

DOCTOR DOG

CAN OUR CANINE COMPANIONS SNIFF OUT CANCER?
SCIENTISTS SAY EARLY TRIALS ARE ENCOURAGING

By Liz Bestic

At 8am every morning, Ollie leaves his house and sets off on the short drive to work at the local laboratory. Eager to get going on his latest project, he greets his colleagues enthusiastically before donning his regulation lab coat and heading for the testing room. Here, Ollie begins his tour of a carousel which has small phials of urine attached to each arm. His job is simple – to take a gentle sniff of each one and let his boss know which of the samples contains a particular type of cancer. It is precise work, but Ollie gets it right over 90 per cent of the time. Not bad for a labrador.

Diagnosing cancer is a hit-and-miss affair. Often the symptoms that prompt a visit to the doctor only emerge when a cancer is relatively advanced. Screening only works for some types of cancer, and diagnostic tools are often unreliable or invasive. Better detection methods are badly needed. Now it seems that dogs could catch a whiff of cancer at an early stage because of small chemical changes that take place within

diseased cells. These chemical signatures are excreted in breath and urine, which dogs like Ollie, at the Medical Detection Dogs charity in the UK, are being trained to detect.

Stories of dogs alerting their owners that they have cancer have been emerging for decades, but will the idea live up to scientific scrutiny? Could dogs be used to save lives?

The appreciation that diseases can have specific smells dates back thousands of years. Ancient texts state that Hippocrates would sniff his patients – particularly their breath and urine – when making a diagnosis. Yellow fever has been said to smell like a butcher's shop, liver failure like raw fish and typhoid like freshly baked bread. Some nurses claim they can tell by smell alone when their patients are at death's door.

These signature smells of disease come from chemicals known as volatile organic compounds (VOCs), hundreds of which are excreted by the body in sweat, urine, breath and other body fluids. The VOCs we excrete are a reflection of the metabolic processes in our cells, and combine to give us an individual "odour fingerprint" that differs with age, diet and gender. It also changes

Life-saver: Claire Guest with her dog Daisy, who detected her breast cancer

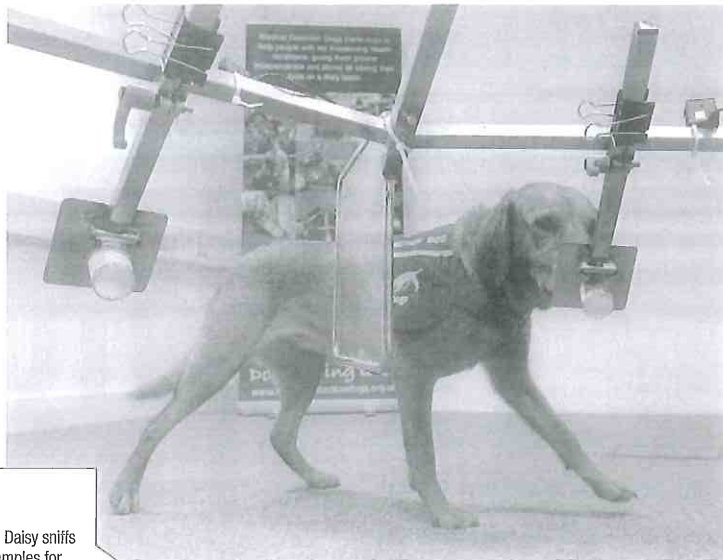
with health, because diseased cells metabolise differently to healthy ones.

Cancer VOCs were first identified in human urine in 1971, but the idea that dogs could use them to help diagnose cancer was first floated in 1989. Two dermatologists wrote to *The Lancet* citing a case in which a woman claimed she had been sent to them by her dog. The headline read: "Sniffer dogs in the melanoma clinic?" The woman had a dark spot on her upper leg that her doctor had said was a mole, purely cosmetic and not worth removing. The woman was content with that diagnosis. But her dog wasn't, and continually sniffed and scratched at the mole. One day the dog pounced on her and nipped at the mole, apparently trying to bite it off. It was enough to make the woman seek a second opinion, and the mole was found to be a malignant melanoma – the most deadly form of skin cancer.

To the dog, the cancerous tissue clearly smelled different in some way, although how the dog "knew" something was wrong is still a mystery, says Claire Guest, CEO and director of operations at Medical Detection Dogs. Her own dog, Daisy, alerted her to the fact she had breast cancer. "The assumption is that the VOCs cause a change to your normal odour which the dog is interested in, and our anecdotal reports all seem to tally that the dogs seem anxious about it. Our domestication of dogs mean they wish to protect us," she says.

In 2001, a similar story of a 66-year-old man whose dog had provoked him to get a second opinion about an unusual mole set orthopaedic surgeon John Church thinking. He wondered whether these stories amounted to anything more than urban legend, and decided to put the dog nose to the test. In 2004, with a team from High Wycombe Hospital where he worked, he ran the first proof of principle study to see whether dogs could identify cancer from urine samples. After seven months of training, six dogs of various breeds were presented with urine samples from people who had bladder cancer, along with control samples from people who were either healthy or had other diseases. "We discovered that the dogs could pick out the correct samples 41 per cent of the time," says Church. "It may not seem impressive these days but it was statistically significant. Nowadays we have better methods of training the dogs and results are much more accurate."

Being able to pick out samples from people who have cancer from those who don't was the



Lab work: Daisy sniffs urine samples for signs of cancer

first step. The next was to see how dogs compare to diagnostic tests that are already available. "The beauty of the VOCs the dogs detect is that they show up in the body as soon as cancer cells start to proliferate," says Guest. "That means cancer detection could be done at a far earlier stage."

While some cancer types, such as cervical cancer, can be picked up early through screening, others are harder to spot and can involve painful and invasive biopsies. Prostate cancer is notoriously hard to detect because one of the few biomarkers of the disease is the presence of prostate specific antigens (PSA) in the blood. Even then, elevated levels only suggest increased risk, and the only way to confirm a diagnosis is with an invasive biopsy. Two-thirds of men with

raised PSA levels won't have prostate cancer (it can spike due to other factors such as inflammation), and up to 20 per cent of men who do have prostate cancer have normal PSA levels, meaning they get missed.

In some countries, PSA is considered too unreliable to be used as a screening test for prostate cancer. Could dogs help? Last year, Gian Luigi Taverna at the Humanitas Clinical and Research Centre in Milan, Italy, spent five months training two German shepherds from the Italian Ministry of Defence to detect the smell of prostate cancer and sit down in front of offending samples. When asked to analyse 900 urine samples, both dogs managed to accurately identify those that came from men with prostate cancer at various stages about 98 per cent of the time. Overall, the dogs had 16 false positives and four false negatives – a much better strike rate than PSA tests. With this level of accuracy, it should be possible to use dogs to reduce the number of biopsies and identify people at risk, says Taverna. The control group included people with different types of cancer, and those who were on medication, but even these smells didn't flummox the dogs. This hints that different types of cancers may have individual smell-prints, although this has yet to be confirmed.

Ollie and his pals at Medical Detection Dogs in the UK are attempting to replicate the Italian study. "We hope this research will help doctors determine which men genuinely need a biopsy or invasive surgery," says Guest. "This will ultimately save lives."

Dogs have been trained to sniff out cancers including bladder, breast, lung and skin cancer,



Sensitive snout: a dog is trained to detect ovarian cancer in Pennsylvania, US

and are now being used to unmask some of the most elusive cancers much earlier than is currently possible.

George Preti of the Monell Chemical Senses Centre and colleagues at the University of Pennsylvania are training a team of dogs to sniff out ovarian cancer in samples of blood plasma. Ovarian cancer is often called the silent killer because it has very few symptoms. Caught early, before it has spread, the five-year relative survival rate is 92 per cent. However, only 15 per cent of ovarian cancers are found at this stage. There is currently no screening tool and the only diagnostic tests available are transvaginal ultrasound or antibody tests. These are often not sensitive enough to catch the disease before it has spread, by which time survival rates drop to 25 per cent.

Analysing people's breath might show up some cancers, too. Colon and breast cancer have been shown to produce characteristic chemicals, but theoretically any cancer could be picked up in this way. Guest and her team are running canine tests on breath and urine samples from people with breast cancer to see which works best.

The final hurdle will be to apply the dogs' sensitive snouts to real-life screening and diagnosis. There are lots of logistical reasons why the role of dogs will always remain behind the scenes rather than in the doctor's office, but nonetheless they are about to start work in screening and testing samples from real patients. "We believe we can apply the dog's superior olfactory system to screening protocols and introduce this tool into clinical practice," says Fabio Grizzi, a co-author of the Italian prostate cancer study.

He and the rest of the team are planning a multi-centre study to see whether dogs could pick up the signs of prostate cancer before a biopsy does. All the men enrolled will have had a positive PSA test, followed by a biopsy which came back negative – suggesting they get the all-clear. After testing the urine samples on the dogs the team will continue to monitor the men to see whether any of them go on to develop cancer, and whether – in hindsight – the dogs could have served as an early warning.

Prostate cancer is also the focus of a similar trial under way with the medical detection dogs in the UK. First the dogs are being trained to detect prostate cancer VOCs. If successful, they too will be put to work on urine samples from men coming to a local hospital for PSA tests. "Currently we look at the symptoms, give a rectal exam and feel the prostate for size and hardness. Then there is the PSA blood test,"

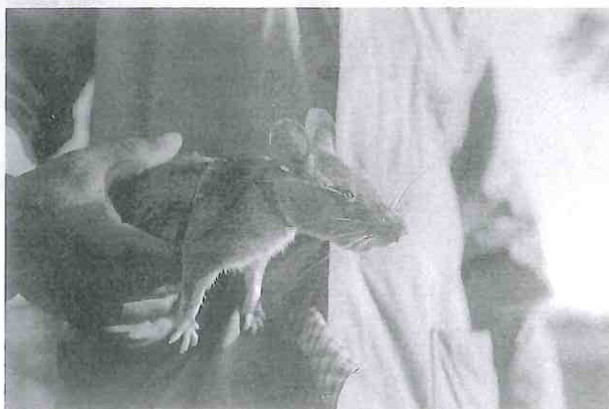
says Iqbal Anjum, a consultant urologist at Milton Keynes University Hospital and principal investigator on the trial. "Now there will be the urine screen as a second opinion." The combination of PSA tests with sniff tests should make diagnosis extremely accurate, Anjum says. "With such predictive accuracy the doctor can then make a quick decision about whether a man needs further investigation or not. We don't want to be doing unnecessary biopsies and damaging healthy prostates."

One big question remains: what is it that the dogs are smelling? "We are not sure exactly what the dogs are picking up but it is not PSA," says Guest. This is something that Preti and his team are trying to determine using traditional techniques such as gas chromatography. Others are analysing cancer cells in culture to better understand the chemicals given off by changes in cell metabolism. Armed with this knowledge, it would be possible to build electronic "noses"

that could do the same job as the dogs, but on the spot and with fewer resources.

Work is already under way to develop such a test for lung cancer, but developing electronic noses for other cancers is proving harder. That's because, even with advanced lab equipment, it's tricky to strip the complex VOCs that the dogs pick up into their individual parts, says Preti. A dog's nose is also sensitive enough to pick up these smells against the backdrop of other VOCs present in the sample. "Dogs are far more sensitive than any technique I know of," Preti says. "They can demonstrate that an odour signature is present, even though we may not smell it or see it with our instruments."

For now, Guest is convinced that the dogs remain the best bet for picking up a whiff of disease where other tests fail. "We are not talking about a couple of volatile markers that constantly appear at the same level. We're looking at complex pattern recognition," she says. "If the dogs can't find VOCs in the sample, nobody can." ●



RATS, FRUIT FLIES JOIN THE PACK

Dogs aren't the only animals capable of sniffing out disease. In Maputo, the capital of Mozambique, giant African pouch rats (above) are being used to detect tuberculosis, which killed 480,000 people in Africa in 2012. In the first 16 months of the Maputo program, the rats evaluated samples from around 12,500 people who had been tested for TB. Of those, 1700 had tested positive in local health clinics. The rats detected a further 764 cases, according to APOPO, the organisation behind the work, which is best known for using rats to find land mines.

Fruit flies have recently joined the party, with findings that they too can detect smells given off by cancer cells. This is thanks to their sensitive antennae, which are covered in receptors that let them recognise very low concentrations of odours.