

Hot, toxic and healing

A nasty infection might kill you, but it could also cure you of cancer. Cell biologist **Uwe Hobohm** may know why. He says it's time to resurrect an old technique

AFTER he lost his first patient to cancer in 1891, William Coley was desperate to find an alternative treatment to offer next time, not just surgery and morphine.

That desire must have led the US surgeon to the first published account of “fever therapy” – treating cancer with pathogenic bacteria. It was an 1868 paper by the German physician Wilhelm Busch, describing how he had deliberately infected a neck sarcoma patient with dangerous bacteria. The infection almost killed her, but her huge tumour softened and shrank.

Though the surgeon did not invent fever therapy, he was the first to do it systematically. After some of the first people he tested it on died from the infection, he started to use heat-sterilised bacterial extracts, with good results. From 1895 until his death in 1936, Coley and his contemporaries treated hundreds of people with cancer by injecting them with pathogenic extracts. The starting dose was small and increased over subsequent shots until the patients developed a fever above 39 °C. Though there were failures, he achieved many cures and the technique came to be known as “Coley’s toxins”.

Despite this, with the rise of chemotherapy and radiotherapy, the treatment fell out of favour. Recently, there has been renewed interest in using bacteria to treat cancer, but the approach faces a major hurdle. As you might expect, regulatory authorities do not readily approve drugs containing unspecified substances and where there is no clearly known biological mechanism of action. But this is where my recent work with colleagues could help: we have found that there might be a simple immunological explanation for Coley’s successes.

Coley’s case studies and publications have

been reviewed several times. In a 1953 report in the journal *Acta Medica Scandinavica*, Coley’s daughter Helen Coley-Nauts re-examined the clinical cases described by her father. It wasn’t easy. His records were not comprehensive and the bacterial extracts had often been prepared in different ways. Coley-Nauts found that her father had used 15 different preparations, 11 of which she deemed “not potent enough”.

Even so, there is no doubt that Coley achieved some spectacular cures. In a 2008 review, Alberto Mantovani of the University of Milan, Italy, wrote that Coley “documented cases of the long-term survival of individuals with malignancies that remain a major challenge to treat now” (*Nature*, vol 454, p 436). For example, he treated a group of sarcoma patients with fever-inducing injections two to three times per week for several months. Many were late-stage, inoperable cases. Yet their five-year survival rate was higher than 80 per cent, according to Coley-Nauts’s analyses.

Why did such treatment work at all, especially given that around 20 per cent of all cancers are caused by chronic infections? And in drug testing, fever is seen as a toxic adverse event, according to the US Food and Drug Administration. In other words, the belief is that fever usually signifies harm, not benefit.

But does it? Some years ago, I stumbled across a 1951 paper reporting that among 300 cases of childhood leukaemia, 26 spontaneous remissions were observed. Of those, 21 were

PROFILE

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Century-old fever therapies might offer more effective ways to treat cancer

preceded by a feverish infection (*The American Journal of Medicine*, vol 10, p 238). Although this was a small study, an 80 per cent correlation of spontaneous regression with fever seemed too odd to be a coincidence. When I started to analyse case studies and reviews of spontaneous cancer remission, it turned out that in a surprisingly large fraction a preceding infection – of the type known to cause fever – was reported.

The fever and cancer regression could just have been a coincidence, but what if there was a causal link? To test this, I looked at analyses of cancer across large populations. To my surprise, I found more than 30 studies showing that people who developed fever-causing infections such as measles, herpes and mumps more frequently over their lifetimes had a lower risk both of developing cancer and of relapsing after standard treatment.

So what do Coley's treatments, spontaneous remissions and the epidemiological studies have in common? And what could be the molecular explanation?

The answer might be a diverse range of chemical danger signals known as "pathogen recognition receptor ligands". These PRRL are produced by invading pathogens such as bacteria, viruses and fungi and they can put our innate immune system on red alert within minutes. But could PRRL protect against cancer? To find out, we need to look more closely at the immune system.

For a long time it was assumed that cancer cells are more or less invisible to the immune system. Millions of people die from cancer each year and if the immune system could respond, we would expect to see a much larger proportion of spontaneous regressions – or so the argument went. However, we now know many tumours are infiltrated by immune cells, such as cytotoxic lymphocytes, indicating that there is an active anti-cancer response. So while tumours are not invisible to the immune system, it seems the reaction is usually too weak to stop the cancer. What if PRRL could lift this immune reaction above a threshold needed for tumour shrinkage?

To mount a vigorous attack against invaders such as bacteria, viruses or cancer, immune cells called T-cells need to be activated. A T-cell can recognise cancer cells, but if it has not been properly turned on, it will remain relatively harmless to the invader. Dendritic cells are responsible for activating T-cells, but they in turn require PRRL for their

own activation. Our hypothesis is that PRRL-activated dendritic cells can turn on several types of T-cells at once. So the immune response to a pathogen could also trigger an immune response to cancer cells.

Last year I tested this hypothesis in mice, working with Claudia Maletzki and Michael Linnebacher of the University of Rostock and Rajkumar Savai of the Max Planck Institute for Heart and Lung Research, Bad Nauheim, both in Germany. We found preliminary evidence that treatment with a single type of PRRL can slow tumour growth in mice and that a mix of PRRL can cure them, provided the treatment is given at regular intervals over a long period (*Cancer Immunology, Immunotherapy*, vol 62, p 1283). In our case, this was every other day for three weeks; adjusted for human life expectancy, this is analogous to a treatment over months, as Coley preferred.

Coley also thought that higher fevers correlated with greater success, but is fever necessary for PRRL to work? We don't know, but when the mice in our experiment were

"The belief is that infection and fever are always signs of harm. But are they?"

given a single dose of PRRL, their body temperature went up by about 1 °C for a day.

Coley's treatments fit within a wider story of beneficial effects from infections and fever. In 1927, Julius Wagner-Jauregg won the Nobel prize for demonstrating the therapeutic value of malaria inoculation for treating syphilis. Today a standard treatment for bladder cancer is the injection of live bacteria – in the form of the BCG vaccine – but the mechanism is not fully understood. PRRL could be the explanation.

We believe that a PRRL mix could replace bacterial extracts, avoiding many of the regulatory obstacles. However, we are clearly a long way from it becoming an approved cancer treatment. To begin with, to test PRRL, the patient's immune system should not be too badly damaged by prior chemotherapy or radiotherapy. Yet a way round this would be to test on cancers for which chemotherapy is not very effective, such as pancreatic or liver cancer, or slow-growing prostate cancer.

Usually drugs are tested in mice first and then in humans, but thanks to Coley, human trials for the treatment of cancer with bacteria were carried out a hundred years ago. Perhaps we can finally provide the molecular explanation for his remarkable results. ■