LAURA MUELLER WOODS (2020)

Peter Moore suddenly began to have severe allergic reactions to meat at the age of 25.

The meat-allergy mystery with a tick-bite link

An unusual reaction to mammalian meat is challenging the immunological understanding of allergies. **By Bianca Nogrady**

Peter Moore woke up in the middle of the night with his throat so tight he struggled to breathe, his torso covered with huge red welts, and no idea why. Earlier that evening in June 2001, Moore — then a 25-year-old teacher living in a coastal suburb of Sydney, Australia — had eaten pork spare ribs at a neighbour's house, then gone to bed content and in perfect health. Until he woke in a panic.

Moore's partner, Christina, immediately called an ambulance. She and the neighbour bundled him into a boat and ferried him across the short stretch of coastal waters to Church Point, where an ambulance could pick him up.

As they waited, seated on a sandstone wall under a street light, Moore remembers watching tiny black ants run back and forth on the ground in front of his feet. "There are certain moments in your life which are super vivid, and that one of the street lights, the ants, the sound of the ambulance, it doesn't dissipate," he says.

The medical team at the hospital where Moore was taken were puzzled. They treated him with adrenaline, antihistamine and steroids, and he recovered. A couple of months later, it happened again, this time after a dinner of spaghetti and meatballs. And again in November that year, after eating beef nachos. Each time, he was hospitalized. Each time, no one was sure what it was he was reacting to.

The allergist he saw after his third episode suggested it might be some kind of additive in the meat, so he started avoiding meat altogether. Then, around six years later, he discovered that a neighbour had experienced similar reactions after eating meat. The chance conversation led him to allergist and clinical immunologist Sheryl van Nunen at Sydney's Royal North Shore Hospital.

Van Nunen diagnosed him with mammalian-meat allergy, a rare condition that she had first seen in a patient in 1987. Since then, she has managed more than 400 cases — and noticed something common among them. "After you've seen a couple of people and the story's the same, I like to know what's happening to them, so I always take a family history of allergy," she says. These patients said they had experienced a large, localized reaction, or a more extreme systemic reaction, when they'd been bitten by a tick.

outlook

As more and more patients arrived at her clinic with similar stories, van Nunen deduced that it wasn't just any tick causing these reactions: it was a specific type from Sydney's northern beaches.

Breakthrough

Half the world away, in North Carolina and Tennessee, researchers conducting clinical trials of a monoclonal antibody treatment for colorectal cancer — cetuximab — were seeing unprecedented rates of severe allergic reactions to the drug. Just over one in five people who had received the intravenous drug were experiencing full anaphylaxis[1] — something that hadn't been seen in cetuximab clinical trials in other parts of the world.

What was especially strange — aside from the high frequency of the reaction — was that many of these people had no history of allergies or previous exposure to the drug. Typically, an allergic reaction to a drug is built up over multiple exposures. "The patients were reacting on the first infusion, which made you think something had to be there ahead of time," says Scott Commins, an allergist and immunologist at the University of North Carolina at Chapel Hill who was among those investigating.

After studying the molecular structure of cetuximab and the immunological markers of the response, researchers hypothesized that the sugar molecules attached to the monoclonal antibody might be important. The manufacturer provided an alternative form of the drug without those sugars, and it was tested. Suddenly, all the previously positive antibody responses turned negative. "We had played this hunch, and then for the data to be so clean, and really support that hunch — it was a good day," Commins says.

Further analysis revealed the exact culprit: a sugar called galactose-α-1,3-galactose, or α-gal. Many mammals produce α-gal, but humans and some other primates do not, having lost the ability to do so around 28 million years ago. This is a major barrier to transplantation of organs between animals and humans, because humans produce substantial quantities of natural antibodies against α-gal. Cetuximab was produced using a mouse cell line, which was the source of the α-gal.

This was a breakthrough, but it still didn't explain why the rate of hypersensitivity reactions to cetuximab was so high in that particular part of the United States. So researchers dug deeper. Using a newly developed test for the type of immunoglobulin E (IgE) antibodies that target α-gal, they discovered that α-gal sensitivity was surprisingly common in the southeastern United States compared with other parts of the country.

Then came the second breakthrough. In 2009, Commins and his colleagues found that 24 patients at the University of Virginia allergy clinic in Charlottesville had IgE antibodies against α-gal[2] — and all of them had shown allergic reactions within three to six hours of eating mammalian meat. Just a few months later, van Nunen and her colleagues published a paper on the association between mammalian-meat allergy and tick bites[3], and the pieces of this food-allergy puzzle finally fell into place. In the southeastern United States, just as in Sydney, a tick was the key.

"The tick is altering us," van Nunen says. When a tick bites a person, it introduces α-gal to the human immune system, which in some people leads to the development of an allergy to mammalian meat products. Exactly how this happens, however, is still shrouded in mystery.

Tick link

The tick is a cunning parasite. It has to be, because unlike other blood-sucking arthropods, it needs to stay attached to its host for a long time — in some cases, for up to ten days.

To suck blood for such a prolonged period, the ticks need a way to manipulate the defences of their host so that they remain unrecognized, says Mária Kazimírová, an entomologist at the Slovak Academy of Sciences in Bratislava. The key to this lies in their saliva, which contains anticoagulants to keep the blood flowing, anaesthetics to dull the skin around the bite, and immunosuppressants and immunomodulators to stop the host's skin from initiating an inflammatory reaction that might prematurely end the tick's feeding.

> **"With his couple of most severe episodes, he actually lost consciousness."**

This sialome — the proteins expressed in the salivary glands of ticks and other blood-sucking parasites — varies between species as well as between individual ticks. It can even vary in one tick over the course of a single feeding, as a mechanism to avoid immune detection. The source of the α-gal is still being investigated: it could be produced by the tick or its microbiome, or ingested from a host.

Not all species of tick produce α-gal, says Shahid Karim, a vector biologist at the University of Southern Mississippi in Hattiesburg. In Australia, the main culprit in mammalian-meat allergy is *Ixodes holocyclus*, which is also known as the paralysis tick. It is found across the east coast, but especially around Sydney's northern beaches, where Moore lived and where so many of van Nunen's patients come from.

In the United States, *Amblyomma americanum*, or lone star tick, is the species whose bite is most commonly associated with the development of mammalian-meat allergy. The tick is distributed across the east and central United States, including North Carolina, Tennessee and New York.

Allergist Erin McGintee had only just started up her practice a decade ago at the east end of Long Island, New York, when she saw a man who thought he had a shellfish allergy. "He would wake up in the middle of the night, usually with severe abdominal symptoms, like he was going to have diarrhoea or he was going to vomit," says McGintee. "He'd jump up out of bed, run to the bathroom and break out in hives. And with his couple of most severe episodes, he actually lost consciousness."

But before some of these episodes, the man hadn't knowingly eaten shellfish. He'd been at a steakhouse, then at a barbecue. McGintee recalled seeing an abstract about mammalian-meat allergy, so she looked into it. When she tested the man for α-gal antibodies, the results came back positive.

"Now that I am an expert in this allergy and I've taken care of it for so many years, his presentation was absolutely classic," McGintee says. She has since seen around 600 people with the allergy, which fits with the high prevalence of the lone star tick in east Long Island.

But the condition is not solely caused by lone star ticks and paralysis ticks in the United States and Australia. In Europe, it can be triggered by *Ixodes ricinus* (the castor bean tick), *Rhipicephalus bursa* (the brown ear tick) and *Hyalomma marginatum*. In Japan, it's linked to *Haemaphysalis longicornis* (the Asian longhorned tick), and in Brazil it's caused by *Amblyomma sculptum*.

There are also clusters of cases in South Africa. However, Tshegofatso Mabelane, an allergist in Pretoria who has been studying a large cohort of people with mammalian-meat allergy, says the cause there has yet to be identified. The cases are clustered in rural areas, which suggests that the people affected would have had the opportunity to come into contact with ticks. But Mabelane's patients don't necessarily report the history of tick-bite reactions that van Nunen has observed. Mabelane speculates that there could be another type of blood-sucking arthropod that is sensitizing these people to α-gal.

The clinical presentation of mammalian-meat allergy also varies between locations. Mabelane conducted a food-challenge trial (in which a person is intentionally exposed to the allergen) in 131 South Africans who had

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***Ixodes ricinus*, the castor bean tick, has been linked to mammalian-meat allergy in Europe.**

experienced adverse reactions to meat[4], giving them a meal of beef sausage. She expected the reaction to take a few hours to manifest, on the basis of what had been reported in other parts of the world. But that wasn't the case. "I had people presenting within 45 minutes," she says. Furthermore, they predominantly showed gastrointestinal symptoms. "I'm expecting skin manifestations, and I'm running around [with] buckets."

Van Nunen has identified two other forms of allergic presentation in tick-bite-induced mammalian-meat allergy — food protein-induced enterocolitis syndrome and the much rarer food carbohydrate-induced enterocolitis syndrome. She is also investigating a possible third presentation, T cell systemic contact dermatitis, in a person whose contact dermatitis resolved when they took mammalian meat out of their diet.

"Now the spectrum of mammalian-meat allergy is across all of the known descriptions of hypersensitivity to food," van Nunen says. "This allergen can do everything any other allergen can do." And it presents across all ages, from children to elderly people; McGintee has seen it in a child aged three.

Paradigm shift

Most humans happily consume mammalian meat throughout their life without becoming allergic, despite our lack of α-gal. But the number of cases of α-gal syndrome is growing: it is estimated to affect more than 5,000 people in the United States, and it is a leading cause of anaphylaxis in the southeast of the country.

Why this allergy has emerged in such numbers only relatively recently, when ticks have been around for a long time, is unclear. One theory is that the ticks themselves have changed. Karim is investigating whether the tick's complement of microbes has altered in response to environmental factors, and this has led to ticks producing α-gal in response. Van Nunen also suggests that the tick might be producing α-gal as a defence mechanism against microorganisms that live in and on it.

Researchers also don't know why the allergy develops only in some people bitten by ticks bearing α-gal, or even why it develops at all. "It really breaks this whole paradigm that tolerance is established in early childhood and is therefore never bendable or breakable," says Commins. The immunological understanding has been that once tolerance to a food is established, IgG antibodies are made to record that. "So what we're really talking about is a new set of IgE antibodies that seem to somehow override the IgG that you've made for years."

There are relatively few clues in the patients themselves as to what might be predisposing them to developing mammalian-meat allergy. Some clinicians have observed that it runs in families, and that individuals of blood group B are less susceptible than those of blood groups O or A. Studies have also shown that although people with mammalian-meat allergy have high levels of IgE antibodies against α-gal, not all people with high levels of those antibodies have mammalian-meat allergy.

McGintee theorizes that there might be a window after a tick bite in which the conditions exist for mammalian-meat allergy to develop, and that it is exposure to additional stimulating factors during that window that determines whether a person will become allergic. When someone is bitten by an α-gal-producing tick, they begin to manufacture antibodies against α-gal over a period of a month or two, she says. At that point, the person might not be producing enough antibodies to have a noticeable reaction to any α-gal that they consume. But if, during that time, they were to eat a substantial quantity of red meat, or be bitten by another tick, the cumulative effect on levels of α-gal antibodies in their system might be enough to provoke an allergic response.

"My theory is that there's probably a lot of people who make some α-gal antibodies following a lone star tick bite, but maybe they never hit that threshold," she says. "They miss the window, and they never have a reaction."

Support for this comes from the observation that the allergy does seem to wane over time if patients are not exposed to any more tick bites. "In quite a few people, you can get them back onto meat within three to four years, but the secret to that is no more tick bites," van Nunen says. Another tick bite can send antibody levels — and allergic responses — soaring again.

This is why van Nunen has focused some of her attention on identifying methods of preventing tick bites, such as treating clothing with insecticide, as well as techniques for removing embedded ticks in a way that reduces the amount of saliva they discharge into their host. "Tick-bite prevention and management strategies have been proven to work," she says.

Moore, who left Australia for the United States in 2009 and is now a teacher in North Carolina, had a close encounter with a lone star tick in the summer. It was crawling across his arm but hadn't yet attached, so he was able to flick it off. He is careful to avoid meat, and he uses his personal experience to help students with food allergies, their parents and other teachers understand the risks and realities of potentially fatal food allergies.

Despite his awareness, he has had a couple of allergic episodes in recent years after being inadvertently exposed to mammalian meat products. Moore says he still lives in fear of another severe reaction that might land him in hospital. "People say is it hard, not eating red meat or pork? And I say, when you know something could kill you, it's really easy to avoid."

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