



# Can Hookworms Cure Coeliac Disease?

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**Coeliac disease patients infected with hookworms can tolerate gluten-containing foods, revealing the potential for these parasites and their secretions to treat a range of inflammatory diseases.**

People have co-existed with parasites throughout history. To enable their survival, the parasites evolved sophisticated strategies to avoid attack by their human host's immune system.

At the same time, the human immune system needed to develop strategies to deal with large and complex creatures such as parasitic worms, since any vigorous inflammatory response directed against the worm may have detrimental effects on its own tissues. This co-evolution has forced us to “tolerate” worms to a point where exposure to these pathogens, as well as other infectious and commensal microorganisms, is critical for shaping the normal development and function of our immune system.

In the past century, however, urbanisation, improved sanitation and health care measures in the developed world have reduced our exposure to many infectious diseases, including parasitic worms. During this period, incidences of allergic and autoimmune inflammatory disorders have risen dramatically. These disorders occur when the immune system, which evolved to combat infections with viruses, bacteria or parasites, inappropriately responds to harmless stimuli such as environmental factors, food and the body's own tissues.

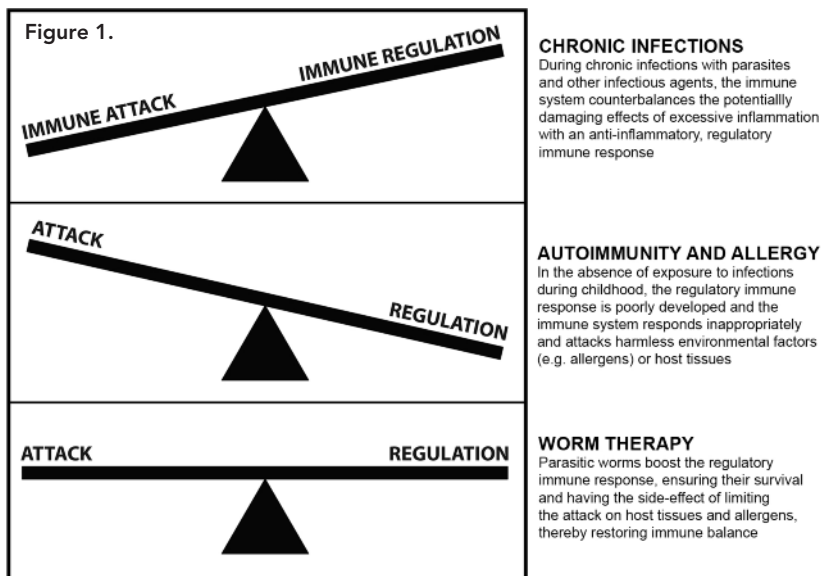
One theory to explain the rise in inflammatory disorders was that by losing contact with “immune-training” microorganisms

during childhood, our immune systems develop improperly, leading to inflammatory diseases such as asthma, inflammatory bowel diseases and autoimmune diseases such as multiple sclerosis and coeliac disease.

This “hygiene hypothesis” or “old friends theory” is supported by a number of epidemiological and observational studies in human populations. For example, studies where worm-infected children from developing countries were treated with drugs to cure their infections showed that allergic skin reactivity increased, while children who retained their worms were allergy-free. These observations were supported by animal studies that revealed the potent ability of worms to suppress inflammation in a variety of experimental inflammatory settings.

## Worm Therapy

These findings have led to the concept that a novel approach for treating autoimmune or allergic disorders would be to reintroduce parasitic worms into humans (Fig. 1). While the idea of deliberately infecting people with parasites may be unpleasant for some people to fathom, these trials would be critical initial proof-of-principal studies that demonstrate how worms may produce factors that could one day be purified and synthesised as novel therapeutic drugs.



Clinical trials of “worm therapy” have predominantly used either the human hookworm (*Necator americanus*) or the pig whipworm (*Trichuris suis ova*; TSO).

Hookworm is a blood-feeding intestinal parasite and is one of the world’s most prevalent and debilitating infections in regions of sub-Saharan Africa, South America and south-east Asia, where infections can involve hundreds of worms that can persist for years. They cause anaemia, malnourishment and impaired development, especially in children. However, clinical trials involving hookworms use a carefully controlled dose of parasite (10–20 larvae that cannot reproduce in the host). Infection of otherwise healthy individuals with an adequate diet have proven safe and well-tolerated, with no lasting side effects.

On the other hand, pig whipworm does not cause patent infections in humans because the larvae cannot reach maturity in the gut. Hence TSO could conceivably be used as a safe and marketable biological therapeutic, but has the disadvantage of needing to be continuously administered every few weeks.

The results of clinical trials using TSO or hookworm to treat a variety of inflammatory diseases have been mixed but encouraging. Promising preliminary results were achieved in small trials with TSO and hookworm in treating inflammatory bowel diseases such as Crohn’s disease or ulcerative colitis, but larger trials of TSO in Crohn’s disease revealed limited efficacy.

Similarly encouraging preliminary results were reported when hookworms were used to treat asthma, and TSO has recently shown promise in people with multiple sclerosis or autism.

### Hookworms for Coeliac Disease?

Our research team has had a long-standing interest in developing the untapped potential for worm-based therapies. In 2010 Prof Alex Loukas from James Cook University and Dr John Croese from Prince Charles Hospital in Brisbane embarked on a clinical trial examining the effect of experimental hookworm infec-

tion on gastrointestinal symptoms in people with coeliac disease.

Coeliac disease is a debilitating autoimmune condition affecting approximately one in every 100 Australians where the immune system attacks the intestinal wall after ingestion of gluten, a major component of foods that contain wheat, barley and rye. While people with coeliac disease can, for the most part, effectively manage their disease by consuming a gluten-free diet, these foods are significantly more expensive and difficult to locate. In addition, there is an ever-present risk of accidental exposure to gluten, particularly when eating out of the home. Hence there is a great need for more effective ways of treating coeliac disease.

The results from the 2010 clinical trial were at first disappointing: hookworm infection was not able to prevent gastrointestinal symptoms in people given a heavy dose of gluten (consistent with a liberal diet). However, further analysis revealed an interesting finding: the people who received hookworm had a significantly reduced proinflammatory immune response to gluten. This led to the hypothesis that while hookworms may not be sufficient for preventing pathology during an intense and abrupt gluten challenge, the potent immunoregulatory capacity of the worms may enable patients to tolerate a gradual reintroduction of smaller amounts of gluten into their diet.

Thus a new trial was designed to test this hypothesis. Between 2012 and 2013, 12 volunteers with diet-managed coeliac disease (at least 6 months on a gluten-free diet) were recruited from the Brisbane metropolitan area and all were infected with 20 hookworm larvae (Fig. 2). The infection was allowed to establish for 12 weeks, and then the subjects were provided with their first gluten challenge, starting with 50 mg of spaghetti (less than one spaghetti straw) each day for 12 weeks. While this dose may not seem like much gluten, previous reports have shown that most people with coeliac disease will predictably react to this level of gluten exposure.

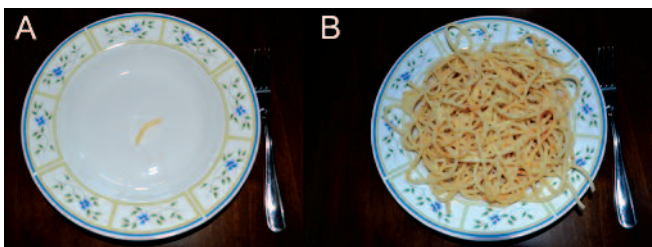
The subjects were then exposed to substantially higher doses of gluten, initially with 1 gram of gluten (14 spaghetti straws) provided twice weekly for 12 weeks, and culminating with a 2-week challenge of 3 grams of gluten every day – equivalent to a medium bowl of pasta (Fig. 3). Based on previous research, each of these gluten-containing meals should induce serious intestinal symptoms in people with coeliac disease, such as diarrhoea, cramps and vomiting. The results from our trial were remarkable and unexpected.

While four subjects withdrew from the trial early (mostly for reasons unrelated to gluten), the remaining eight subjects experienced no ill effects from any of the gluten challenges. Detailed





**Figure 2.** Mature hookworms in the small intestine of a trial participant observed during an endoscopic procedure. The female worm is approximately 10 mm long and the male is approximately 8 mm long. Subjects received 20 worms at the beginning of the trial, and regular monitoring of faecal samples revealed the presence of parasite eggs throughout the duration of the 12-month trial. Each of the subjects elected to keep their worms after the trial ended.



**Figure 3.** (A) As little as 10 mg of gluten – the equivalent of eating as little as a 2.5 cm stick of spaghetti – is sufficient to cause a significant reaction in people with coeliac disease. (B) However, the hookworm-infected subjects involved in the clinical trial were able to tolerate ingestion of the equivalent of a medium bowl of pasta daily.

analysis of the intestinal tissues from each subject by pathologists and immunologists revealed that gluten exposure did not cause any damage to the intestinal lining, and inflammatory responses were lowered compared with pre-trial levels.

In fact, the subjects appeared to have a complete switch in their immune responses, with hookworms seemingly attracting anti-inflammatory immune cells to the intestine. Furthermore, there was no evidence of an autoimmune reaction to gluten, since levels of antibody against host enzymes were not elevated in the blood – a major diagnostic factor for active coeliac disease.

Perhaps most significantly, these subjects felt great throughout the trial eating moderate amounts of gluten, and at the end of the trial elected to keep their worms despite being offered medication to cure their infections. All subjects were instructed to return to their normal gluten-free diet at the end

of the trial, and there is no risk of transmitting the infection to people in the community.

The findings from this small proof-of-principle clinical trial were very encouraging as they provide realistic hope that worms, or some factor that the worms release into the body, could be a potential new therapy for managing coeliac disease. In particular, a hookworm-based therapy could be envisaged as a “pro-biotic” treatment, giving peace of mind to coeliac sufferers that if they deliberately or accidentally eat a small amount of gluten they would not experience adverse effects. This would be an enormous health as well as social benefit for people with coeliac disease.

### Hard to Stomach or a Medical Gold Mine?

Much more work needs to be done to establish the potential for hookworm in managing coeliac disease, most importantly a much larger clinical trial where subjects receive either hookworm or a “mock infection” placebo treatment followed by gluten challenges.

The second issue is that hookworm infection is unlikely to become an acceptable therapy in the mainstream due to its pathogenic nature and the “ick factor” regarding intestinal worms. While the latter point could be debated, especially considering the reasonably widespread use of faecal transplants for other gastrointestinal disorders, the fact that hookworm infection is a devastating health problem in third world countries does raise safety considerations. De-worming drugs are widely used in developing countries, but poor sanitation leads to repeated hookworm infections due to the parasite’s masterful ability to manipulate and evade the human immune response. As such, there are currently no vaccines on the market that can protect us against any species of parasitic worm.

Our research group, and many others around the world, is actively working on a solution to this problem. However, given the potential benefits of worm-based therapies in developed countries such as Australia, there is great interest in studying these parasites to identify the specific molecules that worms produce to suppress the immune system.

Studies have shown that culturing worms in the laboratory stimulates the release of a complex mixture of proteins and chemicals, most of which have not been characterised. Critically, these molecules alone, in the absence of the worm, can be sufficient to limit inflammation in several experimental models of disease.

Hence, the future of worm therapy is likely to involve the manufacture of synthetic versions of these worm proteins in the laboratory in the hope that eventually they could become a pill-based medication to treat a variety of inflammatory diseases, including coeliac disease.

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