

WHAT MAKES SENSE

Around the world, millions of people testing positive for Covid – including journalist Paola Totaro – lost their sense of smell. Now scientists are starting to unravel its mysteries



Ten months ago, I fell ill. Four days of textbook Covid lungs on fire then, as quickly as the burning pain had come, it went – and with it my sense of smell and taste. I remember vividly the moment that I noticed its absence: London had been in lockdown for a week and Prime Minister Boris Johnson was in isolation after testing positive for SARS Cov-2. I'd been washing my hands for what felt like the hundredth time when the moisturising lotion I always use, a heady mix of mandarin rind, cedar atlas and rosemary leaf, yielded nothing, not even the hint of a fragrance. Confused, I uncapped and sniffed several of my perfumes desperately, one by one. Nada. Panicked, I scrubbed for a floral bleach-based toilet cleaner that normally makes you pull back in shock and put my nose right into it. Zilch. The sensory vacuum was so intense that for a few seconds it made me feel as if I were in free-fall in a faulty elevator.

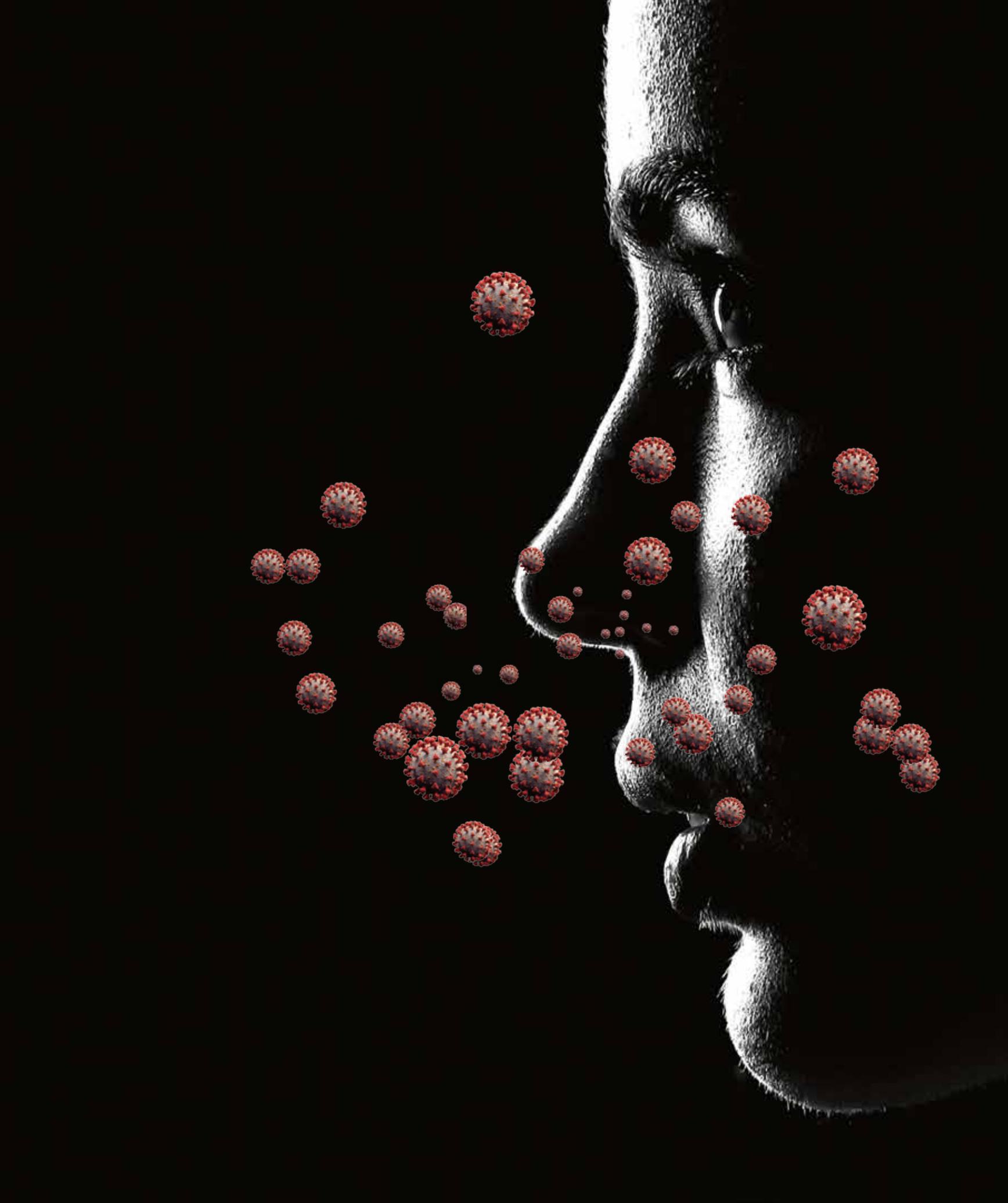
I had been immersed in reporting the earliest days of the Covid-19 crisis in northern Italy at the time, noting an increasing number of anecdotal reports from Milanese physicians about the sudden onset of anosmia – loss of smell – in patients testing positive for the virus. Locked in a frightening sensory desert in those first dark days, I began to Google anosmia. I learnt months later that a global surge in search engine requests for “loss of smell” by patients desperate for information had occurred around this time and that this, combined with Twitter and other social media discussion about the strange and sudden syndrome, had also galvanised chemosensory scientists around the world. Within weeks, they had recognised the extraordinary research potential in what was occurring and created an international collaboration called the Global Chemosensory Research Consortium.

Fast forward to 2021 and about 95 million people have been infected with Covid-19 and two million have lost their lives. Another 67 million have recovered or are in the process of recovery and of these, neuroscientists estimate that between 43 per cent and 60 per cent have experienced some form of sudden olfactory and taste dysfunction. A study published on January 5 in the *Journal of Internal Medicine* found that 86 per cent of patients who suffered mild Covid-19 experienced anosmia compared with just four to seven per cent of moderate to severe cases.

So far it has been the unimaginable speed and collaborative nature of the scientific work achieved to find a vaccine that has dominated the public spotlight, likened to the Apollo moon missions as one of modern history's greatest scientific achievements. But as many nations embark on the gargantuan logistical task of inoculating entire populations, there is another, less known story unfolding. It involves the never-ending cohort of new Covid-19 patients helping scientists to study and explain aspects of human olfactory physiology and perception that, until now, have remained mysterious.

Smell and taste are the oldest of the senses. A product of evolution, they play a key role in human survival, are fundamental to reproduction and protective against dangers such as fire or toxic foods. Smell and taste systems effectively work together, allowing our bodies to take molecules from the external world into the body through the nose and mouth, binding to them and bringing them directly to the brain, which processes their meaning.

The sense of smell is triggered when airborne particles inhaled through the nose attach to the millions of receptor cells that line the mucus



membranes at the top of the nasal bridge. There are about six million of these receptor cells on an area the size of a postage stamp but only 400 or so different types of sensory receptors: some respond to a specific range of molecules while others are much more broadly tuned – what researchers describe as “promiscuous”. As they bind to the odorant they switch on, sending signals upwards to the olfactory bulb and into the brain for interpretation.

Unlike hearing and sight, which can be measured and mapped physiologically, the olfactory sense is the product of a complex neurological process and science still cannot explain in absolute detail how humans code odours. Just as importantly, without smell you cannot detect flavour because taste buds only tell you if your food is salty, sweet, bitter or sour or savoury (umami). The olfactory system decodes the vast array of other flavours unleashed by odour molecules as you chew.

And who among us does not use smell to protect ourselves? We all sniff a bottle of milk before pouring or smell-check fish before cooking. I would learn very quickly that just how often we use our noses to navigate the world only becomes apparent when this fundamental signpost disappears.

On February 27, just a couple of weeks before I, like thousands of others, began to report smell loss, Chrissi Kelly, founder of UK-based charity AbScent, was busy presiding over the official launch of an Anosmia Awareness day, oblivious to what was about to unfold.

A zooarcheologist by training, Kelly lost her sense of smell in 2012 after suffering a heavy bout of flu. Over several years she has become a vocal and powerful advocate, collaborating with the country’s top ear, nose and throat physicians and chemo-sensory scientists to try to understand and develop techniques to hasten olfactory recovery.

Less than two weeks after the launch, Kelly found herself at the epicentre of what is probably best described as one of the world’s largest citizen science projects – spurred by the pandemic. “We launched with the original 1500 AbScent members on our Facebook page,” Kelly tells me via Zoom. “But by the end of the following week, Covid-19 patients had overwhelmed the original group... On March 24, I decided we needed to create a separate, Covid anosmia page. I found a free image of a virus on the net and placed it on the top banner and opened the page. It was 10.30pm and I didn’t even advertise.”

Today, 18,000 people around the world have joined the AbScent Facebook page, all reporting

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the loss of smell and taste. However, as the months have passed, vast numbers have also begun to document entering a phase of recovery characterised by parosmia, a less reported condition in which smells are terribly distorted, often sparking nausea and disgust. Some even described experiencing phantosmia, in which sufferers detect a smell that simply isn’t there – everyday foods suddenly smell of rotting fish or acrid chemicals, sulphurous or burnt. For others like me, a smell would become “locked in”, a haunting constant you cannot shake. The phantom smells I perceived were wood smoke, which persisted for a couple of months, replaced by a cloying, sugary smell I could only liken to sweet potato roasting. These were odours I could live with: I cannot imagine what it must have been like for the thousands who smell the stench of raw sewage everywhere.

Suddenly, a little understood cluster of chronic olfactory conditions endured silently and invisibly in the past has morphed into an acute symptom suffered by thousands around the world. This has created a cohort of patients who can not only be studied but can explain their perceptions and experiences, offering a unique opportunity to enhance understanding in the context of a global pandemic.

Professor Anne Sophie Barwich, a German-born cognitive scientist and philosopher, has

described smell as the Cinderella of the senses because it has been dismissed by philosophers and scientists throughout history as the most dispensable. Even Charles Darwin concluded in 1874 that olfaction was “of extremely slight service” to mankind. But in her book *Smellosophy: What the Nose Tells the Mind*, Barwich argues that all this changed in the early 1990s with the discovery of olfactory receptor genes.

The characteristics of odour perception and its neural bases, she writes, are key to an understanding of the mind but while neuroscience has unlocked new knowledge, we still don’t know how the brain organises olfactory information. “You won’t find a map of stimulus representation in the brain such that chemical groups [which produce fruity, pungent smells] like ketones would sit next to aldehydes or perceptual categories like rose were right next to lavender,” she writes.

This historical neglect of smell and taste by Western thinkers is illustrated more widely by a general belief that they are less important than the other senses. A study in 2018, for example, revealed that teenagers would rather lose one of their senses than their mobile phones, choosing smell as the one they’d prefer to sacrifice. Patients report a similarly dismissive response by their doctors, and many are only now understanding the profound emotional impact of losing the sense of smell and the link between depression and anosmia.

The nose is deeply wired into the part of the brain that is not necessarily conscious or related to learned behaviour but rather is related to instinct and is a gatekeeper not just for wellbeing (detecting smoke and fire is fundamental) but for intimate relationships. Mothers and babies are profoundly linked by smell, while perceiving chemical signals or odours can define who we find attractive. We all know that smells can also trigger powerful memories and emotions: the smell of the sea, freshly cut grass, our mother’s perfume.

I remember, five months after Covid infection, sitting in a neighbour’s garden and suddenly perceiving the faintest hint of the fragrance of jasmine blossom, the essence of spring. I wanted to drink it in, bury my face in the flowers; I was so elated. Months without smell or taste wears you down, makes the world feel colourless, flat, soulless.

This sense of loss is often dismissed by those who have not experienced it, pushing more people into seeking help outside medical care settings. It is here, according to the University of London’s Professor Barry Smith, that groups like AbScent and the human Petri dish it has created with Covid-19 has become so important. Smith, who is

the UK lead for the Global Chemosensory group, believes the experiences reported by the vast new patient cohort created by Covid-19 is integral to the campaign for knowledge.

“The odours we perceive are not predictable from the mixtures of molecules we inhale,” Smith says. “There is no equivalent of primary colours or musical scales. We respond to each molecule with many receptors and each receptor responds to different molecules. Odour mixtures are much more mysterious and that’s what we mostly smell. For all that we do know, science still struggles to work out how we code odours.”

Scientists now generally agree that SARS-CoV-2 uses an enzyme called an ACE2 receptor, a cell surface receptor abundant in the nose, to enter by binding with spike proteins. The virus also appears to need another kind of enzyme known as TMPRSS2, which helps to prime the spike proteins and ready them for infiltration, before it hijacks the lot in order to keep replicating. Some of the most recent studies suggest that anosmia is experienced by 34 to 68 per cent of people infected with Covid-19 – much more than occurs with other known respiratory infections – and that it appears to be more prevalent among women.

Dr Federica Genovese is a young Italian neuroscientist working at the Monell Chemical Senses Centre in Philadelphia. Her specialty is exploring the role of the trigeminal nerve, the system that triggers protective responses against powerful stimuli such as wasabi, mustard or chillies that make you cough, sneeze or your eyes water, as they do when cutting onions.

For me and many others, this absence of response to powerful “tastes” or sensations was one of the most confusing and distressing aspects in the early days. To chop and fry onions – surely one of the most enticing and delicious of odours – and smell nothing is unnerving and I found myself actually mourning this most banal of rituals.

For years, Genovese says, scientists have believed that the olfactory and trigeminal systems might share a location but that they are independent systems that work in parallel. Recently, this has been questioned and the sudden loss of both functions together in the wake of Covid-19 infection seems to confirm they work in tandem. Laboratory work on mice and hamsters, which share very similar olfactory structures to humans, has also revealed for the first time the key role of the scaffolding cells (known as sustentacular cells), which express the ACE2 receptor used by the protein to anchor itself to the cell and infect it.

“We have now realised [in Covid-19] that there is a giant gap in our knowledge about what maintains health in the olfactory epithelium [tissue] and the role of these cells, which are like scaffolding structurally,” Genovese says. “They create order but if you knock them out, the whole system goes nuts.

“Obviously in less than a year we cannot bring results, just hypotheses, but so far the most credited thesis is that parosmia is part of the recovery process from anosmia: during the regeneration and rewiring of the neurons from nose to brain there is mistargeting, but the more we use the network, keep smelling, training and retraining, the more it will redefine.”

AbScent’s Kelly says that just as stroke victims can learn to use different parts of their brain to compensate for neural loss, anosmia sufferers can help the rewiring process in the olfactory system by training the nose daily with essences such as eucalyptus, citrus and rose oils.

While much of the work published has related to the mechanism and physiology of Covid-19 infection in the nose, professors Kelly, Smith and Dr Claire Hopkins, professor of rhinology at London’s Kings College, have taken a different path, collaborating with two other scientists to document and analyse the experience of 9000



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Covid-19 anosmia and parosmia sufferers who joined the Facebook group between March and September. Their paper (published on medRxiv, a pre-publication site for health sciences) concluded that altered taste and smell can lead to severe disruptions to day-to-day life. Sufferers reported that Covid’s impact on the olfactory system was broad, spanning flavour perception, affecting the desire and ability to eat and prepare food, intimacy and social bonding and even an erosion of individual’s sense of reality.

Many sufferers reported weight gains as they craved salty or sweet foods to compensate for the sensory loss while others were so bored or disgusted by parosmia that they’d lost weight and found it difficult to eat at all. Mothers described the sense of mourning when they could no longer smell their babies, couples the shock of being without smell or worse, the condition making their partner smell unfamiliar or bad.

“It’s been hard for people even close to me to understand the severity of the loss and how it’s affected my life,” wrote one respondent. “I feel discombobulated – like I don’t exist,” wrote another. “I can’t smell my house and feel at home. I can’t smell fresh air or grass when I go out. I can’t smell the rain. I would say I am mildly depressed about it and cry sometimes.”

I remember feeling such relief when I read that thousands of others had lost their ability to smell anything organic – what the anosmia community call “poo” smells – which was funny in the beginning but truly disconcerting in the long term.

“I think it’s really important for us to partake in these research projects because we are the research,” wrote one respondent. “For those of us who have been dealing with this for over five months, we are the longest known cases of this craziness that no one really has answers for.”

Professor Smith, who is also director of the University of London’s Institute of Philosophy Centre for the Study of the Senses, says smell not only governs food intake but modulates our interactions with the environment and with others. “It constantly modulates our everyday experience in a way we mostly fail to recognise,” he says. “We don’t know what we’ve got until it’s gone.” ●

Postscript: Ten months after I lost my fifth sense I’m edging ever closer to normality. I still have to check with my husband if what I’m smelling is “real” and still pile the chillies on to boost the taste. I’m joyfully back to wearing perfume, look forward to spring and its fragrances – but still cannot smell my dog’s poo (or any bathroom smells). Which is my Covid silver lining.