

Restoring scent

Treatments for people who have lost their sense of smell are scarce. With millions of people newly affected as a result of COVID-19, researchers are pursuing the problem with renewed vigour. **By Sarah DeWeerd**



Rhinologist Zara Patel uses an endoscope to visualize the olfactory cleft in a patient's nose.

Nearly a year after he contracted COVID-19 in March 2020, Marc Pilchman sat down with a plate of Chinese noodles with beef. Pilchman, who is 80 years old and lives in New Jersey, had found the recipe in a newspaper article, whose author wrote that it had helped him when he was suffering from a loss of smell after recovering from COVID-19. Pilchman had promptly gone online and ordered a long list of ingredients for the recipe.

The heat from the dish's strong spices burned Pilchman's mouth, but he forced the noodles down anyway: he was willing to try anything that might revive his sense of smell. Yet when it came to the dish's aroma or the subtleties of its taste, he experienced the same blankness that had plagued him since the onset of the virus: "Nothing," he says.

Olfactory loss of is a common symptom of COVID-19. Nearly half of those who contract the virus notice that their senses of smell and taste (which are closely related) are affected¹. Loss of smell is often the first and can even be

the only symptom of the virus, although it is less common with some variants such as Omicron (see page S5).

Most people who recover from COVID-19 find their sense of smell returns in a few weeks. But for others – up to 7%, according to one estimate¹ – the loss can persist for months or even years. Physicians refer to this total or near-total loss of smell, as Pilchman has experienced, as anosmia – or in less extreme cases, hyposmia, meaning a reduced sense of smell.

"There are now millions of people around the world that still have persistent olfactory loss" after COVID-19, says Claire Hopkins, a rhinologist at King's College London. "It is still very much a neglected area, both in terms of research funding and support from health-care systems, and it is dismissed in terms of the impact it has on people."

Despite being often overlooked, smell is crucial to many everyday pleasures and social bonds. We're drawn to sniff a baby's head and revel in the scent of a lover. Human connection and conviviality often takes place over food

and drink; without being able to share fully in the sensory aspect of these experiences, people who have lost their sense of smell might withdraw and become socially isolated.

Pilchman, a food and wine lover whose friends used to encourage him to start a food blog, has cobbled together a way to appreciate food on the basis of basic taste elements such as sweet, salty and bitter (which are detected through taste buds on the tongue), the sight and texture of food, and his memory of its taste. "But I don't get the real, full impact and enjoyment," he says.

COVID-19 has put the loss of smell in the spotlight as never before, highlighting both the unique regenerative capacity of the olfactory system and the need for better treatments. The virus has provided insights into the mechanisms behind losing the sense of smell, and has resulted in a large group of people with a persistent olfactory impairment who can take part in clinical trials of potential treatments. If progress can be made in this group of people, those whose sense of smell is impaired for other reasons could stand to benefit, too.

A common affliction

Although loss of smell received little public attention before COVID-19, "the reality is smell loss is something that is quite prevalent", says Aria Jafari, a rhinologist at the University of Washington in Seattle. Between 5 and 15% of the general population, and nearly half of those between the ages of 65 and 80, have experienced impairment of their sense of smell².

The treatment for smell loss and the chances for recovery both depend on its cause, Jafari says. Apart from ageing, one of the most common causes of smell loss is chronic rhinosinusitis – persistent inflammation in the nose and sinuses that is thought to affect around 5–12% of people in industrialized countries³. It is often due to allergies, repeated bacterial infections, or benign growths in the nose called polyps.

Treatment for chronic rhinosinusitis is well developed and effective. Physicians can surgically remove swollen tissue or polyps that block the nasal passages, use oral or topical steroids to calm inflammation in the nose and prescribe antibiotics to get rid

of any nasty bacteria that linger. And in the past few years, monoclonal antibodies such as dupilumab, which block inflammatory signalling molecules, have become available to relieve the hardest-to-treat cases.

“In the last decade or so, as the understanding and treatments for chronic sinusitis have improved, there’s been much greater interest in addressing olfactory disorders,” says David Gudis, a rhinologist at the Columbia University Irving Medical Center in New York.

Yet, despite increasing attention to smell loss from physicians and scientists, treatments for most forms of the condition are scarce. Loss of smell can be an early symptom of neurodegenerative diseases such as Parkinson’s disease or Alzheimer’s disease. There is no treatment for this form of smell loss, which probably involves the same mechanisms that cause damage elsewhere in the brain.

Smell loss can also be caused by exposure to toxic chemicals, certain medications or injuries to the nose or to brain regions that process and interpret smell information. Sometimes, the sense of smell recovers spontaneously after injury. The olfactory nerve is the only cranial nerve that can repair itself when damaged, and olfactory sensory neurons – cells in the upper part of the nose that recognize different odorant molecules – renew themselves periodically throughout life. But smell loss from a head injury can be permanent if the trauma completely severs the olfactory nerve, which occupies a vulnerable position close to the bridge of the nose.

Respiratory viruses – such as influenza and the common-cold-causing rhinoviruses, parainfluenza viruses and endemic coronaviruses – have been known to trigger smell loss that can persist long after recovery. But even compared with other causes of smell

loss, post-viral anosmia has been “relatively understudied and poorly understood”, says Jonathan Overdevest, a rhinologist at the Columbia University Irving Medical Center.

Lack of testing for many respiratory viruses and delays in seeking treatment for smell loss meant that before COVID-19, it was difficult to trace the problem back to specific infections. “So the true incidence of that was really underappreciated,” Overdevest says. SARS-CoV-2 appears to be much more likely than other viruses to cause lingering smell loss, and Overdevest and his collaborators have launched a study to track the effects of long-term post-COVID smell loss on people’s lives.

Training the nose

The mainstay of treatment for post-COVID smell loss is olfactory training – a procedure that many rhinologists compare to physical therapy for the nose. Individuals are instructed to sniff a sequence of four essential oils, deeply inhaling each one for 15 seconds while concentrating on their memory of the corresponding smell. They repeat the procedure twice a day over the course of months.

Olfactory training has its roots in the established understanding that the sense of smell is mutable and improvable. For example, people in professions that involve smell – sommeliers, perfumers, tea merchants and chefs – often develop keen noses, says Thomas Hummel, an olfaction researcher at the Technical University of Dresden in Germany, who conducted some of the first studies of the procedure in the 2000s (ref. 4).

In early studies, Hummel and his team provided participants with jars containing cotton balls soaked with pure odorants. In the early 2010s, Zara Patel, a rhinologist at Stanford University in California who was frustrated

by the lack of treatment options for people with non-rhinosinusitis smell loss, set out to simplify the procedure for everyday clinical practice by using readily available essential oils. The quartet of odorants most commonly used, both in Hummel’s early studies and by physicians today, are rose, eucalyptus, lemon and clove. Each represents a different category of smell, and is therefore expected to stimulate different olfactory neurons, Patel explains.

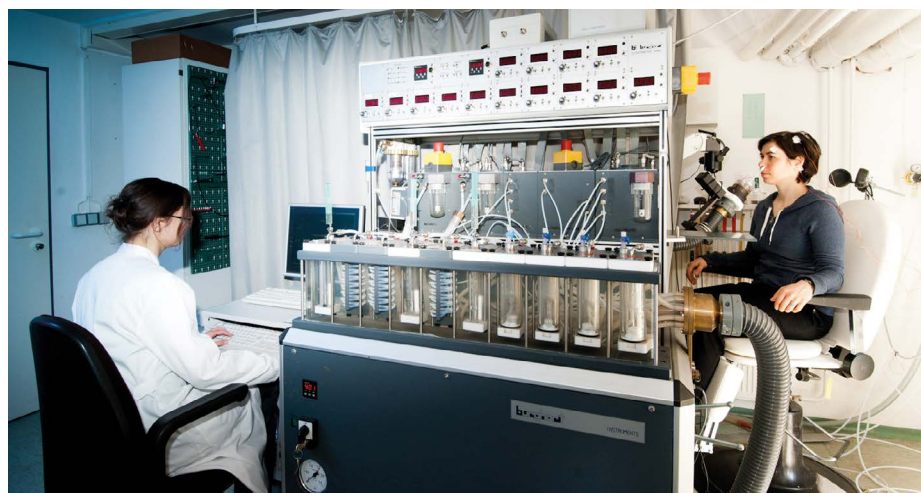
“Early intervention is key. Don’t wait six months to see if it gets better.”

The high rate of spontaneous recovery in post-viral and some other forms of smell loss can make it hard to establish the effectiveness of treatments. But multiple studies of olfactory training – including several randomized, controlled trials – “show that this is helpful in post-viral olfactory loss, in post-traumatic olfactory loss, and possibly also in ageing”, Hummel says.

There is some evidence that switching to a different set of four scents after three months (typically menthol, thyme, tangerine and jasmine) is more beneficial than sticking with the initial quartet². And the sooner olfactory training is initiated, the greater the chances of success. “Early intervention is key,” says Gudis. “Don’t wait six months to see if it gets better.”

Some physicians and scientists were initially sceptical of olfactory training. But acceptance of the decidedly low-tech treatment has increased as evidence for its efficacy has accumulated, and the advent of COVID-19 provided a big boost. With little else to offer their sudden influx of patients with smell loss, clinicians have embraced the approach – which after all is inexpensive and carries almost no risk of side effects.

Many clinicians (including those interviewed for this story) recommend olfactory training for people experiencing post-COVID anosmia and hyposmia, as well as other changes to their sense of smell that can occur after infection (see ‘When good smells go bad’). Many rhinologists also recommend other low-risk treatments that have shown effectiveness in people who have lost their sense of smell from non-viral causes. These supplementary treatments can include steroids, which are widely used in chronic rhinosinusitis, and high doses of omega-3 fatty acids. A small trial showed that omega-3 fatty acids can aid recovery in people who experience olfactory loss after undergoing surgery in which instruments are passed through the nose⁵.



An olfactometer evaluates the effects of smell training.

THOMAS HUMMEL

None of these treatments work miracles. Pilchman followed the olfactory training protocol for months. “I ordered my essential oils and lined them up like little soldiers,” he says. He also used a steroid nasal spray, and is still taking an omega-3 supplement. The combined therapies have yielded no improvement: Pilchman remembers that he could smell the clove essential oil the first time he uncapped the bottle, and this remains the only odour he can reliably detect.

A new opportunity

Efforts to improve the treatment of anosmia have been handed a significant boost by the surge of people affected as a result of COVID-19. Greater attention will surely bring fresh funding, and the large number of people presents an opportunity for trials of therapies.

For example, Patel is conducting a trial of platelet-rich plasma in people with post-COVID smell loss (see go.nature.com/3wmtkqd). This blood concentrate, produced from a person’s own blood, has anti-inflammatory effects and also contains growth factors and other molecules that might help to encourage repair and renewal of tissues – including perhaps the olfactory epithelium.

Many treatments now under investigation aim to promote the regeneration of neurons and calm inflammation, researchers say, and thus might be applicable to multiple causes of smell loss. But drug development would also benefit from a more detailed understanding of the mechanism of olfactory loss on a cellular and molecular level, says Jafari. Researchers have made strides in working out how SARS-CoV-2 damages support cells in the olfactory epithelium and plays havoc with olfactory neurons (see page S5). The next step is to learn more about which biochemical mechanisms and signalling pathways underlie these effects, says Sandeep Robert Datta, a neuroscientist at Harvard Medical School in Boston, Massachusetts.

Such information could come from studies of olfactory tissue biopsied from people with post-COVID smell loss. “Then we can begin to look for molecular or cellular changes that correlate with your actual loss of smell,” says Datta, who is conducting such studies. These investigations could yield benefits for people with olfactory loss not just resulting from COVID-19, but from other causes, too. “We don’t know really anything about how other viruses – or other causes – change your sense of smell,” says Datta. “So if there’s a silver lining here, it’s that we’re finally paying attention to all of the cell types in the epithelium and their interactions.”

For Pilchman, now entering his third year of anosmia, the slow march of scientific progress

WHEN GOOD SMELLS GO BAD

People recovering from COVID-19 can experience a variety of olfactory problems, including distortions of their sense of smell.



Michele Horwitz lost her sense of smell.

After many months of diligently following an olfactory training programme, Michele Horwitz has regained the ability to detect several scents, including clove, tangerine and jasmine. When she opens her bottle of rose essential oil, “I can smell some fragrant something,” she says, but it’s a vague impression. The 55-year-old from New York lost her sense of smell and taste when she came down with COVID-19 in February 2021. She keeps a slowly expanding list of tastes she is able to discern: lemon, red peppers, banana, cucumber and Parmesan cheese.

However, this improvement has been accompanied by several distortions of Horwitz’s senses. The smell of garlic or onion cooking in hot oil has become disgusting to her. Most sweet foods now make her gag. And many previously distinct smells now share a gross sickly scent. “My deodorant, my shampoo, my conditioner and soap — they all smell the same to me,” she says.

This distortion of smell is known as parosmia. Some clinicians think that it is more common in people who have experienced COVID-19 than other viral

illnesses. In one study, nearly two-thirds of people with disruptions to their sense of smell after COVID-19 reported experiencing parosmia⁶. It can develop either along with other symptoms of the virus, or after a person has recovered.

Parosmia — and phantosmia, perceiving smells that aren’t there — are thought to arise from some kind of mis-wiring of olfactory neurons that are recovering from an injury, or misinterpretation of olfactory signals in the brain. But the details are murky.

For people experiencing post-COVID parosmia or phantosmia, rhinologists generally recommend the same regimen of olfactory training as they do for anosmia; there is little evidence about how to treat parosmia and phantosmia specifically. But the large numbers of people affected by COVID-19 could provide an opportunity to change that. “We are going to learn something about how to treat parosmia and phantosmia with this patient population,” says Zara Patel, a rhinologist at Stanford University in California. “It was just never common enough to garner a lot of research interest in the past.”

Paradoxically, physicians generally consider these symptoms to be a promising sign for a person’s recovery: they suggest that the olfactory system is trying to repair itself. One study found that olfactory training was more likely to lead to improvement in people with post-viral smell loss who experienced parosmia than in those with post-viral smell loss who didn’t⁷.

But these symptoms can be just as distressing for people as the total loss of smell — or even more so. The unpredictability of Horwitz’s senses puts her off social activities such as dining out, and is difficult to explain to friends and colleagues, making her feel isolated and alone. “It’s taken a huge part of my life away,” she says.

can be difficult to bear. “I am beginning to feel that it’s just not going to happen for me,” he says.

But some researchers say that even for those with long-term smell loss, there’s reason for optimism. In rare cases, people have recovered from post-viral olfactory loss lasting many years, Hopkins says. This suggests that if scientists could devise a way to activate the nose’s regenerative capacity they could reawaken even a long-dormant sense of smell. “We still think that there is hope for that group,” she says.

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