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 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.”
A
n 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 can-
cer, but now, his voice has become gravelly. If
his vocal cords have tumors, he’ll probably
have his voice box removed.

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 disfig-
uring 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 treat-
ment that involves epidermal growth factor
receptor (EGFR), which is found on the sur-
face 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 low-
est 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 muta-
tion—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 ther-
apy and new drugs, Grandis believes inhibit-
ing EGFR is unlikely to be sufficient as a pri-
mary or adjunct therapy for head and neck
cancer. Even when EGFR is inhibited, anoth-
er 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 nor-
ma lly set into motion by EGFR. (These events
ultimately lead to unrestrained cell growth.)
So it may be necessary to inhibit both recep-
tors. Fortunately, GPCR inhibitors exist.
Grandis and Siegfried are planning a clinical
trial that will look at the effectiveness of com-
bining EGFR and GPCR inhibitors in treat-
ing 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.
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: 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.