

Can Worms Tame the Immune System?

Researchers are investigating the use of parasites as remedies for inflammatory bowel disease and other disorders of hyperimmunity

In a stunt reminiscent of the TV reality show *Fear Factor*, dozens of unpaid volunteers have recently been gulping Gatorade laced with 2500 live eggs from parasitic worms. The host, so to speak, of this experiment was gastroenterologist Joel Weinstock of the University of Iowa in Iowa City. The hoped-for reward for the participants was remission of the disruptive and painful symptoms of inflammatory bowel disease (IBD). Weinstock is among a small but growing group of researchers who believe that parasitic worms, or substances derived from them, could provide effective treatments for not only IBD but also a range of autoimmune disorders.

The idea may sound crazy, but it is buttressed by studies showing that treating mice with eggs, larvae, or extracts of helminths—parasitic worms such as flukes, flatworms, tapeworms, and pinworms—can dampen, and perhaps prevent, allergic reactions, reduce the severity of a multiple sclerosis (MS)-like disease, and block the development of type I diabetes (see sidebar). Recent data indicate that helminths may protect against disease by invigorating so-called regulatory T cells, which function as the immune system's police officers and keep it from running amok. Deficits in or problems with these cells could contribute to many types of immune disorders. "This is the first inkling there is a common thread between diabetes, asthma, and other immune disorders," says Richard Maizels, an immunologist at the University of Edinburgh, U.K. "We suddenly see a huge potential for establishing just how these immune pathologies are regulated."

Worm therapy is still experimental. Weinstock's IBD trials, which use pig worms that seem to be benign in humans, are the only real human tests of worm therapy thus far; it has yet to be tested in a large double-blind trial. "By no means is this [treatment] ready for prime time," says gastroenterologist Stephen Hanauer of the University of Chicago. Most researchers will not believe the early

laboratory and clinical findings until they are reproduced, better explained, or possibly extended to other disorders. But if the data hold up, they could point the way to new medicine. The hope, says Maizels, is "to work out how helminths are doing it and reproduce that with a nonliving intervention." Adds Weinstock: "We're opening up the possibility of whole new classes of drugs."



Man and his worm. Joel Weinstock holds a dose of eggs from *Trichuris suis* (inset), which he is using to treat inflammatory bowel disease.

Microbe medicine

Weinstock, Maizels, and others were inspired by a decades-old theory known as the hygiene hypothesis: For millennia, the theory goes, microbes have trained the immune system—and so too much cleanliness may cause immune system disease.

The first research team to suggest that helminths might confer some benefits, along with their well-recognized hazards, was that of allergy researcher Neil Lynch of Central University of Venezuela in Caracas. In the 1980s, Lynch and his colleagues found that children infected with helminths had fewer allergic disorders than uninfected children. In 1993, Lynch's team reported that giving antihelminth drugs to the infected children greatly raised their sensitivity to environmental allergens in skin and blood tests.

By the mid-1990s, Weinstock began to wonder whether helminths might also protect against IBD, a disorder seen almost exclusively in wealthy, developed societies in which virtually no one had worms. Parasitic worms were known to make peace with their

hosts by damping down the hosts' immune responses. "It occurred to me," Weinstock says, "maybe this is protective." In particular, helminths were known to stimulate anti-inflammatory T helper 2 (Th2) cells, which were thought to counterbalance the overwrought inflammatory Th1 cells in IBD and autoimmune disorders.

The T helper cell theory soon began to fall apart. For one, it could not explain data suggesting that helminths could also protect against allergy and asthma, which are characterized by too much Th2 activity. But emerging data—including mouse data from Weinstock's lab—began to support an alternative mechanism: Helminths seemed to stimulate regulatory T cells, an increasingly studied class of immune cells that work to dampen and control immune responses, including both the Th1 and Th2 variety.

Then in 2000, immunoparasitologist Maria Yazdanbakhsh of Leiden University Medical Center in the Netherlands and her colleagues reported that schoolchildren in Gabon, Africa, who were infected with the intestinal helminth *Schistosoma haematobium* were much less likely to be allergic to house dust mites—a major risk factor for asthma in Africa—than children who were free of worms. The same study showed that concentrations of the cytokine IL-10—a product of regulatory T cells—were significantly higher in infected children and were negatively associated with reactivity to dust mites.

In the same year, parasitologist Achim Hoerauf, now at Bonn University in Germany, and his colleagues implicated regulatory T cells in the immune response to the roundworm *Onchocerca volvulus*, which can cause river blindness. Infected Africans from the Republic of Guinea, Hoerauf's team found, showed high levels of IL-10 and another regulatory cytokine, transforming growth factor β , presumably as a way to tame the inflammatory reaction to the worms in the skin. The team went on to clone the cells secreting these cytokines from peripheral white blood cells in infected individuals and identified them as regulatory T cells.

Unpublished mouse studies, including some by Weinstock, also now support the idea that helminths buttress regulatory immunity. Some of the work shows higher concentrations of regulatory cytokines such as IL-10 and more regulatory T cells in helminth-infected mice protected against disease. "The old concept was that the two sides—Th1 and Th2—were antagonistic," says John Fleming, an MS researcher at the

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University of Wisconsin, Madison. "Now we think that both sides are probably overactive because of a lack of regulation."

Regulatory T cells may not be the whole story, however. Data from Yazdanbakhsh's team published in March, among other studies, suggest that helminth infection also alters the innate immune system, the array of molecules in the body designed to recognize antigens.

Diet of worms

As the regulatory T cell theory emerged, so did stronger data indicating that helminths were protective in IBD. Last year, Weinstock published results showing that eggs from the fluke *Schistosoma mansoni* protected mice from developing a severe, chemically induced inflammation of the colon. In a separate study published last September, the group reported that all seven IBD patients who were initially treated with eggs from porcine whipworm, *Trichuris suis*, improved substantially, and six of them went into remission. There were no reported side effects, presumably because the pig worm does not fully develop in humans.

In May, at Digestive Disease Week in New Orleans, Louisiana, Weinstock reported that the treatment worked in two larger trials. For patients with ulcerative colitis, in which inflammation of the large intestine produces persistent diarrhea, biweekly worm-egg treatments for 3 months resulted in major improvement for 13, or 43%, of 30 patients. By contrast, a placebo drink helped only four, or 17%, of another 24 patients. Reversing the placebo and treatment groups for another 12 weeks resulted in big gains for 60% of the treatment group but only 13% of the controls. In the test of the therapy in patients with Crohn's disease, a painful disorder that typically affects the small intestine, 23 of 29 patients showed substantial improvement, with 21 achieving remission.

"These preliminary data look very promising," says Gary Lichtenstein, an IBD researcher at the University of Pennsylvania in Philadelphia, "and there is a large amount of interest [in the therapy] given the lack of toxicity." However, Lichtenstein warns that the Crohn's disease trial lacked a placebo group and the colitis results fell short of remission, the usual endpoint for trials. Adds Hanauer of the University of Chicago, "No one has seen good double-blind controlled trials" of the therapy. In part to address such concerns, Weinstock is now working with Dr. Falk Pharma, a pharmaceutical firm based in Freiburg, Germany, to develop a worm-egg capsule for use in a several-thousand-patient trial in Europe that could begin as early as this fall. "It's moving to clinical utility very quickly," says Weinstock.

—INGRID WICKELGREN

Wielding Worms at Asthma And Autoimmunity

Despite an unappealing image, worm therapy is drawing the enthusiastic interest of researchers and clinicians in several fields. Promising targets include—in addition to bowel disorders—asthma, allergy, and autoimmune diseases such as diabetes and multiple sclerosis (MS).

• **Allergy.** In March, Maria Yazdanbakhsh of Leiden University Medical Center in the Netherlands and her colleagues published results from a randomized, controlled intervention study in schoolchildren in Gabon, Africa. Among 152 helminth-infected children treated with medications to kill their worms, 29, or 19%, developed allergic sensitivity to dust mites after 30 months of treatment and follow-up. By contrast, only 20 of 165 children, 12%, given a placebo developed dust-mite sensitivity by the end of the study, a "highly significant" difference, Yazdanbakhsh says.

• **Asthma.** Pulmonary immunologist Joel Kline of the University of Iowa and his colleagues have shown in unpublished studies that helminth infections protect against allergies and signs of asthma in mice. Kline reported at the American Thoracic Society meeting in May that the airways of worm-treated mice that were sensitized and exposed to an allergen contained many fewer asthma-associated white blood cells called eosinophils, and were less prone to spasms, than those of untreated mice. Richard Maizels and his team at the University of Edinburgh, U.K., have similarly shown that mice infected with a gut helminth are protected against allergic reactions in the airways to dust mites or egg-white protein.

• **Diabetes and MS.** Anne Cooke's team at the University of Cambridge, U.K., reported last year that extracts of *Schistosoma mansoni* eggs could completely prevent the onset of type I diabetes in diabetes-prone mice if treatment began at 4 weeks of age. And neuroimmunologist Zsuzsa Fabry and her team at the University of Wisconsin, Madison, along with the University of Iowa's Joel Weinstock, found that either of two species of worm eggs greatly improved symptoms such as hindlimb weakness and paralysis in mice afflicted with an MS-like disorder called experimental autoimmune encephalomyelitis. The egg treatments also minimized the number of autoreactive T cells that infiltrated the mouse central nervous system to attack nerves there, the researchers reported last year.

Fabry's Wisconsin colleague John Fleming hopes to treat 10 to 20 MS patients with the same pig whipworm eggs used in Weinstock's studies, given orally every 2 to 3 weeks for several months. He proposes following them with monthly MRI brain scans to see if the treatment slows down the development of new brain lesions. "Aesthetically, it's a lot to swallow," Fleming admits, but he adds: "We need better treatments for MS, so I want to look in different places."

—I.W.



Worms and dust. Allergy tests on children in Gabon (close-up in top image) found that treatment for helminth infections raised the incidence of allergic reactions to dust mites.