



There must be better options for treating pain than opioids, which are the best medicine has to offer many people. Pittsburgh is building a new pain-research enterprise to pursue such a dream. In these pages, Doris K. Cope, Pitt's expert on today's remedies, and new recruit Gerald Gebhart, considered by many to be the world's preeminent pain researcher, share their visions and insights. (Shown immediate left, *Papaver somniferum*, from which opioids are derived, with other flowers.)

CONVERSATIONS ABOUT PAIN
INTERVIEWS BY JOE MIKSCH

EVERYBODY HURTS

Buddha thought pain was endemic to the human condition, a natural partner of desire. Athletes wear T-shirts advising us that pain is weakness leaving the body.

Your little sister can be a pain.

The consideration of pain at the University of Pittsburgh School of Medicine is a slightly different animal, less a philosophical pursuit than one dedicated to alleviating hurt born of cancer, nerve disorders, or surgery.

On the clinical side of things is Doris K. Cope, Pitt professor of anesthesiology and division chief of the UPMC Pain Medicine Program. Cope came to Pitt in 1997 to found and lead the program. During the early years, the program saw hundreds of patients a year. Last year, with the program having grown to seven sites from one, program staff saw more than 22,000.

The tools of Cope's trade are nerve blockades, electrical stimulation, radio-frequency current, medication, and intrathecal pumps—which deliver medicine directly to the spinal cord. Physical therapy, psychological therapy (Cope has a master's degree in clinical psychology in addition to her MD), exercise, and nutritional and sleep counseling also are often part of the pain-treatment regimen.

In her office at UPMC St. Margaret, Cope—who speaks quickly, but with a gentle lilt true to her Georgia roots—explains that though pain has always been with us, pain medicine per se is a newly recognized subspecialty. Having a core group of physicians dedicated to treating pain, she says, improves care and, frankly, has become something of a necessity as humans live longer.

“Now, cancer patients with successful treatment can live decades,” says Cope. “People live until their bones wear out.”

She adds it only makes sense that those who live long want to live well:

“People want to function and be happy. They’re not content to sit on the porch and knit afghans and moan about their arthritis. They want to go to the beach. They want to go to the mountains. They want to fly fish. They want to entertain. They want to do things.”

On the flip side of the pain coin is Gerald Gebhart, basic scientist and new recruit for the School of Medicine. Gebhart hails from the University of Iowa College of Medicine, where he led the Pain Interest Group. (P.I.G., for short. Who says pain researchers in the heartland don’t have a sense of humor?) At Pitt, the PhD professor of anesthesiology, neurobiology, and pharmacology heads the newly established Pittsburgh Center for Pain Research.



Cope

It’s clever-acronym-free, yet Gebhart has high aspirations for the center, which represents a collaboration of the anesthesiology and neurology departments as well as the gastroenterology, hepatology, and nutrition division.

“Simply stated, I want to make the University of Pittsburgh the preeminent pain research center in the world,” he says.

The achievement of this goal requires the recruitment of existing world-class pain research talent, bright young minds interested in pain research, and a balance between the clinical and the basic science sides.

“I’m kind of ambitious about that,” Gebhart concedes.

Gebhart, as one might suspect, is no slouch himself, having developed a reputation as one of the world’s most sophisticated pain researchers during his tenure at Iowa. Among his more recent honors is the \$50,000 Purdue Pharma Prize for Pain Research, which recognizes a lengthy heritage of research, a dedication to training young researchers, and a deep and broad range of research interests.

If Gebhart is known for his work in any one area, it’s visceral pain, the kind of agony associated with damage or disease affecting the internal organs. Pancreatic cancer patients usually experience visceral pain. It’s difficult to treat. Finding the pathways and systems at the root of visceral pain has been his focus. His work may lead to new targeted drugs.

In an effort to tease out the nature of pain, *Pitt Med* sat down separately with Cope and Gebhart. In wide-ranging conversations, each spoke about where we’ve been and where we’re going in treating humanity’s common yet unwelcome companion. —JM



DORIS K. COPE

PM: What are the differences in types of pain?

DKC: Okay, when you pinch yourself, when you feel something, there are certain molecules, certain channels that are opened that cause a response, and it’s an appropriate response. You stop pinching yourself, and it stops hurting.

Chronic pain, a pinch that goes on and on for days or weeks or months, sets up entirely new pathways in the central nervous system. New feedback loops, new proteins are being synthesized. We think even new genes are being expressed, so it’s kind of a self-perpetuating abnormal state. Chronic pain is not warning you that, “Ouch, I touched the stove, and it’s hot.” We call it a wind-up phenomenon. It’s a revving up of the central nervous system. It’s almost like a seizure of pain. A seizure is just out of control.

PM: How has treatment of pain progressed?

DKC: I think the options have changed. At one time, for surgery, for example, they didn’t have anesthetics, so they gave people whiskey and a bullet to bite on. ... They had the orderlies hold people down, and they would pin them to the table, operate as fast as they could without sterile technique, and hopefully the person survived the shock of it.

So we’ve progressed to better analgesics. In addition to anesthetic and analgesic drugs, we now have neuropathic pain medicine. We know that some of the antidepressants work for pain on some of the same neurotransmitters that are involved in both pathways. We have a lot of interventional options. We have radio-frequency [current], we have certain

nerve blocks, injections. We have steroids; we have surgical techniques for implantation. If I give you an intrathecal pump, I'm literally giving you less than one-hundredth of a [standard opioid] dose, but it's going directly to the spinal pain receptors, and it's much stronger—with fewer side effects.

We also have more psychological understanding. People can be distressed, and it's not a "pain problem." It can be depression, anxiety. It can be opiate seeking, you know, "I want to feel euphoric, and I perceive this as pain."

I sometimes see patients who had a very traumatic childhood, who have been abused or suffered, and it's not okay to talk about psychic pain, it's not okay to even acknowledge psychic pain, but [patients may be able to say], "I'm not quite right. I feel pain. My stomach. My pelvis is just not right."

They feel they're not right, but they can't put [a] finger on it. It's very diffuse, free-floating anxiety and pain. Because, to go back to the memory of what they went through—they've almost distanced themselves from that. So we talk about pain, but it's not really a pain syndrome.

So, there's pain, and there's suffering.

Old people who live a long time, I tell them, "You live your life, and your body keeps score."

People who have been active in sports, who've been steelworkers, who've been heavy lifting all their [lives], they come in at 75 or 80, and their [bodies] keep score. It's not the same as the person who has been trim, exercised, not done heavy, strenuous things to [her] body.

PM: What's the "next big thing"? Where is pain medicine heading?

DKC: Maybe gene therapy, targeting specific brain chemistry that we can change. Maybe we'll be able to produce certain neurotransmitters in our own body. Maybe we'll be able to diagnose genetic likelihoods, a tendency toward developing neuropathy.

[If we were] able to more specifically measure the ravages of pain, maybe [we could] target our therapy more specifically to those mechanisms. Right now, you take morphine—it gets the acute pain, the chronic pain, it gets the brain, it gets everything. So it makes you constipated, nauseated, and dopey, though it does take away the pain. If we could find more specific drugs and more specific receptors, [the therapy] would not

make you constipated and confused and give you euphoria. It would just work with the pain changes molecularly. That would be a huge leap forward.

PM: If there's one thing you could understand about pain and the treatment of pain, what would that be?

DKC: I would like to have some kind of objective measure of the changes that have happened in the brain chemistry or in the spinal cord from pain—some way to objectively quantify both the pain that's there, the type of pain, and also the response to treatment. Right now, patients get some better, or some worse, or they stay the same. And we do multimodal therapy, so we're not even sure if physical therapy is 10 percent [responsible

"You live your life, and your body keeps score."

for a success in treatment] and medicines are 20 percent and injections are another 20. If you put it all together, that's a 50 percent reduction, which is significant. The function's good. The pain's better. But it would be nice to be able to do a blood test like you do for diabetes. You can follow that.

PM: How does what Dr. Gebhart is doing complement what you do?

DKC: I would like to see more interdisciplinary collaboration. Maybe we can come up with some cross-training opportunities. Maybe we can be present in each other's clinics. I'm thinking we can really transcend boundaries here and work collaboratively with others. An institute without departmental boundaries.



GERALD GEBHART

PM: When did we start to understand the mechanisms behind pain?

GG: The actual study of pain mechanisms,

if you will, probably goes back to the early 19th century. [Much earlier were] people like Descartes who were involved in conceptualizing what pain was. There were some physicians in the Civil War who wrote about pain as a consequence of injury. There's the stump pain, they call it, subsequent to an amputation. Weir Mitchell was a physician who studied the effects of damage to nerves from gunshot and the bizarre neuropathic type of pain that results.

So then, with clinical writings, observations of patients in the 19th century were the first, at least among the earlier documented histories, systematic investigations.

But it wasn't until the end of the 19th century, the beginning of the 20th century that [Nobel Prize-winning neurologist Sir] Charles

Sherrington actually began to study reflexes to noxious stimulation. He's sort of the father of pain experimentation. He provided for us a lot of the operational definitions of stimuli and responses that are still used today in the study of pain.

PM: Are there different kinds of pain, or is pain pain?

GG: Pain can be characterized in many, many different ways. So the simplest differentiation is acute pain as opposed to chronic pain.

But then there's also pain that's defined by its location. There's cutaneous pain and deep pain, like muscle, joints, and viscera. And people categorize pain in that context because deep pain, particularly visceral pain, is organized anatomically in a different way and associated with greater emotional responses to the pain. So if you slam a car door on your hand and in the process you break a finger or two, you look at that—it's bleeding, it hurts, but you know you're not going to die from this.

If you get pain subinternally in your chest that radiates up to the shoulder, the emotional import of that is [it's] potentially life threatening. So pain that arises from the internal organs is almost always associated with greater emotional importance than other kinds of pain.

Then there's other pain that's associated with specific injuries. So there's what's called

neuropathic pain, which is pain due to nerve injury. There are many different ways in which pain is categorized. I guess [how you think about it] depends upon your medical specialty and discipline.

Interestingly, the mechanisms are different for deep pain, for cutaneous pain, for neuropathic pain, and understanding those mechanisms will potentially lead to better strategies for managing the treatment of pain. That's the reason why we study mechanisms of different kinds of pain.

PM: What are these mechanisms?

GG: Let me give you an example from visceral pain. Each visceral organ receives

So it's easy to understand how the viscera are different from other tissues. And it's easy to understand that if you can understand the mechanism of visceral pain, it's going to be different than cutaneous pain, and it also maybe provides a different therapeutic target. It may have different receptors associated with it or different ion channels associated with the mechanism of the pain.

The same is true of neuropathic pain. When you damage a nerve, or sever a nerve, as opposed to cutting your skin, that nerve will heal, but even though it does there may be some permanent damage. So when the nerve is damaged, you get bizarre sensations: tingling, numbness. If you fall asleep on your

tal in three or four days. And you recover.

The other kinds of pain are very difficult to treat because they're associated with insults that don't heal properly or heal inappropriately and then lead to continuing pain. The usual strategies for management, like opioids, if they work, usually have to be given in high dosage. That's pretty undesirable, because opioids have unwanted effects. They make you drowsy and sedated and make you constipated. They can affect your breathing. And then long-term use of opioids is associated with development of tolerance and maybe dependence and maybe abuse.

So if you look at the drugs we have available for pain management now, we still rely on those that have been around for quite a while. The nonsteroidal drugs like aspirin ... there are many new aspirin-like drugs, but in terms of efficacy, they're not that much different than aspirin. There are new opioids, but an opioid is like a rose—it may differ in color, but it's still a rose.

Opioids are the most efficacious drugs we have for pain. Opioids are capable, in sufficient dosage, of relieving virtually all pain. But sometimes you have to be nearly unconscious for that to happen. And that's not good. So we're looking for new drugs all the time, and the molecular revolution in biology has permitted us to identify some specific molecular targets, such as ion channels and new receptors that are associated with pain mechanisms. The hope is that identifying these new molecules that are in neurons and are associated with pain will allow us to develop new chemicals, new drugs, that target those molecules.

The downside of identifying all of these molecules is you identify and target a single molecule, and you can very effectively block that molecule, but pain is not associated with activation of just the single molecule. It's multiple molecules. That's why opioids, for example, are so good. They do more than just a single thing. The drugs that have been developed that do just a single thing typically work just a little bit. We want to know what the molecules are, but targeting them has not been particularly fruitful in developing new drugs.

Presumably some very new strategies are effective in combining targets. The [drug] industry [has been] saying, "Let's develop



Gebhart

input from two separate nerves, whereas your finger receives input from one nerve. So, immediately, there's an anatomical difference between the internal organs and skin, muscle, and joints. Skin, muscle, and joints are all the same [in anatomical organization]. One nerve goes here, and that's it. If this were your bladder, there would be a nerve from here, and there'd be a nerve from there. [Gebhart gestures to opposite ends of an imaginary bladder.]

This complicates things enormously, if you think about it. It makes visceral pain difficult to localize, so if you get a pain in your abdomen or thorax, because of the anatomical organization of the nervous innervation, it's hard to localize. So the mechanisms are different, because each nerve has a different function.

arm, and you wake up, you can't move it. Then when it sort of begins to wake up it tingles a little bit. Neuropathic pain is sort of like that. You have incomplete sensory properties, but you have tingling, you have numbness, sometimes you have shooting pain associated with it.

PM: How does that complicate treatment?

GG: I think that acute pain and acute postoperative pain management [are] pretty straightforward. You go in for a surgical procedure, they cut into your belly and remove your appendix, and they sew you back up, and you've got pain. But it's treated with opioids and nonopioids very effectively. They make you walk around, and you're out of the hospi-

this specific drug that acts on a selected target.” But now I think they know they need to develop a chemical that has selectivity for several targets, two or three targets. I think that’s what’s on the horizon.

PM: Any research into nontraditional forms of pain treatment?

GG: There’s great interest in the pain community to understand why some of these things are effective in people. I take the view that some of these folk medicines and these nontraditional approaches are helpful and useful. It’s part of our job to find out what is contained in those folk medicines or ... strategies that is the useful principle.

People drink green tea or they take some herbs ... and some of these things have been proven to be useful. And others have been shown to be totally nonuseful, though they may have a placebo effect.

If you look at the history of effective drugs, they were derived from natural sources.

But some of these things that people have gotten from snakes and spiders and whatnot have very selective actions on certain ... sodium channels. If you could, for example, develop a drug that was effective at one of the sodium channels that’s called the NAV 1.8 channel, it could be useful, perhaps, in pain because neurons that express NAV 1.8 are uniformly associated with pain processing. I think it emphasizes again why it’s important to look at these natural treatments people have used over the years, sometimes centuries, because some of them have active principles that might be extremely useful. And some of them are just hokum, just nothing. Still, I think it’s incumbent on us to find out—to find out the truth.

PM: Is there one question regarding pain that you’d like to have answered? What would you like to know most that you don’t know right now?

GG: Let me preface this by saying, one of the characteristics of many of the pains

their patients, but is not their primary focus.

Pain management is poor because it is not emphasized in education. It’s also poor with respect to the use of opioids because there are societal and legal restrictions against the use of opioids. In the current [federal] administration, the Drug Enforcement Agency is very aggressive in seeking out and punishing healthcare practitioners, principally physicians, who are prescribing huge dosages of opioids to patients.

There are many, many cases where physicians have been put away in jail for basically distributing opioids, as if they were drug dealers. And it’s a very, very fine line physicians are walking these days in terms of efficiently and effectively managing pain and staying out of legal trouble. We’re trying to do the best we can to educate law enforcement people about the difference between opioid abuse and opioid use at high dosages. But it’s a difficult, difficult fight. And it is a fight. Physicians are under considerable legal pressure not to give prescriptions for high

“There are families who are not happy that grandma is being treated with an opioid for her cancer pain, even though she may be terminally ill.”

es. Opium comes from the poppy plant. We learned about aspirin [after realizing the analgesic effects of] salicylates, which are part of willow bark. So there are many, many natural products out there—some of them that come from toad skin, and others have come from plants, and venoms from snails and snakes—which are complex things when you collect them. But you have to identify what the active principle is. There’s [a new drug] that comes from a cone snail that’s a poison that the snail uses to kill its prey. [It’s] now used as an analgesic in certain pain states.

There are also toxins from snakes and spiders that have been extracted and purified that are being tested in a variety of circumstances. For example, some of these block sodium channels. [You’re probably familiar with local anesthetics like lidocaine that your dentist might administer.] But they’re sort of nonselective in that they block all sodium channels. There are like nine or 10 [channels]. So, you don’t want to give a local anesthetic in great concentration directly into an artery because it will affect the heart and could kill you.

that are chronic and difficult is the fact that people are hypersensitive to normal stimuli.

So, if there was one question that I could answer and address, it’s “What is the mechanism that contributes to the development and the current irreversibility of hypersensitivity in disorders like interstitial cystitis, low back pain, fibromyalgia?”

It may be naïve to think there’s one mechanism, there may be multiple mechanisms, but if we could [ask] about the mechanism that causes the persistence and current irreversibility, that would be the question I would like to see answered. Because that would probably provide an efficacious strategy for management of many, many types of chronic pains.

PM: What problems do physicians face in treating pain?

GG: It’s a complicated issue. First of all, to be blunt about it, most medical school curricula do not include sufficient education about pain and then about pain management. Most physicians, then, when they get out and practice, specialize in things where pain is almost always present in a subset of

dosages of opioids to people in pain.

There’s also the stigma associated with the use of opioids.

So, as bizarre as it may sound, there are families who are not happy that grandma is being treated with an opioid for her cancer pain, even though she may be terminally ill, because, “What are the people in the community going to think? Grandma’s become addicted.”

In some way, it makes them complicit in making grandma addicted and, in some way suggests that they’re a bad family.

If you talk to cancer pain patients who have been told, “You’ve got a certain amount of time to live; it’s inevitable that you’re going to die [soon],” and you ask them, “What worries you most?” You might think they’d say, “I’m scared of dying.” It’s not that. They’re scared of dying in pain. That’s what it is. They’re afraid of suffering.

Most of these people will accept the fact that their [lives are] going to come to an end. It’s going to happen to all of us at some time, so you accept that once you get over the initial shock. But ... they don’t want to die in pain. ■