Early trials suggest a host of allergies and autoimmune ailments could be treated with worm therapy, or infection with live worm-like parasites. But will it ever reach the clinic?

Jim Turk initially put his symptoms down to stress. The self-described "health nut" who was in training to run marathons suddenly found himself unable to jog for more than a couple of minutes before coming to a gasping, staggering halt. His speech began to slur. Turk, then in his early thirties, blamed the combined pressures of juggling a full-time job, studying for a master's degree and his parenting responsibilities. When he collapsed in the middle of a baseball field one sunny afternoon in 2008 while coaching his son's team, he realised it was time to seek help.

At the hospital, magnetic resonance imaging (MRI) scans revealed plaques peppered throughout Turk's brain and spine. The diagnosis was obvious: multiple sclerosis, the autoimmune condition in which the body eats away at its own nerve cell casings. The cure: not known yet.

A month later, Turk saw an ad on the news seeking multiple sclerosis patients to try out an unusual new treatment at the University of Wisconsin, in his hometown of Madison. Patients were being asked to infect themselves with live pig whipworm eggs to see if the parasites alleviated any of their symptoms or slowed the spread of telltale brain and spine lesions. "I've always had a research interest so I decided to put my money where my mouth is," Turk says. "Plus I was terrified and didn't know what to do."

When Turk arrived at the clinic, John Fleming, a professor of neurology, presented him with a vial of clear liquid. "It tasted a little bit salty but otherwise it was just water," says Turk. "I couldn't see the eggs or anything."

For the next three months, he and four others visited the lab every two weeks to swallow doses of 2,500 parasite eggs. At the start of the trial, MRI scans showed patients had an average of 6.6 active lesions — scars on the protective layer around nerve cells that disrupt the transmission of electrical messages in the brain and spinal cord. By the end of the study, that number had dropped to two. Two months after discontinuing the worm treatment, the lesions rebounded to an average of 5.8.

"The beauty of this is that the number of new lesions is really an objective, brutally honest answer," Fleming says. "It's not proof, it's not definitive, but at least it's promising."

Old friends

Fleming's trial in 2008 was the first to infect multiple sclerosis patients with live parasitic worms, also known as helminths, but others were also investigating their therapeutic potential. The field has its origins in the early 1980s. Joel Weinstock, now chief of the division of gastroenterology/hepatology at Tufts Medical Center in Boston, struck upon the idea during a six-hour delay on the runway at Chicago's O'Hare airport.

"Over the years, people had looked for environmental factors that caused inflammatory bowel disease and hadn't found anything," Weinstock says. "While on the plane, I decided to play a game and pretend that it's caused by the loss of something rather than the addition of something." It was as if "a light suddenly went off", Weinstock says, as parasites came to mind. Hygiene does wonderful things, he realised, but there's always a price for change.

The price might be the surge in cases of asthma and allergies we've seen in western countries over the past 40 years. Likewise, rates of autoimmune and immunoregulatory conditions such as Crohn's diseases, type 1 diabetes, inflammatory bowel disease and multiple sclerosis have been on the rise. Yet in developing countries, such conditions remain rare.

In 1989, David Strachan, an epidemiologist at St. George's University in London, published a landmark study proposing that improved hygiene in the developed world could explain trends in hay fever incidence. Strachan's idea was that changes to sewage treatment, availability of clean water and food, and a shift away from farming lifestyles decreased our contact with soil, faeces and contaminated food where bacteria and parasites like helminths live.

The so-called "hygiene hypothesis" quickly took off, but in recent years a growing number of scientists have said the picture is more complex. The rise in allergies and inflammatory diseases may not necessarily be caused by a general lack of microbes in hygienic environments, but rather by a lack of certain organisms that have, over the course of evolution, trained our immune system to be more tolerant.

One of those organisms could be the worm-like parasite. Many of our human ancestors would have been infected with helminths, as are large numbers living in developing nations today. When helminths infect individuals and attach themselves in their hosts' gastrointestinal tracts, the immune systemlaunches an attack, while at the same time issuing a chain of anti-inflammatory orders to ensure the response does not get out of hand. People who survived infection have passed on immune
advantages to future generations. In the modern, developed and sterile West, the theory goes, immunoregulatory effects no longer develop normally, leaving some particularly vulnerable to allergies and inflammatory diseases. "It's not that you're diseased or abnormal, it's just that the world has changed," says David Elliott, hepatologist at the University of Iowa, and Weinstock's research colleague.

**Market forces**

In 1999, when Elliott and Weinstock first found that helminths protected mice against colitis, news spread fast. Six years later, the group published the result of two preliminary trials in humans. In one, involving 54 ulcerative colitis patients, 43% of those given pig whipworm eggs improved, compared with only 17% who received placebos. In a second trial 29 patients with Crohn's disease took whipworm eggs every three weeks. By the end of 24 weeks, 79% had reduced disease activity and 72% had gone into remission. Researchers and biomedical companies around the world began to investigate the potential of helminthic therapy for treating conditions ranging from asthma to autism to psoriasis.

Helminthic therapy is still at the experimental stage, but some patients are unwilling to wait. In 2007, self-infected entrepreneurs Garin Aglietti and Jasper Lawrence founded a worm therapy start-up called AutoimmuneTherapies in the US by harvesting hookworms plucked and sterilised from their own faeces, and charging between $2,000 to $3,000 per dose. However in 2009, the Food and Drug Administration defined helminths as biological products that could not be sold before having undergone a series of clinical trials, which they had not. Aglietti set up his own WormTherapy operation to Tijuana, Mexico, and Lawrence returned to his native England.

Herbert Smith, a financial analyst in New York bought hookworms, and pig and human whipworms from WormTherapy and AutoimmuneTherapies, either travelling to Mexico or receiving mail-order worms from Lawrence. Smith was diagnosed with Crohn's disease in 1996, and lost a foot of his intestines to surgeries before he stumbled on one of Weinstock's papers. Today, he maintains a healthy population of hookworms, which he says have caused a complete remission. "This therapy could help people who don't have any other treatment options," Smith says.

Not everyone responds so well, however. Moises Velasquez-Manoff, a journalist, also visited Aglietti's Tijuana clinic to receive a dose of 30 hookworms for his allergies and asthma, and to chronicle the experience in his book, An Epidemic of Absence (http://books.simonandschuster.com/Epidemic-of-Absence/Moises-Velasquez-Manoff/9781439199381). Once infected, he suffered diarrhoea and a dull, constant gut pain, and his allergies failed to improve. After a year and a half he took medication to flush out the invaders. "The idea is very, very powerful," Velasquez-Manoff says. "They just weren't doing anything for me."

Researchers across the board are keen to discourage self-infection, which they say puts patients at risk of taking the wrong dose or purchasing contaminated batches. Fleming says he advises the multiple sclerosis patients who email him at a rate of around one a week against self-infecting with helminths. "People might say they're getting better or worse, but they don't really know," he says. "Outside a scientific trial, it's a muddle."

**Testing stage**

Nowadays, most researchers investigating helminthic therapies have abandoned blood-sucking hookworms in favour of pig whipworms, as they have evolved to colonise swine and therefore cannot complete their life cycle within humans. Patients must re-infect themselves every few weeks but do not risk a chronic infection potentially spiralling out of control, or of accidentally infecting family members. "Pig whipworm is very kosher," Weinstock says.

At New York University, immunologist P'ng Loke found monkeys suffering from chronic diarrhoea not only got better after receiving a dose of pig whipworms but also had significantly different gut microbes post-infection. He is currently enrolling ulcerative colitis patients to repeat the experiment in humans. Gaastroenterologist John Croese, at the Prince Charles Hospital in Brisbane, is inoculating 12 coeliac disease patients, who suffer from gluten intolerance, with hookworms. Gluten is slowly introduced into their diets so to see if the hookworms will suppress the disease's inflammatory response.

Back in Wisconsin, Fleming is continuing his studies on multiple sclerosis. He has enrolled another 15 patients for a longer trial with pig whipworms, the results of which are expected at the end of this year. As for Weinstock and Elliott, they have returned to mouse models, seeking to understand how helminths inhibit disease. Coronado Biosciences, a Massachusetts-based company, hopes to have results from two large studies being carried out in the US into the use of pig whipworm eggs to treat Crohn's disease by the end of the year. Meanwhile, German firm Dr Falk Pharma is collaborating with Coronado in a similar trial.

Coronado also expects results from its multiple sclerosis trials next year. Trials on adults with autism are underway, and the firm is planning studies on psoriasis, ulcerative colitis, type 1 diabetes and children with autism. "Our most important task now is to identify which diseases to pursue and which patient populations to target," says Karin Hegenberger, Coronado's chief medical officer.

**Worm factory**

None of these trials have reached phase 3, the final testing stage required to gain approval. Even if they are successful it is likely to be a few more years before treatments are made available to patients. Frustrating though it may be for some, developing new modes of therapies simply takes a long time. Gaining approval for trials, recruiting patients and waiting to evaluate the effects are all time-consuming.

It's not just a case of demonstrating helminthic therapy is safe and effective, researchers will also have to figure out how to administer it. A live organism's many complex molecular interactions with its host may be key to triggering the desired immune-suppressing reaction. It may therefore make sense to administer helminths as "living probiotics". In the case of whipworms this means patients swallowing doses of live eggs; in the case of hookworms they apply gauzes containing live larvae to their skin. "When you give someone a live worm, it's like giving them the factory that makes the products and letting the factory do what it needs to do," Elliott says. "Evolution has already created this thing."

Others oppose this approach. "These worms are not benign," says Peter Hotez, dean of the National School of Tropical Medicine at Baylor College of Medicine, Houston. "We can design better, bona fide treatments based on the biology of the worms that can be scaled up and manufactured without the complexities or safety issues that go along with administering live parasites."

Hotez and others including Weinstock's group are working on identifying the molecules responsible for the effects of treatment with worms so they can be purified and synthesised as pharmaceuticals, just as scientists did with penicillin. Several discoveries have already been made with hookworms, such as a protein that inhibits white blood cell activity and another with antiinflammatory properties.

Back in Wisconsin, Turk, who has no desire to travel to Mexico or England to attain illicit worms, awaits the trial results. He occasionally speaks to multiple sclerosis support groups about his experiences, encouraging others to take part in research to speed the discovery of better medications. He is taking interferon beta-1a, a drug that reduces relapse rates, but he hopes the trials of helminthic therapy prove successful, and would gladly switch to it if it gained approval. Without a tried and tested cure, Turk says he has good days and bad days. "A lot of people look at me and don't think there's anything wrong, but that's just because I do a good job at hiding it," he adds.

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