DOES THAT HURT?

SOMETIMES, IT'S ALL IN YOUR HEAD, AND THAT'S REAL, TOO

BY KRISTIN OHLSON

When Stuart Derbyshire was 10, a teacher played a mean, if enlightening, trick. The teacher sent Derbyshire and a few of the boy's friends out of the classroom and also left the room himself. He returned with a pot of boiling water, which he lugged past the children

into the classroom. While Derbyshire and his friends waited in the hallway, wondering what was happening, another boy crept out of the room. *The teacher is going to plunge your hands into boiling water!*, he warned them. In a few minutes, everyone was summoned back into the classroom. The teacher pointed out the pot of water, blindfolded Derbyshire and his friends, led them across the room, and one by one, dunked their hands into the pot. The children screamed and yanked out their hands, yet the teacher had replaced the hot water with tepid water before they'd returned to the room.

"I distinctly recall that the water felt hot, even though it was actually tepid," says Derbyshire, now a Pitt assistant professor of anesthesiology and radiology. "I really perceived it as hot." His teacher had taught them a lesson about how sensations are not absolute but can be influenced by context.

Ever since, Derbyshire has been interested in pain, especially in the relationship between pain and perception. "Pain is capricious," he says. "If you're playing football and get kicked in the shin, it won't hurt much, but if you say something inappropriate at a dinner party and your partner kicks you in the shin, that hurts a lot. Pain has many layers of context and subjectivity. That's what makes it fascinating but also hard to understand."

Derbyshire has cast some light on what is known as functional pain, which is pain that has no discernable physical cause. An estimated 5 to 20 percent of the population suffers from mysterious ailments that involve functional pain. One such ailment is fibromyalgia, characterized by widespread, chronic pain, fatigue, and sleep problems; researchers believe abnormal sensory processing causes the condition. One fibromyalgia patient told Derbyshire that it hurt just to put on her clothes. Sometimes, these patients become frustrated, because they feel no one believes they are in pain. Derbyshire's study lends credence to their claims. He and researchers at the University College London have shown, for the first time, that the brain can generate the experience of pain on its own, without any physical cause.

In the study, eight healthy young adult volunteers with no history of functional pain were hypnotized while they were inside a magnetic resonance scanner. Derbyshire scanned their brains functioning under three circumstances. First, the volunteers were told to hold a thermal probe in their hands, and, after they were alerted to the beginning of the experiment by a tap to the foot, the researchers heated the probe to 119 degrees Fahrenheit for 30 seconds. Nearly all the volunteers found this to be painful. In a second scenario, researchers told the volunteers that their probes were going to be heated to the same level following another tap to the foot, even though the probes actually were turned off. In a third scenario, volunteers were asked to imagine the pain caused by the hot probe after the foot tap but were informed that the probe would not be turned on.

During the first two circumstances, the volunteers reported similar levels of pain. If they were warned that the probe would be hot, people believed that their hands hurt even when the probe wasn't heated.

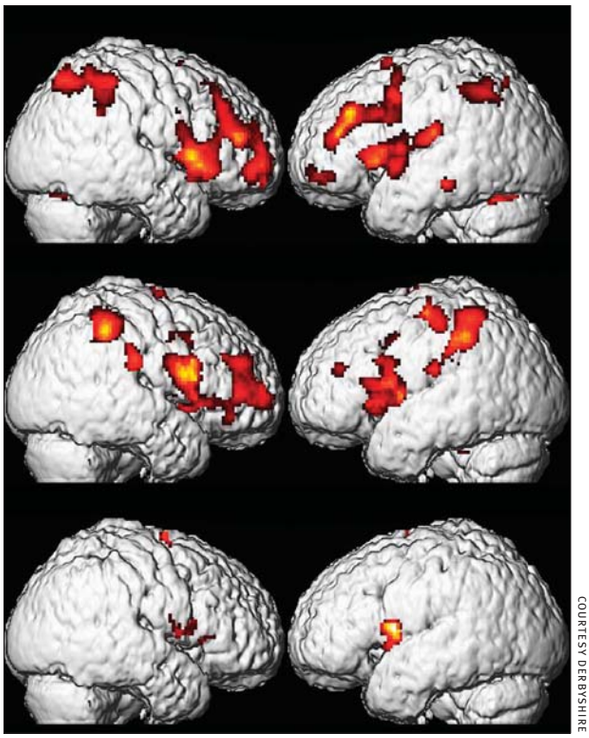
And when Derbyshire and his colleagues examined the scans from the first situation, they found activity in areas of the brain that are already known to be associated with pain. In the second situation, they found similar activity. The brain had actually created the experience of pain in the absence of physical stimulus.

(There were fewer reports of pain from the third situation, when the volunteers knew the probe would not be hot. The brain scans of imagined pain were not similar to the scans from the first two situations.)

The study results have been independently replicated by a group in Finland and will be published in the journal *NeuroImage*.

Hypnosis was useful in this study, because it does not alter the perception of reality but makes people more open to suggestion. Derbyshire wonders if the same psychological mechanisms may be involved in both hypnosis and functional pain. In an upcoming study, he will use hypnosis to try to decrease the pain experience of fibromyalgia patients while they're in the MRI scanner, then examine scans to see which brain areas are affected when the patients feel better. In another study, he'll compare brain scans from healthy people who can be easily hypnotized and are able to lessen the amount of pain they feel to scans from people who are not able to alter their pain experience during hypnosis.

"It's intrinsically fascinating to get someone to experience something out of nothing," says Derbyshire. "Now when we say that the brain can generate an experience of pain, we're not talking hot air—we've shown it. And, hopefully, that will get us closer to understanding functional pain." ■



COURTESY DERBYSHIRE

Sometimes doctors can find no physical cause for a patient's pain. Magnetic resonance imaging may help explain the brain's role in experiencing such pain. Composite scans from volunteers holding painfully hot probes (top) look a lot like scans from volunteers who are holding probes they've been told are hot, even though they really aren't (middle). But when volunteers just imagine touching a hot probe (bottom), their brain activity looks very different. Volunteers were hypnotized in all three circumstances.

GETTY/ HULTON ARCHIVE

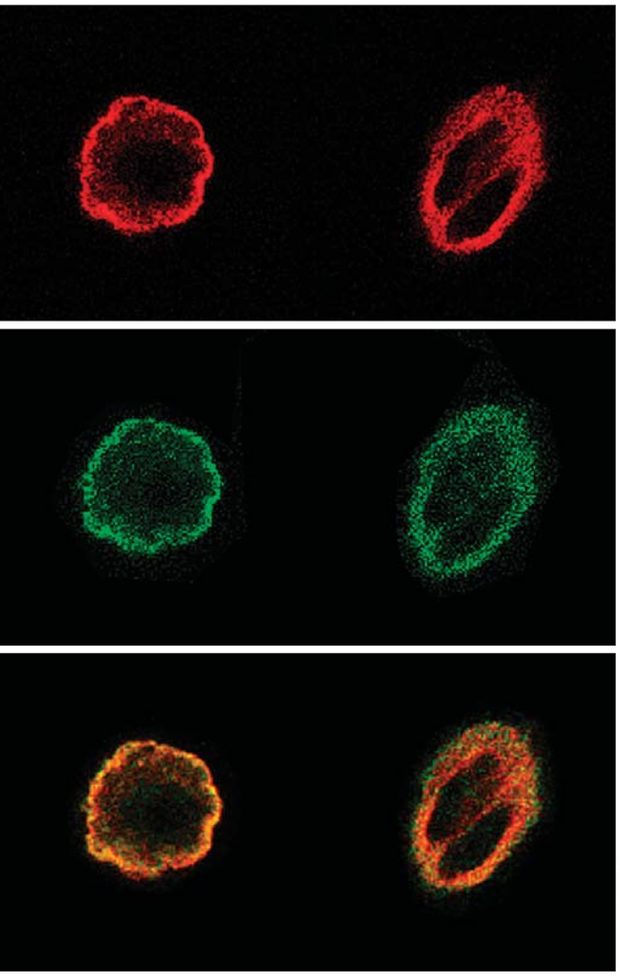
RAMPANT RECEPTORS

NEW STRATEGIES FOR HEAD AND NECK CANCER

BY SUSAN GULLION AND DOTTIE HORN

An imagined patient, Ronald, has a malignant tumor removed from the wall of his throat. The surgery is followed with chemotherapy and radiation, but two years later, cancer reappears. The first time, his vocal cords were free of cancer, but now, his voice has become gravelly. If his vocal cords have tumors, he'll probably have his voice box removed.

New drugs have shown promise against head and neck cancer—but the interplay between two protein receptors (EGFR and GPCR) may limit the effectiveness of those drugs. This image shows that two proteins involved in communicating between the EGFR and the GPCR are located in the same part of the cell. (The bottom image is the digital overlay of the first two images, each of which shows a separate protein. The areas where the proteins overlap are orange.)



COURTESY GRANDIS

Ronald is fictional, yet his story is not unlike that of many patients with head and neck cancer. The recurrence rate is high, and only 50 percent of patients with the disease survive five years. The treatment can be disfiguring and make it difficult to swallow, talk, or breathe. There has been no improvement in the cure rate in the past 50 years.

However, work by Jennifer Grandis (MD '87), professor of otolaryngology, and Jill Siegfried, professor of pharmacology, may offer new hope for treating this devastating disease. Gene therapy is one treatment strategy that looks tentatively promising.

The researchers are testing a new treatment that involves epidermal growth factor receptor (EGFR), which is found on the surface of epithelial cells, like skin cells and the cells that line the esophagus and the gut. This receptor's role in normal cells is unknown. In 1998, Grandis and Siegfried showed that EGFR is overproduced in tumors from patients with head and neck cancer. The patients with the highest EGFR production died from the cancer, and those with the lowest production levels survived. What if they could inhibit EGFR?

The researchers then demonstrated that in animal models of head and neck cancer, inhibiting EGFR resulted in decreased tumor size. That work helped set off a flurry of research activity into ways of manipulating EGFR.

Recently, the FDA approved the first EGFR-inhibiting drugs. In 2003, Iressa (manufactured by AstraZeneca) was approved for treating lung cancer; in 2004, Erbitux (manufactured by Imclone) was approved for use against colon cancer. A recent paper in *The New England Journal of Medicine* showed that certain lung cancer patients—those with a specific EGFR mutation—responded well to Iressa.

Erbitux has been tested against head and neck cancer with mixed results. One study compared head and neck cancer patients who were treated with chemotherapy to those treated with a combination of chemotherapy and Erbitux. The addition of the drug did not improve patient outcomes. In another study, Erbitux proved beneficial when combined with radiation therapy. Many new trials are under way that will test the addition of Erbitux to more typical treatment protocols.

What if doctors were to deliver a gene into the tumor cells that would inhibit EGFR? Siegfried and Grandis are in the early stages of a phase I clinical trial designed to evaluate such a gene therapy. Although they've only enrolled three patients so far, their anecdotal evidence has been exciting: One patient's tumor, which was too large for surgical removal, completely disappeared after gene therapy. (However, the patient had another tumor that was positioned too deeply to be injected with the therapy.)

Despite the possible value of the gene therapy and new drugs, Grandis believes inhibiting EGFR is unlikely to be sufficient as a primary or adjunct therapy for head and neck cancer. Even when EGFR is inhibited, another receptor, the G-protein coupled receptor (GPCR), can be a source of trouble. Think of GPCR as a generator waiting in the wings—shut down EGFR, and GPCR can take over—stimulating the same sequence of events normally set into motion by EGFR. (These events ultimately lead to unrestrained cell growth.) So it may be necessary to inhibit both receptors. Fortunately, GPCR inhibitors exist. Grandis and Siegfried are planning a clinical trial that will look at the effectiveness of combining EGFR and GPCR inhibitors in treating head and neck cancer.

In another effort, they're searching for a means to predict how a given tumor will respond to a given therapy. They'd like to not only develop better treatments, but also help physicians choose which treatment option is best for a particular patient. ■

TOO MUCH OF A GOOD THING?

IN CYSTIC FIBROSIS, QUALITY CONTROL GETS OUT OF HAND

BY DOTTIE HORN

Destroying mutant protein sounds like a good thing, and often it is. Many diseases result when mutant proteins aren't destroyed. However, in the case of cystic fibrosis, the mutated gene that causes the disease results in a protein that, even though it is abnormal, isn't completely dysfunctional. It can still do its job—it's just less efficient than the normal protein. The cell's quality-control system, however, sees the mutant protein and destroys all of it. None is left to perform the critical role of forming an ion channel at the cell membrane. If only the protein weren't completely destroyed, studies suggest, a person with CF might have enough functional protein to cure or curtail the disease.

In the case of CF, the mutant protein wouldn't cause any damage to the cell, says Jeffrey Brodsky, associate professor of biological sciences and medicine. "That's the whole problem, the quality-control mechanisms are overzealous, hyperactive," says Brodsky. "That's what makes it so frustrating, because the cell's doing too good a job."

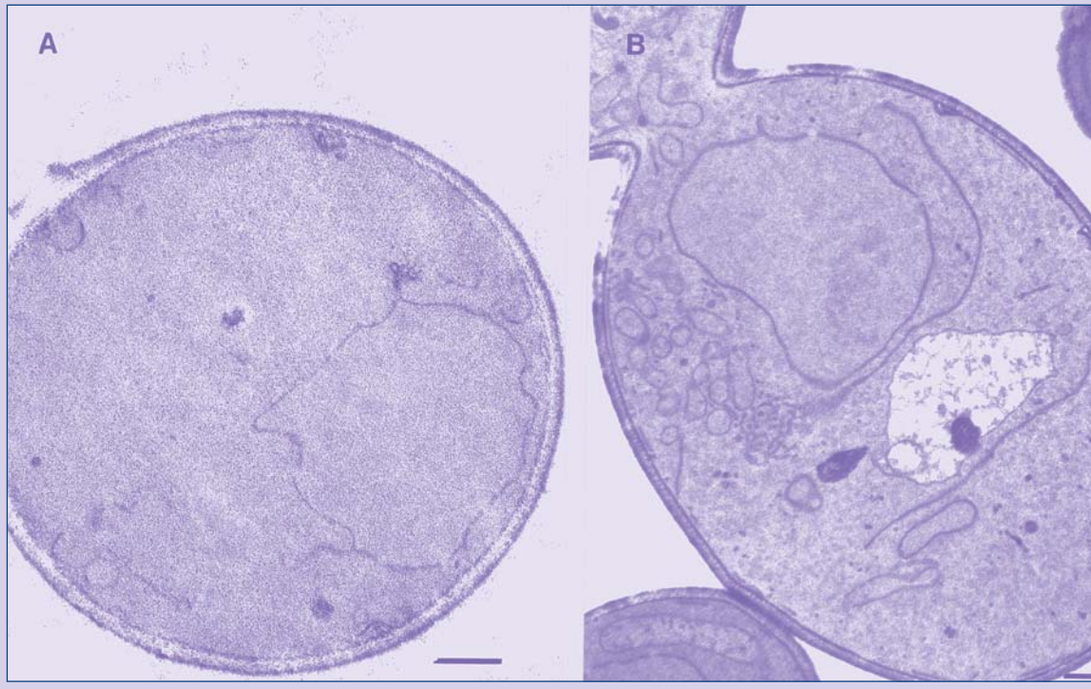
He wonders: If we could modulate the quality-control mechanisms, make them a little less ardent, could we change the course of CF? To study this question, he uses yeast, the same yeast used to make bread and beer. Although yeast is a single-cell organism (simple compared to multitrillion-cell people), it shares many proteins in common with humans.

Brodsky starts with healthy yeast, which he grows in a nutrient-rich broth in glass flasks. (His microscopic yeast cells are cannibals—as part of their diet, he feeds them extract derived from other yeast.) He puts into the yeast the mutated gene that codes for CFTR, the protein that's defective in CF. The cells start making the abnormal CFTR protein. But they also destroy it as soon as it's made, and the cells remain healthy.

Then Brodsky applies microarrays to the yeast; this tool allows him to look at the expression level of every single gene in both the normal yeast and the yeast with the CFTR gene. He looks for differences, genes whose expression changes dramatically in the yeast with the mutated CFTR gene. His finding: "Whoops, a few things go up, big time."

One of the "things" that goes up is the expression of what's known as a molecular chaperone, Brodsky explains. Chaperones are key players in the cell's quality-control system; they pick out the damaged proteins that should be eliminated. Brodsky tried knocking out the gene for this particular molecular chaperone; when he did, the CFTR protein was no longer destroyed. It was this chaperone, then, that was condemning the mutated protein to destruction.

A clinical trial is under way at Johns Hopkins University, looking at whether curcumin, an agent derived from the spice turmeric, might be effective against CF. Curcumin is believed to inhibit the action of some molecular chaperones. It's not yet known whether inhibiting these chaperones might allow other malformed proteins, which really should be degraded, to go unchecked. ■



If the cell's policing of mutants was not so diligent, people with cystic fibrosis might fare better. The yeast cell on the left is normal. The cell on the right is working overtime to destroy a protein that is mutated in cystic fibrosis patients.