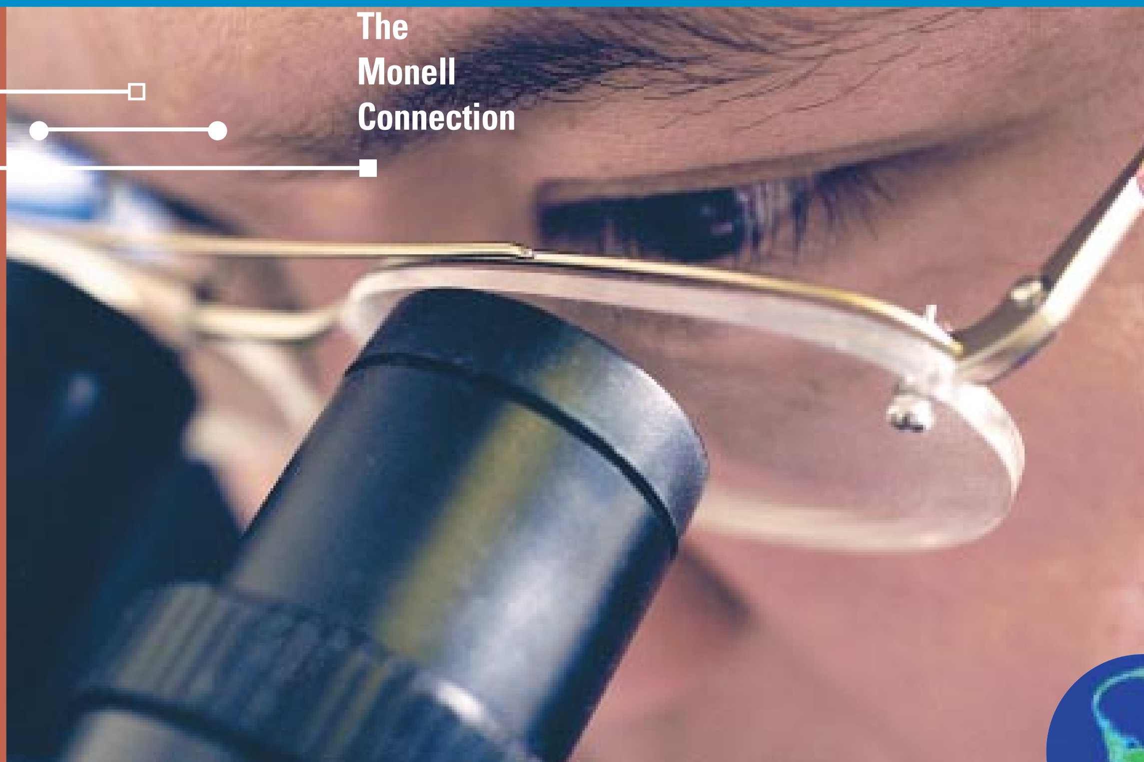
Monell

Fall 2002

The Monell Connection



Small Things Mean A Lot

The Medical and Scientific Journey of an Olfactory Cell

What's So Special About a Cell?

Sometimes, it's the smallest things that can tell us the most.

About medicine.

About science.

About the process of discovery and application.

About the value of teamwork and collaboration among physicians and research scientists seeking to discover and disseminate knowledge for the benefit of us all.

This is a story about a cell inside the nose. The cell is called an olfactory receptor neuron — ORN for short. As indicated by their name, ORNs contain sensory receptors that detect the thousands of odorants that make up our olfactory world. Scientists have already learned much about the sense of smell using ORNs from animals. Now, the exciting ability to study living human ORNs in the laboratory is advancing our understanding of human olfactory function in health and disease.

ORNs have two more important properties. In addition to being sensory cells, ORNs also are nerve cells directly connected to the brain. And, they can easily be obtained from a living human. By exploiting these features, Monell scientists and their colleagues are using ORNs to probe underlying mechanisms responsible for neural changes associated with aging and with neurodegenerative disorders, including Alzheimer's disease. ORNs also provide investigators with a tool

Continued from cover page

to explore potential causes and treatments for neuropsychiatric diseases such as manic-depressive disorder (bipolar disease) and to study basic scientific processes such as cell regeneration, signal transduction, and gene expression.

How scientists at Monell and its affiliated institutions study that simple cell provides a vista on contemporary medicine and science. The journey from clinic to donor to laboratory and eventually back to the clinic demonstrates how basic science research can be applied to health care problems, translating to discoveries which eventually benefit patients. This process — aptly called "translational science" or "translational medicine" — lies at the heart of the pharmaceutical and biotechnology industries. Translational science, effected through multidisciplinary research, knits together institutions, people, and programs in a shared effort.

The journey of the ORN promises to have several different endings. It conveys the excitement of how science actually happens: how a chance observation or a seemingly simple question can redirect an entire line of research, how multidisciplinary scientific and medical collaboration can result in novel perspectives, and how Monell provides the opportunity and resources to "follow the question," no matter where it may lead and what detours may be encountered along the way.

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The Monell-Jefferson Taste & Smell Clinic

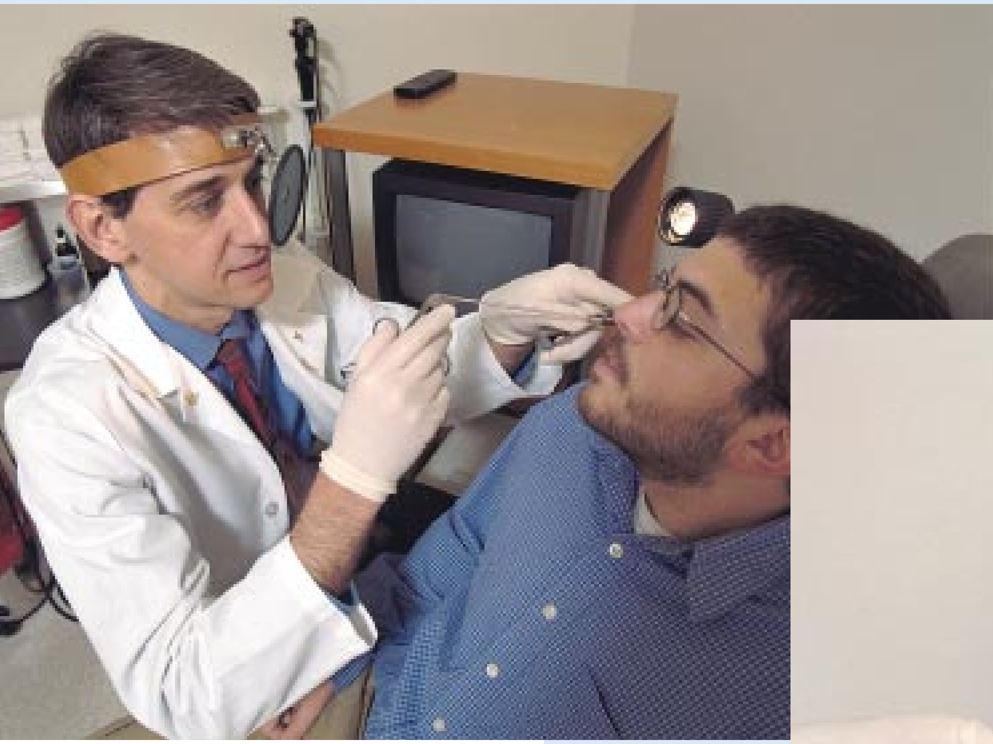
It all begins in the Monell-Jefferson Taste & Smell Clinic. There, for the past 12 years, hundreds of patients, along with healthy volunteers, have donated ORNs through a simple biopsy procedure.

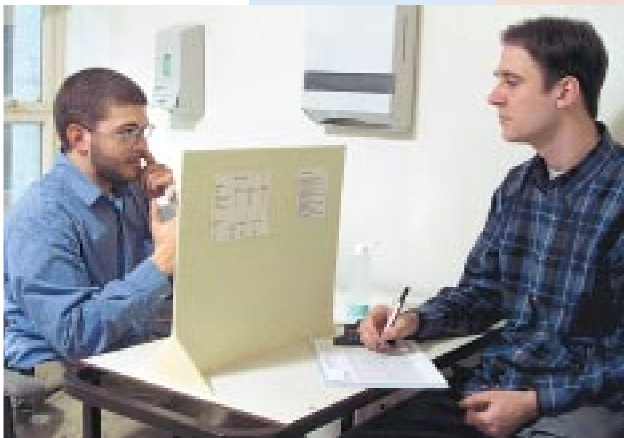
The Clinic is part of the Monell-Jefferson Chemosensory Clinical Research Center (CCRC). Funded by the National Institutes of Health since 1986, the CCRC brings together research scientists from Monell and physicians from Thomas Jefferson University to advance the understanding of clinical issues related to taste and smell. One of several projects currently under the CCRC's umbrella is entitled "Cellular Mechanisms of Human Olfaction in Health and Disease." Researchers and clinicians working on the project want to understand exactly how human ORNs translate chemical information from an odorant into electrical information used by nerves in the brain. Cellular biologist Nancy Rawson, an Associate Member who first came to Monell as a graduate student, has headed the project since 1997.

Nancy Rawson, PhD

At the Clinic, ORN donors undergo sensory testing to determine their sensitivity to odorants that will be used later that day in physiological studies at Monell. Then, through the surgeon's expert hands, the ORNs are extracted from the nose to begin the journey of discovery and application.

Jefferson otolaryngologist Edmund Pribitkin performs the biopsy procedures. His interest in the sense of smell derives from his surgical work on the sinuses. "What happens when you operate on the nose and sinuses is that you're altering





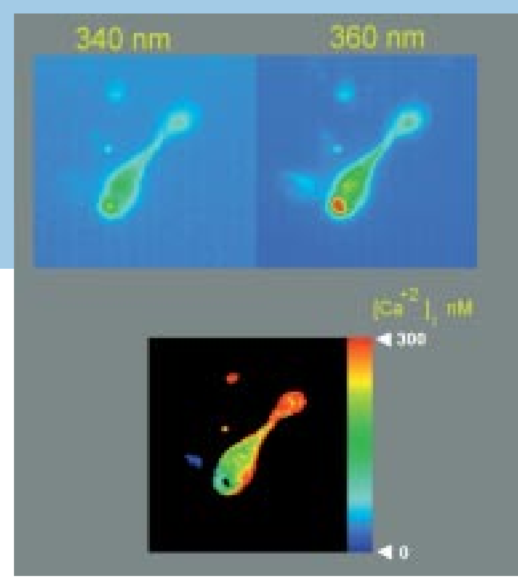
not only the function of the sinuses but also of the sense of smell. What we're able to do by working with investigators at Monell is find out right at the very basic roots how things function, and then translate that into possible cures for patients."

Monell neurobiologist George Gomez often transports the ORNs from Jefferson to Monell, needing only 20 minutes for the trip from downtown Philadelphia to University City. At Monell, the human ORNs are distributed to various laboratories for study.

The Fluorescence Imaging Lab — Doing the Science of Smell

In Monell's Fluorescence Imaging Lab, Gomez places the ORNs into a solution containing the fluorescent dye fura-2, giving the dye time to move into the cells. Fura-2 has two useful properties: it binds to calcium inside the ORNs, and it emits visible light when exposed to ultraviolet wavelengths. Calcium is involved in the cell's response to stimulation; a change in how much calcium is inside the cell tells the researchers when a cell responds to the application of a specific odorant. Every few seconds, a sophisticated computer and camera set-up measures the light intensity and calculates how much calcium is in the cell. The intensity of light is translated into colors, which are shown on the computer's monitor — red signifies high calcium, blue is low, green is in-between.

Rawson and her co-workers have taken advantage of these properties to characterize how human ORNs respond to odorants. As that knowledge accumulates, scientists are also beginning to understand some of the changes of olfactory function that accompany aging and disease.



The team has made several significant discoveries. Rawson summarizes the first as, "A human is not a rat." Unlike ORNs from rats and other non-human species, which always respond to odors with an increase of intracellular calcium, a significant number of human ORNs show a decrease in calcium after odor stimulation. Rawson reflects, "Much of what we know is based on animal models. We need to look at species adaptations. Humans, for instance, have only 40% of the number of different olfactory receptors that rats do. Are there adaptations that our systems have gone through to compensate for that?"

When the ORNs are ready, Gomez shuts off the overhead lights. Strands of small blue lights intertwined around the equipment faintly illuminate the microscopes and electronic instruments, while computer screens glow with multi-colored images. Gomez explains, "The room must be kept dark because the cameras are very sensitive to light. But they don't pick up the blue wavelength, so we can use these blue lights to help us see what we're doing." Gomez and postdoctoral fellow Gloria Adamek situate themselves at workstations on either side of the room. They peer through their microscopes, each using the ORN's characteristic shape — "They look like bowling pins..." — to select up to five cells to monitor. Working separately, the researchers apply odorants to the cells and closely observe the computer screens to watch for a response.

Different sets of odorants are used to identify which of several possible biochemical

George Gomez, PhD

Beverly Cowart, PhD

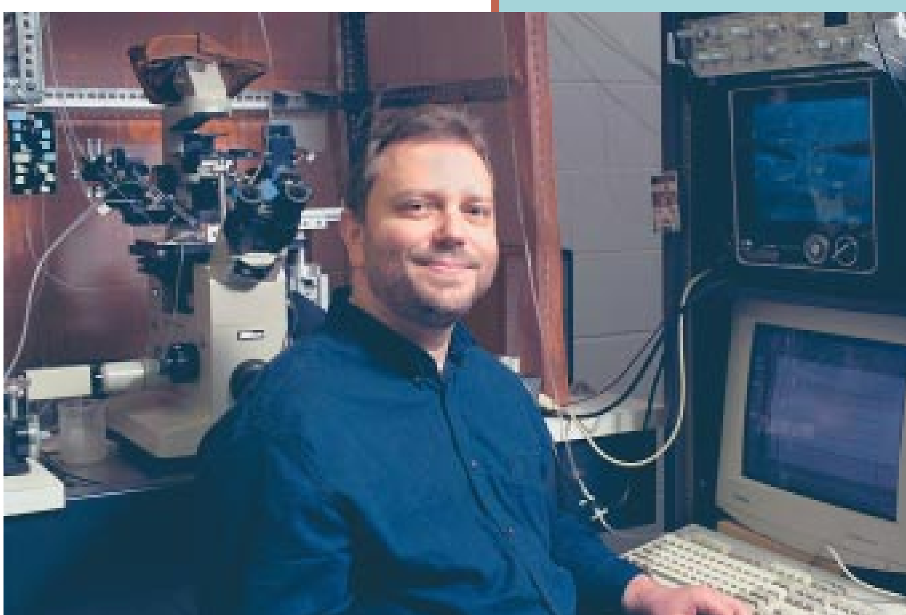
pathways is involved when a cell responds. These studies have revealed a second unusual feature of human ORNs: they appear to be more selective than ORNs from other species. Olfactory cells from younger humans rarely respond to more than one odorant, whereas many rat ORNs respond to multiple unrelated odorants. This suggests that the coding of olfactory qualities, the identification process that allows us to distinguish one odor from thousands of others, may be accomplished differently in humans than in other species.

By applying the same odorants used earlier that day for sensory testing at the clinic, the researchers can try to relate the ORNs' responsiveness to a donor's ability to perceive that odorant. This type of study is leading to major insights into changes of olfactory perception that accompany normal aging. Nancy Rawson remarks, "This turned out to be much more interesting than we expected. As you age, you tend to lose your sense of smell, so we thought we'd have difficulty finding neurons in our older subjects. But after several hundred biopsies, we discovered this was not the case. We get just as many neurons from older subjects as we do from younger subjects. Even more surprising, rather than being less likely to respond to odors, they're actually more likely to respond."

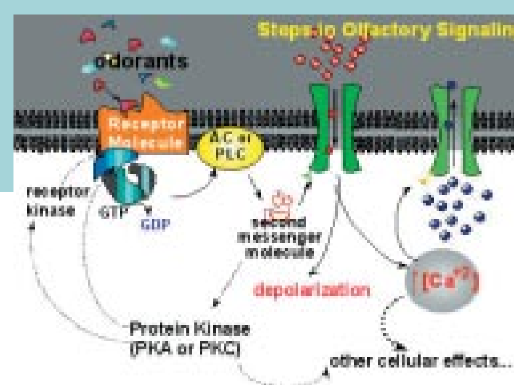
The researchers hypothesize that human olfactory cells may become less selective with age. An individual cell from a young person will only respond to one odor, or occasionally to a very few related odors. But in older subjects, a single cell often responds to several odors that differ substantially in structure or quality. The findings have led the scientists to re-think how aging might affect the sense of smell. Sensory psychologist Beverly Cowart, Director of the Taste & Smell Clinic, remarks, "The age-related changes are fascinating, in part because they don't seem to make any sense. One thought is that, because of their propensity to respond to multiple odorants, many ORNs in older individuals may be in a state of chronic adaptation. The net effect would be a functional decrease of olfactory sensitivity." Cowart and her colleagues have developed several sensory tests to explore this possibility. She continues, "We have a unique opportunity to look at relationships between perceptual measures and neurophysiological measures and how those might tie together."

The Electrophysiology Lab — The ORN Reaches Out to Touch the Brain

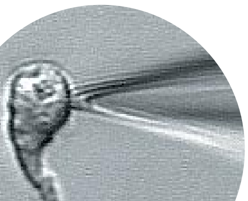
Meanwhile, Research Associate Fritz Lischka takes some of the ORNs and heads into his laboratory. Lischka, an electrophysiologist, measures electrical currents caused by the movement of positively- and negatively-charged ions across a cell's membrane. When an odor molecule interacts with an olfactory receptor on the ORN's surface, a chain of biochemical events is triggered inside the cell. The result of this biochemical cascade is to selectively open and close various ion channels that span the cell's membrane. This allows ions (such as potassium, sodium, or calcium) to flow in and out, ultimately changing the electrical charge of the cell. When this process reaches a critical level, the ORN sends an electrical signal to the next cell. That second cell is located in the olfactory bulb — the part of the brain that processes incoming odor information.



Fritz Lischka, PhD



By measuring current changes across the ORN's membrane, Lischka can identify which ion channels open and close in response to specific odorants. All these events take place within tens of milliseconds. Measuring electric currents in a living cell that's only 10 micrometers in diameter is not an easy thing to do, and Rawson and Lischka often tap into the extensive experience of project colleague John Teeter. Teeter, who came to Monell as a graduate student right after the Center was founded, is a recognized expert in electrophysiological recording of sensory receptor cells. His research on ion channels and intracellular events in olfactory and taste



receptors, primarily in fish, makes him an important partner in the design of experiments and the interpretation of results.

Looking through his microscope, Lischka carefully positions the tip of a micropipette near an ORN. Using a plastic tube attached to the pipette, he applies a slight suction to create a seal between the tip and the cell wall. Then he sits back to wait. Will he get a tight seal? Will the cell respond to stimulation? Only about 35% of the human ORNs do. After a few minutes, Lischka lets out a sigh of relief; the cell is responding.

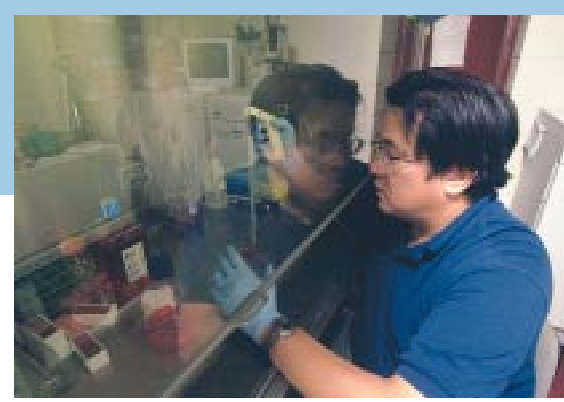
Nancy Rawson describes Lischka's work as "the bottom line — if you don't have that current, you won't get the signal in your brain." Rawson continues, "Fritz's experiments are among the most important and technically demanding that we're doing. Electrophysiology is the only way that we can actually see which ions are going where and when. That's how we learn precisely how the cell functions. After the sodium comes in, what goes out? Is there also chloride coming in? Potassium? Calcium? Do human cells differ in this regard from those of other animals?"

Even on good days like today when the ORNs are cooperating, Lischka's job is not easy. Since a recording of a given cell will remain stable only for about 30 minutes, Lischka must soon start over. "It's very hard and often frustrating," Lischka admits with a rueful smile. "There aren't many groups who are doing these types of studies. You have to have a certain mindset and a lot of patience. You can have days or even weeks where the experiments just don't work." He continues, "Eventually, we'll figure it out."

The Cell Culture Lab — Exploring the Secrets of Regeneration

Unlike most other neurons that are part of the brain, ORNs can regenerate throughout the adult lifespan. Yet another focus of the project is to understand this unique ability. The findings could have major implications in the treatment of olfactory disorders that are caused by missing or dysfunctional ORNs. In addition, treatment of neurodegenerative disorders such as Alzheimer's or Parkinson's diseases may be aided by the discovery and development of medications that promote neuronal growth and maturation.

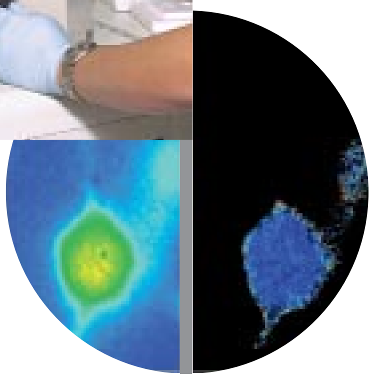
Earlier, Gomez had carefully inspected the tissue sample, explaining "I'm looking to see how deep the biopsy extended into the epithelium." The olfactory epithelium — the patch of skin within the nose where the ORNs are located — contains ORNs in various stages of development. The less mature cells are found in deeper layers and migrate towards the surface as they develop. Gomez places some biopsy tissue into a tube containing growth factors, a cocktail of nutrients and proteins that stimulate development of immature cells into mature olfactory neurons. After a few days, he will see new cells growing in about two-thirds of the samples.



In an ongoing study, Rawson and Gomez are comparing ORNs grown in culture to those obtained from biopsies to learn more about how structure and function are related in the developing ORNs. Which growth factors stimulate the cells to proliferate? Which factors trigger them to mature into functional neurons — or prevent them from doing so? At what point in its growth does a cell become responsive to odorants? And, what components of the ORN's cellular machinery are necessary for it to start responding?

At the same time, postdoctoral fellow Hongyan Wang is looking at cellular regeneration from another angle. Wang, a molecular biologist, is seeking to identify the genes that direct the process. This information will help the researchers understand how ORNs are different from other neurons that don't regenerate. Rawson comments, "We're taking the project to a molecular level, looking to understand how the cells regenerate. What genes are turned on at each step and what factors regulate that process?" She smiles and adds, "It's at a really exciting stage — I just can't wait until the next piece of data comes in."

Understanding the factors that guide growth and maturation of ORNs would also have the benefit of providing the researchers with a convenient and plentiful source of cells for future studies. Gomez envisions,"Instead of getting 1000 cells from 1000 biopsies, I want to be able to get 1000 cells from one culture and do my experiment with that."



ORNs Offer a Window Onto the Brain

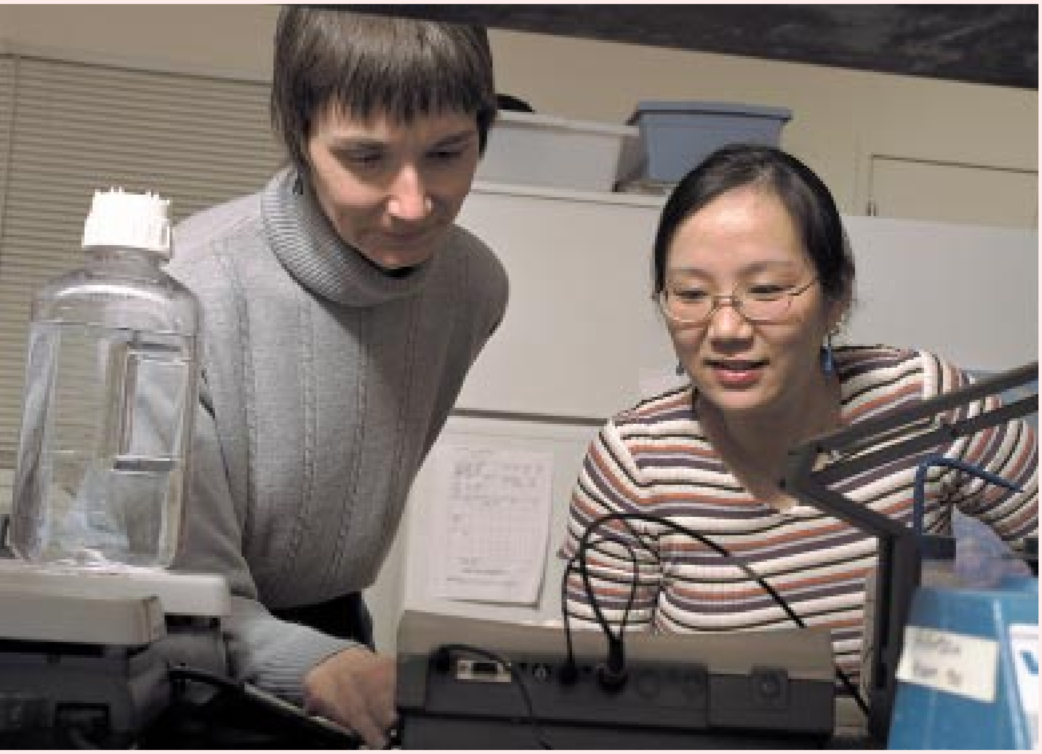
According to Nancy Rawson, ORNs provide "a unique window on the brain." Because they share characteristics with other neurons in the brain, ORNs provide scientists with a useful model to study the neural effects of aging and of certain neurodegenerative diseases, including Alzheimer's and Parkinson's diseases.

Alzheimer's disease is the most common form of age-related dementia, afflicting up to four million people in the United States. Currently, the causes are unknown and there is no cure. The disease involves changes within the brain, making it difficult to study nerve cell function in living patients afflicted with Alzheimer's.

A decrease in olfactory function is one of the earliest clinical signs of Alzheimer's. This led Diego Restrepo — the project's original principal investigator and a current collaborator from his present position at the University of Colorado — to propose that studies of olfactory neurons might provide clues as to what was happening in the brains of Alzheimer's patients. Rawson comments, "Our preliminary data are quite promising, and suggest that we can use these neurons to identify functional differences that occur early in the progression of the disease." The researchers hope that continued study of ORNs from patients with Alzheimer's disease may eventually provide insight into the causes and perhaps treatment for some of the changes that accompany this debilitating disorder. Rawson predicts, "I think we will have a very exciting story to tell."

Bipolar (manic-depressive) disorder is another disease for which the ORNs may provide important insights. Bipolar disease is a severe mood disorder characterized by unusual shifts in a person's mood, energy, and ability to function. Like Alzheimer's disease, bipolar disease affects nerve cells in the brain, making it difficult to study underlying neurobiological causes of the disease during its actual course.

Rawson has been collaborating with Chang-Gyu Hahn, a psychiatrist and neuroscientist at the University of Pennsylvania, to explore biochemical and functional changes in ORNs from patients with bipolar disease. Hahn first contacted Rawson to discuss how changes of calcium within nerve cells might be related to depression. He also was intrigued by the possibility that these calcium changes might be affected by lithium. Lithium is a drug commonly used to reduce symptoms in bipolar patients, but — as for many drugs currently used to treat neuropsychiatric disease — scientists and clinicians do not



understand how this medication exerts its effects.

Hahn and Rawson recruited bipolar patients from Hahn's practice and were able to obtain ORN biopsies before and after lithium treatment. Rawson describes the results, "The data showed a very striking difference in the calcium responses from these patients. These results may potentially give us a better understanding of the underlying neurobiological causes of the disease and what the medications are doing at a cellular level." Hahn is enthusiastic about the collaboration, explaining "For the first time in the field of biological psychiatry, we have been able to study intracellular signaling in cells from living patients with bipolar disorder."

Helping Patients

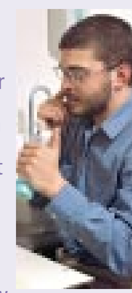
Until recently, smell and taste disorders have received little attention from the medical community, and many of the people who call the Monell-Jefferson Taste & Smell Clinic are desperate to understand what's happening to them. Beverly Cowart, the Clinic's Director, explains, "People come to us because they want to know, 'Does this mean I have a brain disorder? Do I have some disease?'"

Depending on the nature of their complaint, patients are tested to determine their ability to perceive, identify, and discriminate a variety of odors, tastes, and chemosensory irritants. Following the sensory tests, they see Jefferson otolaryngologist Edmund Pribitkin for a thorough medical examination and, when warranted, also are examined by Roy Feldman, a periodontal surgeon associated with the Philadelphia Veterans Affairs Medical Center.

Over 1200 patients have been evaluated since the clinic was first funded by the National Institutes of Health in 1986. About two-thirds complain of problems with both taste and smell, while another 20% present only with an olfactory complaint. The remainder report problems only with taste. More than 200 normal healthy controls have also been assessed to provide a baseline for the diagnostic tests.

For about 15% of patients, the tests do not reveal any major abnormalities or dysfunction. The large majority of the remaining patients are diagnosed with a smell dysfunction. Taste dysfunctions are identified in a smaller number, and a few patients have both taste and smell disorders. Many who thought they had a problem with taste are surprised to learn that the problem actually involves their sense of smell.

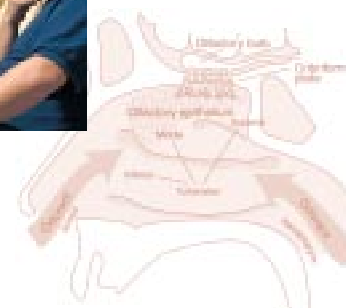
For most patients, the prognosis is not entirely welcome. Except for those with sinusitis or a nasal obstruction, the usual treatment is time. Nancy Rawson sees their plight as one objective of her research with ORNs, "This is why it's important to support the whole range of research from basic science all the way through clinical trials. People should look at our research and know that there is somebody trying to get a better understanding of human olfaction, somebody trying to come up with a treatment for some of these diseases and problems."



Follow-up phone calls and re-evaluations allow researchers and clinicians to provide patients with more accurate information about recovery from their specific disorders. Cowart remarks, "It helps patients to feel better when they have an idea of what proportion of people like them do improve, and of how long it is likely to take."

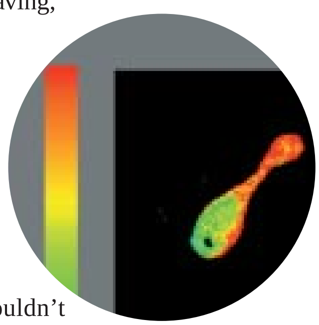
To contact the Monell-Jefferson Taste & Smell Clinic, call 215.955.5652.

Bringing it Together



Rawson applauds the promise of the Monell-Jefferson clinical and research relationship to improve human health. "This is the only place in the world where we have psychophysical data, we have medical data, and we have functional and genetic characteristics of human olfactory neurons, all obtained from living patients. The information that you can gain from this type of multidisciplinary approach is incredibly powerful. These studies have the potential to give us new insights that no other approach can into neurodegenerative and neuropsychiatric diseases and the neural effects of aging."

Like Rawson, Cowart is a firm believer in the "bedside-to-bench-to-bedside" model and the multidisciplinary research approach, which Monell and Jefferson do so well in tandem. "At the [monthly] CCRC meetings, we talk about the problems we're having, we talk about the patients, we talk about weird results. People come at it from different perspectives and I think it can really provide novel insights."



Monell scientists are eager to point out the importance of the Jefferson physicians to the success of the ORN project. According to Rawson, "The project probably wouldn't have happened without Dale Lowry, who was chair of the Department of Otolaryngology at Jefferson at the time." And Gomez affirms, "It's a real asset to have the clinic and to have surgeons like Ed Pribitkin who are interested — genuinely interested — in science."

Penn's Chang-Gyu Hahn makes a similar point. His collaboration with the project, which started over five years ago, "has been a very productive experience. The expertise of the Monell investigators makes it possible for us to investigate clinically-relevant questions at the cellular and molecular levels."

What makes it all work? Cowart believes "Monell is what holds us together. It's the stability of the interdisciplinary institution that supports the clinical studies."

For his part, Jefferson surgeon Pribitkin appreciates the insights he gets from his side of the collaboration. "It's very exciting, because we get to take things from the benchtop to the clinic. The new understanding we glean from the basic science helps us to explain things better to our patients. They get a better comprehension of their difficulties and we can treat them better as physicians."

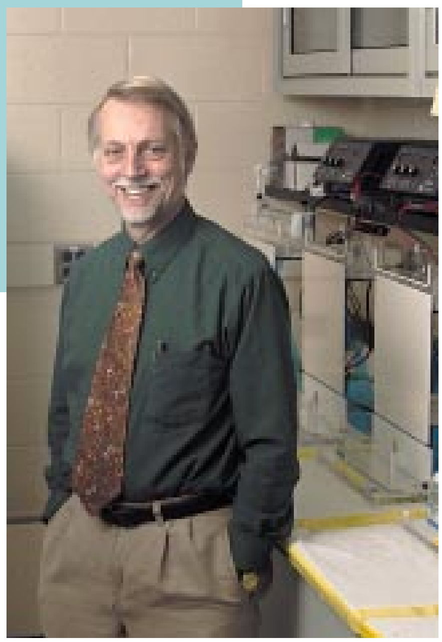
Pribitkin thoroughly enjoys the opportunities that the collaboration brings and is particularly excited about a neuro-anatomical outcome that has accompanied his participation in the biopsies, explaining, "One of the things we've done at Monell is re-map the olfactory epithelium. We used to think that the sense of smell was located in a little patch of tissue at the top of the nose, but now we realize that those olfactory cells actually extend halfway down the side of the nose. It becomes very important to treat maladies with that in mind." He continues enthusiastically, "We're pushing the boundaries of our knowledge. Then we're bringing all that knowledge not only into a laboratory where people are looking at cells, but we're also taking it out of the laboratory and bringing it into our patients' lives."

From Jefferson to Monell, from sensory psychologist to surgeon to neuroscientist to physiologist to biologist to molecular geneticist to psychiatrist, the ORN is opening new panoramas onto the intersection of science and medicine. The outlook includes olfactory perception and much more — basic biological processes and the understanding, detection, treatment, and prevention of human disease. And the story is far from over, as Nancy Rawson tells us:

"It has always been my feeling that each person's olfactory world is as individual as his or her fingerprints, and we now have the tools to determine whether that is indeed the case. We can also explore the extent to which our experience, exposures, and health history impacts on our olfactory world.

The great success of the Chemosensory Clinical Research Center is demonstrated not only by the publications produced from the work directly, but also in the new projects that have sprung up as a result of our work and the doors that have been opened into entirely new areas that would never have occurred without the CCRC in action. In the future, the Clinical Center will allow us to translate our findings into therapeutic approaches and test them with patient populations."

Perspective



Gary K. Beauchamp, PhD
Director

Olfactory Identity

The story of the olfactory neuron vividly illustrates the guiding research strategy of the Monell Center: collaboration across scientific disciplines. Many other projects at the Center also embody this ideal of multidisciplinary cross-fertilization. One of these involves the study of individuality of odor that I have been pursuing for many years with my Monell colleague Kunio Yamazaki, a behavioral biologist.

The immune system is responsible for the recognition of self from non-self, acting to protect the body from unrecognized outside "invaders." Many years ago we discovered that the set of genes that regulates immune function also somehow codes for individual identity, which in mice is communicated via odorants in urine and other body fluids. These genes, broadly known as the Major Histocompatiblity Complex (MHC), are called Histocompatibility Leukocyte Antigen (HLA) in humans, in whom information on identity may be conveyed by odorants in sweat.

Our original behavioral and genetic experiments were followed by chemical studies to identify the odorants. After much work with organic chemist Alan Singer, we concluded that it was the pattern of volatiles that conveys the individual's olfactory fingerprint, or "odorprint." By analogy, the characteristics that allow us to visually recognize a person as a particular individual also are a pattern. The essential characteristics of this pattern still command a lively research interest in the vision field.

Now consider the odor of urine. On one hand it is obviously a very complex mixture of volatiles. From a simple-minded perspective, one would assume that it would therefore stimulate many different olfactory receptor types. However, we know from our own experience that when we sniff urine — or coffee or a flower or a person — the initial impression is not perceived as a diverse array like an orchestra tuning up, but as a single experience that we respond to emotionally and grasp as an entity, like a musical chord. Somehow the brain takes a very complex input and organizes it. How and where does this happen?

Our collaborators, Diego Restrepo, a former faculty member at Monell who also contributes to the ORN studies, and his graduate student at the University of Colorado, Michele Schaefer, have begun to answer this question. They are studying patterns of neural activity in the brains of mice exposed to urine odors from mice with dissimilar MHC genes. Diego and Michelle have discovered that the olfactory system is organized so that the first steps in information transmittal involve simplification and pattern formation. They generated brain (olfactory bulb) maps that identify the specific locations activated by these odors and found that the maps differ for different individual odors. Strikingly, the degree of difference in the brain activity maps almost perfectly parallel the degree of difference we obtained in our chemical and behavioral studies. That is, individual animals that have similar patterns of chemical secretions in their urine smell alike and produce similar patterns of brain activity in other mice.

These studies may have significant practical applications. In collaboration with Kazumi Osada, a visiting scientist from Taisho Pharmaceuticals (one of our Sponsor companies), and Monell chemists Ben Smith and Ann Belcher, we are working to further specify the chemical identity of these odorant signals of individuality, and to see if this work translates to humans. Because of the fundamental nature of the immune and olfactory systems, this seems to me to be highly likely.

Can individual humans be identified by their genetically-determined odor? If so, this could have obvious implications (and concerns) for security; we have been awarded a grant by the Department of Defense to pursue this work, with the ultimate goal of providing a non-invasive way to identify individuals. In related research, we are also exploring the possibility of using changes in body odor to diagnose disease. And, with other scientists, including Alan Gelperin, a computational biologist and neuroscientist who has joined Monell's faculty from Bell Labs, we are working to develop an electronic nose that can discriminate individual odors, enabling these odor-based differences to be put to practical use.

These studies, like many at Monell, span the spectrum from behavior and genetics to chemistry to neurophysiology. To do them requires a collaborative group of individuals possessing diverse skills and a desire to work together. And in many cases, such as this one and the ORN research, the results are remarkably satisfying. When it all begins to make some sense, it is as if a curtain has opened. This is why we do what we do.

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