

Could the diabetes epidemic be down to pollution?

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10 July 1976, a reactor at a chemical plant near the small town of Seveso in northern Italy exploded, sending a toxic cloud drifting into the summer sky. Around 18 square kilometres of land was contaminated with TCDD, a member of the notorious class of industrial chemicals known as dioxins.

The immediate after-effects were relatively mild: 15 children landed in hospital with skin inflammation and around 3300 small animals were killed. Today, however, the accident casts a long shadow over the people of Seveso, who are suffering increased numbers of premature deaths from cancer, cardiovascular disease and, perhaps surprisingly, diabetes (American Journal of Epidemiology, vol 167, p 847).

To some diabetes researchers, Seveso serves as a warning to us all. Ask why diabetes is epidemic in the 21st century and most people will point the finger at bad diet, laziness and obesity. According to a small but growing group of scientists, though, the real culprit is a family of toxic chemicals known as persistent organic pollutants, or POPs. If these researchers are right, POPs - which include some of the most reviled chemicals ever created, including dioxins, DDT and PCBs - may be key players in the web of events that lead people to develop the disease.

The claim has yet to attract widespread attention from mainstream diabetes research. Even its champions were initially surprised by it. "I had never even heard of POPs until 2005," says Duk-Hee Lee, an epidemiologist at Kyungpook National University in Daegu, Korea, who led the work. Lee and her co-workers are now convinced, albeit reluctantly, that they are onto something. "The hypothesis is one that I wish were not true," says her colleague David Jacobs of the University of Minnesota, Minneapolis.

Diabetes, and particularly its commonest form, type 2 (see "Diabetes basics"), is practically everyone's business. The World Health Organization estimates that it already affects 180 million people worldwide, with the number predicted to more than double by 2030. Last year the epidemic cost \$174 billion in the US alone, according to the American Diabetes Association.

The standard explanation for type 2 diabetes is that it is a "lifestyle disease" caused by laziness and gluttony. For at least a decade, however, epidemiologists have known that people briefly exposed to high concentrations of POPs face a modest increase in their risk of developing diabetes later in life. Those affected include the people of Seveso and US veterans who were exposed to dioxin-contaminated Agent Orange during the Vietnam war.

Two years ago, Lee, Jacobs and others decided to see whether everyday exposure to POPs is also linked to diabetes. To their surprise and horror, they found that it is.

For most people, POPs are inescapable: meat, fish and dairy products all contain them. They enter the food chain from sources such as pesticides, chemical manufacturing and incinerated waste, and accumulate in animals higher up in the chain. Once in the body they take up residence in fat.

POPs have long been recognised as nasty substances: their effects include birth defects, cancer, immune dysfunction and endocrine disruption. Since the 1970s, various measures have been put in place to phase them out - 12 of the worst POPs, known as the "dirty dozen", (see table) were banned in 2004 - but despite these efforts, POPs remain a significant presence in the environment and food chain, partly because many are still in use in the developing world, and partly because these chemicals can take decades to break down.

Role of Fat

Prior to her 2005 introduction to POPs, Lee was working on a humble enzyme called gamma-glutamyltransferase (GGT), which is essential for maintaining antioxidant levels in the liver. She was puzzled to find that obesity combined with an elevated level of GGT is a strong predictor of diabetes, but obesity alone isn't. "I searched the literature and finally got an idea," she says.

As it turns out, GGT has an essential role to play in removing some pollutants, including POPs, from inside cells (*Diabetologia*, vol 51, p 402). Could increased GGT activity simply be a marker of exposure to POPs?

To find out, Lee and her colleagues analysed data from more than 2000 people in the US National Health and Nutrition Examination Survey (NHANES), which measured both diabetes status and bloodstream levels of POPs, among other things. They discovered that people with high levels of six different POPs in their bloodstream were much more likely to have diabetes, regardless of obesity (see diagram). The six POPs were chosen because they were detectable in at least 80 per cent of the participants.

Taking into account factors such as weight, age, waist circumference and ethnic group, Lee calculated that in people with the highest combined levels of all six POPs the rate of diabetes was a massive 38 times greater than in those with the lowest levels (*Diabetes Care*, vol 29, p 1638). "The people who disagree with us will say it's all noise," says Jacobs, "but it's pretty hard to get odds ratios of 38 with noise."

To her even greater surprise, Lee found that in people with undetectable levels of POPs the expected link between diabetes and body weight melted away - those who were obese were no more likely to have diabetes than their lean counterparts. "This suggests that POPs may be a more fundamental factor in the risk of diabetes than obesity," says Lee. "The absolute risk of diabetes was extremely low among subjects with very low concentrations of POPs."

"The expected link between diabetes and body weight melted away" But fat is not off the hook just yet. While obesity alone appears not to be linked with diabetes, the study suggests that POPs plus obesity is bad news, and the fatter you are the worse it gets. When the researchers examined the link with body mass index, they found that in people with high levels of POPs the odds of being diabetic were much higher for the obese than the lean. This suggests that something about

excess fat may be enhancing the toxicity of POPs. "It appears that obesity can increase the harmful effects," says Lee.

Of course, the findings do not prove that POPs cause diabetes. "This is an association between two things, not direct evidence of a causal link," warns Oliver Jones, an environmental biochemist at the University of Cambridge. The idea deserves further investigation, though, he says.

Lee and her colleagues acknowledge that their interpretation could be stood on its head. If diabetes causes the body to become less efficient at dealing with POPs, then higher levels of POPs in people with diabetes could be an effect of the disease, rather than its cause. Lee does not rule out this possibility, but thinks it unlikely. She points to a 2003 study by other researchers that found no relationship between diabetes and the rate at which POPs are eliminated from the body (*Journal of Toxicology and Environmental Health*, vol 66, p 211).

The team also examined the link between POPs and a metabolic disorder called insulin resistance, in which muscle, fat and liver cells fail to use insulin properly and which often progresses to full-blown diabetes. Once again, they found that people whose blood contained the highest levels of POPs were most likely to have insulin resistance (*Diabetes Care*, vol 30, p 622). The results add weight to the idea that POPs may be playing a vital role in the disease pathway from insulin resistance to diabetes, says Lee. "I am really excited about this."

Even so, she acknowledges two obvious objections to her work. First, while levels of POPs in the blood of Americans have been falling for a couple of decades, the diabetes epidemic is just taking off. Lee suggests that as obesity seems to make POPs more dangerous, its rising prevalence may have cancelled out any health improvements that should have followed the decline in POPs.

A second question is why, if POPs are central to diabetes, the incidence of the disease is soaring not only in the meat-addicted west but also in countries such as India, where many millions are vegetarian. Lee's answer is that, while many POPs are banned in the west, some are still used as pesticides in developing countries. "The highest rate of increasing risk of type 2 diabetes is observed in Asia and Africa, not North America with the highest obesity rate," she says.

To try to slot POPs into the complex diabetes jigsaw, it is worth taking a brief step into the mainstream to look at the role of fats, or lipids, in the disease. Type 2 diabetes was once seen mainly as a disorder of glucose metabolism. Now, says diabetes researcher Evan Rosen of Beth Israel Deaconess Medical Center in Boston, the focus has shifted, with many scientists considering that the primary problem lies with the metabolism of fats.

For years, physiologists largely ignored fat cells, or adipocytes, seeing them as little more than passive energy silos. Recently, though, they have been revealed for what they are: highly active in producing both hormones that regulate energy, and inflammatory messenger chemicals that are important to the immune system (*New Scientist*, 16 September 2000, p 36). If adipocytes malfunction, the consequences can be widespread.

When we eat energy-rich foods, our bodies have to store any excess energy not burned up by physical activity. Most is stored as fat in adipocytes, but when these eventually fill up, excess lipid spills over into other tissues, particularly the liver, muscles and the area around the heart. The presence of this "ectopic fat" has been linked to all sorts of health problems, including insulin resistance and diabetes.

Just how might ectopic fat help to trigger diabetes, though? There is no simple answer and researchers still disagree about the possible mechanism. However, there are some clues.

In animals ectopic fat is known to attract the attention of the immune system, which produces inflammatory messenger chemicals around it as though it were an infection. Interestingly, people with diabetes have chronically raised levels of these inflammatory chemicals, raising the question of whether inflammation caused by ectopic fat could be a factor in the disease.

Ectopic fat also causes problems when muscle cells try to burn it to generate energy. In obese people this is a highly inefficient process, probably because their mitochondria - the cell's power plants - function at a reduced capacity, says Rosen. Mitochondria in muscle cells are already known to work less efficiently in people with diabetes, and this year a team at Helsinki University Central Hospital in Finland found similar changes in obese people with no symptoms of diabetes (*American Journal of Physiology - Endocrinology and Metabolism*, vol 295, p E148). "You end up with a half-burned lipid," says Rosen.

He speculates that this half-burned lipid acts like a magnet for reactive oxygen species (ROS), including free radicals and peroxides, which then inflict damage to the muscle cells themselves. There is now clear evidence that chronic damage from ROS - known as oxidative stress - helps to drive cells into insulin resistance. "If you block ROS, you can block insulin resistance," says Rosen.

If Lee is right, however, and POPs are at the root of diabetes, these ideas tell only half the story. So how might POPs be involved? Again, there are tantalising hints. Jones points out that POPs are known to bind to a family of receptors on cell nuclei known as PPARs. These are involved in lipid metabolism and are known not to work properly in people with diabetes; the diabetes drug troglitazone works by activating one member of the family, PPAR-gamma. People with an inherited disorder of this receptor are unusually prone to insulin resistance. Another intriguing link is that POPs are known to cause mitochondrial dysfunction, which some researchers think is the root cause of diabetes (*Science*, vol 307, p 384).

But none of this explains how POPs interact with obesity. It may be that obese people simply have a higher load of POPs in their bodies. Another possibility is that POPs in ectopic fat are particularly dangerous. Perhaps, speculates Lee, adipocytes are a relatively safe storage site for POPs. "Our body has to find some place to store them," she says, "and in this sense, adipose tissue is a relatively safe organ." The trouble might start when POP-contaminated ectopic fat starts to build up in the muscles and liver, exposing the organs to a direct toxic assault. "That way, the harmful effects of POPs could become more serious," Lee suggests.

Clearly more work is needed to establish the precise link between POPs and diabetes. For Jones,

it is surprising that Lee's research has remained relatively neglected, especially given its public health implications. He does note, though, that other teams are starting to investigate the hypothesis. Julian Griffin and others at Cambridge have found that low-level mixtures of POPs can cause metabolic disturbances similar to those seen in type 2 diabetes.

Rosen stresses that the lack of attention given to this research should not be seen as an indictment of the work, but instead reflects how deeply scientists specialise in their own areas. "We generally stay inside our silos," he says. "It's incredibly difficult to move outside of them." Another problem, says Jacobs, is that testing the hypothesis to destruction would require complex and long-term studies of the type that funding bodies are often reluctant to commit money to.

If Lee is right, it is not good news for the diabetes epidemic. Even though many POPs are being phased out, they will take decades to clear from the food chain. Meanwhile, newer POPs such as brominated flame retardants continue to be manufactured in large quantities.

There is perhaps one silver lining. If you need an extra incentive to stay lean, eat less meat and keep active, then knowing that toxic chemicals lurking in your body fat could be a sure route to diabetes might just be the motivation you're looking for.

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Diabetes Basics

Diabetes has two main forms: type 1 and type 2. About 90 per cent of diabetics have type 2.

Type 1 diabetes is an autoimmune disease in which insulin-producing cells in the pancreas are progressively destroyed.

Type 2 diabetes usually develops in adulthood, although it is now increasingly common in children. In this form, the pancreas either produces too little insulin, or cells in the liver, muscles and fat tissues fail to use it properly. Type 2 is most common in inactive, overweight people who carry their fat on their midriff.