COMMENT

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CONSERVATION Suburbanites' conflicted relationship with wild animals **p.188**

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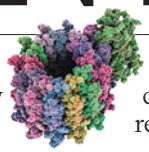


OBITUARY Keith Campbell, creator of Dolly the sheep, remembered **p.193**

JOEL WEINSTOCK LAB

The whipworm *Trichuris suis* is currently in trials for treating Crohn's disease and ulcerative colitis.

The worm returns

Joel V. Weinstock explains why several clinical trials are deliberately infecting people with helminths to treat autoimmune diseases.

For as long as modern humans have existed, they have carried parasitic worms. That is around 200,000 years. Like many bacteria, some roundworms and flatworms (helminths) reside harmlessly in the gut. Others can cause problems.

Before antibiotics and improvements in sanitation, gastrointestinal infections — mostly with bacteria — killed perhaps one in five children and many adults. Now, thanks to clean food and water and hygienic sanitation, it is rare for a child in the Western world to die from such infections. These advances in hygiene have also 'dewormed' much of the developed world.

Meanwhile, the twentieth century saw a rapid increase in an entirely new set of diseases, such as inflammatory bowel disease (the focus of my research). These once-rare diseases, caused by autoimmunity, have become relatively common in less than a century. Why?

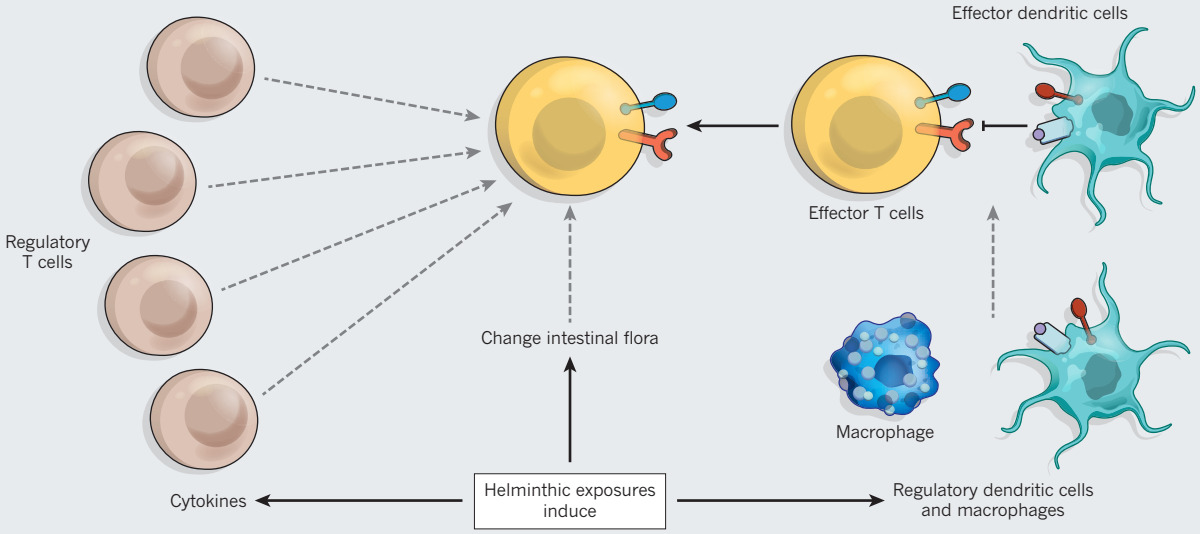
This question was plaguing me as I sat in a plane on the runway of Chicago's O'Hare airport for five hours one day during the mid-1990s. I was on my way to a grant-review session for the Crohn's and Colitis Foundation of America when lightning struck the control tower, forcing us to wait until the airport could get up and running again.

NATURE.COM
Treating multiple sclerosis using helminths:
http://doi.org/jnq

I was writing a review article at the time, on inflammatory bowel disease, and editing a book about parasites. That day, I was focusing on a chapter about how the 'evil' properties of intestinal parasites are often overblown. Considering the vast number of people who have carried them throughout history, the occurrence of associated disease is surprisingly infrequent. I was reminded of a classic teaching in parasitology, that a 'good' parasite imparts some advantage to its host — because if the host dies, so does the worm. Clearly, after thousands of years of co-evolution, the human immune system ▶

PATH OF A PARASITE

Infection with helminths prevents effector T cells from triggering autoimmune reactions through three mechanisms: increasing the activity of regulatory T cells and stimulating cytokine release that dampens effector T cells (left); turning on macrophages and regulatory dendritic cells that prevent effector dendritic cells from activating T cells (right); and changing intestinal flora to boost 'probiotic' bacteria.



has evolved to handle the presence of most parasitic worms, which have, in turn, developed adaptations that enable them to live for years in a human host.

Was it possible that improved hygiene, by ridding our bodies of parasitic worms and beneficial bacteria alike, made way for the newer problem of immune-mediated diseases? And could reintroducing parasitic worms protect people against those diseases?

That brainstorm in the middle of a lightning storm has turned into an active area of research. Several ongoing clinical trials, in which patients with inflammatory bowel disease or multiple sclerosis are colonized with an intestinal worm, have produced early evidence that the treatment may be safe and effective.

This counterintuitive hypothesis has captured the imagination of the popular press, and drawn the opprobrium of sceptics. The World Health Organization estimates[1] that nearly 50 million children under the age of five were treated for parasitic worms in 2006. Some of these parasites can damage the liver, bladder or eyes. How could such an infection actually improve health?

TOO CLEAN

Helminths, being parasitic, evolved independently of the 'worms' people often think of, such as earthworms. Some take up residence in the gut after the host swallows their eggs in contaminated water or food. Even gardening in contaminated soil or playing in the mud can cause an infection. Others, such as hookworm, burrow into the body through the skin and ride the blood to the lungs. Humans then cough up and swallow the larvae, which grow into adult worms in the gastrointestinal tract. Other helminths have even more complex life cycles.

Today, most helminths are found in developing countries in which poor sanitation contaminates water and soil. In Europe and the United States such infections are rare, but as recently as the 1930s and 1940s, up to 70% of children in some rural parts of the southern United States carried helminths[2].

At the time of my insight on the O'Hare tarmac, I had been researching intestinal parasites for many years. Different species of worm cause a variety of effects. Some, such as *Schistosoma*, can impair the liver or bladder. Biliary flukes and some species of schistosome can predispose people to biliary and bladder cancer, respectively. Heavy acute infections with some helminths can cause diarrhoea and nausea. Hookworm can cause iron-deficiency anaemia in heavily infected, susceptible hosts.

> ***"The first patient eagerly consumed the 2,500 nearly microscopic eggs."***

Despite the potential dangers of some helminths, when I proposed the connection between the decrease in parasitic infections and the rise of autoimmunity, I had some historical facts on my side. In the United States and Europe, Crohn's disease first emerged in affluent populations living in hygienic conditions in the more northerly latitudes, where colder temperatures are less hospitable to soil-borne helminths[3]. One of the last US groups to present with Crohn's disease was African Americans[4], who are, on average, poorer than their white counterparts. Similarly, in Europe, autoimmune diseases are more common in the richer Western Europe than in Eastern Europe.

Today, Native American reservations, which have relatively high rates of infection with parasitic worms, also have lower rates of inflammatory bowel disease. Latinos born and raised in South America rarely develop this gut disorder. If their children are born in the United States, where conditions are often more sanitary, they have a much higher risk of the disease.

TESTING A THEORY

When I returned to my laboratory (then at the University of Iowa in Iowa City), I told my colleagues about my theory. Some of them were intrigued and wanted to start experiments. Others thought I was joking.

We had access to parasitic worms — already a focus of our research — and to mouse models of inflammatory bowel disease. Sure enough, when we gave the mice enteric worms such as *Heligmosomoides bakeri* or *Trichuris muris* by feeding tube[5], or schistosome eggs by injection[6], the animals were protected from autoimmune disease.

To test the therapy in humans, we selected *Trichuris suis*, a whipworm that typically infects pigs but can survive for a few months in people. Evidence suggested that this was a safe choice — if swallowed, the worm remains in the gut and does not pass into the bloodstream, and pig farmers are commonly exposed to it without

medical reports of associated illness.

We began with a dose of 2,500 eggs — one investigator in an earlier study had given themselves a similar dose to prove that this organism could colonize the human intestine, and reported no clinical symptoms[7]. We infected pigs with *T. suis* eggs, then isolated adult worms from the infected animals and cultured them *in vitro*. The worms survived long enough to produce eggs that could be harvested and cleaned for clinical use.

Our institutional review committee gave us permission to try a dose in one patient. It was not hard to find a volunteer; many patients with inflammatory disease do not do well on conventional therapy and readily seek alternative approaches. The first patient in the study had untreatable Crohn's disease, and he eagerly consumed the 2,500 nearly microscopic eggs, which we gave to him in a popular sports drink. We held our breaths.

After six weeks — the time it takes for *T. suis* eggs to mature into adult worms — he reported no adverse events and showed improvement in disease symptoms that lasted for several months. In another trial, three more patients with Crohn's and another three with ulcerative colitis all reported substantial improvements (or complete remission), with no side effects.

Eventually, we administered live eggs every two weeks for 24 weeks to 29 patients with Crohn's disease. By week 24, nearly 80% of them reported a decrease in symptoms, and 72% were in remission — more than one would expect from a placebo effect. None reported side effects[8]. In another trial of 54 patients with ulcerative colitis, about half of whom were given placebo, 43% of helminth-treated patients improved after 12 weeks, compared with only 17% of those given a placebo[9].

Several pharmaceutical companies have since taken on the task of developing *T. suis* eggs as a drug. Both the US Food and Drug Administration and the European Medicines Agency have formally approved the manufacturing process and allowed further testing.

At present, a multi-centre trial in Europe conducted by drug firm Dr Falk Pharma, based in Freiburg, Germany, is enrolling nearly 300 patients with Crohn's disease; an interim analysis of the data suggests the treatment is safe. Coronado Biosciences, a firm based in Burlington, Massachusetts, and for which I am a consultant, is running a similar multi-centre, double-blind trial for Crohn's disease. There are trials under way in multiple sclerosis and autism, and others set to begin in ulcerative colitis, psoriasis, type 1 diabetes and other immune-mediated diseases.

Some investigators worry that helminths could weaken patients' immune systems and leave them more vulnerable to some types of infectious disease, even under careful medical supervision. But as long as society maintains its current modern hygienic standards, I consider this risk to be negligible. Given the lack of side effects from helminth therapy, morbidity from immune-mediated diseases and the toxicities of modern therapies for them almost certainly exceed the risk from helminthic exposure.

HOW IT WORKS

Worms seem to have three major effects on the immune system (see 'Path of a parasite'). First, they seem to cause changes that activate regulatory T cells such as T_{reg}. These cells dampen immune responses and curb autoimmunity — by, for example, ramping up the production of regulatory molecules such as interleukin-10 and transforming growth factor-β.

Second, helminths seem to act on other cells — regulatory dendritic cells and macrophages. These prevent the switching on of dangerous effector T cells, which normally leads to inflammation and disease.

Both of these effects seem to protect from autoimmunity in a redundant fashion. My colleagues and I have found that when we block regulatory T cells or regulatory dendritic cells in helminth-infected mice, the animals are still protected from developing colitis[10] — either type of cell is sufficient in its own right to protect the mice. This redundancy may be one of the reasons why helminths are so effective in controlling these immune-mediated diseases.

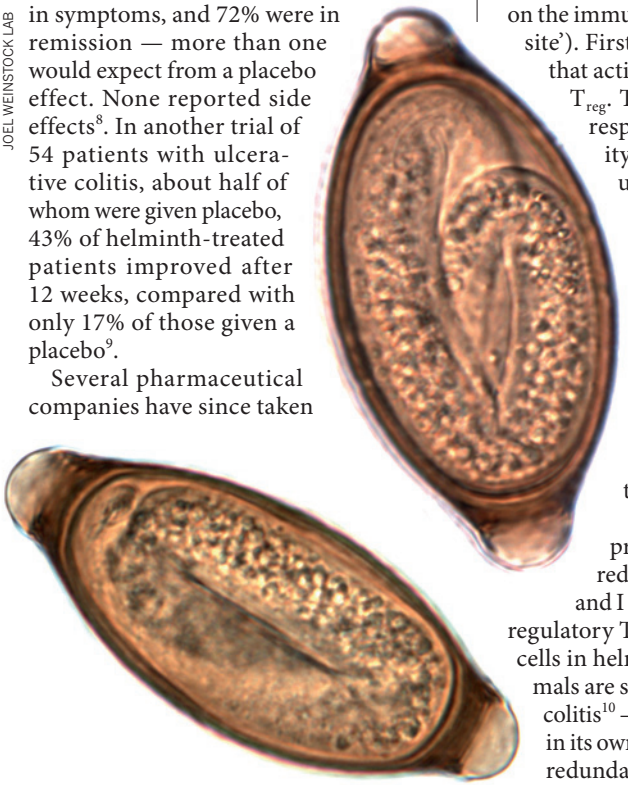
Third, worms seem to alter the bacterial composition of intestinal flora. Research in mice suggests that helminths promote the growth of gut microorganisms typically considered to be 'probiotic', which help to maintain intestinal health.

The more we learn about the changes that helminths induce, the more we will understand about how autoimmunity develops and be able to devise more therapies — consisting of either helminths or agents that mimic their actions in the gut.

"Worms seem to have three major effects on the immune system."

For me, the project has generated the gamut of emotions for nearly 20 years now. The scientific and medical community initially received the hypothesis with a mixture of fascination and vocal scepticism. Thankfully, this research eventually obtained funding from the US National Institutes of Health and support from organizations such as the Crohn's and Colitis Foundation of America. Most of my colleagues took a neutral stance, waiting for more data. Today, studying the effects of alterations to intestinal flora and fauna on health and disease is one of the hottest areas in medical research, and investigations of the impact of helminths are increasing.

The public-hygiene measures and vaccine programmes to eliminate enteric and other types of infections have vastly improved quality of life during the past 100 years, with many more lives saved than taken. The goal now is to reintroduce organisms into people in a controlled and predictable way, to prevent immune-mediated disease without increasing the risk of serious infection. ■



JOEL WEINSTOCK LAB

Several pharmaceutical firms are developing eggs of the pig parasite *Trichuris suis* as a drug.

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Competing financial interests declared; see tinyurl.com/blhntgo for details.