



Q&A Joel Weinstock

Worm charmer

Helminths are worms that can live in the human intestine. Joel Weinstock, a gastroenterologist at Tufts Medical Center in Boston, Massachusetts, studies how they affect inflammation and the body's immune response. He spoke to Nature about how helminths might lead to treatments for inflammatory bowel disease (IBD).

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What do intestinal parasites have to do with IBD?

Immune-mediated diseases such as ulcerative colitis, Crohn's disease, type 1 diabetes and some allergies were very unusual problems before the twentieth century. It could be that an infection has made these diseases more common, but nobody has found a link with any particular infectious agent. The rise must be driven by environmental change.

Until the early nineteenth century, most people were farmers. Their floors weren't terribly clean, they didn't have refrigeration and they didn't bathe very often. Humans evolved over thousands of years in that environment. But now we live in clean houses where food is refrigerated and we're using antibiotics. It occurred to me that this change may have made us more susceptible to immune-mediated diseases. Maybe there were things that were protecting us. Scientists have known since the 1970s that helminths are powerful modulators of hosts' immunity, so maybe the loss of these worms changed our immune responses. This is the IBD hygiene hypothesis: the loss of worms from our bodies altered our intestinal bacteria, and is one of the factors that has made IBD common.

What evidence is there to support this idea?

In 1999, I did some mouse studies with a few varieties of worm — *Schistosoma mansoni*, *Trichuris muris* and *Heligmosomoides*

polygyrus — that showed that they might be able to prevent ulcerative colitis or reduce inflammation. And many groups have shown that worms can block other immune-mediated diseases in mouse models. There's also epidemiological data from developing countries such as India that, although not definitive, suggest IBD and allergies are higher among children and adults who have had treatment for worms. And there is some discussion that changes in bacterial composition of the gut could be a risk factor.

How would a gut-flora imbalance lead to IBD?

The worms change the immune response to gut bacteria. In the gut, you have tons of bacteria. Normally, your immune system is reacting just enough to keep the organisms where they belong, on the surface lining of the intestine; it's not trying to sterilize. What we think happens in people with IBD is that the immune system gets confused. It starts seeing the intestinal flora and other things in our gut as dangerous and mounts a damaging response — far beyond what's necessary to keep you safe. The worms turn off these destructive pathways, such as those that create type 1 helper T cells.

How does an absence of worms affect the immune response?

Worms can live inside you for a couple of years; to do that they have to avoid the attention of your immune system. So they sense how you react to them, and make molecules

that modulate your immune responses so you don't kill them. This modulation doesn't do us any harm. In fact, our immune systems have evolved in such a way that some of us may need the worms — they block the SYK signalling pathway, which is involved in immune receptor signalling, and prevent the T-cell activation that leads to inflammation. In the absence of these worms, you become more susceptible. This has been shown in mouse models, and some studies suggest the same is true in people, but it's not completely accepted yet. We're currently identifying the molecules that mediate these pathways.

Can knowing the mechanisms involved lead to treatments?

We've already identified two crucial immune pathways that involve dendritic cells and regulatory T cells that can prevent IBD, and we know that worms make molecules that act on these pathways. So one option is to develop medicines based on molecules that modulate these regulatory pathways. Another idea is to either find or bioengineer worms that live inside you safely, stay stable over time and act predictably — you swallow a dose of worm eggs and forget about them for a year.

We did a double-blind study using pig whipworms (*Trichuris suis*) in people with ulcerative colitis that showed efficacy. A pharmaceutical company picked it up, but their study wasn't great: over 55% of people receiving a placebo went into clinical remission, which suggests that patient selection was not very good. The study needs to be done again in a different way, but right now there are no ongoing clinical trials that use live worms. I'm convinced helminth therapy does something, but the definitive studies and therapeutic agents that we know will help people are not yet there; we don't treat people with worms.

What about the people who are treating themselves?

If you're trying a therapy that hasn't been absolutely proved to work, you're taking a risk. You can get hold of worms that you can use, but the problem with buying things over the Internet is that you never know what you're getting. Is it the real thing? Is it contaminated? It's expensive too, because it's not covered by insurance in the United States.

What I tell people who want to experiment is that they should always have a doctor following them to ensure that they're not doing themselves harm by taking something with negative effects or by letting their condition get worse. They mustn't risk permanent damage just to try to avoid IBD medicines that can often be given with reasonable safety. People can feel desperate, but even in those cases I caution against experimenting on themselves. It's a risky thing. ■

INTERVIEW BY NEIL SAVAGE

This interview has been edited for length and clarity.