

The Monell Connection

Fall 1997
The Monell Connection...
from the Monell Chemical Senses Center, a nonprofit scientific institute devoted to research on taste, smell, and chemosensory irritation.

A Tingle on the Tongue

For a new and different oral sensation, try a bit of *timurol*. The accompanying buzz on the tongue is variously described as resembling a shock from a low-voltage battery, a sudden explosion of a million tiny bubbles, or the early stages of numbness from local anesthesia.

Timurol, a chemical compound isolated from the Nepalese spice *timur*, produces a unique kind of irritation that most people find to be pleasing. With its tingling, somewhat vibrating component, this little-described sensation is a form of chemosensory irritation that offers intriguing opportunities for both scientific exploration and commercial use.

Although well-known in Asia, where the description of the sensation the spice imparts is translated as “electric shock,” *timur* just recently came to the attention of Monell scientists. A neurobiologist received a small amount from an anthropologist friend working in Nepal with the suggestion, “Here — try this!” As soon as he felt the buzz, it was apparent that it was unlike anything he had previously experienced.

The compound was named *timurol* by Monell scientists. This name reflects both the origin of the compound (*timur*) and the chemical structure of the molecule, which contains a hydroxyl group and is designated an alcohol.

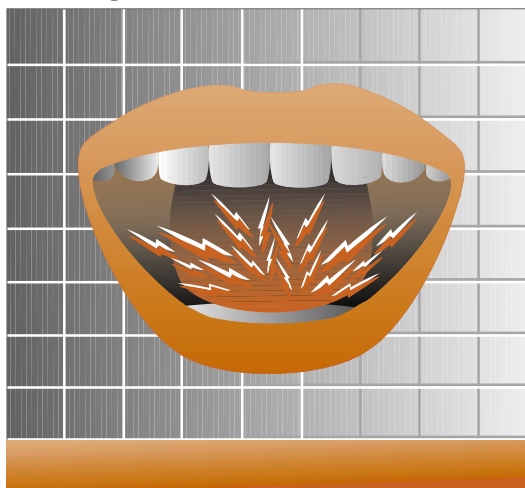
While humans find *timurol*’s buzz pleasing, non-human animals appear not to like *timurol*. For example, rats, voles, deer,

and blackbirds eat less when *timurol* is sprinkled on their food. All species tested made their dislike very clear; some were repelled by just the citrus-like odor.

A similar chemical compound is found in the Prickly Ash, known in rural areas of America as “The

Toothache Tree.” A bitter aromatic tonic is made from the bark, roots, and berries for use as a general stimulant, and also as a remedy for toothache, upset stomach, poor circulation, fever, and other ailments. Also, the bark is ground into

powder and mixed into a paste to be applied as an anesthetic to wounds, skin ulcers, and rashes.



Because *timurol* activates different neurons from those that respond to other chemosensory irritants, it can lead to new information on sensory neural function. Researchers at Monell are now observing patterns and combinations of neural activity that give rise to this unique sensation, and are using *timurol* to identify sensory neurons not previously thought to be involved in chemosensory irritation.

Timurol, with its ability to chemically excite nerves that lead to an irritating sensation, might be a way to mimic the spontaneously-occurring pain syndrome

continued on page 4



Writing about the Chemical Senses

his classic autobiography, *Father and Son*, written in 1907, Sir Edmund Gosse, the literary critic, described the odor in the house of his uncles: “Their home had a strange delicious smell, so unlike anything I smelt anywhere else, that it used to fill my eyes with mysterious pleasure. I know now that this was the odour of cigars, tobacco being a species of incense taboo at home on the highest religious grounds.”

Perhaps these and other literary observations have stimulated scientific investigation of phenomena such as odor memory and the special role odors may have in arousing emotional memory. In fact, a direct test of the potency of odor memory and emotions, as distinct from emotional memories aroused by stimulation of other senses, forms the central theme of the research of a Monell scientist.

In my own research, a paragraph in *Gulliver's Travels* was important. Swift writes: “I was at first at a great loss for salt; but custom soon reconciled the want of it; and I am confident that the frequent use of salt among us is an effect of luxury...when I left this Country, it was a great while before I could endure the taste of it in anything that I eat.” Subsequent research, more than 250 years later, confirmed Swift's observation.

On a lesser literary plane, one of my colleagues at Monell gave me a book with the intriguing title *Sweet Salt*. It is a first-person account of a man's experience as a prisoner of war in World War II, starving in the hold of a ship. Significantly, the author indicated that when he was depleted of sodium, the taste of salt changed from salty

to sweet. We tested this with humans, but could not confirm it. However, we might not have sufficiently depleted our human subjects to see the phenomenon experimentally, since there are some animal model data consistent with this hypothesis.

Just because an idea comes from a literary source is not a reason for scientists to reject it. Conversely, non-scientist writers are sometimes obtuse, lacking in rigor, and often just plain wrong. There are many careful and excellent scientific writers and journalists. At Monell, we work with some of them to our mutual benefit. But since one of Monell's missions is to help ensure accurate dissemination of the scientific fundamentals of our field, poor or sloppy science writing is an annoyance.

The journalist and scientist often have opposing goals. The scientist should want to ensure that accurate information is available to the public. The journalist wants to tell a good story, and might not be sufficiently inspired by the restraint and resistance of scientists to make pronouncements about what is or is not true. Sometimes the journalist virtually ignores the content of a lengthy interview with a credible scientist from Monell or elsewhere, and instead cites others who are willing to be much more dogmatic, dramatic, quotable — and perhaps misleading.

A clear example of this involves recent articles about human pheromones. It is true, but not newsworthy, that at this point we do not know whether pheromones exist in humans. More exciting, but in my view erroneous, are confident statements about the absolute certainty of their existence, their exact chemical nature, and their function.

This brings me back to our book reviewer. In his final sentence, he expresses horror that the literary critic (and I would assume he might extend this to the non-scientist journalist) could presume to partake of the scientific enterprise. Obviously, I do not agree with this. As with most generalizations, it is too inclusive — but certainly highly quotable.

Both good literary works and good journalism will benefit the scientific enterprise. From the former we can find useful ideas. From the latter we can have our often obscure activities transformed into something understandable and capable of being appreciated by readers, who ultimately provide the support and encouragement for our work. ■

Recently there appeared in the prestigious science journal *Nature* the following quotation in a review of two books, one by a scientist and the other by a distinguished literary critic: “A comparison of the two texts shows that, as is usually the case, the prose style and clarity of the scientist are far superior to those of the professor of English. In this postmodernist world, literary criticism might well fare better if it were taken over by scientists. But God help science if literary critics reciprocated the gesture.”

This pithy quote, by a reviewer who is a scientist, is brimming with confidence — and also arrogance. It set me to thinking about differences in the ways the literary writer and, more generally, the non-scientist writer represent the chemical senses.

Proust's *Remembrance of Things Past* probably has the most famous literary allusion to the chemical senses, in describing the power of odors to evoke long lost memories and to elicit strong emotions. In

Thinking about Ion Channels... and Beyond



Paola Tagliamonte

From his childhood attempt to perform a heart transplant on a tadpole to his current research on ion channels and taste receptors, Dr. Ralph Puchalski likes to attempt new things and break new ground.

After graduating from college with a major in economics, he was the first of several Americans to obtain a permanent position in a large Japanese trading and retail conglomerate. After two years in Japan, he was well on the way to a successful international business career. At the same time, however, he was coming to realize that “the more I worked in business the more I knew that it wasn’t what I wanted to be doing.”

Fortunately, he had a good sense of what he did want to be doing. “Everything pointed to science,” Puchalski recalls. That path was reaffirmed while spending his days off in a laboratory at the University of Tokyo Medical School. “I knew it was the kind of place where I wanted to be,” he says.

The turnaround wasn’t easy, in part because he didn’t have the necessary background in math and science. Puchalski used savings accumulated in Japan to finance a year of catch-up courses required for entering graduate school. He persevered and obtained his Ph.D. in Oncology and Biochemistry at the University of Wisconsin (Madison).

As a postdoctoral fellow at The Salk Institute for Biological Studies, Puchalski again ventured into an unfamiliar area to study molecular neurobiology. His decision to focus on ion channels associated with glutamate receptors in the central nervous

system was made in part because he liked the fact that he didn’t yet know anything about them. “They were exciting, new, and different,” he explains.

“What really drives me in the scientific endeavor,” Puchalski says, “is developing new ideas and new ways of thinking about problems and process.” He adds, “The really exciting projects are the ones I haven’t even started.”

A molecular biologist in pursuit of something new is precisely the kind of scientist that Monell was seeking to help obtain deeper knowledge of taste transduction. Although considerable progress has been made towards describing the events involved in olfaction, taste transduction — the process in which taste stimuli interact with receptors on taste buds and then trigger nerve impulses to the brain — is still not clearly understood at the molecular level.

Because ion channels, and potassium channels in particular, are thought to be essential to the way all taste cells send messages to the brain, Puchalski’s postdoctoral research provided an ideal basis for the

search for potassium channels involved in the taste process. He was particularly interested in finding new ion channels and taste receptor proteins that have not yet been identified.

His search has been successful. Since coming to Monell in 1995, Puchalski and coworkers have identified and cloned a new type of potassium channel in catfish and are currently extending this work to find out if the channel is also present in rats. Of particular interest is that the channel is located in taste buds, but not in the surrounding non-taste tissue. Studies are currently underway to determine whether the new channel is active in other organs.

Ion channels are pores in cell membranes that permit ions, such as sodium, potassium, and calcium, to flow in and out. They are a key factor in creating and controlling electrical signals that transmit information to the brain.

Collaborative work at Monell has also revealed that this channel appears to have unique electrophysiological properties not

o n d

previously seen in other potassium channels. Current projects are focused on further understanding how the channel functions in the taste transduction process.

Puchalski's research interests have both economic and medical potential. Once an ion channel or other protein involved in taste transduction is identified, it may be possible to develop synthetic compounds or identify natural substances that would lead to discovery of new taste stimuli or taste modifiers. In terms of medical investigation, ion channels or receptors discovered in the taste system might also be required for proper functioning of other organ systems. Puchalski speculates that knowledge of how these channels or receptors function — or fail to function — could lead to insights into the cause, development, or progression of a disease.

Puchalski uses techniques of molecular biology to clone new ion channels. Once the genetic material that codes for the channel's structure is identified and isolated, he expresses the channel and uses biochemical and electrophysiological methods to study its function in the taste process.

An interesting series of parallel studies has identified yet another potassium channel. This one appears to influence salty taste preference in mice. When the channel is made non-functional, the mice's preference for salts decreases. Future studies will determine whether this decreased preference is due to an alteration in the taste system, and whether the effect is specific for salts or extends to other taste modalities.

Puchalski doesn't try to predict where his research will lead. He is confident that the search to identify and understand ion channels and other taste-related proteins will not only lead to new knowledge about taste transduction, but will also have an impact beyond what is known about taste. And most important, it will satisfy his desire to discover "something I can't even predict is there and that hasn't been thought of yet." ■



Ralph B. Puchalski, Ph.D.

Tingle on the Tongue *continued* *from page 1*



known as *paresthesia*, characterized by feelings of burning, pricking, and tingling. Research using timurol may provide insight into the causes of paresthesias and help to identify methods to provide relief from this and other kinds of pain.

In terms of consumer products, a compound that provides a strange and wonderful oral sensation and also deters animals can certainly be put to many intriguing uses, particularly in oral hygiene and healthcare products and animal repellents.

People were asked to describe the three predominant oral sensations they experienced after trying timurol. Most of them had difficulty coming up with appropriate words because it was so new and strange. In addition to expected responses of "tingling," "buzzing" and "pins-and-needles," other descriptors included "crackling," "scratchy" and "tickles my throat." Quite a few also characterized it as salty, sour, bitter — or a combination of the three.

Right now the potential for timurol is spurring several avenues of scientific and commercial exploration. No matter what the use, there are many unknowns. For example, there's quite a bit of variability from person-to-person in how timurol is perceived — for some, it's just a little tingle; for others it's painful. Also, the rate of onset ranges from slow diffusion on the tongue to an immediate buzzing vibration. Obviously, commercial efforts to add new zing to familiar products will need a way to standardize and control the sensation.

With all that is yet to be discovered about the mechanisms and function of nerves involved in oral sensation, timurol provides a valuable tool for obtaining new information. At Monell, chemists are trying to produce the compound synthetically so as to come up with a more potent version for use as a repellent, as well as to determine which parts of the molecule are necessary to produce the buzzing sensation. Electrophysiological recordings and intracellular imaging techniques are identifying those nerves that are stimulated by timurol, and also comparing them to nerves known to be involved in other forms of chemical and tactile sensations.

With such a range of scientific possibilities to be investigated — gustatory, thermal, tactile, olfactory, sensitivity to pain — there's a great deal to be done in untangling the tingle of timurol. ■

Q&A

How do odors affect work performance?

Whether in offices, factories or schools, people frequently seek ways to improve their performance. As part of this effort it is often proposed that environmental factors, including scent, can improve the accuracy and speed of task performance.

Although scenting might potentially be a relatively inexpensive and easily implemented way to improve task performance, research on this topic has produced diverse findings.

Several studies have found that odor has no effect on task performance. Of note is the fact that in two of these studies even malodors had no influence on performance. In some studies using pleasant odors, the odors did have a positive effect. In other studies, however, odor was found to have a negative effect on performance — even when pleasant odors were used. These findings seem to indicate that it is unwise to assume that the effect of pleasant odors will always be positive.

The mixed and often contradictory results may be due, in part, to variables that have not yet been systematically studied. For example, it may be that odor characteristics such as intensity or timing of delivery influence how odors affect performance. Similarly, the type or duration of the task itself and the subject's personality might have an impact.

Additional research is needed to determine the effects of different combinations of odor, task, and subject characteristics in order to understand how odors influence performance and the significance of their role.

What do people who have lost their sense of smell miss most?

More than 3-million people in the United States suffer from some type of chronic smell or taste disorder. Although a small number of individuals are born without a sense of smell, the most frequent causes of loss are injury or illness. These include head trauma, viral infection, and inflammatory disease of the nasal or sinus passages.

Because of the close link between smell and “taste,” whereby food flavors are mostly recognized through the sense of smell, the most frequent complaint from people with olfactory loss seems to be its negative impact on the pleasures of eating. This is particularly bothersome for people such as professional chefs who rely on sampling foods to adjust seasonings. Of even greater cause for concern

are the hazards of being unable to smell tainted food, leaking gas, toxic fumes, and smoke.

In order to compensate for the loss of food flavor, more attention can be given to texture (e.g., crunchiness or creaminess), temperature, and use of non-olfactory flavorings such as lemon juice and pungent spices. In terms of safety, gas and smoke detectors can provide some protection.

Loss of sensitivity as a result of damage to the olfactory neurons is usually permanent, although these nerves sometimes regenerate and an individual's sensitivity returns. In most instances, a problem caused by sinus infection or polyps can be treated through medication, surgery, or both.

Why, in spite of good oral hygiene, do some people have persistent bad breath?

Many individuals work hard to keep their mouths in good health, yet they still suffer from persistent bad mouth odor and taste.

This problem may stem from two possible causes. The first is that keeping teeth and gums clean does not eliminate excessive build-up of bacterial plaque on the back of the tongue.

Most people do not know that the tongue is an odor-producing area, yet recent research has determined that almost all persistent cases of bad breath stem from plaque build-up there. Therefore, it is important to clean the back of the tongue by gentle scraping and brushing.

A second explanation for bad breath and a bad taste in the mouth could involve a metabolic problem. The most prevalent one is trimethylaminuria (TMAU), a frequently undiagnosed, odor-producing metabolic disorder that often includes sporadic oral symptoms.

Many dentists and physicians do not have enough information about TMAU. This creates a frustrating situation for patients whose symptoms are sometimes viewed as subjective and psychological, and unrelated to any disease process.

Although there is no known cure, an individual with TMAU can take steps to lessen the symptoms. After consultation with a knowledgeable healthcare professional, these measures might include keeping the mouth moist by drinking water or citrus juice, and avoiding choline-rich foods such as egg yolks, certain fishes and organ meats, and some legumes. ■

Contributors: Beverly J. Cowart, Ph.D.; Susan C. Knasko, Ph.D.; George Preti, Ph.D.

Cravings by Young and Old

Although the population is aging, little is known about the incidence of food cravings or the types of foods craved by elderly adults. To describe how food cravings — defined as an intense desire or longing to eat a particular food — vary between young and elderly adults, Dr. Pelchat interviewed approximately 50 individuals from each of these age groups.

Elderly adults (over 65 years of age) differed from young adults (ages 18-35 years) in several aspects of craving behavior. Fewer elderly adults reported food cravings. Elderly subjects also described craving a smaller number of different foods, and were better able to resist or postpone their cravings. There were no differences in frequency of cravings, with cravings occurring about once per week in all the groups. Overall, women reported more

cravings for sweet foods than men, but elderly women were less likely to crave sweet foods than were young women.

Some theories that have been proposed to explain the causes of food cravings suggest cravings are triggered by sensory factors. Because aging is sometimes accompanied by loss of olfactory and gustatory function, the decline in food cravings with age is consistent with these theories. Further, the age-related decrease in cravings for sweet foods by women supports a role for ovarian hormones in at least some types of cravings. Based on these data, future studies will explore mechanisms of food cravings in both young and elderly adults.

Food cravings in young and elderly adults. Marcia Levin Pelchat. *Appetite*, 1997, 28, 103-113.

Does the Brain Tell the Nose?

Variability among individuals in ability to perceive odors is usually attributed to biologic factors, such as age-related or genetically-determined differences in sensitivity. The purpose of Dr. Dalton's experiment was to explore how information concerning the presumed health risk of an airborne odor can influence perceived intensity of that odor.

Subjects in a climate-controlled chamber were exposed to isobornyl acetate, which smells like balsam, for 20 minutes. They were asked to rate the odor's intensity once every minute. Groups differed only with regard to the information each was given about the odor: one group was told that the odor was a positive health-promoting natural extract, while the other group was given negative information and told the odor was a potentially hazardous industrial solvent.

Intensity ratings reported by the groups differed during the test period. Subjects in the

group given positive information showed a typical adaptation pattern, with intensity ratings decreasing continuously to a final rating of "weak." However, intensity ratings of the group that was told the effect of the odor was negative increased over the second half of the session and were perceived as "strong" at the end of exposure. Threshold sensitivity tests showed that the groups were equally able to detect the odor.

These data confirm that non-sensory factors such as cognitive information can have an effect on odor perception. For example, assumption or expectation of risk may influence discomfort of individuals who report extreme sensitivity to odors and may interfere with adaptation to environmental odors.

Odor perception and beliefs about risk. Pamela Dalton. *Chemical Senses*, 1996, 21, 447-458.