Researchers *Sniff Out* a cure for smell loss

By Karen L. Brooks

STORY SUMMARY

- Anosmia, or the inability to smell, seriously affects quality of life and currently has no cure.
- Jefferson's Edmund Pribitkin, MD, is partnering with researchers at the Monell Chemical Senses Center to examine ways to treat anosmia using regenerative medicine.
- The team aims to grow nasal stem cells in the lab, engineer them to function as olfactory nerve cells and transplant them into patients' noses.

Next time you sit down to a meal, pinch your nose before taking a bite. Keep it pinched the entire time you're chewing and swallowing. What do you taste?

Maybe you'll detect notes of sweetness, sourness, saltiness or bitterness — but you won't be able to distinguish flavors.

This is what Sherri Geller tells people to do when trying to show them what her everyday life is like. Geller has anosmia, or the inability to smell. And since sense of smell plays a powerful role in sense of taste, losing the former means also losing the latter.

Even after the nose-pinching exercise, "I still don't think anyone understands," Geller says. "My daughter tries to cook for me ... 'How about garlic?" she'll ask. 'No? Then how about Tabasco sauce?' But everything smells and tastes the same: like nothing."

Estimates on the incidence of anosmia vary, but experts believe two to five million Americans suffer from a smell disorder. Hundreds of medical problems — from the common cold to nasal polyps to head trauma — and some medications have been associated with olfactory loss. Sometimes the condition improves over time, but for those whose sense of smell fails to return on its own, no cures exist. Edmund A. Pribitkin, MD, professor and academic vice chair of Jefferson's Department of Otolaryngology-Head and Neck Surgery, hopes to help change that.

Stop and Smell the... Danger?

In collaboration with researchers at the Monell Chemical Senses Center in West Philadelphia, Pribitkin is studying new ways to treat smell loss. Living without a sense of smell might sound more like an inconvenience than an urgent health concern, but he says anosmia is far more serious than most people realize, and a cure would save lives.

"We're quick to correct anyone who says, 'Big deal, it's not like it kills people' — because, in fact, it has," Pribitkin says. "People can become very sick from eating spoiled food they could not smell. People have died in their homes because of fires or gas leaks they didn't detect."

Research has shown that people lacking a sense of smell are at least three times more likely to experience a hazardous event than those without olfactory problems. In addition to causing physical danger, the condition affects general quality of life. Smell is tied to the limbic system, the part of the brain that governs emotions and memory. The inability to taste takes the joy out of eating and can interfere with appetite, and people with chronic anosmia can't draw pleasure from scents others take for granted.

"If I had never smelled or tasted before, maybe I wouldn't realize what I'm missing," says Geller, who mysteriously lost her sense of smell two years ago. She sustained a traumatic brain injury in a car accident in 2001 but didn't lose the sense for more than a decade, and while her injuries could have sparked a delayed reaction, physicians believe a virus might be the real culprit.

"Now, when I cook, I have no way of knowing if something I make is wonderful or terrible. My husband took me to dinner for my birthday, and the food looked delicious, but there was no flavor," she says. "He buys me flowers, but I cannot smell their beautiful aroma. I only know I'm near freshly cut grass when I start sneezing."

Missing out on sensual experiences can devastate patients, who feel disassociated from the "real world" and often develop anxiety.

"There is a very high correlation between smell loss and clinical depression," Pribitkin says. "You can treat the depression itself, but wouldn't it be nice if we could instead treat the cause?"

What Causes Anosmia?

Most people who lose their sense of smell have experienced a recent illness or injury, but a variety of circumstances can induce temporary or permanent anosmia.

Causes include:

- Aging (sense of smell generally declines after age 60)
- Allergies
- Sinus and other upper respiratory infections
- Viruses, like the flu or common cold
- Smoking
- Growths in the nasal cavities, like polyps or tumors
- Head injury
- Brain tumors
- Radiation therapy for head and neck cancers
- Exposure to certain chemicals, such as insecticides and solvents
- Various medications, including some antibiotics and antihistamines
- Hormonal disturbances
- Dental problems
- Conditions that affect the nervous system, such as Parkinson's disease, Alzheimer's disease and multiple sclerosis

Looking to Regenerative Medicine

Treating anosmia requires understanding how sense of smell works.

High inside your nose, at the back of your nasal cavity, lives a small patch containing hundreds of special receptors called olfactory sensory neurons. Different from other neurons because they come into direct contact with air, olfactory sensory neurons have hair-like projections called cilia.

Odors are caused by microscopic molecules that are emitted by an object and float through the air into your nose. These molecules bind to the cilia and activate the neurons, which transmit a signal to your brain, enabling you to perceive a smell.

Each neuron is encoded by a different gene to recognize a specific odorant. The environment has more smells than the nose has receptors, and any given molecule can stimulate a combination of neurons to produce a unique representation that the brain identifies as a particular scent.

When the system is working correctly, a human can distinguish more than 1 trillion smells. But if the genes that should be encoding neurons — or the neurons themselves — are missing or damaged, a person becomes unable to detect some or all smells.

Pribitkin and his Monell colleagues are hoping olfactory stem cell regeneration holds the key to solving this problem. They aim to engineer stem cells in the laboratory and grow them into functional olfactory sensory neurons that can be transplanted into patients' noses.

First, Pribitkin harvests nasal tissue from healthy volunteers and sends it to Mridula "Meera" Vinjamuri, PhD, a geneticist at Monell. Vinjamuri then works to isolate stem cells in the tissue and coax them into producing odor-detecting neurons.

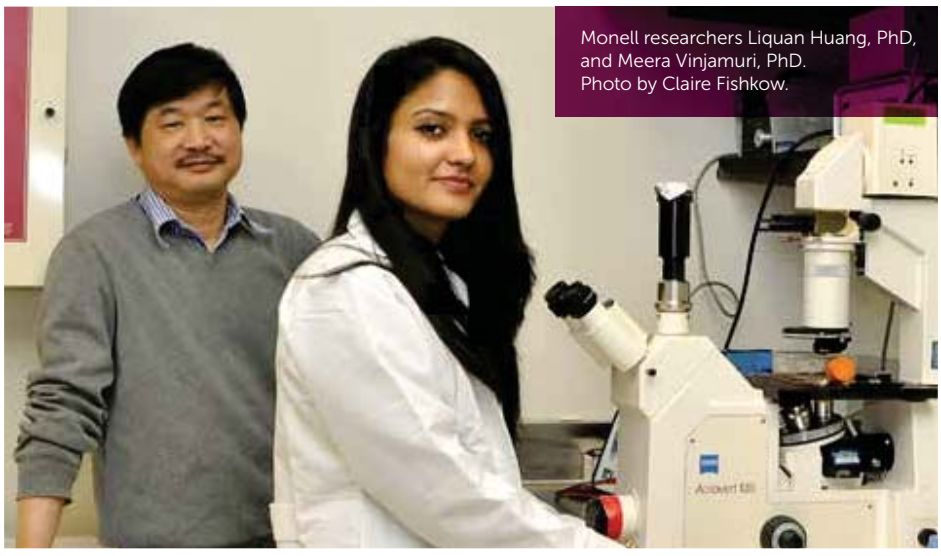
"We lose nerve cells all the time because nasal tissue is so close to the air that we breathe — so the nerve cells die pretty quickly from toxins and pollution. Our nasal stem cells regenerate whatever is lost," Vinjamuri says. "We want to replicate this process in a petri dish."

Because neurons in the nose are coded individually to recognize specific odors, Vinjamuri says the goal is more complex than it seems. "We really need to create subsets of neurons that will send the right signals to the brain and distinguish vanilla as opposed to strawberry or coffee or something else."

If Vinjamuri succeeds in doing that, the next phase would involve finding a way to place the stem cells into the noses of anosmic patients, which would lead to clinical trials.

Pribitkin acknowledges these ambitions are lofty.

"This is what we call a 'swinging for the fences' approach," he says. "Because there are so many research steps we have to complete incrementally, it's a long process. We've only just gotten to the point in terms of stem cell research and growing neurons that we can envision the possibility of this whole method actually working."



Monell researchers Liquan Huang, PhD, and Meera Vinjamuri, PhD. Photo by Claire Fishkow.

Edmund Pribitkin, MD, academic vice chair of Jefferson's Department of Otolaryngology-Head and Neck Surgery.

Three Decades of Teamwork

The anosmia stem cell study is not the first collaboration between Jefferson physicians and Monell scientists but rather the latest of many projects generated by a nearly 30-year partnership.

In 1986, the Monell-Jefferson Chemosensory Clinical Research Center (CCRC) — for many years the only center of its kind funded by the National Institutes of Health — was founded to advance discovery related to smell and taste disorders through clinical research projects. The CCRC no longer exists as a formal entity, but collaborative studies continue and have built the foundation for today's stem cell research, Pribitkin says.

"Just one example of a past study we're relying on today involved olfactory cells we harvested and that a colleague at Monell, Dr. Nancy Rawson, blew odors over to see if the cells depolarized. She was able to show when and how a particular cell responded to, say, the smell of a rose," Pribitkin explains. "This informs our research now because as Meera (Vinjamuri) is growing neurons, she needs to be able to tell not only that they look like olfactory neurons, but also that they work like olfactory neurons."

Pribitkin is optimistic that continued Jefferson-Monell teamwork will eventually provide the first real cure for anosmia.

"The beauty of this sense of community is that every scientist involved has provided a little piece of the puzzle, and now we're positioned to frame the puzzle so all the pieces fit together into a solution for a very difficult problem."

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Big Ideas Lead to Big Impact

However long this project will take, Pribitkin, Vinjamuri and their colleagues are committed to sticking with it. Pribitkin finds motivation in the progress he has seen in repairing another sense — hearing — throughout his career.

"When I was a medical student and resident, cochlear implants were crude and controversial. Now, cochlear implantation is accepted as the primary form of treating deafness around the world," he says. "Within my short career, we've gone from having generations of deaf children to having generations of children who can hear. If you would have asked me 20 or 30 years ago if cochlear implantation would be as far along as it is today, I would have said probably not."

The fact that smell is a chemical sense — not a physical one, like hearing — complicates the process, and this study promises to span decades.

"These kinds of big ideas make big differences in science and in people's lives if they pan out," Pribitkin says. "It doesn't matter that we have a ways to go, because this has the potential for changing millions of lives, and that means it's worth it." ■

Jefferson and Monell are partnering to raise funds for their anosmia research collaboration. To learn more or to make an investment in this project, contact Jonathan Agree, director of development, clinical departments, at ***215-503-6058*** *or* ***jonathan.agree@jefferson.edu****.*