

ScienceNews

MAGAZINE OF THE SOCIETY FOR SCIENCE & THE PUBLIC

<http://www.sciencenews.org/view/feature/id/58906>

Home / May 22nd, 2010; Vol.177 #11 / [Feature](#)

Destination brain

[Inhaled pollutants may inflame more than the lungs](#)

By Janet Raloff

May 22nd, 2010; Vol.177 #11 (p. 16)



ENLARGE

DESTINATION BRAIN

Tiny inhaled motes can travel beyond the lungs; new research suggests these particles may ravage the brain.

Stephanie Maze/Getty Images

When Lilian Calderón-Garcidueñas recruited children for a study probing the effects of air pollution, Ana was just 7. The trim girl with an above-average IQ of 113 “was bright, very beautiful and clinically healthy,” the physician and toxicologist recalls.

But now Ana (not her real name) is 11. And after putting her and 54 other children from a middle-class area of Mexico City through a new battery of medical and cognitive tests, Calderón-Garcidueñas found that something has been ravaging the youngsters’ lungs, hearts — and, especially troubling, their minds.

Brain scans and screening for chemical biomarkers in the blood pointed to inflammation affecting all parts of the brain, says Calderón-Garcidueñas, of the National Institute of Pediatrics in Mexico City and the University of Montana in Missoula. On MRI scans, white spots showed up in the prefrontal cortex. In the elderly, she says, such brain lesions tend to denote reduced blood flow and often show up in people who are developing dementias, including Alzheimer’s disease.

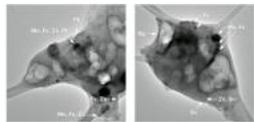
In autopsies of seemingly healthy Mexico City children who had died in auto accidents or other traumatic events, Calderón-Garcidueñas uncovered brain deposits of amyloid-beta and alpha-synuclein, proteins that serve as hallmarks of Alzheimer’s and Parkinson’s diseases. Several years earlier, she had found similar abnormalities in homeless Mexico City dogs and exaggerated versions of the abnormalities in local 20- to 50-year-olds.

She has published studies linking the insidious changes to the metro region’s air quality. The area’s 20-plus million inhabitants make it one

of the world's largest megacities, a roughly 7,000-square-kilometer region choking with smog and particles containing carbon, metals and more (*SN: 9/8/07, p. 152*). Most are nanoparticles — too small to see but just the right size to migrate into tissues throughout the body. Further clouding the air are solvents and other reactive gases — as well as toxins contributed by livestock feces.

Scientists have known that air pollution can impair airways and blood vessels. The emerging surprise is what it might do to the brain. Increasingly, studies have been highlighting inflammation-provoking nanopollutants as a potential source of nerve cell damage.

Calderón-Garcidueñas has been correlating Mexico City's stew of air pollutants with a suite of symptoms in people of all ages. In March in Salt Lake City at the annual meeting of the Society of Toxicology, Calderón-Garcidueñas unveiled some of her latest data. At age 11, Ana shows persistent, growing brain lesions, the toxicologist reported. As do the other Mexico City children surveyed. They also exhibit cognitive impairments in memory, problem solving and judgment and deficiencies in their sense of smell compared with age-matched children from a cleaner city 120 kilometers away.



ENLARGE



METALS IN THE AIR

Particles collected from the air above Mexico City (two shown) contain metals including manganese, iron, zinc, tin, lead and mercury (labeled). New research suggests that the particles can end up in the brain.

Kouji Adachi and Peter R. Buseck/*Environmental Sci. Technol.* 2010

Other

toxicologists at the meeting presented data, largely from animal studies, tracking the movement of billionth-of-a-meter-scale particles into the brain, where they triggered inflammation and abnormalities characteristic of Alzheimer's or Parkinson's.

Until recently, most air pollution toxicology has focused on impacts to the lungs and heart, observes James Antonini of the National Institute for Occupational Safety and Health's lab in Morgantown, W. Va. The challenge now, he says, is to identify which pollutants are harming the nervous systems of Ana and others who live in areas with particularly dirty air.

Fuzzy thinking

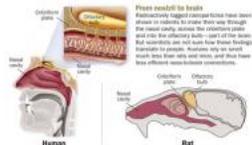
Mexico City is not the only source of real-world pollution that has been linked to mental impairments.

Ulrich Ranft and colleagues at the Environmental Health Research Institute at Heinrich Heine University in Düsseldorf, Germany, studied 400 or so highly functioning local women in their mid- to late 70s. Elderly women who lived within 50 meters of very busy streets exhibited poorer memory skills than did women of the same age whose homes were well removed from highly trafficked roadways, the team reported in the November 2009 *Environmental Research*.

The study turned up no similar link between cognitive scores and average levels of particles in the women's communities. That makes sense, Ranft says, because the levels of ultrafine motes emitted by traffic can be quite high along streets, "but drop off very fast, falling to almost background levels when you get just 100 meters away from the road."

Young children's minds may be especially sensitive to tiny airborne particles spewed by traffic, according to Shakira Franco Suglia of the Harvard School of Public Health in Boston and her colleagues. In studies of roughly 200 Boston 10-year-olds, the researchers found that those living in areas with the highest average airborne concentrations of soot, a pollutant primarily associated with traffic, had lower IQs and lower scores on memory tests.

The



ENLARGE



FROM NOSTRIL TO BRAIN

Human: BSIP/Photo Researchers, Inc.; Rodent: T. Dube

team divided the kids by exposure levels into four groups. The average IQ drop between one group and the next averaged about three points — comparable to that seen in kids whose mothers had smoked during pregnancy, Franco Suglia's group reported in 2008 in the *American Journal of Epidemiology*.

Taking note of non-scents

A few studies, including the recent one by Ranft's group, have also observed a somewhat impaired sense of smell among people living in polluted regions.

At the toxicology meeting, Calderón-Garcidueñas reported that kids and young adults in Mexico City have a somewhat worse sense of smell than those living in cleaner cities. Roberto Lucchini of the University of Brescia in Italy reported much the same for adolescents living in communities around now-closed iron-alloy manufacturing plants. Both groups' data also turned up signs the youngsters have

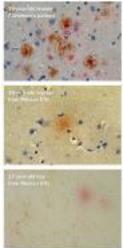
been experiencing at least subtle nerve damage.

The findings, the researchers say, are especially worrisome since a number of studies have shown that a sense of scents wanes in people developing Alzheimer's and Parkinson's.

Though metal pollution hasn't been confirmed as a cause of these diseases, Lucchini was able to link pollution in Brescia to reduced smelling abilities and to motor impairments.

Until 2001, alloy plants in northern areas of the province spewed a number of metals into the air. Manganese remains a substantial pollutant in the air, soil and house dust in this part of Italy. Work by Lucchini's team uncovered unusually high rates of symptoms including tremors, slowed movement and rigidity among adults living near the now-defunct plants. The local prevalence of these and other Parkinson's-like symptoms is about 400 per 100,000 inhabitants. That's two and a half times the usual rate in Italy.

Lucchini's



ENLARGE



UNNERVING SIGNS

Diffuse amyloid plaques (brown blotches), like those seen in Alzheimer's patients (top), have shown up in adults (middle) and children (bottom) from Mexico City.

L. Calderon-Garciduenas

team, which had already planned to examine 300 middle schoolers for neural effects of local pollution, included a smell assay in the tests. To measure exposures, the researchers collected blood and urine from the 11- to 13-year-olds. A third of the kids also carried a backpack fitted with an air-sampling device and a GPS to pair up readings and precise locations. Some children lived near the former alloy plants, others at Garda Lake, a relatively clean comparison region in the province.

At the toxicology meeting, Lucchini reported that among kids living near the alloy plants, "Odor identification was clearly impaired compared to children living in the [Garda Lake] region." The smell-threshold reduction was "preclinical," he explains, meaning the children wouldn't notice the change but it could be picked up with testing.

His team also linked exposures to manganese-rich dust particles with

motor impairments — such as a reduction in the speed at which children could clench their hands or sequentially touch the fingers of each hand to the thumb. Though it's too early to speculate about whether the symptoms will evolve into something resembling Parkinson's disease, Lucchini says, these are the first data to link such motor impairments to inhaled manganese.

Nosing out the problem

While these data are just coming in, a growing body of evidence suggests that nerves in the nose can provide a highway along which some inflammatory pollutants, such as metals, motor directly from the outside world to the brain.

How efficient the conduit is varies by pollutant particle, according to new experiments by Wolfgang Kreyling of the Helmholtz Center and the German Research Center for Environmental Health in Munich. In rats, 20-nano-meter-diameter agglomerations of at least 100 radioactively labeled iridium particles entered the brain whether inhaled through the nose or pumped directly into the lungs.

By comparing what has been deposited after one-hour exposures via the two routes, Kreyling's team showed that for such small particles, two-thirds of what ends up in the rat brain comes directly from the nose, the rest via a more circuitous route that starts in the lungs, moves into the bloodstream and then goes to the brain.

Well under 1 percent of inhaled particles made it to the brain via either route, Kreyling reported at the toxicology meeting. However, he added, once those insoluble particles arrive in the brain, "we do not see much clearance." So continuous exposure over time could leave substantial amounts of inflammatory particles in the brain, he speculates.

Change the 20-nanometer iridium to same-sized soot particles and the uptake rate falls by 75 percent. Expose animals to 20-nanometer particles made from titanium dioxide or to 80-nanometer particles of iridium, and the rate of brain uptake drops by about 90 percent.

But no one's sure how well such studies model what happens in people, points out David Dorman of North Carolina State University in Raleigh. Long-snouted rodents depend far more than humans do on the sense of smell and have evolved a much bigger and more efficient system linking the outside environment to the brain. For instance, Dorman notes that half of the nasal cavity of a rat is lined with olfactory-system cells. In humans, this receptive area is much smaller, he says — "only about 3 to 5 percent."

His team has shown that even for particles that begin moving up the olfactory highway, some stop partway. One type that does seem to go the distance: manganese. When Dorman's group exposed rats to manganese, the same metal that taints the dust Lucchini has been

studying in Italy, nearly all of the pollutant particles entering the nasal tissue migrated at least as far as the olfactory bulb, a structure in the brain.

Regardless of what percentage of particles make it all the way, such data suggest that inhaled airborne motes can enter the brain, where they would be expected to foster inflammation, a primary underlying trigger of tissue damage and neurodegenerative disease.

Moreover, Calderón-Garcidueñas has linked the pollutants with a breakdown in the lining of the nose, which could facilitate particles' access to olfactory highways serving the brain.

A burning issue

Although the source and chemistry of air pollutants affecting the brain differ, all seem to share the same toxic modus operandi: inflammation. Some pollutants turn on genes that release inflammatory chemicals, others call out immune cells that quash invaders and clean up trash using inflammatory mechanisms. Still more induce biologically destructive electron-stripping chemical reactions that won't quiet down without a copious release of antioxidants.

Krishnan Sriram, a neurotoxicologist with NIOSH, reported at the toxicology meeting that following 10-day and 28-week exposures to manganese welding-fume particles, rodents developed brain changes resembling many of those in Parkinson's patients — nerve-cell inflammation, tissue damage from oxidation and loss of nerve cells from a region of the brain that makes dopamine.

In addition, his team looked at some of the family of *Park* genes; mutations in these genes are associated with an elevated risk of developing Parkinson's disease. In rodents exposed to manganese, the researchers saw a reduction in the genes' production of proteins that normally help rid the body of misshapen nerves and that quash the oxidation responsible for excessive inflammation.

Bellina Veronesi of the U.S. Environmental Protection Agency and Lung-Chi Chen of the New York University School of Medicine laboratory in Tuxedo reported data at the toxicology meeting from mice exposed to dense concentrations of pollutants collected from outdoor air. Animals without functioning apolipoprotein genes, which normally help control the production and activity of certain fats in the bloodstream, experienced runaway brain inflammation and nerve damage. This finding suggests that properly working apolipoproteins may be essential for coping with tiny inhaled particles.

People born with a particular apolipoprotein gene variant — known as *APOE-4* — face a greatly elevated risk of developing late-onset Alzheimer's disease and more general cognitive declines. In North America, Calderón-Garcidueñas says, roughly one-fifth of people carry

this variant. And in Mexico City, she has found that children and young adults with the variant exhibit the most inflammation, the greatest cognitive declines and the most rapid deposition of amyloid-beta.

But Calderón-Garcidueñas has yet to prove that deposition in the brain of air particles primarily explains the brain inflammation she's measured, says Dorman. One has to wonder, he says, whether the "widespread nasal damage" that she depicted was a major contributor to inflammatory brain damage or independent of it.

Calderón-Garcidueñas is aware of the issue. She notes that work by others has shown that inflammation-provoking cells or chemicals have the potential to migrate from distant sites into the brain, triggering fallout damage there.

But whatever the source of inflammation in the brain, Calderón-Garcidueñas would like to see people who may face an elevated risk for pollution-triggered neural damage identified and counseled about lifestyle changes that could reduce that risk. For instance, people with the *APOE-4* gene variant might give up cigarettes, take low-dose anti-inflammatory drugs or find jobs that won't expose them to inflammatory agents, such as the endotoxin in chicken manure.

These people might also look to change their diet, eating foods rich in inflammation-limiting antioxidants, like brightly colored fruits and vegetables, or dark chocolate. She recently began feeding commercially available chocolate rich in polyphenols, a class of natural antioxidants, to treat inflammation ravaging the hearts and minds of mice.

The data are still preliminary, cautions Calderón-Garcidueñas. But from all appearances, she chuckles, the chocolate "works wonders!"

SUGGESTED READING :

Perkins, S. 2007. What goes up. Science News 172(Sept. 8):152.b

CITATIONS & REFERENCES :

L. Calderón-Garcidueñas and M.L. Block. "Air pollution: Mechanisms of neuroinflammation and CNS disease." Trends in Neurosciences. September 2009. M. Aschner. "Nanoparticles: Transport across the olfactory epithelium and application to the assessment of brain function in health and disease." Progress in Brain Research. December 2009. Sayre, L.M., G. Perry and M.A. Smith. 2008. Oxidative Stress and Neurotoxicity. Chemical Research in Toxicology 21 (January):172. DOI: 10.1021/tx700210j