Is Exposure to Helminths Needed for Immunity?

BY NANCY WALSH
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The epidemic of immune diseases that swept through the developed world during the 20th century may have resulted from a disruption in the delicate balance achieved throughout evolution between humans and certain parasitic fellow travelers, according to Dr. Joel V. Weinstock.

Diseases such as inflammatory bowel disease (IBD) were rare before the 1920s, when public health efforts began making significant strides in cleaning up the water supply, modernizing sewage treatment, and improving farming practices. While these efforts clearly had major benefits in curtailing or eliminating exposure to many disease-causing pathogens, they also had the unintended consequence of removing exposure to beneficial or even necessary organisms.

"People today live very differently than they did throughout history. People used to live close to the soil, without indoor plumbing, often with direct exposure to animals," said Dr. Weinstock, professor of medicine, Tufts Medical Center and Tufts University Sackler School of Graduate Biomedical Sciences, Boston.

The result was near universal colonization with helminths, which are complex wormlike animals that inhabit the gastrointestinal tract of mammals. Like the myriad bacteria also found in the gut performing important tasks such as producing vitamins and aiding in digestion, some helminths can cause disease in the host but many are relatively harmless and, in fact, are important regulators of our immune systems.

"We have known for many years that helminths exert a powerful effect on immunity in the host, primarily by inducing the regulatory arm of the immune system, which is important in reigning in the effector 'fight and kill' arm of the immune system," he said. The regulatory arm hones and shapes the immune response to bacteria, viruses, and parasites, quelling the effects of the effector arm so as to prevent needless tissue damage.

At least one rheumatologist was skeptical. "This is an interesting theory—but just that. We need more documentation," said Dr. Roy D. Altman, professor of medicine, rheumatology, and immunology at the University of California, Los Angeles, in an interview.

"In addition, longevity increases with the elimination of parasites. It may be that people are living longer and this allows them to get immune diseases like rheumatoid arthritis."

When other researchers were investigating possible environmental causes for the increase in these diseases, such as exposure to food dyes or from vaccinations, Dr. Weinstock took a different approach, looking for something in the environment that had been protective and had been lost. "It occurred to us that the deworming of the population—a major public health project early in the 20th century—took place at the same time as the incidence of immunologic diseases really took off," he said.

Moreover, diseases such as asthma, IBD, rheumatoid arthritis, and multiple sclerosis remain uncommon in less-developed parts of the world where helminthic colonization is still widespread.

Because Dr. Weinstock is a gastroenterologist with a special interest in immunology, his subsequent investigations in animals and humans have focused on IBD.

Initial animal experiments determined that helminth exposure could both prevent and reverse induced colitis in mice by inhibiting inflammatory cytokines such as tumor necrosis factor–α and interleukin (IL)-12 or by promoting the production of regulatory cytokines such as IL-10 and transforming growth factor-β (Int. J. Parasitol. 2007;37:457-64).

In a pilot study of 29 adult patients with longstanding, refractory Crohn's disease, patients were given a drink containing 2,500 specially prepared ova of *Trichuris suis*, the pig whipworm, every 3 weeks for 24 weeks. Ingestion of this helminth, which is similar to the human whipworm, causes a short-term colonization in the human gastrointestinal tract.

By the 12th week, 22 patients (76%) had responded to the treatment, with a decrease in the Crohn's disease activity index (CDAI) of more than 100 points or below 150, and 19 patients (66%) were in remission, with a CDAI below 150.

At the 24th week, 23 patients (79%) were responders and 21 (72%) were in remission (Gut 2005;54:87-90).

In a subsequent double-blind trial that enrolled 54 adult patients with ulcerative colitis, participants received 2,500 *T. suis* ova in a liquid drink or a placebo drink every 2 weeks for 12 weeks.

Favorable responses, with decreases in the ulcerative colitis disease activity index of 4 or more points on an index ranging from 0 to 12, were seen in 13 patients receiving the active treatment (43%) compared with 4 receiving placebo (17%).

Similar findings have been shown in several other autoimmune conditions. Prospective data have shown that children with helminths are less likely to develop allergies, and disease has been arrested in patients with multiple sclerosis following helminth colonization. Researchers in the United Kingdom have been investigating modulation of the immune system in rheumatoid arthritis. They tested an anti-inflammatory phosphorylcholine-containing glycoprotein secreted by the nematode *Acanthocheilonema viteae* in collagen-induced arthritic mice, finding a reduction in the severity of arthritis and suppression of collagen-specific T-1 cytokine production (Ann. Rheum. Dis. 2008;67:518-23).

COURTESY DR. JOEL V. WEINSTOCK

Helminths, like this whipworm, could be the next big thing in multiple sclerosis and other autoimmune diseases.

Dr. Weinstock believes that helminths and human hosts evolved to the benefit of both over millennia. Petrified human stool many thousands of years old has been found to contain helminth eggs, and autopsies of mummies have found traces of helminths. The frozen iceman Ötzi, found in the northern Italian Alps in 1991 where he had lain buried in a glacier since 3300 B.C., had *T. trichiura* in his gut.

"We are teeming with life, and we really are part of the environment. When we try to separate ourselves from the environment and exposures to these organisms, we leave ourselves predisposed to disease," he said.

Dr. Weinstock is not advocating a return to 19th-century hygiene. Rather, he and others are working to characterize more fully the interaction of helminths with the immune system and to identify factors responsible for the beneficial exposures so they can be reintroduced at an appropriate time early in life, when the immune system is developing.

Clinical studies in IBD, asthma, rhinoconjunctivitis, and multiple sclerosis are underway and more are planned, and one helminth-derived medication, ASP1002, is under review by the Food and Drug Administration and the European drug monitoring authorities.

Dr. Francois-Xavier Frapaise, CEO of Asphelia Pharmaceuticals Inc., confirmed that his company is about to file an Investigational New Drug application for ASP1002 in Crohn's disease. They also are planning trials in various other conditions including lupus and multiple sclerosis. "RA would also be interesting to investigate," he said.

"There has been a revolution in our thinking," Dr. Weinstock said. "We have learned that we are not insulated from the world around us." ■

After Methotrexate, Glatiramer Acetate Improves MS Outcomes

MADRID — Glatiramer acetate significantly reduced relapse and disease progression in patients with multiple sclerosis who received the drug after a course of methotrexate, according to the results of a small Italian study.

"In our experience, six multiple sclerosis patients treated with methotrexate followed by glatiramer acetate showed a significant reduction of inflammatory activity parameters during the follow-up," Dr. Yasmin Handouk wrote in a poster that was presented at the annual congress of the European Federation of Neurological Societies.

"This was associated with a lack of disease progression," Dr. Handouk added.

Glatiramer acetate received Food and Drug Administration approval in 2001 for use in reduction of the frequency of relapses in relapsing-remitting multiple sclerosis.

The randomized trial included 12 patients with refractory MS (6 with relapsing-remitting disease and 6 with progressive-relapsing disease).

All of the patients had undergone a course of methotrexate after failing to respond to interferon therapy, wrote Dr. Handouk of the Università Politecnica delle Marche, Ancona, Italy.

After methotrexate, patients had magnetic resonance imaging of the brain. Within 3 months of ending methotrexate, six started maintenance therapy with glatiramer acetate 20 mg/day for a mean of 8 months; the rest received no further treatment.

Follow-up assessments were done at 6-month intervals for 2 years.

At the 2-year follow-up, only one patient in the active group had relapsed. Disability, as measured by the Expanded Disability Status Scale, had significantly improved, with patients dropping an average of 1 point on the scale.

There were no new or enhanced lesions. In the nontreated group, two patients had relapsed. The disability score was not improved from baseline. Two patients showed new gadolinium-enhancing lesions.

"[Dr. Jason Ramtahal] previously proved the usefulness of 6-month glatiramer acetate beginning 2 months before ending methotrexate, although a case of acute promyelocytic leukemia was registered [J. Neuro. 2006;253:1160-4]," Dr. Handouk noted.

"Our patients started glatiramer acetate therapy at least 3 months after methotrexate without serious adverse event."

Dr. Handouk made no financial declarations with regard to the study.

—Michele G. Sullivan