



## Can Hookworms Help Humans?

Conditions with an immunological basis, such as multiple sclerosis, might be ameliorated by means of the helminth parasites that cause chronic ill-health in the tropics

**Bernard Dixon**



**T**reating multiple sclerosis (MS) patients by infecting them with the hookworm *Necator americanus*, sometimes known as the “American murderer,” may at first sight appear to be an outrageous idea. But if and when David Pritchard and colleagues at the University of Nottingham, U.K., gain regulatory approval, this is exactly what they plan to do. Moreover, their previous studies in Nottingham and in Papua New Guinea, and those by other groups elsewhere, indicate that this heterodox therapy should be not only safe but also effective. It is one of the most intriguing ideas to emerge from work on the “hygiene hypothesis,” according to which the elimination of pathogens and parasites may lead to the loss of health benefits that formerly accompanied those infections.

Hardly mentioned in the early years of microbiology courses, hookworm infection with the helminth nematode parasites *N. americanus* or *Ancylostoma duodenale* is one of the commonest of all chronic infections. With around 740 million cases in tropical and subtropical areas of rural poverty, it eclipses dengue, schistosomiasis and several other diseases in the burden of illness. It was a key factor that delayed economic development in the southern United States during the early 20th century, and gave China the reputation of being the “sick man of Asia” until halfway through the century.

At first sight again, it is difficult to discern any possible benefit to humans in the hookworm’s fiendish life cycle and its attendant pathology. Attached to the wall of the duodenum, adult females extract blood from the capillary bed, causing iron deficiency anaemia if there are too many of them. After being inseminated by males

in the lumen of the duodenum, the females lay eggs which then pass through the gastrointestinal tract and are excreted in the feces.

In unsanitary conditions, and with appropriate temperature and humidity, the eggs hatch into larvae that go through two further stages before becoming infective. These forms use degradative enzymes to penetrate the skin of human feet and hands, causing a rash called “ground itch.” Entering the local microvasculature and soon circulating further afield, they break out in the alveolar spaces of the lungs. The penultimate stage is when the parasites migrate up the trachea to the back of the throat, when the unwitting host swallows them. They thence find their way to the small intestine, where they mature into adults.

The link between this process and the potential treatment of MS is in the immunological changes triggered by the infection. “Our work in Papua New Guinea points to the fact that individuals with high levels of a T-helper 2 response to the worm, characterised by heightened IgE and eosinophilia in the circulation, harbour smaller and less fecund worms,” Pritchard writes in *The Biochemist* (31:28, 2009). “Furthermore, worm expulsion restored some cytokine responses in the host, indicating a degree of parasite-induced immunosuppression.”

“Taken together, one interpretation of these data is that an immunogenic parasite, in close contact with the immune system throughout its life cycle, is partially controlled by the heightened immune reactivity . . . However, the parasite, in order to propagate the species, actively suppresses the immune system to stay ahead.”

Theory aside, several independent observations have suggested that hookworms and other parasites are associated with a lowered inci-



dence of medical conditions whose aetiology is, at least in part, immunological. These include asthma, Crohn's disease and most recently multiple sclerosis (Correale, J. and Farez, M., *Ann. Neurol.* 61:97, 2007). It's possible that, while the hookworm is undoubtedly pathogenic at high densities, it could be deployed therapeutically at low doses to combat autoimmunity and allergy. Pritchard believes there is no conflict between the continued need to use worm-expulsion chemotherapy (and to develop immunisation, as is happening under the Hookworm Vaccine Initiative funded by Bill Gates) and on the other hand to explore the utility and safety of carefully titrated doses against other diseases.

His first aim has been to determine a tolerable and acceptable dose, and in this endeavour he has joined the historic ranks of microbiological self-experimenters, as well as recruiting campus volunteers. Using sticking plaster, the experimenters administered ten, 25, 50 or 100 infective larvae to the subjects' skin. "Once the intense itching had subsided, caused possibly by vasoactive amine release while larvae entered the dermal vasculature, ten and 25 larvae were well tolerated, with 50 larvae proving problematic in some (the author)," Pritchard writes. "[One hundred] larvae were definitely not well tolerated, causing severe gastrointestinal disturbance and vomiting."

The well-tolerated doses led to an infection density the same as that which, in a field study of the effect of hookworms on asthma, was associated with reduced respiratory wheeze in response to environmental allergens. Importantly, the immune system also recognized these doses, with peripheral eosinophilia and antibody responses to antigens secreted by the adult parasite.

More recent studies (J. Feary et al., *Clin. Exp. Allergy* 39:1060, 2009) have shown that infection of allergic rhinitis patients with 10 larvae did not heighten bronchial reactivity, nor potentiate IgE responses to allergens to which they were already sensitized. Immunologically, the patients responded as in the earlier tests. There were also early signs of the onset of immune suppression, although circulating levels of natural regulatory T-cells did not rise.

While these are promising findings, there are grounds for caution in the course of events since the discovery of IgE in the early 1960s and its

subsequent implication in both allergic asthma and helminthic infections. At first, it seemed that helminths, by potentiating allergen-specific IgE responses, contributed to allergy and asthma. A rival notion was that they were protective against these conditions—either by saturating certain receptors in mast cells and basophils (by polyclonal IgE) or by inducing IgG-blocking antibodies.

Several papers in recent years have demonstrated that chronic intestinal helminth infection can protect children in developing countries against atopic reactivity. Others have indicated that transient, delayed, or milder helminthic infections are positively linked with atopic disorders. And a study by Philip Cooper and colleagues in Ecuadorian schoolchildren showed that antihelminthic treatment for over a year was highly effective but did not increase the prevalence of atopy or clinical allergy. Reviewing all of these studies together in *The Lancet* (367: 1556, 2006), Susanne Lau and Paulo Matricardi of the Charite University Medical Centre in Berlin, Germany, concluded that the hygiene hypothesis is an "extremely complex field."

The challenge now facing David Pritchard and his coworkers is to devise safe protocols to reproduce in human patients the positive effects already observed in animal models, using strategies such as boosting with low level "trickle infection" as occurs in the tropics. "The mean worm burden in our study population in Papua New Guinea was 23 adults, with worms likely to be entering and leaving the body throughout life," he says. "This is the scenario that we may need to replicate in patient populations in order to fully ascertain the potential for benefit."

The Nottingham team's robust approach to their work is illustrated by the two methodologies, external and internal, which they have adopted to bring worms back from Papua New Guinea to their laboratory in Britain. Pritchard uses an external approach "with explanations ready for the airport screening personnel as to the contents of my vials of precious liquid." His colleague Alan Brown prefers an internal technique "and carries a healthy population of Papuan hookworms . . . His fecal cultures provide the 'snek bilong bel,' or snakes in your belly, for today's trials."

Each to their own.