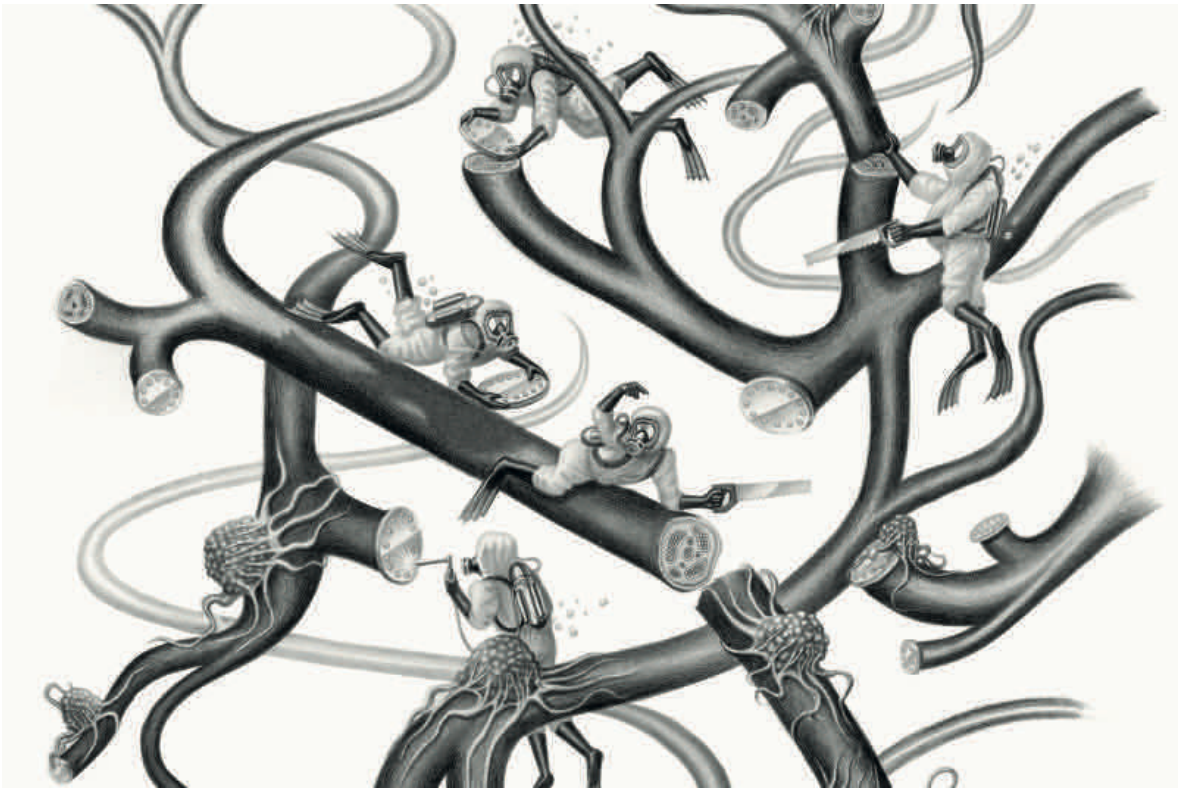
8 October 2017

Getting on cancer's nerves: A surprising way to thwart tumours

A technique for alleviating pain has exposed cancer's weak spot and may finally enable us to stop the disease by disabling the nerves that help it spread



Armando Veve

By **Elie Dolgin**

DAVID MARTINEZ lives with excruciating pain. He has pancreatitis, a condition in which the pancreas becomes severely inflamed. Over the past five months, he has received three injections of a local anaesthetic into nerves in his abdomen to help ease the agony. But eventually the medicine wears off, and the pain returns.

As if pancreatitis weren't bad enough, Martinez, a 41-year-old former forklift operator in Pasco, Washington, has something else to worry about. Chronic inflammation of the pancreas is a major risk factor for cancer. "I'm afraid of it happening," he says.

But what if the painkilling injections Martinez is getting could do more than just ease his discomfort – even help ward off cancer altogether? New evidence is causing a rethink of the way cancer invades our bodies. It now seems that targeting nerve cells might be an effective way to fight tumours – and even prevent them developing in the first place. Some even think that focussing on nerves may be the missing piece in the fight against the disease. As Gustavo Ayala at the University of Texas Health Science Center at Houston sees it, "If you don't take care of the nerves, you're not going to cure cancer."

For a cancer surgeon, it is devastating to discover mid-operation that you are too late – that the disease has already spread its lethal tendrils beyond your reach. But about 30 years ago, pancreatic cancer surgeon Keith Lillemoe realised that, even if he couldn't remove all of the cancerous tissue, he could at least reduce the pain

his patients were feeling. By injecting alcohol into the nerves surrounding pancreatic tumours pressing against the belly and spine he could destroy the fibres that carry pain signals to the brain.

In the late 1980s Lillemoe and his colleagues at Johns Hopkins University in Baltimore, Maryland, tested the technique on 137 patients with inoperable pancreatic cancer. The benefits were obvious: those who got the alcohol injection felt far less pain afterwards than those who got a placebo. But another result was more surprising: patients given the treatment also lived longer.

On average, they survived for at least three months longer, with a better quality of life to boot. "It was a remarkable effect," says Peter Staats, a pain specialist who helped analyse the data.

Like most physicians at the time, Staats assumed these patients lived longer because the pain reduction lifted their moods and enabled them to be more physically active and therefore better able to withstand additional rounds of chemotherapy or radiation. But that wasn't necessarily all that was happening.

The nervous system has long been known to play a critical role in the spread of cancer. Tumour cells can invade surrounding nerves and travel along the body's electrical superhighway, seeding themselves anew in distant sites. That's why, as cancers become more aggressive and metastasise, they often end up spreading to the nervous system's central hub: the brain.

"But the nerves are bystanders in that story," says Hubert Hondermarck, a cancer neurobiologist at the University of Newcastle in Australia. We used to believe that they simply provide routes for the cancer to travel along. Now it's become increasingly clear that, although tumours attempt to infiltrate the nerves to speed their spread, nerves stimulate cancer growth as well. "It's a

two-way street," Hondermarck says.

The fact that tumour biologists have neglected the role of the nervous system for so long could explain why so few cancer therapies actually eliminate the disease.

Precision medicine

But surely deactivating nerves must be harmful? Our nerves serve many essential functions, so if you indiscriminately destroy nerve signalling there can be some real dangers. Sensory neurons are the kind that enable us to feel things and also signal for the muscles to respond, for instance. Switching them off throughout the body – as some early trials of experimental painkillers did – effectively makes people unable to feel scalding heat, a major hazard for anyone who likes hot showers or cups of tea.

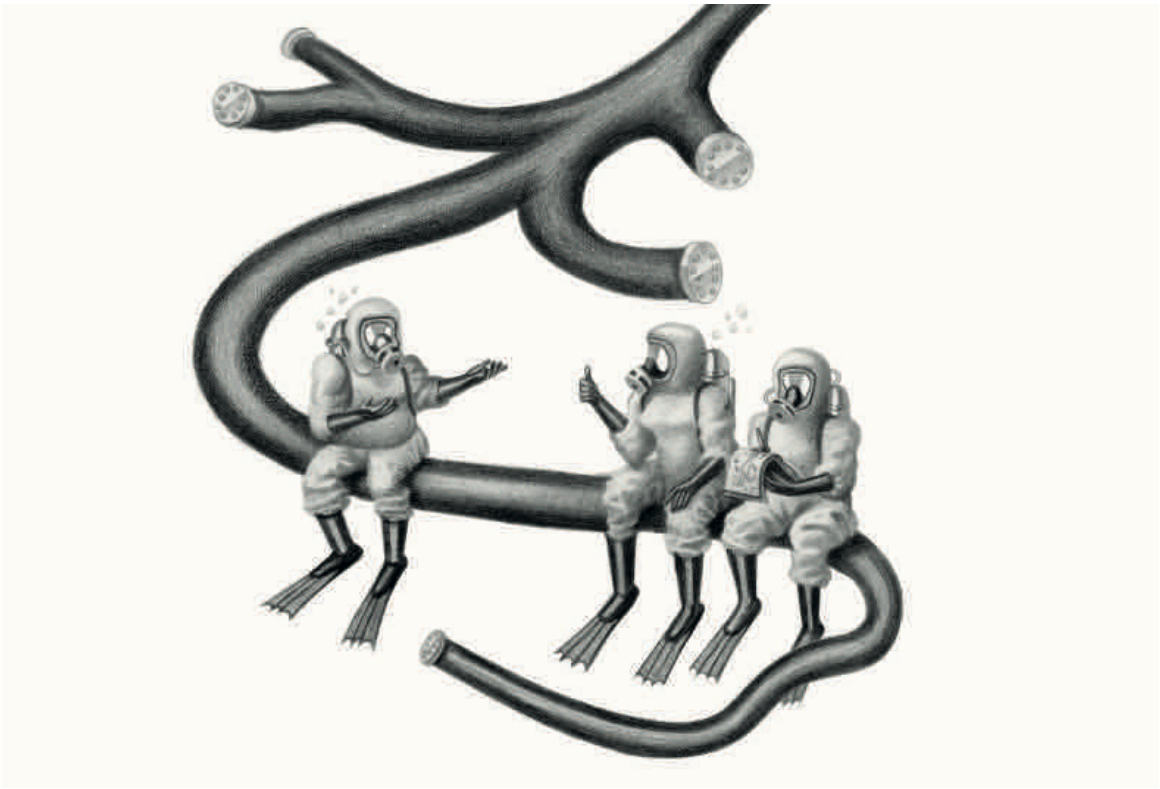
That's why Lillemoe's trial used localised alcohol injections. But alcohol, like many nerve-blocking agents, tends to indiscriminately destroy all nerves – and not all nerves contribute to cancer. The ones we now know are involved tend to lie outside the brain and spinal cord, in the peripheral nervous system, which itself has two subsystems: one to control movement and one to regulate the body's involuntary functions. Both of these contribute to tumour development, but in different ways for different cancers.

In pancreatic cancer, for example, tumours are filled with sensory neurons. "The stimulation of these sensory neurons can actually drive inflammation," says Brian Davis, a pain and cancer biologist at the University of Pittsburgh in Pennsylvania. It's the inflammation that is thought to create conditions conducive for tumours to take hold. So in this type of cancer, trimming away or otherwise destroying the sensory nerves can make a big difference. For Martinez, it might prevent pancreatitis ever leading to a tumour.

In prostate cancer, however, it's not sensory neurons but nerves in our involuntary, "autonomic" nervous system that seem to matter most. This system has two opposing functions: to relax the body, allowing for rest and digestion, and, in times of threat, to regulate the body's fight-or-flight response by, for example, revving the heart to beat faster.

In mice with prostate cancer, the two different functions of the autonomic nervous system have different effects in regulating tumour growth, says Claire Magnon, a cancer biologist at the French Alternative Energies and Atomic Energy Commission near Paris. The one that regulates the fight-or-flight response "controls the initiation," she says, "and the other the dissemination."

That distinction could make a difference as doctors look to use nerve-targeting drugs to treat cancer patients. Beta-blockers, for instance, can help regulate heart rate. It's for this reason that they are routinely prescribed to people with high blood pressure and other cardiovascular problems. They work by targeting nerve receptors involved in fight-or-flight responses. So they're most likely to be useful in treating the earliest stages of cancer, Magnon says. For full-blown disease, drugs that gum up nerves involved in relaxing the body might work better. "It's exciting," says Magnon. "This is the beginning of a new era in cancer research."



Armando Veve

Support for the idea that stopping nerves could stop cancer initially came from large observational studies. People who regularly took medication, such as beta-blockers, which impede parts of the nervous system, often had lower rates of cancer. This idea was backed up by lab research showing that mixing neurons with cancer cells in a dish speeds cancer growth.

The first concrete evidence of a biological cause and effect came in 2013, when Magnon, working in Paul Frenette's laboratory at the Albert Einstein College of Medicine in the Bronx, New York, injected a nerve-killing chemical into mice that had been implanted with human prostate tumours. It stopped the cancer dead in its tracks – and surgically nicking the nerves had the same effect. "We didn't expect any of that," Frenette says. He thought the technique might reduce the spread of cancer throughout the body – by cutting off its route through the nervous system – but instead it halted tumour growth in the prostate.

So could this effect extend to humans? Although certain cancers show little infiltration by nerves – thyroid cancer, for instance – in principle, this approach could have wide application. "You find in almost all cancers an increase in nerves, and you can show that many of these nerves stimulate tumour growth and the tumours secrete factors that bring nerves into them," says Timothy Wang at Columbia University Medical Center in New York.

"Killing the nerves stopped the prostate cancer dead in its tracks"

The immediate focus is on strategies that could augment existing treatments. Research in mice has shown that, even after the cancer has appeared, cutting away nerves can make tumours more susceptible to chemotherapy and other treatments. The job now is to see if the same holds true for us. "All those options are on the table now," Hondermarck says.

For prostate cancer, removing or destroying nerves wouldn't be popular, because it would leave men impotent and incontinent. That used to be the price of treating the disease, but nowadays surgeons can usually remove a man's prostate while sparing the nerves that control erections and bladder function.

But the nerve-blocking botulinum toxin, known as Botox, could provide a solution. By preventing the release of a chemical messenger needed to transmit signals from nerve cells to muscles, Botox causes localised paralysis. This is why it is commonly used to smooth out wrinkles in the face or to treat conditions associated with overactive muscle activity.

A few years back, Ayala ran a small study in men with localised cancer who were about to have their prostates surgically removed. Before surgery, he injected Botox directly into one lobe of the prostate and a saline solution into another, while avoiding any spillover into the surrounding nerves that control sexual and

urinary functions. A month later, when the men had their prostates removed, Ayala inspected the tissues. The effect was clear: the cancer cells were wasting away, but only those on the side that got the neurotoxin.

Other types of injections could work too. Davis and his University of Pittsburgh colleague Jami Saloman are testing a chemical called resiniferatoxin on pancreatic cancer in mice. Found in a cactus-like plant in Morocco, resiniferatoxin is similar to the active ingredient in chilli peppers, but 1000 times as potent at blunting sensory neurons. Unlike alcohol, it also does so without harming the rest of the nervous system. By desensitising nerves around the pancreas, an injection could provide a double whammy, Saloman says: slowing cancer growth to make chemotherapy and radiation more effective, and also stopping horrific pain.

Other drugs are also in the works. Last year, for instance, Wang showed that, when given alongside chemotherapy, a drug that blocks the receptors cancer cells and nerves use to communicate reduced tumourgrowth in mice with stomach cancer. Now, it is being tested in humans. And last month, a team led by Michelle Monje of Stanford University in California identified a drug that prevents neurons in the brain from releasing a cancer-promoting factor into the surrounding tissues, curbing growth of paediatric brain tumours in mice.

Some researchers are trying to repurpose beta-blockers. A team at the Penn State Hershey Cancer Institute recently looked back over 15 years of patient records at their hospital and found that about half of all people with melanoma who were also taking a beta-blocker – ostensibly for their hearts – went into sustained remission for years following immunotherapy. “The effect on survival was the greatest I’ve ever seen,” says Elizabeth Repasky at the Roswell Park Cancer Institute in Buffalo, New York, who collaborated on the project. Repasky recently showed that using

beta-blockers can make immunotherapy more effective against cancer in mice. Now, she and her colleagues are planning trials to see if they can do the same for people receiving immunotherapy to treat breast or skin cancer. Elsewhere, researchers are evaluating whether beta-blockers can make chemotherapy or surgery more effective against ovarian, prostate and other kinds of cancers.

No way through

Wang thinks it is only a matter of time now before nerve-blocking therapies become a routine part of cancer treatment. "They're going to have much broader utility than most precision medicine approaches that others are feverishly working away on today."

As with most cancer treatments, the earlier in the disease's development strategies to disable nerves can be used, the more effective they are likely to be. As cancer emerges, nerves reorganise the cellular environment to make way for tumour growth. No nerves, no reorganisation. "You basically block that early transition," Frenette says.

Of course, preventing cancer from taking hold at all is the ultimate goal. Could we do so by getting rid of nerves before tumours even start to form? That's not a terribly useful strategy unless you know in advance that you're almost definitely going to get cancer, says Andrew Rhim at the University of Texas MD Anderson Cancer Center in Houston. But, he adds, "it would make sense to use this as a preventative strategy for patients who are at a very high risk for cancer".

Women with genes that make them likely to get breast and ovarian cancer could be prime candidates. Today, more than half of all women with *BRCA* gene variants elect to have their breasts or ovaries surgically removed. For those facing this drastic intervention, stripping away or disabling the nerves could be a less

invasive alternative.

“If you were at risk, you could cut off the disease before it ever takes hold”

A similar preventive strategy could be possible for people who are likely to get pancreatic cancer, a particularly deadly disease that’s hard to catch early. Pancreatic tumours don’t usually emerge until someone is in their mid-40s or older. If you knew you carried a gene variant that made you highly susceptible, you could have targeted treatment to destroy just the sensory nerves in your pancreas – cutting off the disease before it ever takes hold. “You don’t sense your pancreas anyway, so you’re not going to miss anything,” says Salomon.

That kind of permanent fix could also provide peace of mind for people like Martinez. He has no family history of pancreatic cancer, but his pancreatitis and his age do increase his risk of developing it.

Our new-found knowledge of the role our nerves play in the development of cancer is rewriting our understanding of the disease – and may revolutionise treatment. In the meantime, for Martinez and others in a similar situation, there is comfort in knowing that efforts to relieve the pain today might reduce the risk of cancer tomorrow. “I hope it’s something that’s helping me,” he says.

This article appeared in print under the headline “Getting on cancer’s nerves”