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News Feature: The worm has turned

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For decades, scientists have struggled to stem the spiking rates of asthma. Could the key to a cure be a belly full of writhing worms? Charlotte Schubert investigates.

The Ogooué river cuts through the center of Gabon, snaking a path through the tropical forest near the equator. Lambaréné, nestled along the banks of the Ogooué, is a fairly typical town in this region of West Africa. Most of its several thousand residents make a living by fishing or farming on small plots.

Children in Lambaréné, Gabon, play in a pool where they probably get infected with schistosomes. The village has negligible rates of asthma, even as tested by responses to dust-mite allergens (inset).

Courtesy: Yvonne KruizeCourtesy: Anita van den Biggelaar

Like many other villages in rural Africa, Lambaréné is filled with children infected with intestinal parasites. And like those villages, it too has negligible rates of asthma. Lambaréné is also home to the Albert Schweitzer Hospital, established by the famed doctor himself in 1913, and its medical research unit. For those reasons, the village has become the perfect crucible to test a long-standing theory—that parasitic worms, despite their ability to maim and kill, shield their victims from asthma and other allergies.

Since 1999, Maria Yazdanbakhsh, a biologist at the University of Leiden in the Netherlands, has tested the theory in a group of Lambaréné's schoolchildren, about 70 percent of whom were infected with intestinal parasites.

Yazdanbakhsh treated half of the students with antihelminth drugs over a period of 30 months and followed their response to dust mite allergen, a common trigger for asthma. In March 2004, she and her colleagues reported that worm-free students became twice as likely to have an allergic reaction[1].

"What seems to be happening today is that children have hyperactive immune systems."

Joel Weinstock
University of Iowa

"[The data] have provoked an enormous amount of interest," says Patrick Holt, a professor at the University of Western Australia in Perth, and an asthma expert.

Yazdanbakhsh's data add to an emerging picture that the devious parasites may protect not only against asthma but from other diseases in which the immune system goes into overdrive. They also support a controversial hypothesis that tries to explain the sharp spike in allergic diseases: the 'hygiene hypothesis.'

How clean is too clean?

Scientists first proposed the hygiene hypothesis decades ago to explain epidemiological data suggesting that cleaner living conditions have gone hand in hand with an increase in allergic disorders such as asthma. The idea is that by wiping out the microbes that keep the immune system in balance, people have become vulnerable to diseases—such as asthma—where the immune system has gone haywire.

When those susceptible are exposed to allergens such as pollen and dust mites, the airways contract and inflammatory cells and antibodies flood the lungs—triggering a full-blown asthma attack. Since the 1960s, the incidence of asthma in westernized countries has mushroomed: asthma now afflicts about 22% of 13–14-year-olds in the US and about 30% in the UK, Australia and New Zealand[2].

"What seems to be happening today is that children have hyperactive immune systems," says Joel Weinstock, an immunologist at the University of Iowa.

More recently, researchers have also begun to recognize an increase in inflammatory bowel disease and in autoimmune disorders such as type 1 diabetes and multiple sclerosis. The rise in these diseases also roughly parallels the emergence of higher standards of hygiene[3], and some researchers say the rising incidence of those disorders might also be explained by the hygiene hypothesis.

No one has been able to pinpoint which changes in lifestyle underlie the increase in immune-related diseases. Explanations range from a drop in viral infections such as hepatitis A to changes in intestinal microbe ecology because of antibiotic use and diet. The more obvious risk factors for asthma, such as air pollution, do not fully explain the increase[4]. Some researchers say that an environmental factor—perhaps even chemicals or allergens associated with western indoor homes—might be to blame.

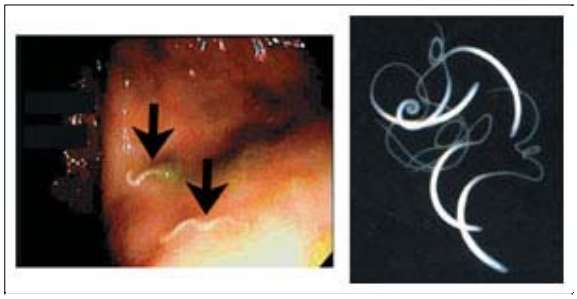
The real answer may lie in a combination of factors, but the 'helminth hypothesis' is increasingly gaining favor. Like many other aspects of hygiene, the decline of helminth infection roughly coincides with the increase in immune disorders and there is increasing evidence that children with helminth infections have fewer allergic disorders. Could worms protect people against asthma?

Intimate immunity

Dozens of worm species infect humans: whipworms, pinworms, roundworms, hookworms—and together they kill about 44 million people a year[5]. The whipworm *Trichuris trichiura*, for instance, embeds itself into the large intestine and causes dysentery, anemia and mental retardation. A single person can be infected with a million of these finger-length parasites.

But many people infected with *T. trichiura* and other helminths don't show any symptoms. "A single worm can live in our system for 20 years," notes Weinstock. "It is like the worm is an organ transplant."

Like a transplanted organ, the worm becomes accustomed to its host, adapting to the assaults of the immune system. About one-third of the human population is infected with helminths, and the numbers might have been bigger through evolution's eons of grime and poor hygiene. Some researchers suggest that we, too, have grown accustomed to the helminths.



An adult *Trichuris suis* worm (right) in the colon of a patient (left) can cause dysentery and mental retardation. It may also protect against asthma.

Courtesy: Joel Weinstock

Different worms wreak havoc in different ways, but recent studies are converging on a common theme: the parasites seem to induce a 'regulatory' response that dampens the immune system. In the case of asthma, this response keeps at bay the airway inflammation, wheezing and other symptoms.

In unpublished experiments, Rick Maizels at Edinburgh University has shown that an intestinal roundworm protects mice from allergic responses by inducing regulatory T cells. Among immunologists, these cells are all the rage for their ability to dampen the immune response. No one knows exactly how regulatory T cells put on the brakes, but the cells are known to secrete interleukin (IL)-10, a powerful immune modulator.

"In the course of time there will be a mechanistic explanation for it, but right now the most likely is regulatory T cells, that is for sure," says Holt.

Yazdanbakhsh's studies in Lambaréné dovetail with the work on mice. She reported several years ago that IL-10 levels are high in helminth-infected children and levels of IL-10 correlate with the degree of reactivity to dust mites[6].

Padraic Fallon, a helminth researcher at Trinity College in Dublin, has found that schistosome parasites can protect against an allergic response in a mouse model of asthma. But instead of regulatory T cells, Fallon's most recent work[7] suggests that B cells that produce IL-10 mediate this effect.

The case for a regulatory response has also gained momentum in studies on the basic biology of asthma. For instance, Stanford University researcher Dale Umetsu has found that regulatory T cells—generated in response to allergen exposure—produce IL-10 and shield mice from airway hyperreactivity to allergens, a cardinal feature of asthma[8]. Work in humans also suggests that strong regulatory T-cell responses protect against asthma[9].

Any theory invoked to explain the increase in asthma would gain credibility if it could also explain the rise in autoimmune disorders and intestinal bowel disease. Helminth researchers note that their favorite organism fits the bill, as the parasites appear to downregulate the immune response in all of these diseases.

Recent mouse work suggests that helminths can guard against intestinal bowel disease, a multiple sclerosis–like disorder and type 1 diabetes. Regulatory T cells appear to modulate symptoms in all of these diseases.

Convinced by these data, Weinstock has launched a project to feed worms to patients with inflammatory bowel disease[10]. Preliminary data suggest that eating a dose of helminth eggs has a protective effect, but some researchers remain skeptical. Even Yazdanbakhsh, who has dedicated much attention to the helminth hypothesis, says "I would never feed helminths to my children."

Worm food

Among the skeptics, there is considerably more interest in isolating specific molecules that guide the helminths' ability to dampen the immune response.

There is sure to be a retinue of candidates, says Maizels. "Think of the [worms'] ability to infect every human... they must have incredible adaptability," says Maizels. Through eons of coevolution, they have come to know our immune systems in detail, he adds. "You could almost argue that the worms are us."

Many researchers suspect that the molecules might work through dendritic cells, which direct T-cell development. Yazdanbakhsh has isolated a substance produced by schistosomes that can tweak Toll-like receptors on dendritic cells and thereby affect T cells[11]. Fallon is chasing down another protein trigger; blocking the protein's activity in mice causes the helminth infection to run wild and kill the animal.

Others say that commensal bacteria in the gut might share common mechanisms with helminths. Already one bacterial substance, CpG DNA, has been shown to protect against asthma, and CpG-containing vaccines have entered phase 3 clinical trials for asthma.

Whether other factors—such as hepatitis A—invoked for the hygiene hypothesis also induce regulatory T cells could become clear within the next few years. In the meantime, skeptics such as Umetsu note that although parasites were probably largely eradicated in the US by 1980, the incidence of asthma has spiked since then.

Yazdanbakhsh says it is unlikely that the hygiene hypothesis can be explained by any one factor. Not all of the drug-treated children in Lambaréné had positive dust-mite allergen tests, she notes, and among those that did, there were few symptoms of asthma. She says there will be much to be learned from how allergic diseases develop in the large cities in Africa, where additional factors like air pollution come into play.

As a therapy, any worm substance that triggers a regulatory response would run the risk of putting too tight a lid on the immune system. But new treatments are sorely needed: an estimated 180,000 people die from asthma each year.

"I have people calling me saying 'can I please have some of your helminths?'" says Yazdanbakhsh. "People are desperate; I would really like to know what molecule to give them."

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