

## Helminth Therapy: A Promising Approach to Treating Crohn's disease and Asthma

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Autoimmune diseases are characterised by a disordered immune response directed towards an individual's own cells that can cause both systemic and organ specific damage (Smith and Germolec, 1999). The increasing prevalence of autoimmune diseases has become a worldwide concern for industrialized nations (Elliot & Weinstock, 2009). For instance, Crohn's disease, an autoimmune disease of the gastrointestinal tract, has similarly shown an increase in prevalence rates from being a relatively rare disease in the 1900's to now affecting 1 in 250 people (Elliot & Weinstock, 2012). Asthma is characterized by chronic inflammation of the airway epithelium due to maladaptive immune responses toward allergens (Maizels, 2005). However, asthma is also observed in individuals where allergies to environmental factors are not the initiating cause of the immune response, suggesting that autoimmunity may play a role in the development of asthma (Tedeschi & Asero, 2008). Due to the strong similarities in features and mechanisms between allergic or non-allergic asthma and autoimmunity, asthma is more commonly being recognized through the paradigm of autoimmune disease (Rottem & Shoenfeld, 2003; Tedeschi & Asero, 2008). In the last 20 years, asthma rates have doubled in western countries and one in seven children in Great Britain are currently afflicted with asthma (Cookson & Moffatt, 1997).

One potential explanation for the recent surge of autoimmune diseases in developed countries is the absence of parasitic infections. Humans and parasites have shared a long and intimate relationship that has led parasites to evolve mechanisms that allow them to regulate and alter host immune responses in order to survive within their human hosts (Elliot & Weinstock, 2009). On the other hand, long-standing parasitic infection in humans has acted as a selection pressure, favouring genes that defend the body against parasitic infection (Elliot & Weinstock, 2009). Over time, this coevolutionary relationship between humans and parasites has influenced immune system regulation and functioning (Elliot & Weinstock, 2009). Thus, the lack of parasitic infections in humans due to industrialization and better hygiene practices may be contributing to underdeveloped and disordered immune systems.

Many epidemiological and correlational studies provide support for the link between parasitic infection and autoimmunity. From 1969 to 2004, whipworm (*Trichuris trichiura*) infections in South Korean school children dropped from 75% to 0.02%, while the rates of ulcerative colitis, a form of inflammatory bowel disease, increased six-fold (Elliot & Weinstock, 2012). In regard to asthma, Selassie et al. (2000) measured IgE antibody, parasite loads, and symptoms of asthma in a sample of 153 people from Ethiopia and found that asthma was negatively correlated to the roundworms *Ascaris lumbricoides*, and *Necator americanus* parasite infections. Furthermore, Biggelaar et al. (2000) employed the skin prick test on 520 Gabonese school children to study skin reactivity toward allergens, and found that children infected with the blood parasite *Schistosoma haematobium* had much lower skin reactivity to environmental allergens than children who were not infected. Additionally, Lynch et al. (1993) found that after treating parasite-infected children with antiparasitic medication, skin test reactivity scores

increased by 50%. These findings suggest that parasitic infections may serve a protective function against immune system hypersensitivity, and that removal of parasitic infections can present an environment for autoimmune diseases to develop.

The protective effect of parasite infection from autoimmune disease can be better understood through the hygiene hypothesis. The hygiene hypothesis argues that exposure to various microorganisms and pathogens protects against autoimmune diseases by stimulating and developing the immune system (Bach, 2017). The hygiene hypothesis was originally developed because of the finding that autoimmune diseases are more prevalent in industrialized countries than non-industrialized countries, where parasite infections are common (Bach, 2017). Improved hygiene from industrialization and hygienic practices such as proper sewage systems, hand washing, and food safety regulations impedes our exposure to parasites that would foster immunological development and suppress excessive inflammation from autoimmune responses (Reddy & Fried, 2007). Consequently, this leaves individuals with disordered immune systems susceptible to autoimmune diseases.

The hygiene hypothesis provides an explanation for why the prevalence of autoimmune disease is higher in countries with less parasitic infection. However, it fails to address how parasites can influence our immune systems on a mechanistic level. While the exact mechanism that parasitic worms, also known as helminths, use to modulate the human immune system is not fully known and differs depending on the helminth, there are several contending hypotheses that have stemmed from research on animal models. One hypothesis is the homeostatic model, which proposes that the human immune system has limited capacity of immunological responsiveness (Wilson & Maizels, 2004). According to the homeostatic model, parasitic infection shifts the focus of the immune system away from maladaptive autoimmune functioning and toward the parasite infection, thus reducing the severity of autoimmunity. This can be thought of as an immunological tug-of-war, with parasite infection on one side of the rope and a faulty autoimmune response at the other, both competing for the attention of the immune system.

A second hypothesis is that chronic parasitic infection downregulates the immune system in order to decrease pathogenicity associated with a prolonged immune response (Wilson & Maizels, 2004). Sustained exposure to antigens from parasite infections causes the body to make an immunological compromise by suppressing immune responses toward the parasite infection in order to reduce damage to the body that results from a chronic inflammatory response.

The IgE hypothesis was developed based on the finding that parasite infection results in the large production of nonspecific polyclonal antibodies, called IgE, compared to parasite specific IgE (Wilson & Maizels, 2004). As a result, receptor sites on immune system cells (called mast cells) become saturated with polyclonal IgE rather than allergen specific IgE, thus reducing the immune response toward allergens (Wilson & Maizels, 2004).

Attempts to use helminth therapy on animal models has provided strong evidence for the ability of parasites to prevent the development of autoimmune diseases, as well as to suppress symptoms. A common method of studying helminth effects on Crohn's disease in animals is to induce colitis, another autoimmune disease of the colon, by chemical exposure or by using genetic knockouts of the regulatory cytokine *IL-10* gene (Elliot & Weinstock, 2012). Rodents infected with the roundworm *Heligomosomoides polygyrus*, the blood fluke *Schistosoma*

*mansoni*, or the tapeworm *Hymenolepis diminuta*, are found to have increased levels of anti-inflammatory cytokine *IL-10*, and decreased levels of pro-inflammatory cytokine IFN $\gamma$ , protecting them from experimentally induced colitis (Elliot & Weinstock, 2012). Additionally, *H. polygyrus* infection can protect *IL-10* gene knockout mice from developing colitis, as well as cure existing colitis (Elliot & Weinstock, 2012).

Concerning asthma, a wealth of murine studies provide support for using helminth therapy to treat asthma in humans. Mice infected with male *S. mansoni* are found to have decreased levels of the allergen cytokine *IL-5* and are protected from airway hyperreactivity, suggesting that *S. mansoni* could be a possible treatment for human asthma (Elliot & Weinstock, 2012). Parasitic infections in mice with the nematode worms *Nippostrongylus brasiliensis* (Wohlleben et al., 2004), *Litomosoides sigmodontis* (Dittrich et al., 2008), *Heligmosomoides polygyrus* (Wilson et al., 2005), and *Schistosoma japonicum* (Mo et al., 2008) were shown to suppress the development of asthma. Furthermore, biological products derived from parasites have been shown to be an effective remedy to prevent and treat asthma in murine models. AcCystatin, a cystatin protease inhibitor of the parasite *Angiostrongylus cantonensis*, significantly reduced airway hyperreactivity in asthma-induced rats (Ji et al., 2015). Additionally, extracts from the parasite *T. spiralis* were shown to lessen airway inflammation in asthma-induced mice (Sun et al., 2019). Therefore, it's clear that in rodents, helminth therapy is an effective treatment for Crohn's disease and asthma.

Clinical studies using helminths to treat autoimmune diseases in humans have shown promising results for helminth therapy. In a clinical study, infection with *Necator americanus* (or hookworm larvae) in patients suffering from Crohn's disease led to an improvement in their symptom scores, providing support for hookworm's therapeutic potential to treat Crohn's disease (Elliot & Weinstock, 2009). In another clinical study, patients with Crohn's disease and ulcerative colitis were infected with 2500 ova from the parasite *Trichuria suis*, also known as pig whipworm, and later found that all patients' symptoms improved (Summers et al., 2003). *T. suis* was further investigated for its therapeutic potential in another study with a sample of 29 patients with Crohn's disease (Summers et al., 2005). Over the course of 24 weeks, patients were infected with multiple rounds of 2500 *T. suis* ova and then had their symptoms measured. 79% of the patients were found to have significant clinical improvements in their symptoms of Crohn's disease.

In humans, outcomes of helminth therapy for the treatment of asthma are mostly limited to information from self-treaters. A study by Cheng et al. (2015) investigated the success rates from helminth self-treatments in a sample of individuals with various autoimmune diseases. Cheng et al. (2015) found that individuals with asthma who used *Trichuris trichiura*, also known as human whipworm, to treat their symptoms reported success rates for treatment of 100%. Additionally, self-treaters using the hookworm *N. americanus* to treat their asthma reported success rates of 77.3% and a 100% success rate for helminth therapy with the combination of *N. americanus* and *T. trichiura* infections (Cheng et al., 2015). While the conclusions that can be drawn from self-report data are limited, the therapeutic effects of helminths for treating and preventing asthma in animal studies suggests that it could potentially be an effective treatment in humans.

So, based on these studies, why are we not infecting people to treat their autoimmune diseases today? While helminth therapy is an effective method of treatment for autoimmune

diseases such as Crohn's disease and asthma, it's not without its challenges. There are many factors like dosage, pathogenicity, life cycle, colonization location, and migratory capacities that influence a parasite's viability as a candidate for therapy. As a result, parasites for helminth therapy must be carefully selected. Sobotkova et al. (2019) describe three main criteria for therapeutic helminth candidates: feasible domestication, controlled exposure to target population, and a positive benefit/cost ratio.

Feasible domestication refers to the practicality of using the parasite for therapeutic purposes. Factors influencing a helminth's practicality for therapy include the number of hosts in its life cycle, the ability of the helminth's life cycle to be completed in controlled conditions, and the longevity of human colonization (Sobotkova et al., 2019). Controlled exposure to the target population refers to the ability for the helminth to infect only the intended population, and not spread or multiply spontaneously in the environment. The last criterion, positive benefit/cost ratio, refers to the greater benefits obtained compared to the costs associated with parasitic infection. Thus, the potential benefits of parasitic infection, such as immune system regulation and inflammatory suppression in patients suffering from autoimmune disease, must outweigh the potential risks resulting from parasite infection.

Another concern for using helminth therapy is that helminths may become pathogenic in patients with autoimmune diseases who are taking immunosuppressants (Elliot & Weinstock, 2009). Elliot and Weinstock (2009) argue that this is not a valid concern, because the typical immune response toward parasite infection is to remove the parasites from the body. Consequently, a weakened immune system as a result of taking immunosuppressants would not lead to increased pathogenicity of the parasite but would instead cause a longer retention of the parasite infection. Furthermore, most pathology associated with parasitic infections is the cause of an activated host immune response in order to combat the parasitic infection, rather than the parasitic infection itself (Maizels et al., 2009).

Helminth therapy has also been criticized from an ethical standpoint (Elliot & Weinstock, 2009). The thought of intentionally infecting patients with parasites for treatment of an autoimmune disease may be troubling for some because of their negative effects in other areas of the world. For instance, it may be difficult for some individuals to view the blood flukes (*S. haematobium*) modulating effect on allergic reactivity as a potential solution for asthma (Biggelaar et al., 2000), especially when the parasite contributes to the epidemic of an important human tropical disease called schistosomiasis (Colley et al., 2014).

Despite the challenges associated with helminth therapy, its potential benefits are plentiful. Pathogenicity of parasite infection can be controlled because most helminths do not reproduce within their human host, so the numbers of active parasites remains stable (Elliot & Weinstock, 2009). Another benefit of helminth therapy is that it does not show the same increase in susceptibility to pathology as occurs with immunosuppressants, thus reducing the concern for secondary infections (Elliot & Weinstock, 2009). Additionally, the side effects for common immunosuppressant medications (such as anti-inflammatory drugs like steroid hormones) for autoimmune diseases can cause dangerous, even fatal, complications (Elliot & Weinstock, 2009). Determining the proper dosage for immunosuppressant medication is an extremely sensitive task, as the range of doses that improves the disease without causing serious toxicity is narrow (Elliot & Weinstock, 2009). In contrast, helminth therapy likely has a wider range of doses that can be tolerated because most natural parasitic infections are

asymptomatic. Furthermore, parasitic infections can be closely monitored and terminated at any time with anti-helminthic drugs. Thus, I argue, helminth therapy is a safer and more effective treatment than immunosuppressants for treating autoimmune diseases, such as Crohn's disease and asthma.

Research on helminth therapy and the immunological modulating characteristic of parasites has provided strong evidence for their protective effect against the development of autoimmune diseases. A collection of epidemiological, experimental, and clinical studies supports the connection between parasite infection and immune system functioning and reveals the vast potential to transform what was previously considered a malady into a treatment for autoimmune diseases. While helminth therapy is an effective treatment and prevention method for autoimmune diseases, more research needs to be conducted in order to determine the specific mechanisms of action on our immune systems. The knowledge derived from research of parasite immune system interactions could lead to advancements in treatments for autoimmune diseases, as well as for new methods of prevention for autoimmune diseases. If parasite infections continue to prove a protective effect against autoimmune diseases, helminth therapy could become a preventative health measure similar to vaccines, where one day you may find yourself lining up to get infected at your local pharmacy.

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