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UPHILL STRUGGLE

The first vaccine against Lyme disease was withdrawn because patients distrusted it. Should market forces be allowed to shape the next one, asks **Alison Abbott**.

The idea that the customer is always right is gospel in most areas of business. Most, you might think, except the business of making drugs and vaccines. Not so. The cautionary tale of the Lyme-disease vaccine is a good example of how consumer power can override science.

Lyme disease is a debilitating infection spread by bites from ticks. Found mainly in the United States and Europe, its prevalence is increasing as civilization encroaches on forested areas — home to the deer on which the ticks feed. A vaccine is badly needed to contain the disease, but the one jab available was pulled from the market after complaints from a group of patients damaged its reputation. Now, a similar vaccine is set to emerge, but some say it has been tweaked in a way that confers no obvious scientific benefit.

Lyme disease made a meteoric entry into medical and public consciousness 30 years ago, when Allen Steere, a rheumatologist now at Massachusetts General Hospital in Boston, described an outbreak of a mysterious illness in Lyme, Connecticut. The disease he identified was caused by a spirochete, a spiral-shaped bacterium called *Borrelia burgdorferi*. It is rarely fatal, but acute infection results in a range of unpleasant and debilitating symptoms, including flu-like effects, a bullseye rash and neurological problems such as facial palsy.

After several weeks without treatment, some patients go on to develop joint pain or arthritis. If left untreated, it can last for years, but even then will usually respond to antibiotics. In a small subset of patients, however, the joint pain and swelling do not respond — the condition is known as treatment-resistant Lyme arthritis.

It was arguments about the long-term persistence of Lyme disease that triggered the first 'Lyme scandal'. In the 1990s, Steere was hounded by patients who claimed to be suffering from a chronic form of Lyme disease that left them persistently exhausted. Steere insisted that they had been misdiagnosed. Although the patients had antibodies to Lyme disease, indicating that they had at one time been exposed to *Borrelia*, Steere maintained that their range of vague symptoms did not correlate with the true course of the disease. He says he wanted to save people from unnecessary antibiotic treatment, but instead found himself under protection of security guards, and dealing with hate mail and even death threats.

Ticked off

The dust had barely settled when another scandal broke, which eventually led SmithKline Beecham (now GlaxoSmithKline) to withdraw its vaccine LYMErix from the US market. Shortly after the jab was introduced, hundreds of vaccine recipients claimed that they had fallen victim to side effects — including autoimmunity, in which the immune system attacks the body. Their claims were based on a scientific hypothesis that is still unproven today: it predicts that people will raise antibodies to a stretch of a particular protein on the outer surface of *Borrelia*, called OspA, that could destroy normal human protein as well as the bacterium. LYMErix happened to work by generating antibodies to this OspA protein — which is why patient advocacy groups latched on to the idea that the jab itself could cause autoimmune disease.

> **"This just shows how irrational the world can be — there was no scientific justification for pulling the first Lyme vaccine."**
> — Markus Simon

One law firm filed a class action in December 1999, and individual suits began to flood in. The US Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention published their own investigation into 900 or so adverse event reports and concluded that there was no evidence of a link between the autoimmunity complaints and the vaccine[1]. But the bad publicity torpedoed sales. In February 2002, GlaxoSmithKline withdrew the vaccine from the US market and abandoned plans to launch a similar one in Europe. Enthusiasm for the jab seemed to have been killed off, and various attempts to generate vaccines against different *Borrelia* proteins fizzled to nothing.

But last year the company Baxter Vaccines in Vienna quietly announced that it was hoping to do clinical tests of a new vaccine candidate in Europe. To the astonishment of Lyme-disease researchers, the candidate turned out to be broadly based on the same *Borrelia* protein, OspA. The vaccine, which has been successfully tested in animals, differs from LYMErix in two ways. Europe is home to two more species of *Borrelia* than the United States, so Baxter's vaccine is designed to protect against infection from all three. And the short stretch of the OspA protein that had been associated with the hypothetical danger of autoimmunity has been spliced out.

The news only deepened the frustration of Markus Simon of the Max Planck Institute for Immunobiology in Freiburg, Germany. Along

First in line: those who work or play in the forest could benefit a lot from a vaccine for Lyme disease.

with his colleagues, Simon was the one who had developed the concept of an OspA-based vaccine in the early 1990s, which was then taken to the clinic by GlaxoSmithKline. "This just shows how irrational the world can be," says Simon. "There was no scientific justification for the first OspA vaccine being pulled."

On the trail

The idea that Lyme infection — and the Lyme vaccine — could cause the immune system to attack the body has its roots in the 1970s, when Steere described treatment-resistant Lyme arthritis. Nothing to do with the 'chronic Lyme disease' that angry patients later claimed had been triggered by Lyme infection, this syndrome, which can last for years, is characterized solely by inflamed joints. The arthritis seems not to be associated with continuing bacterial infection. Indeed, in the decades that followed, bacterial DNA has only very rarely been found in fluid extracted from affected joints, even using modern, sensitive methods of amplifying DNA traces[2]. So scientists began to entertain the thought that this treatment-resistant Lyme arthritis could be an autoimmune response.

The idea was supported by the discovery in 1990 that the immune systems of most patients developing treatment-resistant Lyme arthritis shared some very specific, and genetically determined, characteristics[3]. This subset of people happens also to be particularly susceptible to rheumatoid arthritis, an autoimmune condition afflicting the joints.

If persistent Lyme arthritis were really an autoimmune condition, what might be the mechanism? Scientists first looked to the idea of 'molecular mimicry', which was developed in the 1980s to explain how microbes in general might cause autoimmunity. According to this hypothesis, part of one of a microbe's proteins might be structurally similar to part of a normal protein in the patient — but different enough to be recognized as foreign by the patient's immune system. On exposure, antibodies to the foreign protein would be produced, which would then also attack the patient's normal protein.

"It is essential to err on the side of caution, and it is a simple matter to eliminate the problem."
— Brigitte Huber

To test whether the molecular-mimicry hypothesis might be applicable to treatment-resistant Lyme arthritis, scientists began to look for a host protein that the immune system might mistake for a *Borrelia* one. Looking for matches to OspA was an obvious starting point, and in 1998 Brigitte Huber, an immunologist at Tufts University in Boston, and a number of her colleagues including Steere, came up with a strong candidate. They found that a stretch of the *Borrelia* OspA protein shared a very similar amino-acid sequence with a human protein that helps move immune cells from blood vessels to inflamed tissue[4]. In the test-tube, this protein did the right thing — it prompted immune cells from treatment-resistant Lyme arthritis patients to trigger inflammation processes.

The implications of this for a vaccine whose mechanism depended on OspA antibody production were clear. And patient advocacy groups, sensitized by the battle over 'chronic Lyme disease', were on the alert when LYMErix was approved for the US market by the FDA later in 1998.

But although molecular mimicry has a sound and respectable foundation as a hypothesis, no one has yet shown that it happens in real life. And as time went by, Lyme-disease researchers showed that many other proteins also activated OspA-specific immune cells in the test-tube[5], and some of them did not even share similar sequences. "This all dealt a big blow to the molecular mimicry theory," says Thomas Kamradt, an immunologist at the University of Jena in Germany.

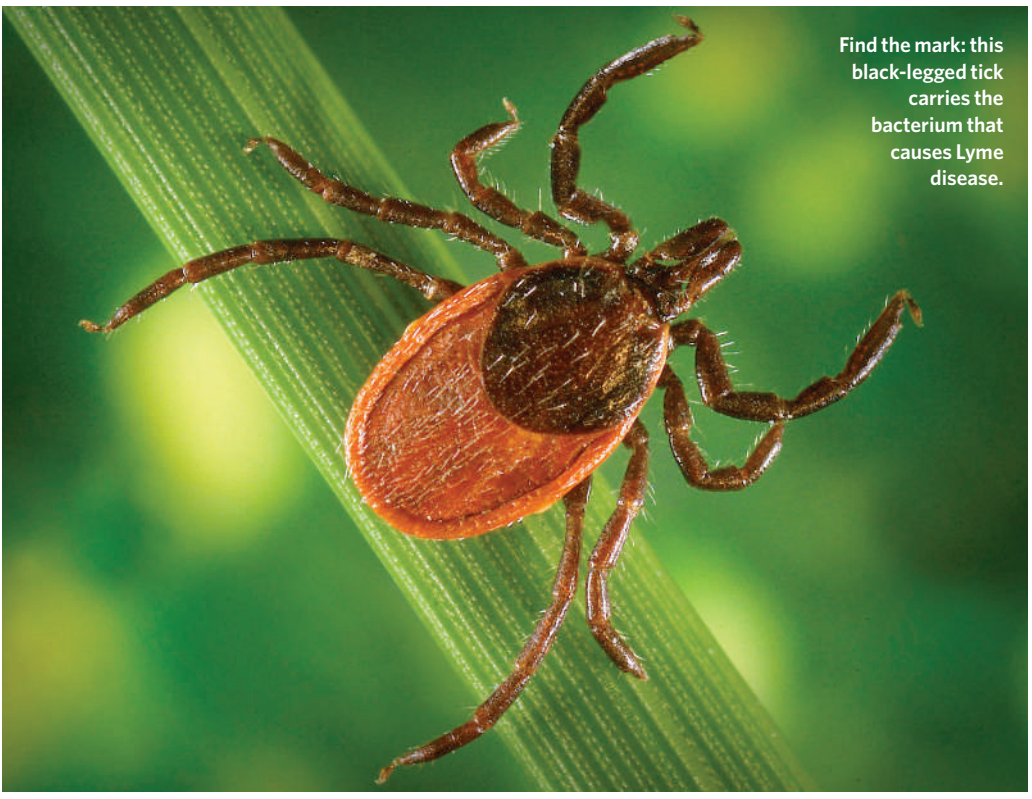
No verdict

Huber says that the jury is still out because there is not yet a good animal model in which to test the hypothesis. But most Lyme researchers are now convinced that molecular mimicry is an extremely unlikely explanation for any autoimmune response that might underlie treatment-resistant Lyme arthritis.

So, given that costly testing for safety and efficacy will have to start from scratch, does it make any sense to modify an earlier vaccine's structure in ways that may not, after all, be necessary? Simon thinks not. "We had years of clinical data with LYMErix — hundreds of thousands were vaccinated, and not one autoimmune response was ever confirmed," he storms. "And who knows if the new vaccine with this sequence spliced out will still be protective in humans?" Only clinical trials will tell. When contacted by *Nature*, Baxter Vaccines declined to comment.

Although no link has been found between LYMErix and an autoimmune response, some researchers are taking a precautionary stance. Steere, who has worked as a consultant for Baxter Vaccines, says: "There is no proof that autoimmunity ever developed in anyone, but it could be a very rare side effect." Splicing out the sequence in question "takes care of this theoretical concern", he adds. Huber agrees: "It is essential to err on the side of caution, and it is a simple matter to eliminate the potential problem."

Steere, whose experience with the angry patients encourages him to keep his head well below the parapet, strongly believes that a vaccine is necessary. And he argues that this need will become clearer to the public as experience of Lyme disease expands: "Most people who want a vaccine are those who have already had the disease." ■



Find the mark: this black-legged tick carries the bacterium that causes Lyme disease.

CDC/J. GATHANY

Alison Abbott is *Nature*'s senior European correspondent.

1. Food and Drug Administration www.fda.gov/ohrms/dockets/ac/01/briefing/3680b2_06.doc
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