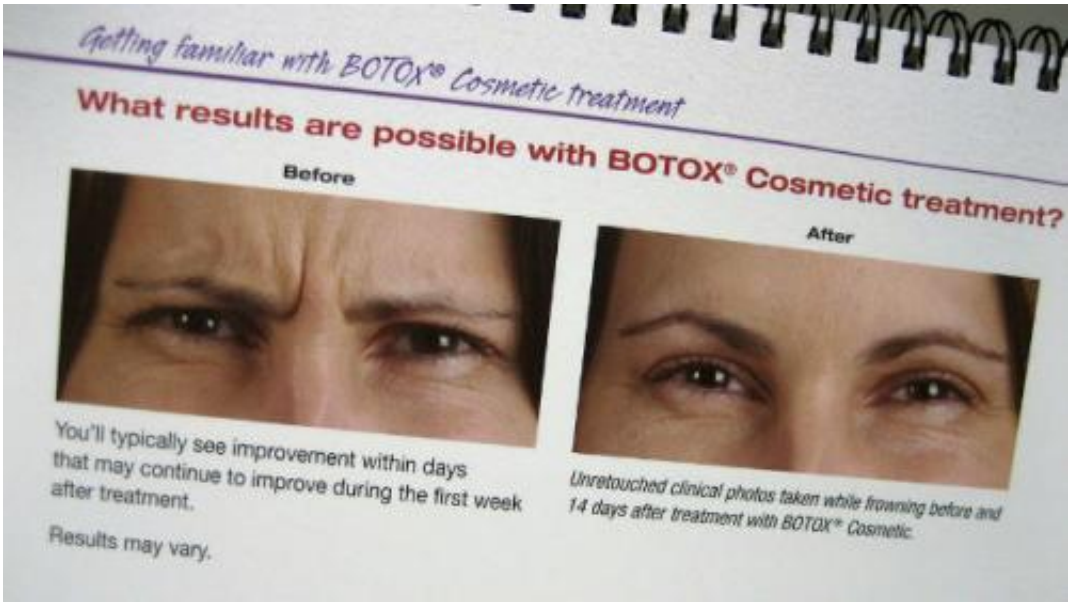
Botox for stomach cancer? No, but the research is fascinating

August 25 2014, by Henry Scowcroft



Research on Botox and stomach cancer is more complex than headlines suggest

Amid continuing tales of global woe, Thursday morning's news carried one of those quirky 'fancy-that!' medical research stories that often captures the imagination, but which can inadvertently raise false hope in patients.

According to several news outlets, Botox injections – better known for their face-freezing properties – 'could be used to treat stomach cancer'. The Irish Independent's headline even went so far as to say it was a

'highly effective' treatment.

As is so often the case, that's going way beyond what the underlying research actually found: the study was mainly carried out in mice, and doesn't yet prove that Botox could help stomach cancer patients.

But with that important caveat out of the way, the research itself is worth a closer look. It highlights a very poorly studied but fascinating topic – the potential link between the body's nervous system and the way cancer develops.

To find out more, we spoke to one of the UK's top gastroenterologists – Liverpool University's Professor Mark Pritchard – about the wider context, and whether this research could, one day, help patients.

Stomach cancer, infections and stem cells

"How nerves are involved in stomach cancer isn't a very well-advanced area of study," says Professor Prichard, chair of the British Society of Gastroenterology's gastro-duodenal section, who's spent many years studying how this cancer develops.

This is because most of the limelight has been hogged by a relatively common infection called Helicobacter pylori, which more commonly causes stomach and duodenal ulcers (you can read an in-depth post about H pylori and cancer here).

"Most stomach cancers are linked to H pylori, an infection which can kick off a complex series of events that can, in some people, lead to cancer," says Professor Pritchard.

"But even so, only one or two out of every hundred people infected with H pylori ever goes on to get stomach cancer," he told us.

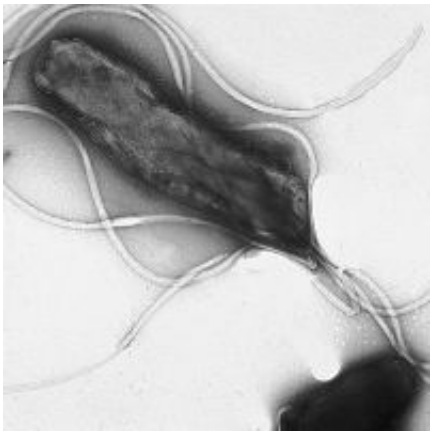
So the big question, Pritchard says, is to work out what's going on in this minority of infected people that leads to cancer.

To solve this puzzle, researchers have been studying the molecules involved when the bacteria inflame the stomach lining, and when cancer then develops.

And they've made progress – most crucially by identifying the involvement of a set of molecular signals sent and received by the cells of our body called 'Wnt' signalling. Many lines of evidence have now shown that these signals, switched on inappropriately by H pylori, seem to activate a small group of cells in the stomach - called stem cells - and these somehow develop into cancer.

But clearly there's more going on, and many unanswered questions. So researchers have begun to look at other processes in the stomach, whether they're involved, and, if so, how.

One such process will be familiar to anyone who's suffered pangs of hunger, nerves or nausea – the stomach's nervous system.



The H pylori bacterium can trigger stomach cancer

Getting on your nerves

The stomach is in constant contact with the brain via a long 'cable' called the vagus nerve. This transmits subconscious signals telling your gut to do a variety of things – contract, release acid and so on – while simultaneously reporting the stomach's state back to the brain.

On a molecular level, this involves chemicals called neurotransmitters, which affect the cells of the stomach in different ways. Could they somehow be involved in cancer?

Tentative evidence is emerging that they might be. Before H pylori was discovered, patients with stomach and duodenal ulcers were sometimes treated with an operation to cut their vagus nerve – a vagotomy – rather than being given antibiotics as they are today.

In the early 1980s, a large study looked at the risk of subsequent stomach cancer among patients with ulcers who'd had a vagotomy, compared to those who hadn't. Careful scrutiny of the long-term results in 1994, revealed that, although no effect was seen immediately, after a decade their risk of stomach cancer began to drop.

Over the following years, more intriguing observations began to accumulate. Some tumours were found to be able to stimulate the growth of nearby nerves. Neurotransmitter 'receiver' molecules – called receptors – were found on certain types of cancer cell. And last year, scientists studying prostate cancer found that nerves in the prostate seemed to help fuel the disease.

So do nerve signals provoke stomach cancer? To find out, a team of Norwegian and US researchers led by Professor Timothy Wang – a former collaborator of Professor Pritchard's – carried out a series of elegant experiments in mice. And it's these experiments, published in a

paper in *Science Translational Medicine*, that led to yesterday's headlines.

What did they do?

The researchers worked with a variety of different types of mouse that had been painstakingly developed by Professor Wang's lab at Columbia University in New York, all of which were predisposed to stomach cancer, but through different mechanisms.

The team showed that, in all the different mice, interrupting signals from the vagus nerve – either through giving the mice a vagotomy, or by using Botox (which works by blocking nerve signals) – stopped Wnt signals in the mice's stomachs, affecting the growth of stem cells. And this slowed down the growth of cancer, or prevented it from developing.

They also showed that interrupting these signals made chemotherapy more effective, and – separately – that a particular molecule, called the M3 receptor, seemed to be the link between nerve impulses and Wnt signalling in stem cells.

Finally, to see if their laboratory findings would be worth following up in patients, they looked at stomach cancer samples taken from a variety of clinical studies. In some, they found overactive Wnt signalling. In others, they checked for excessive nerve growth, and found that too.

As a result of their findings, the Norwegian researchers have started a very small-scale clinical trial, in very advanced stomach cancer patients, to begin to test the idea that injecting Botox into stomach tumours might be helpful.

So what next?

Despite these findings, the study has crucial limitations which means we need to temper our excitement.

"For a start," says Professor Pritchard, "none of the mouse models they used involved cancers exclusively triggered by H pylori infection, so we can't yet say for certain that these results are applicable in people."

There's a fair bit more work needed to really understand what's going on, he says.

He's also sceptical about the way the study was presented to the media, and of raising hopes of new treatments.

"This study doesn't look at all at the really important problems – disease that's spread beyond the stomach. The mice only had early-stage, localised cancers."

That's important. For most patients whose cancer hasn't spread, the best option will almost always be surgery to remove the cancer. "Only a minority of patients with localised cancer will be unsuitable for surgery, so would need a theoretical nerve-blocker instead."

Even then, says Pritchard, Botox itself wouldn't necessarily be a good treatment: "Its effects tend to wear off after a month or two, and you'd probably have to keep injecting it into the stomach – and that's assuming it's proven to work."

But once the cancer's spread, you need to look for drugs that can target these distant tumours, "and a nerve-blocker like Botox isn't going to solve that problem," he says. Encouragingly, yet unreported by most of the media, the research does point to one potential avenue to do this, centring on the M3-receptors the team found at the heart of the stem cells' signal transmission.

"This looks like a good target for future treatments – much more interesting than anything about Botox," says Pritchard. A drug targeting M3-receptors, darifenacin, is already approved for treating incontinence, and is a good candidate for testing out in stomach cancer, Pritchard thinks.

"All in all, this is a fascinating, thorough piece of research that clearly points to new and exciting avenues for researchers to explore," says Pritchard.

But, he says, it's "a long way" from saying that Botox has any use for people with stomach cancer today – despite the headlines.

More information: Zhao, C., Hayakawa, Y., Kodama, Y., Muthupalani, S., Westphalen, C., Andersen, G., Flatberg, A., Johannessen, H., Friedman, R., Renz, B., Sandvik, A., Beisvag, V., Tomita, H., Hara, A., Quante, M., Li, Z., Gershon, M., Kaneko, K., Fox, J., Wang, T., & Chen, D. (2014). "Denervation suppresses gastric tumorigenesis "*Science Translational Medicine*, 6 (250), 250-250 DOI: 10.1126/scitranslmed.3009569

"Gastric cancer risk after vagotomy." Lundegårdh G, et al. *Gut.* 1994 Jul;35(7):946-9. www.ncbi.nlm.nih.gov/pubmed/8063222

"Cancer-Related Axonogenesis and Neurogenesis in Prostate Cancer." Gustavo E. Ayala, et al. clincancerres.aacrjournals.org … tent/14/23/7593.long

" Autonomic nerve development contributes to prostate cancer progression." *Science* 12 July 2013: Vol. 341 no. 6142 1236361. DOI: 10.1126/science.1236361