To biologist Robyn Hudson, Mexico City was the opposite of the much cleaner city of Tlaxcala, where she had lived for nearly a decade. Her move to the Universidad Nacional Autónoma de Mexico (UNAM) in the sprawling city of 21.3 million meant that Hudson would need to adjust to urban living, including Mexico City’s notorious air pollution.

What had long interested Hudson about her new hometown’s air pollution was not its effects on the lungs or cardiovascular system—two issues repeatedly linked to chronic exposure to fine particulate matter (PM$_{2.5}$)—but its effects on the olfactory system. She hypothesized that daily inhalation of car exhaust, diesel fumes, and other pollutants might damage the delicate layer of sensory cells in the nasal lining as well as the surrounding epithelial tissue in residents of Mexico City and other major cities with poor air quality around the world.

Work conducted by Hudson and other environmental health scientists appears to support that hypothesis. Although relatively few human studies have been conducted in this area, there is evidence that air pollution can damage olfactory sensitivity (the concentration of an odor required for someone to smell it) and the ability to distinguish between different smells. This research has opened up a new avenue of inquiry about the health consequences of poor air quality.

When scientists first began to investigate the health impact of air pollution, they focused on its effects on the respiratory tract. By the mid-1990s advances in cell biology and genetics began providing evidence that ground-level ozone could damage the DNA in alveolar macrophages and tracheal endothelial cells.

Around this time, UNAM environmental health scientist Lilian Calderón-Garcidueñas (now at the University of Montana) began to study whether ozone and other air pollutants might also harm the olfactory epithelium. Calderón-Garcidueñas compared a small group of long-term residents of Mexico City (91 adults and 16 children) with controls living in Manzanillo, a relatively clean port city on Mexico’s Pacific coast. The investigators also studied a group of 22 young men who had recently come to the capital city from small towns across Mexico, following them over a period of 12 weeks.

The results, published in 1996, suggested an increased number of single-strand DNA breaks in the olfactory epithelium of the long-term Mexico City residents, compared with controls, as well as increases in the number of single-strand breaks in the.
young men who had just moved to the city. A study published the next year reported preliminary evidence of similar damage, based on comparisons of small numbers of students living in different parts of Mexico City. Although these studies did not measure olfactory damage and were limited by small sample sizes, they did lay the initial groundwork to show that air pollution may harm nasal tissue.

An Elusive Sense

Olfactory impairments are strongly associated with aging and neurodegenerative diseases but have also been noted in relation to autism spectrum disorders. Brain injury and certain medications are both known to cause anosmia (the loss of olfaction), and recent findings also associated acute high-level pesticide exposures with impaired sense of smell later in life. The location of the olfactory bulb in the brain (tucked under the front of the brain, right behind the eyes) provides close links with the limbic system, which may help explain why so many people with olfactory issues also develop major depression.

Although not as immediately apparent and disabling as the loss of sight or hearing, anyone with an impaired or absent sense of smell can explain just how much this sense contributes to the human experience. People with anosmia or hyposmia (reduced olfactory function) have a hard time tasting their food. They also are less able to detect warning smells, such as the odor of spoiled food or a natural gas leak.

Impaired olfaction affects more than just a small slice of the population. A 2015 study estimated that 10.6% of American adults over 40 years of age had reported problems with their sense of smell in the preceding year. Despite the large number of people who may have difficulties with smelling, the amount of research on causes of olfactory loss lags behind that for sight and hearing, says Thomas Hummel, an olfactory scientist at the Technical University in Dresden, Germany.

One of the reasons for this disparity may be the difficulty of measuring olfaction and making subsequent comparisons across time and geography. In order to assess damage to olfaction, scientists first needed methods to quantify olfactory abilities, similar to standardized hearing and vision tests. But smell is a much more subjective sense than hearing and sight. A lack of objective standards has made it difficult to measure olfaction in large populations. And without standards, Hummel says it has been difficult to assess how environmental factors may impact the sense of smell.

Establishing Standards

Initially, researchers would simply ask individuals if they had any issues with their sense of smell. Some of the earliest tests involved asking patients to identify specific odors. One problem with these tests, according to Hummel and Hudson, is that they rely on cognition and memory to assess olfaction. Given that olfactory loss is one of the first signs of neurodegenerative conditions such as Alzheimer’s and Parkinson’s diseases, the results of these tests could be questionable.

Over the years, scientists began testing olfactory sensitivity by asking individuals to sniff concentrated odors and providing...
squeeze bottles that blow out various concentrations of odorants. In the early 1980s, investigators led by Richard L. Doty, a professor of psychology in the University of Pennsylvania Department of Otorhinolaryngology, developed the 40-odorant scratch-and-sniff University of Pennsylvania Smell Identification Test (UPSIT).

The widely used UPSIT is a reliable indicator of olfactory function, but it includes odors (for instance, bubble gum, wintergreen, and root beer) that are not universally recognizable. So Doty and two other colleagues adapted the UPSIT to produce the Cross-Cultural Smell Identification Test. This test consists of 12 scents deemed familiar to cultures across North and South America, Europe, and Asia—banana, chocolate, cinnamon, gasoline, lemon, onion, paint thinner, pineapple, rose, soap, smoke, and turpentine.

A product known as Sniffin’ Sticks was introduced in the late 1990s. These sticks, which Hummel helped design, resemble a felt-tip pen, but the interior sponge is soaked in specific concentrations of different odorants instead of ink. Sniffin’ Sticks are used to assess performance in odor threshold (sensitivity), odor discrimination, and odor identification.

Early Olfaction Studies

In 1990, Doty led a study measuring olfaction in 638 current, former, and never smokers after physicians began to document a self-reported loss of smell in some cigarette smokers. Their results, which relied on the UPSIT, suggested “long-term but reversible adverse effects” of smoking on olfaction. Importantly, this work provided evidence for a dose-dependent relationship, meaning that the more cigarettes a person smokes, the greater his or her loss of smell is likely to be.

Earlier animal studies showing damage to the nasal epithelium after exposure to cigarette smoke had belied the idea that the odor of smoke simply masked other smells. Subsequent human studies confirmed that smoking can cause real olfactory damage. A 2017 meta-analysis of studies on smoking and olfactory damage, coauthored by Helen Suh, a Tufts University professor of environmental epidemiology, supported the results of the initial 1990 study.

To Hudson, work linking impaired olfaction and smoking was important not just because of its ability to show that particulate matter could blunt the sense of smell, but also for its implications for neurology. “Olfactory neurons are a direct window to the brain,” she says. “They are one of the most exposed neurons in the body, covered by just a little bit of mucus.”

It might seem biologically disadvantageous to have a direct route to the brain so open to potential toxicants. But olfactory neurons need to be easily accessible if they are to sense odor molecules in the environment. This portal also means that ultrafine particles can actually enter the brain through the olfactory system. But before these particles reach the brain, Hudson believes they may first affect the sense of smell.

Mexico City and Beyond

Hudson and UNAM colleague Marco Guarneros wanted to see whether the damage caused by air pollution to the olfactory
The epithelium actually affects the sense of smell. A study they published in 2006 suggested that it does.25

The investigators compared olfactory abilities of 82 residents in Mexico City to 86 in Tlaxcala. These two cities are similar in terms of their elevation and temperate climate. However, Mexico City has many more emission sources and much higher levels of air pollution than Tlaxcala.26

They found that the Tlaxcalans could detect odors from instant coffee and a powdered orange drink at much lower concentrations than people in Mexico City. They also did better at distinguishing between two similar-smelling Mexican beverages. Overall, 10% of the adults in Mexico City met the investigators’ criteria for a poor sense of smell, compared with 2% of those in Tlaxcala.27

Hudson and Guarneros performed a follow-up study in 2009 of 30 male and female university students from Tlaxcala and Mexico City. They used Sniffin’ Sticks to compare participants’ ability to smell different concentrations of 2-phenyl ethanol and to distinguish among multiple odorants. Using a squeeze-bottle test, the team also measured functioning of the intranasal trigeminal system, which registers sensations such as burning, stinging, and tickling. In all areas, the Tlaxcala group outperformed their Mexico City counterparts.27

Other groups of scientists began comparing olfactory abilities among people from very different environments and cultures. Hummel was part of a team that compared odor detection thresholds in adults from the industrialized city of Dresden, Germany, to members of the Tsimané tribe in the remote Bolivian rainforest. On average, the 151 Tsimané tested could detect smells from Sniffin’ Sticks at lower concentrations than the 286 German adults. One in four of the Tsimané did better than any of the German participants.28 Then the same researchers compared the Germans and the Tsimané with residents of the Cook Islands in the South Pacific, which are highly developed but among the world’s least polluted areas. In these tests, the Cook Islanders performed better than even the Tsimané.29

None of these studies, however, prove a link between a diminished sense of smell and exposure to air pollutants. Any number of factors, from air pollution to culture-specific sensitivity to certain smells,30 could be the cause. However, various studies on human tissue do support the hypothesis that air pollution can harm the sense of smell.

Nasal biopsies from 54 young nonsmokers living in Mexico City and 12 living on the Mexican island of Isla Mujeres showed that the males living in the urban area were more likely than island dwellers to have lesions in the roof of the nasal cavity, where olfaction is centered.31 When Calderón-Garcidueñas and colleagues necropsied tissue from residents of Mexico City, they found signs of neuroinflammation in the olfactory bulb and other brain regions,
as well as the accumulation of particulate matter in the olfactory bulb and sensory neurons. By comparison, 12 controls from Tlaxcala and another low-pollution city (Veracruz) were much less likely to show such characteristics.

Notably, this study (and another by the same team) reported evidence that particulate matter may contribute to neuroinflammation and accumulations of β-amyloid peptide that resembled Alzheimer's disease. Calderón-Garcidueñas and colleagues have also found especially high levels of manganese, chromium, and nickel in the olfactory sensory neurons of 47 deceased Mexico City residents compared with 12 controls from Tlaxcala and Veracruz.

Potential Mechanisms
Guarneros says that damage to peripheral neurons in the nose lowers sensitivity to odorants, whereas damage to central neurons in the brain—which his work has associated with manganese exposure—reduces the capacity to name odors and to distinguish between them.

There are a few potential mechanisms by which pollutants might impair olfaction. One is through direct damage to the sensory neurons themselves. Although researchers have found some evidence of neuronal regeneration in younger individuals, this damage likely results in more permanent effects, according to Hudson.

Toxic injury to both olfactory sensory neurons and the surrounding respiratory epithelium may also result from inflammation and oxidative stress. When toxic compounds enter cells, the cells respond by producing a variety of inflammatory chemicals to repair the damage. In addition to directly damaging cells, inflammatory processes also recruit monocytes, neutrophils, and (in the brain) microglia, which can sometimes harm cells if inflammation is chronic or dysregulated. Inflammation is also associated with free radical damage.

Some types of air pollutants, such as diesel exhaust and cigarette smoke, are also nasal irritants, causing inflammation, congestion, and sneezing. These irritants can stimulate overproduction and secretion of mucus in the nasal airways. The resulting stuffy nose may prevent odorants from reaching the olfactory sensory cells.

Where Are We Now?
Ambient air pollution is a highly heterogenous mixture, which makes it hard to identify which components—or combinations of components—may be most toxic. Most animal studies of nasal toxicity and olfaction have focused on specific air pollutants, such as black carbon and ozone. They also are limited to short-term exposures at high chemical concentrations, says Jack Harkema, an inhalation toxicologist and respiratory research pathologist at Michigan State University. “We need to know more about the effects on olfaction after long-term chemical exposures and at realistic environmental concentrations,” Harkema says.

If olfaction tests are to yield usable information, they must include odors that are familiar to the test taker. The Cross-Cultural Smell Identification Test consists of 12 scents deemed familiar to cultures across North and South America, Europe, and Asia—banana, chocolate, cinnamon, gasoline, lemon, onion, paint thinner, pineapple, rose, soap, smoke, and turpentine. Image: © iStockphoto/Rawpixel.
In a review on the effects of ambient air pollution on olfaction, published in *Environmental Health Perspectives* in 2016, Suh and colleagues noted several other limitations in the current body of evidence. For example, most studies to date have used proxies for pollution exposure in small convenience samples. Studies should be larger and encompass more diverse populations—including subgroups who may have disproportionately high exposures to air pollution. The use of personal exposure monitoring would provide a more robust basis for assessing dose–response relationships. And, as Harkema suggests, longitudinal studies could give insight into the relationship between exposures in childhood and young adulthood and the risk of olfactory impairment later in life.

Because impaired olfaction is significant as a proxy marker of neurological and cognitive damage and because of its profound impact on quality of life, it is a health outcome worth exploring further. Although the field does not yet have the epidemiological data needed to make the conclusive case between air pollution and olfaction the way it has with heart and lung health, Suh says that researchers like Hudson and Calderón-Garcidueñas have been conducting important research that may lead to new insights on the matter. As the number of people living in heavily polluted cities continues to rise, researchers will have no shortage of potential subjects.

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