Chapter 7
Helminth Therapy

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7.1 Introduction

The best solutions address root causes of a problem. The therapeutic use of helminths (parasitic worms) proposes to treat a root cause of autoimmune disease, loss of exposure to these organisms due to modern hygienic lifestyle. There are many types of helminths. Two are being explored for potential medical application. The first is *Trichuris suis* or porcine whipworm. The second is *Necator americanus*, a human hookworm. There are more than 80 different autoimmune diseases, which afflict people in highly-developed industrialized countries. Most of these diseases are rare in tropical lesser-developed countries, where helminth exposure is common. Diseases currently being studied for treatment by helminths include Crohn's disease, ulcerative colitis, multiple sclerosis, celiac disease, rheumatoid arthritis, and autism.

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7.2 General Historical Aspects

Our immune system protects us from invading organisms like viruses and bacteria. To do this, the immune system must identify an invader and then mount a defense. If the immune system inappropriately identifies normal cells or commensal bacteria as an invader, the misguided defense will injure healthy tissue. Diseases caused by misguided immune reactions are named autoimmune and immune-mediated inflammatory diseases. These types of diseases were very rare before the 1930s but now afflict more than 10 % of the population in the United States and Western Europe. The dramatic increase in autoimmune and immune-mediated disease that occurred over the last 75 years, suggests that environmental changes, associated with advanced industrialization, result in an increased risk for immune-mediated disease. Indeed, there is now a great deal of data showing that as lesser-developed countries become more developed, autoimmune and inflammatory diseases emerge.

Many lifestyle changes occur as countries become more developed. One change with profound immunologic impact is the loss of natural exposure to helminths. Helminths influence their host's immune system to promote anti-inflammatory immune regulatory responses. Loss of exposure to helminths means loss of this immune regulatory influence. In theory, loss of the helminthic immune regulatory influence permits development of an autoimmune or immune mediated inflammatory disease. If this theory is true, then exposure to helminths should serve to protect individuals from these types of diseases.

We and others have used animal models to test the theory that helminth exposure protects individuals from developing immune-mediated disease. An animal model is a well-defined experimental setting where an animal, usually mice or rats, develops an illness that mimics a human disease. Mice or rats given helminths are protected from developing illnesses that mimic inflammatory bowel disease (Elliott et al. 2000, 2003, 2004; Khan et al. 2002; Reardon et al. 2001), multiple sclerosis (La Flamme et al. 2003; Sewell et al. 2003), type 1 diabetes (Cooke et al. 1999; Zaccone et al. 2003; Saunders et al. 2007; Liu et al. 2009; Espinoza-Jimenez et al. 2010), rheumatoid arthritis (Salinas-Carmona et al. 2009; Osada et al. 2009; He et al. 2010; McInnes et al. 2003), and asthma (Wilson et al. 2002; Kitagaki et al. 2006; Mangan et al. 2006).

The theory that helminth infection protects from autoimmune disease can be tested in people by comparing the prevalence of a disease in helminth highly-exposed and less- or non-exposed groups. These epidemiologic studies show that wheezing or allergic skin reactions (Scrivener et al. 2001; Araujo et al. 2004; van den Biggelaar et al. 2000, 2004; Endara et al. 2010; Flohr et al. 2010), multiple sclerosis (Correale and Farez 2007), and inflammatory bowel disease (Kabeerdoss et al. 2011) are less common or much milder in people often exposed to helminths. In patients with multiple sclerosis, removal of naturally acquired helminths results in worsening neurologic symptoms (Correale and Farez 2011). In a case report of ulcerative colitis, treatment of pinworm resulted in a flare of the inflammatory bowel disease (Büning et al. 2008). These observations suggest that exposure to helminths does protect individuals from developing immune-mediated illness.

7.3 General Mechanisms of Action

Biological organisms need to respond to challenges quickly in order to remain alive. To accomplish this task, most systems within an organism are maintained in a state of balance so they can move in either a positive or a negative direction depending on need. After meeting a challenge, the system moves back to a baseline or neutral position. This state of dynamic balance is called homeostasis. The immune system demonstrates active homeostatic balance. Many different cell types make up the immune system. Each cell type has members that pull toward a maximal response and members that push to reduce (regulate) that response. The interactions of these varied components result in a homeostatic network that responds to invading bacteria and viruses, while ignoring normal cells and helpful commensal organisms. Autoimmune and immune-mediated inflammatory diseases occur when this immune regulatory network becomes dysfunctional. Helminths need to live in their host, while causing as little damage as possible. Therefore, they have evolved mechanisms that augment immune regulatory responses. In our laboratories, we are studying how helminths suppress inflammatory responses and strengthen immune regulatory networks.

A major immune regulatory network is composed of "helper" T lymphocyte cells. These cells recognize and respond to proteins displayed on antigen-presenting cells (APC; dendritic cells, macrophages, and B lymphocytes). To sense proteins displayed by APC, T helper cells use a surface component named CD4 and are often called CD4+ T cells. There are several different subtypes of T helper cells known as Th1, Th2, Th17, Th3, Tr1, and Treg cells (Fig. 7.1).

These subtypes are identified by the hormone-like molecules (called cytokines or interleukins (IL)) that they produce. Th1 cells make IFNγ, which instructs macrophages to make toxic substances used to kill intracellular bacteria and viruses. Th2 cells make IL-4, which helps the growth of B cells that make antibodies, while Th17 cells make IL-17, which promotes growth of neutrophils to kill extracellular bacteria. Th3 cells make TGF-β that helps suppress activity by Th1 and Th2 cells. Tr1 cells make IL-10 that suppresses activity by Th1, Th2, and Th17 cells. Tregs suppress growth of Th1, Th2, and Th17 cells. How the immune system responds to a challenge or to normal cells depends on the mix of Th1/Th2/Th17/Th3/Tr1/Treg lymphocytes. Animals exposed to helminths have reduced Th1 and Th17 cell activity but augmented Th2, Th3, Tr1, and Treg activity as compared to helminth naïve animals (Elliott and Weinstock 2012). Similar patterns are seen in people from regions where helminth infection is commonplace (highly endemic) (Elliott et al. 2000; Borkow et al. 2000; Sabin et al. 1996; Bentwich et al. 1996). Exposure to helminths also increases regulatory subtypes of CD8+ T cells, dendritic cells, macrophages, and B cells (Elliott and Weinstock 2012).

There is strong evidence that helminth exposure results in changes to the immune system, which decreases risk for developing immune disorders. Therefore, exposure to helminths may prevent onset of the immune-mediated diseases that have become common in developed countries. In addition, previously established colitis improves

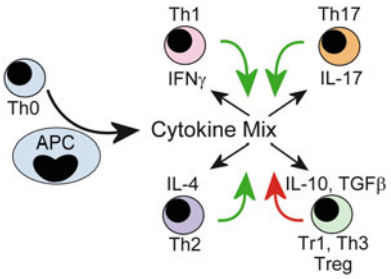

Fig. 7.1 T helper cell subtypes. Naïve T cells (Th0) respond to proteins displayed by antigen-presenting cells (*APC*) can develop into different subtypes (Th1, Th2, Th17, Tr1, Th3, Treg) depending on the mix of different cytokines/interleukins they are exposed to. Th1 cells make cytokines that promote differentiation of more Th1 cells. Th2 cells make cytokines that promote differentiation of more Th2 cells. Th17 cells make cytokines that promote differentiation of more Th17 cells. Tr1, Th3, and Treg cells suppress differentiation and function of Th1, Th2, and Th17 cells to help the immune system stay in homeostatic balance

in mice treated with helminths (Elliott et al. 2004). This suggests that helminths may be used to treat patients that have already developed autoimmune and immune-mediated inflammatory illnesses.

Investigators are working to identify how helminths are able to alter their host immune systems. For example, helminths make products that can alter how the cells of the immune system react (McInnes et al. 2003; Schnoeller et al. 2008). There are many different types of helminths and each type likely has a unique set of products that shape immunity. Helminths are divided into three major groups: round worms (nematodes), flukes (trematodes), and tapeworms (cestodes). The ability to live inside and at the expense of another organism (parasitism), developed independently in each of these groups. Furthermore, many of these parasites live in different parts of the body (niche) or use different ways of gaining access to their host. Therefore, the exact methods used by parasitic worms to alter host immune systems likely varies between these groups and probably even varies by parasite species within a group. In addition, helminths are very complex multicellular organisms that have influenced human genetic variation (Goncalves et al. 2003; Fumagalli et al. 2009). We expect that a given helminth utilizes several mechanisms to evade and suppress host immunity.

7.4 Helminths Currently Being Studied to Treat Human Diseases

Left untreated, autoimmune and immune-mediated inflammatory diseases cause significant damage to patient's tissues. However, many of the medications we use to combat these diseases have significant risks. Commonly used medications include: glucocorticoids (e.g. prednisone) that can cause infections, diabetes, osteoporosis,

cataracts, muscle weakness, avascular necrosis of the large joints, and growth arrest; methotrexate that can cause low blood counts, lung scaring, liver inflammation, mouth sores, diarrhea, birth defects, and abortion; purine anti-metabolites (e.g. azathioprine, mercaptopurine) that can cause low blood counts, hair loss, pancreatic inflammation, liver inflammation and lymphoma; mitoxantrone which can cause hair loss, nausea, vomiting and severe heart damage; TNFα blockers (e.g. infliximab, adalimumab, certolizumab, etanercept), which can cause severe viral, bacterial or fungal infection, liver failure, heart failure, demyelinating disease (similar to multiple sclerosis), and lupus-like disease; and natalizumab, which is rarely associated with an irreversible brain infection called progressive multifocal leukoencephalopathy (PML). When medications fail, we are often left with attempts at surgical repair of damage caused by immune mediated disease. With current medical therapy, about 50 % of patients with Crohn's disease will require at least one bowel resection. A similar percentage of patients with ulcerative colitis require colon removal either due to ongoing inflammation or colon cancer associated with longstanding disease. Patients with rheumatoid arthritis often require joint replacement when feasible. Each of these surgeries carries its own set of risks, therefore, alternative approaches to treat these diseases are needed.

Experiments using animal models and studies of people from endemic areas suggest that helminth exposure can prevent and treat immune-mediated disease. There are many species of helminths that can infect people. One challenge to using helminths therapeutically is to identify species with little risk for causing disease on their own. Although most infections cause no symptoms, some helminth species can cause significant problems to their hosts over time. Examples of these helminths include *Wuchereria bancrofti* and *Brugia malayi*, which cause elephantiasis from severe swelling of the lower extremities. While the biologic behavior of most helminths does not change in patients with altered immune systems, some are able to multiply by autoinfection in immune compromised patients. The usually asymptomatic helminth *Strongyloides stercoralis* can exponentially multiply in patients placed on glucocorticoid medications causing a potentially fatal disease named "fulminant strongyloidiasis". Some helminth larvae have the capacity to migrate to parts of the body where they can cause damage. For example, instead of laying eggs to reproduce, adult *Onchocerca volvulus* release microfilaria that migrate to the skin where they are ingested by biting flies that then transmit infection to other people. *O. volvulus* microfilariae carry a symbiotic bacteria called *Wolbachia pipientis.* When microfilariae die in the skin before they are ingested by a fly, they release bacterial products that causes a mild itch. Microfilariae also can inadvertently migrate into the eye. If they die while in the eye, the release of bacterial products prompts an inflammatory response that can cause irreversible blindness. Helminths that have the ability to cause significant disease are poor candidates for therapeutic use. Yet, there are many helminths that produce few symptoms and little or no disease.

Compared with current medications and surgeries, the clinical use of selected helminths has very low risk. We have performed early clinical studies using *Trichuris suis* or *Necator americanus* to treat patients with active immunologic disease. These helminths are discussed individually below.

7.4.1 Trichuris suis: *Porcine Whipworm*

7.4.1.1 Choice and Biology of *Trichuris suis*

Trichuris suis is a helminth that is closely related to the human whipworm, *Trichuris trichiura* (Cutillas et al. 2009). People can briefly become colonized with *T. suis* (Beer 1976) though there are no reports of illness due to occupational exposure in farmers. *Trichuris* species have a simple lifecycle. The helminth is acquired by swallowing microscopic eggs (ova) that contain an infective worm larva. The ova hatch in the intestine to release larvae that attach to the lining of the intestine and mature into adult worms. Adult worms mate and lay immature ova that are deposited in the stool and are passed with a bowel movement. Once out of the body, the ova slowly mature (embryonate) in the soil over several weeks. Mature ova can survive for years in the soil waiting to be swallowed by a new host.

T. suis provides some unique advantages for use as a therapeutic agent. Helminths need to live in hosts to reproduce. Although closely related to *T. trichiura*, *T. suis* can be grown in specially bred pigs. This permits production of the significant numbers of mature ova needed to treat many patients with immune-mediated disease. The ova are easy to isolate in pure form from infected pigs. The ova are very stable permitting storage and distribution through normal pharmaceutical channels. *T. suis* worms do not multiply in their host permitting accurate dosing of exposure. Because the ova take weeks to mature in the environment, people cannot easily transmit the *T. suis* to close contacts. In humans, *T. suis* colonization is transient. Ova can be taken orally every 2 or 3 weeks to maintain exposure. These characteristics make *T. suis* an unusually robust choice for clinical use (Fig. 7.2).

7.4.1.2 Potential Indications, Contraindications and Side Effects

Many if not most autoimmune and immune-mediated inflammatory diseases could improve with helminthic therapy. These diseases result from inadequate or dysfunctional regulation of the immune response. Helminths induce immune regulatory responses that restrain immune-medicated disease. Illnesses currently targeted for study of "helminthotherapy" include: Crohn's disease, ulcerative colitis, multiple sclerosis, Type 1 diabetes, rheumatoid arthritis, psoriasis, food allergy, and autism.

There are no human diseases attributed to *T. suis*. In pigs, *T. suis* increases infections caused by known bacterial pathogens like *Campylobacter jejuni* (Mansfield et al. 2003). Therefore, *T. suis* should not be given to people with known pathogenic intestinal bacterial infections (eg. *Clostridium difficile*, *E. coli* O157, *Klebsiella oxytoca*, *C. jejuni*, *Shigella* sp., *Salmonella* sp.). It is currently standard of care to test for these infections before starting medications in patients with intestinal symptoms. Helminths are resistant to most antibiotics and are probably not affected by generally used medications. There are current plans to test pigs colonized with *T. suis* with common medications to determine if they influence helminth viability.

Fig. 7.2 *Trichuris suis* ova (TSO). (*Left*) Bottle containing 2,500 microscopic embryonated ova in 30 ml of fluid. (*Right*) Close up micrograph of an embryonated egg. Each *Trichuris suis* ova is about 25–30 µm wide and 65–75 µm long. For comparison, the *gray circle* is the size one human red blood cell

Helminth infections usually cause no symptoms. No side effects were noted in initial studies of *T. suis* in Crohn's disease and ulcerative colitis. Studies in allergic rhinitis and multiple sclerosis suggest that some patients may experience soft stools or diarrhea that resolves without stopping continued dosing with *T. suis* ova (Bager et al. 2010; Fleming et al. 2011). However, these mild, transient side effects are not apparent in patients with inflammatory bowel disease.

7.4.1.3 Diseases Studied

The earliest clinical studies of *T. suis* were "open label" meaning that the patients and health care team knew who was receiving helminth eggs. We performed a small trial of four patients with Crohn's disease and three patients with ulcerative colitis. Each patient received one dose of 2,500 embryonated *T. suis* ova. Each patient had improvement in his/her disease symptoms (Summers et al. 2003). We then did a second open label study that tested repeated dosing with embryonated *T. suis* ova. Approximately 2,500 *T. suis* ova were given to 29 patients with Crohn's disease every 3 weeks for 24 weeks (Summers et al. 2005a). After this period, 79 % responded with a drop in their disease activity scores, and 72 % had resolution of their Crohn's symptoms (Summers et al. 2005a). There were no side effects or complications attributable to *T. suis* colonization. These safety and early efficacy trials suggested that patients with inflammatory bowel disease may improve with exposure to *T. suis* and that this helminth is safe to use in people with intestinal inflammation.

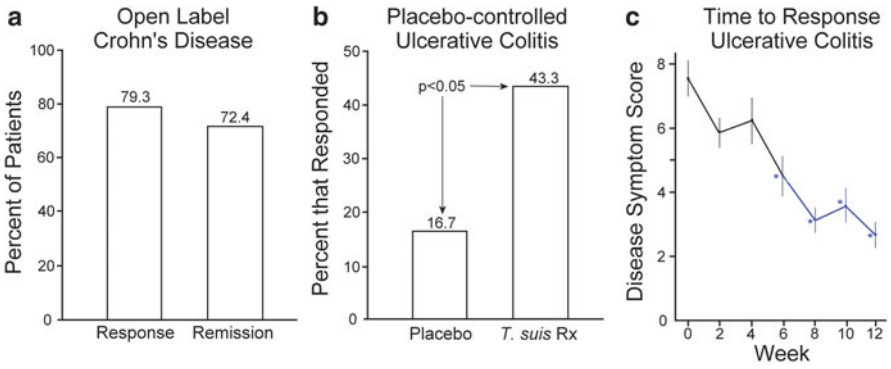

Fig. 7.3 Results of clinical studies in IBD. (**a**) Open label study of *T. suis* every 3 weeks for 24 weeks in Crohn's disease. Response is a drop in Crohn's disease activity index (CDAI) of 100 or more points. Remission is a CDAI below 150 points at end of study period. (**b**) Double blind placebo controlled study of *T. suis* every 2 weeks for 12 weeks in ulcerative colitis. Response is a drop in the ulcerative colitis disease activity index of 4 or more points at end of study period. (**c**) Time to response. Disease activity (Simple index) was measured serially in ulcerative colitis patients receiving *T. suis*. Significant ($p<0.05$) sustained drop in disease activity occurred about 6–8 weeks after starting treatment. Please see text for citations

Open-label studies show if a treatment is safe. However, to show that a treatment is effective, randomized double-blind placebo-controlled studies are used. In these types of studies, patients are randomly assigned to groups that are given either the treatment being studied or an inactive look-a-like (i.e. placebo control). Neither the patient nor members of the health care team know, which group a patient is in until the study is completed (i.e. double blind). We performed randomized double-blind placebo-controlled trial of *T. suis* in 54 patients with ulcerative colitis (Summers et al. 2005b). Patients received either 2,500 *T. suis* ova or placebo every 2 weeks for 12 weeks. Many of the patients repeatedly exposed to *T. suis* had significant improvement in disease activity compared to those given placebo (43 % vs. 17 %, $p<0.05$, Fig. 7.3b). The study also included a crossover phase, according to which, after the initial 12-week study, patients with continued symptoms that were originally on placebo were switched to *T. suis* and those on *T. suis* were crossed-over to placebo. The patients and team members remained "blinded" to the treatment groups. In the crossover phase, 56 % of the patients given *T. suis* responded compared to 13 % of patients given placebo ($p=0.02$) (Elliott et al. 2005). It took about 6–8 weeks for ulcerative colitis patients to respond to *T. suis* treatment (Fig. 7.3c). This study suggested that exposure to *T. suis* is safe and effective for reducing symptoms and disease activity in patients with ulcerative colitis.

A randomized double-blind placebo-controlled study testing the effect of *T. suis* exposure on grass pollen-induced allergic rhinitis was conducted in Denmark (Bager et al. 2010). During allergy season, 96 rhinitis patients received placebo or 2,500 *T. suis* ova (TSO) every 3 weeks for a total of up to eight doses. However, test subjects received between two and five (median 3) doses of TSO or placebo by the

peak of allergy season. By the end of the trial, 24 % of the patients had not received the full eight doses. Patients that received *T. suis* eggs had increased eosinophil counts and titers of anti-*T. suis* antibody as compared to those in the placebo group. Although patients in the *T. suis* group used fewer medications, symptom scores and response to skin prick tests did not differ between the two groups; suggesting that exposure to *T. suis*, as administered in this study, may not help seasonal allergy symptoms. This study has been criticized for timing of exposure to *T. suis* in relation to the onset of allergy season and for assuming that the same dose that reduces symptoms in inflammatory bowel disease would be effective in rhinitis (Hepworth et al. 2010; Summers et al. 2010). Circulating allergen-specific IgE antibodies bind to mast cells causing these cells to release histamine and other mediators upon allergen exposure and triggering the symptoms of allergic rhinitis. Thus, it is reasonable to assume that *T. suis* therapy will require long-term administration well before the allergy season to allow the naturally occurring allergen-specific IgE levels to wane. But, this study did show that *T. suis* exposure influences some immunologic responses in people. Also the agent appeared safe though some patients receiving helminths reported more loose stools, upper abdominal discomfort and flatulence than did those who received placebo. The reported symptoms dissipated quickly. Further studies are required to determine if *T. suis* is effective in allergic rhinitis.

Helminthic therapy of multiple sclerosis is also being investigated. A series of publications from South America suggest that natural infection with helminths arrests the further development of brain lesions in patients with multiple sclerosis. This has led to independent clinical trials both in the United States and Germany testing *T. suis* in patients with this disease. An open label trial of repeated *T. suis* exposure in five patients with relapsing-remitting multiple sclerosis showed that helminth colonization resulted in less neurological symptoms and development of fewer CNS lesions as measured by magnetic resonance imaging (Fleming et al. 2011). Disease activity returned after stopping *T. suis* administration. These researchers found that exposure to helminths increased the peripheral blood eosinophil count, increased production of anti-*T. suis* antibodies, and increased the level of circulating IL-4 and IL-10 cytokines. It was found that repeated doses of *T. suis* were well tolerated but some patients had a brief period of low grade intestinal symptoms and loose stools. A group working in Germany performed an open-label study of *T. suis* on four patients with progressive multiple sclerosis (Benzel et al. 2011). Clinical symptoms stabilized in three of the four patients. Helminth exposure resulted in slight increase in eosinophil counts and suppression of pro-inflammatory cytokine (IFNγ) production by peripheral blood T cells. Similar to scientists in the USA, they also found that helminth exposure was well tolerated by patients with multiple sclerosis.

7.4.1.4 Case Report

A patient with unresponsive ulcerative colitis, whose symptoms did not improve with medications, went into remission after traveling to Thailand and purposefully acquiring *T. trichiura* (human whipworm) infection (Broadhurst et al. 2010).

However, the patient's symptoms returned when the helminths died off. The person then reacquired *T. trichiura* and went back into remission. It should be noted that human whipworm is closely related to porcine whipworm (*T. suis*).

7.4.1.5 Future Clinical Trials with *T. suis*

The pharmaceutical industry presently is conducting large multi-center randomized double blind trial testing this agent in patients with inflammatory bowel disease. There are trials underway in Crohn's disease in Europe and in the United States (ClinicalTrials.gov Identifier NCT01279577). A large multi-center trial for ulcerative colitis is slated for the United States. Also underway are, a single center investigator-initiated study of *T. suis* in peanut food allergy (NCT01070498), a single center investigator-initiated study of *T. suis* in autism (NCT01040221), and three independent single center investigator-initiated studies of *T. suis* in multiple sclerosis (NCT00645749, NCT01006941, NCT01413243). Many of these studies also plan to start evaluating how *T. suis* may alter human immune responses. For one study of patients with ulcerative colitis, that is the major focus of the investigation (NCT01433471).

Over the next few years, *T. suis* treatment will be tested for efficacy in many of the major autoimmune and immune-mediated inflammatory diseases like psoriasis and Type 1 diabetes. Alongside those clinical trials, translational studies in people and experiments in animal models of human disease will define the mechanisms by which helminths manipulate their host to suppress inflammation. Hopefully, we eventually will identify helminth-derived factors that reproduce at least some of these effects.

7.4.2 Necator americanus*: Human Hookworm*

7.4.2.1 Choice and Biology of Organism

Necator americanus, a hookworm, was chosen because of its propensity to re-infect immunologically primed individuals indicating the ability to moderate the immune system. This was further demonstrated in epidemiological studies, where hookworm infection was associated with a reduction in allergy, and supported by the identification of a number of immune-modulatory molecules in parasite secretions. This work has recently been comprehensively reviewed (Pritchard et al. 2012).

Our current understanding is that this hookworm species induces an allergic phenotype in the infected host soon after infection, a phenotype, which affords the host some protection. However, the phenotype would appear to be transient, implying counter immune regulation by the parasite.

Nevertheless, this parasite exhibits a dark side to its biology; *Necator* enters the body trans-cutaneously, causing a pruritus in the process. This is called "ground itch"

in the tropics, and is a key feature of experimental infection during trial. Once in the skin, the worms migrate to the lungs, enter the air space, to be coughed up and swallowed. The potential for lung damage is real, hence the requirement to conduct short–term, low infection intensity safety trials. Once in the gut, the worms feed on mucosal tissue and blood, again a cause for concern for patients and physicians alike.

Consequently, the early human trials with this parasite were safety orientated, with small numbers of worms resident for a short period of time (12 weeks). The trials were designed to choose an asymptomatic dose that did not adversely affect lung or gut function.

Physicians are currently confident that doses of up to 25 larvae can be safely administered. This dose will induce a natural immunological phenotype, with what one would hope to be a parallel natural immune-regulatory response, conducive to disease suppression.

7.4.2.2 Diseases Studied

Following on from safety trials, *N. americanus* is currently being used in an attempt to moderate relapsing remitting multiple sclerosis. The immunology of this disease suggests that it would be amenable to moderation by a parasite, which promotes a T helper 2 phenotype. Patients will be infected with 25 larvae during remission, as indicated in the Worms for Immune Regulation of Multiple Sclerosis (WIRMS) clinical trial (NCT01470521) documentation, and the worms will remain in residence for the duration of the trial. Disease progression will be monitored by MRI, and patient immunology screened in parallel.

7.4.2.3 Future Research

Views on the direction of future research are outlined in a recent opinion piece (Pritchard 2012). Should TSO or *Necator* prove to be of benefit in any of the medical conditions described above, there will be a natural tendency towards experiments, which will help clinicians to understand the molecular and cellular mechanisms of immune-moderation. Our view is that parasite immunologists should also mine proven therapeutic parasites for non-proteinaceous and non-immunogenic immune suppressants. This view is based on the hypothesis that parasites need such molecules to evade host-immunity, i.e., to survive. Immunogenic parasite secretions that elicit targeted immune responses would not benefit the parasite for prolonged colonization (Pritchard et al. 2012). Any therapeutic effect of parasites in immunological disease could be the result of bystander effects of parasite-derived molecules on an over-active dysregulated immune system. On the other hand, helminths, which are complex animals, can certainly use more than one molecule to evade host immunity. It seems likely that the whole living organism, rather than a single molecular product, will remain most effective at controlling immune mediated disease.

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