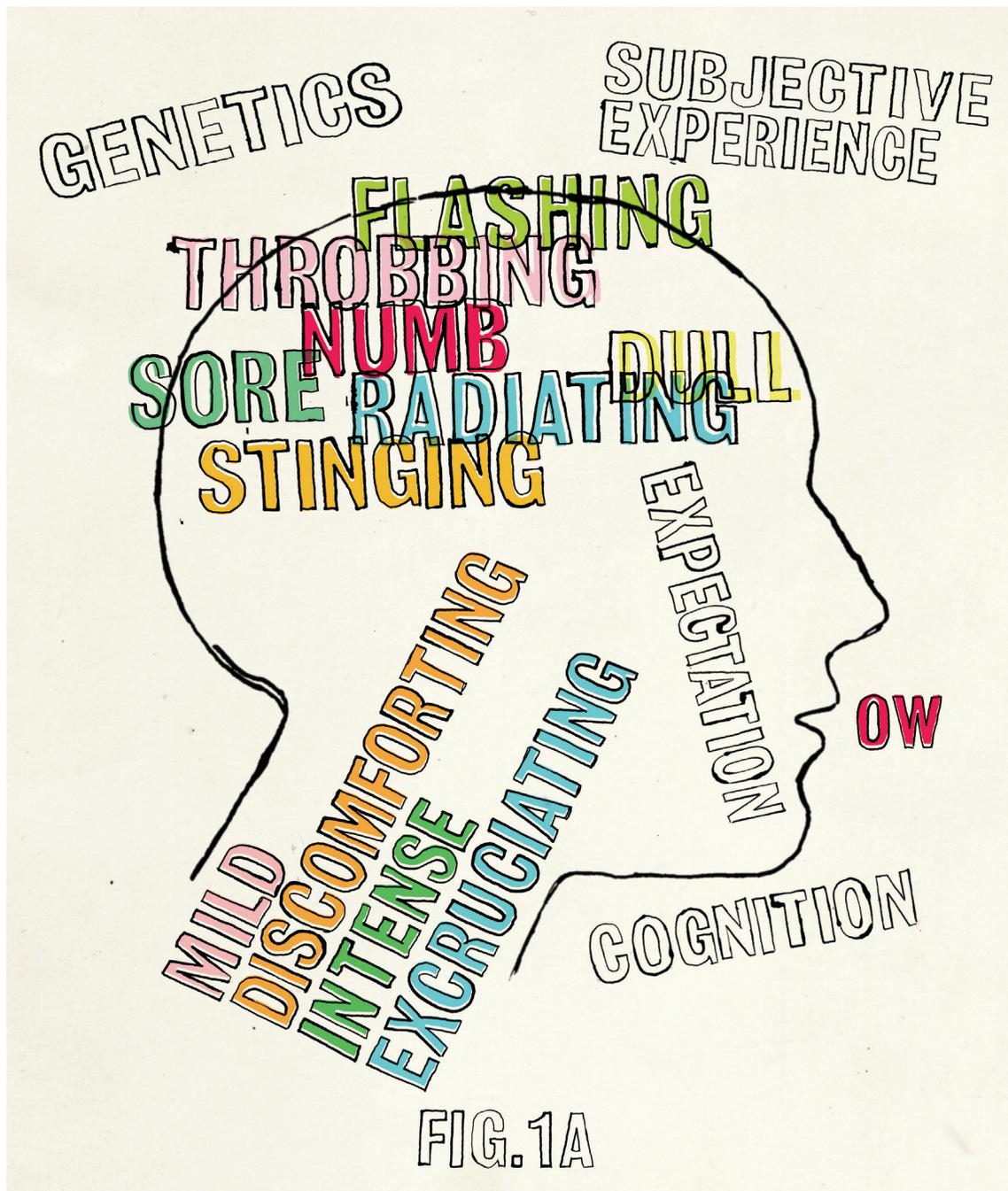


FIG. 1A

TRPA1. So, it's pretty obvious why finding a way to block these bad actors (which are also good actors, to an extent) might be a way to alleviate pain.

"One of our postdocs, Erica Schwartz, used drugs that blocked TRPV1 and TRPA1 in [Albers'] model for pancreatitis," Davis says. "She not only blocked the inflammation, but blocked the pain. If you can block the sensory neurons from releasing their peptides [known as CGRP and substance P], you not only can block the pain, but you can

block the inflammation, block the disease itself."

Blocking TRPV1 and TRPA1, though, can't yet be done without a cost. The good things that TRPV1, TRPA1, NGF, and artemin do—help us perceive heat, regulate vasculature—can be blocked this way, as well. Some experimental TRPV1 blockers, for example, caused some participants in a drug company clinical trial to develop fevers and burn themselves with hot liquids. An anti-NGF drug may have caused the death of

blood vessels in participants' hips. (The drug company contends that people felt so free of pain that overexertion caused the injury.)

There still is a lot to sort out, Gebhart says. "There are physiological differences (between individuals), plus there are emotional, cognitive, and affective contributions that influence the way you interpret pain." But not delving into such complexities, he concludes, means no new targets and no new therapies. It means that chronic pain will continue to have no future but itself. ■