Cynthia Otto: Sniffing out diseases

Humans have long taken advantage of dogs' superior sense of smell. The 300 million scent receptors in a dog's nose are routinely used to detect bombs, drugs, firearms and people. But dogs are now being used experimentally to sniff out human disease. Cynthia Otto, a veterinarian and director of the Penn Vet Working Dog Center at the University of Pennsylvania in Philadelphia, spoke to *Nature* about how sniffer dogs could help in improving medical diagnostics.

Veterinarian Cynthia Otto trains dogs to detect COVID-19 and other diseases.

SHELBY WISE

What evidence is there that dogs can sniff out human disease?

Dogs have been recognizing changes in odour in humans for a long time. The first evidence for their ability to smell disease, published in *The Lancet* in 1989, was of a dog sniffing and biting a woman's mole, which turned out to be a melanoma[1]. That raised the idea that cancer might be detectable by smell, and that dogs could be used in diagnostics.

The field got a huge boost in 2004, when a UK charity called Medical Detection Dogs reported that the animals could sniff out bladder cancer in people's urine[2]. Since then, researchers have been looking at how dogs could be used to diagnose other cancers as well as diseases such as diabetes, malaria and COVID-19.

What makes dogs right for the job?

Dogs are built to experience the world through their noses. When they inhale, they divert up to 15% of that incoming stream of air directly to the olfactory epithelium. This membranous tissue is densely populated with olfactory receptors that help the animals to detect odours in tiny concentrations. And because they have so many scent receptors, dogs can distinguish many different compounds. Information about the odour molecules is then transmitted to the olfactory bulb in the dog's brain — the bulb is about 30 times bigger than ours, relative to the size of the brain.

Many other animals have the capacity to sniff out diseases. Elephants, sharks and bears have some of the best senses of smell — but we cannot practically work with any of those. There are other animals that could do the job, such as the Gambian pouched rat (*Cricetomys gambianus*), which can detect landmines and tuberculosis. But the great things about dogs are their cognitive function, their communication, their ability to respond and their desire to belong. Those make a huge difference. We jokingly say cats could do it, but they probably wouldn't want to, or it would be on their terms. Dogs, however, are such good partners that we can work with them and get that information back.

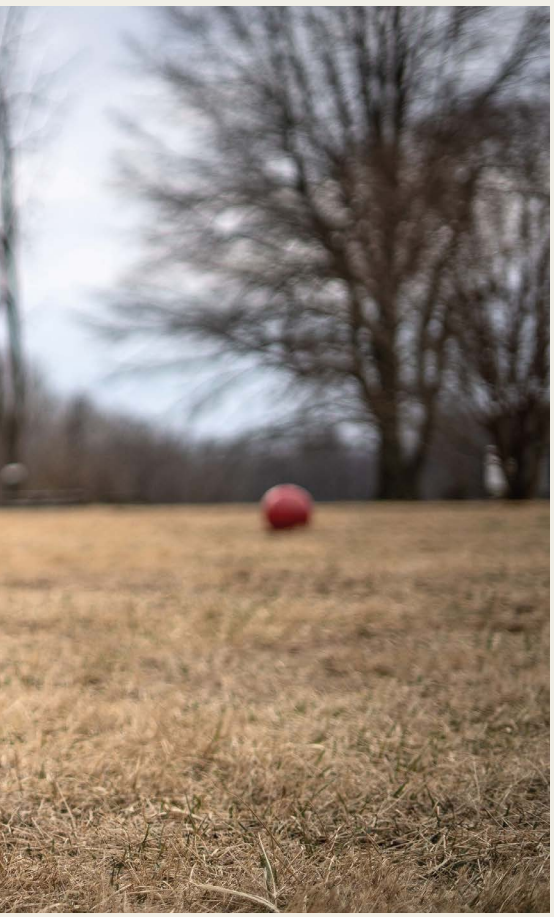
What are dogs detecting in disease?

We don't know exactly what the dogs are smelling, but when we think about basic physiology, we know that cancer, or a bacterial or viral infection, changes our metabolism. So it's not surprising that there is an odour difference. The problem is that it is probably so subtle that even sophisticated analytical methods, such as gas chromatography–mass spectrometry, are not sensitive enough to detect it. It might even differ from one disease to another. And in any case, it is probably not one smell but a distinct pattern of smells that dogs respond to.

We are now working with chemists at Monell Chemical Senses Center in Philadelphia to break up disease-related odours into constituent parts. After all, we know from explosives detection work that not all dogs respond to the exact same parts of an odour. Some use chemicals A and B, whereas others use A and C — whatever is the easiest difference for that particular animal to pick up.

How are dogs taught to detect diseases accurately?

Training is similar to how we teach dogs to detect bombs and drugs. We take biological



samples such as sweat and urine from people who have a particular disease and from people who don't. We then allow the dog to sniff the container with the samples, and reward the dog with a treat for the correct behavioural response to each one and ignore other behaviours.

However, you have to use many samples from a variety of individuals. If you use only a few, the dogs learn to differentiate the scent of the individuals rather than the disease. The dog's job is to generalize, and realize that even though all these odours are different, they still have that one correct thing in common. We also have to be aware of other variables, because dogs can use whatever cue is the easiest for them. For example, if we took all our positive samples from a hospital and all our negative samples from a community centre, dogs would probably tell you who is in the hospital rather than who has the disease. The greater the variety of samples, the broader the generalization and the better accuracy the dogs will have.

We have been advocating for training and quality-control standards to ensure that the dogs are absolutely doing what we think they are doing — we don't want people to be misled by human error.

How have you got on using dogs to detect COVID-19?

At the beginning of the pandemic, we felt like we needed to do something, so we began to train dogs to detect samples from people with COVID-19. Some of my colleagues at the medical school provided us with urine and saliva samples from people with COVID-19, but we had only a limited number so the dogs had trouble generalizing[3].

In another study we are working on, we moved out of the hospital setting and into a more public one. We recruited people from the community to better match real circumstances. All participants took a COVID-19 test and we sent them a plain white T-shirt to sleep in. We then trained the dogs on sweat samples from the T-shirts. We wanted the dogs to be able to distinguish between individuals with and without COVID-19, and they could do it — dogs can definitely detect the disease.

However, the biggest challenge is translating what we see in the research setting into an operational setting. Dogs that work well in the laboratory don't always work well in a community environment. Also, having a small sample of an odour in a lab is very different from having a huge amount of odour coming from various sources out in the real world. Dogs can have a hard time picking people out as they stand in line or walk by, so a trial at an airport in Finland set up testing stations at which the dogs could sniff samples from people one by one[4].

Will dogs ever become a regular part of clinical practice?

That is certainly what people imagine, but there are many reasons why dogs are not yet in your local doctor's surgery — despite their accuracy. For example, receiving a diagnosis of cancer can be unnerving and upsetting, and if a dog is in the room at the time, our reactions to the situation, to the physician and to the dog itself could influence how the dog responds. They could sniff samples in a back room away from patients, but the dogs usually only work for about ten minutes at a time. And dogs are fallible, just like people: they have good days and bad days.

Instead, we could have dogs teaching machines to detect diseases — something we are doing for ovarian and pancreatic cancer and for COVID-19. We are working with several people and groups, including Charlie Johnson, the director of the Nano/Bio Interface Center at the University of Pennsylvania, and a company we co-founded along with others, called VOC Health, to develop handheld electronic devices that recognize the odour signature of various diseases accurately and reliably, just as dogs do.

What lies ahead for the use of smell in medical diagnostics?

The future is really exciting. We don't make much use of olfaction in diagnostics. The Ancient Greeks talked about physicians using their sense of smell to make diagnoses, but the idea has mostly been overlooked. Now, people's eyes have been opened. For example, diabetes alert dogs, which are trained to smell when their owner's blood-sugar levels are too low or too high, are becoming much more accepted.

I think dogs will have a role in early diagnoses, but we haven't worked out the best way to do it yet — we need to keep exploring that from both a scientific and animal-welfare standpoint. The biggest challenge has been funding. Our research is a little outside the box, some people think we are wacky, but this view is shifting. People are realizing that there is a role for medical detection dogs, and with enough support, I think we can save a lot of lives.

Interview by Julianna Photopoulos

This interview has been edited for length and clarity.

1. Williams, H. & Pembroke, A. *Lancet* **333**, 734 (1989).
2. Willis, C. M. *et al. BMJ* **329**, 712 (2004).
3. Essler, J. L. *et al. PLoS ONE* **16**, e0250158 (2021).
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