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Invited review

Helminths as governors of immune-mediated inflammation

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Abstract

Immune-mediated diseases (e.g. inflammatory bowel disease, asthma, multiple sclerosis and autoimmune diabetes) are increasing in prevalence and emerge as populations adopt meticulously hygienic lifestyles. This change in lifestyles precludes exposure to helminths (parasitic worms). Loss of natural helminth exposure removes a previously universal Th2 and regulatory immune biasing imparted by these organisms. Helminths protect animals from developing immune-mediated diseases (colitis, reactive airway disease, encephalitis and diabetes). Clinical trials show that exposure to helminths can reduce disease activity in patients with ulcerative colitis or Crohn's disease. This paper summarises work by multiple groups demonstrating that colonization with helminths alters immune reactivity and protects against disease from dysregulated inflammation.

Keywords: Immune regulation; Inflammation; Inflammatory bowel disease; Asthma; Multiple sclerosis; Autoimmune type 1 diabetes; Immune-mediated inflammatory disease; *Trichuris suis*; Whipworm; Hookworm

1. Introduction

Although a robust immune response protects us from recurrent infections, when misdirected it will cause disease. Crohn's disease and ulcerative colitis (together comprising inflammatory bowel disease (IBD)), asthma, multiple sclerosis (MS) and autoimmune (type 1) diabetes (T1D) are examples of immune-mediated diseases. These diseases result from targeted tissue destruction due to chronic inflammation orchestrated by lymphocytes. Immune-mediated diseases are prevalent in industrialized, highly developed countries but rarely occur in less-developed countries. This rarity is not due to inability to diagnose these illnesses in less-developed settings. What is it that makes people in highly developed countries susceptible to immune-mediated disease?

In this article, we will review some of the observations showing that immune-mediated diseases are increasing in prevalence in areas where exposure to helminths is rare, that anti-helminthic treatment increases symptoms of atopy, that helminths protect against illness in animal models of immune-mediated disease by promoting regulatory responses, and that treatment of patients with helminths reduces disease activity. These observations suggest that helminths, although parasites, may contribute something in return to their hosts and the loss of helminths removes a natural governor that helped to prevent disease due to immune dysregulation.

2. The emergence of immune-mediated disease

IBD, asthma, MS and T1D are examples of immune-mediated diseases. Over the last 70 years, these immune-mediated diseases have become common in industrialized, highly developed countries but remain rare in less-developed countries.

IBD results from chronic inflammation of the small and/or large intestine. It is treated with immune-suppressive medications such as glucocorticoids, azathioprine,

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methotrexate and anti-cytokine mAbs. IBD was uncommon prior to the 1940s but now afflicts more than three million people in the United States and Europe (Loftus Jr., 2004). As IBD emerged within developed countries, it was most common in people living in cities (Ekbom et al., 1991), northern latitudes (Sonnenberg et al., 1991; Shivananda et al., 1996) and with white collar type jobs (Sonnenberg, 1990). As countries develop economically, the prevalence of IBD in the population increases (Loftus Jr., 2004; Lakatos et al., 2004) and when people move from a country with low prevalence to a developed country with high prevalence of IBD, their children acquire a higher risk of developing IBD (Jayanthi et al., 1992; Carr and Mayberry, 1999). This suggests that growing up in an industrialized, developed country increases the risk of acquiring IBD.

A similar situation exists with asthma. Asthma is caused by chronic inflammation of the airways, often with allergic provocation. Asthma has increased dramatically in developed countries over the last 40 years and is becoming prevalent in urban centres of developing countries (Braman, 2006). Children of Mexican immigrants born in the United States are more likely to report asthma symptoms than children born in Mexico and immigrating to the U.S. at older ages (Eldeirawi and Persky, 2006). Again, this suggests that the environment in developed countries promotes or permits asthma (Asher et al., 2006).

MS results from immune-mediated inflammatory destruction of neural pathways in the central nervous system. Like IBD and asthma, it is treated by suppressing immune cell function. The prevalence of MS has a strong geographical distribution (similar to IBD and asthma), has increased in frequency over the last century and is high in children of immigrants born in developed countries (Marrie, 2004). As countries develop improved sanitation, the prevalence of MS increases (Cabre et al., 2005).

T1D is caused by immune-mediated destruction of pancreatic β-cells that make insulin. It is treated by insulin replacement rather than immune suppression, although such therapy is contemplated (Cernea and Herold, 2006). T1D is much more common in the United States, Canada and Europe than in other geographical regions but much of this difference in distribution is explained by the genetic risk conferred by specific human leukocyte antigen haplotypes. However, within a given population, the incidence of T1D has increased dramatically over time (Onkamo et al., 1999). This suggests that like IBD, asthma and MS, a change in environment promotes or permits T1D.

3. Loss of helminths as an agent of change

Our ancestors were colonized with helminths (Goncalves et al., 2003). Paleoparasitological specimens dating back 10,000 years show that infections with nematodes (e.g. *Trichuris trichiura*, *Ascaris lumbricoides*, *Enterobius vermicularis*, *Trichinella spiralis*), cestodes (e.g. *Taenia* spp., *Diphyllobothrium* spp., *Hymenolepis nana*) and trematodes (e.g. *Fasciola* spp., *Schistosoma* spp.) were common. Indeed, every mammal in a natural environment is likely colonized with helminths. Human infections with these organisms remain prevalent in lesser developed countries (Crompton, 1999; Bethony et al., 2006) (Table 1). This longstanding exposure permits selection of genetic traits that are optimised for the presence of helminths (Elliott et al., 2000).

Prior to the 1930s, colonization with helminths was nearly universal (Fig. 1) (Elliott et al., 2000). Modern sewage treatment, cement sidewalks, improved animal husbandry and regulated food industries in developed countries have eliminated lifecycle pathways required to maintain helminth colonization. For example, U.S. autopsy studies in the 1940s suggested that about 17% of individuals were previously exposed to *T. spiralis*. Now, fewer than five patients a year contract that infection, usually due to ingestion of exotic meats (Fig. 2). Even helminths with simple lifecycles such as *E. vermicularis* (pinworm) appear to be declining in the United States (Vermund and MacLeod, 1988) and Europe (Gale, 2002).

No one is bemoaning the loss of helminth parasites, but it is possible that eradication of these organisms has unforeseen consequences. Epidemiological studies suggest that helminths may protect against some immune-mediated diseases. People with *A. lumbricoides* or hookworm (*Necator*) infections reported less wheezing (a sign of asthma) than people without those infections (Scrivener et al., 2001). A positive skin reaction to an allergen helps identify atopic individuals. Gabonese school children infected with *Schistosoma hematobium* had decreased prevalence of dust-mite skin-test positivity compared with children without that helminth (van den Biggelaar et al., 2000). People living in areas endemic for *Schistosoma mansoni* reported less wheezing and use of anti-asthmatic medications than individuals living in non-endemic areas (Araujo et al., 2004). Children repeatedly treated for *T. trichiura* and *A. lumbricoides* had increased dust-mite skin responses compared with children that were not treated for asymptomatic geohelminth infections (van den Biggelaar et al., 2004).

The epidemiological evidence for helminthic protection from IBD and MS is not as strong as that for asthma but it is as suggestive. Soldiers who served in Vietnam or

Table 1
Prevalence of common helminths

Helminth	Estimated number of people colonised
Ascaris lumricoides	1.221 billion
Trichuris trichiura	795 million
Ancyclostoma/Necator	740 million
Schistosoma spp.	200 million
Wuchereria bancrofti	120 million
Strongyloides stercoralis	100 million
Taenia spp.	87 million
Hymenolepis nana	75 million

Note: These are estimates of the number of people with active infections. The number of people potentially exposed or with sub-clinical helminth infections is much higher.

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Fig. 1. A nurse brings hookworm medicine to a rural Alabama family in 1939 (National Library of Congress photo LC-USF34- 051377-D). One of the first public health programs in the United States was the eradication of hookworm infection initiated by John D. Rockefeller in 1909.

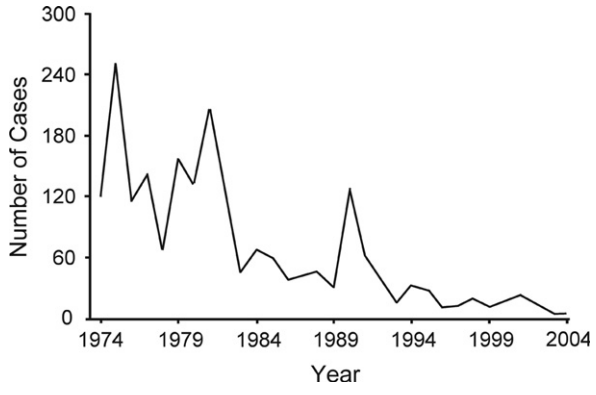

Fig. 2. Decline in the number of U.S. cases of trichinosis reported to the Centers for Disease Control and Prevention over 30 years (from Summary of Notifiable Diseases – United States 2004, MMWR 53:1–79).

who were prisoners of war are at lower risk for IBD (Crohn's disease) (Delco and Sonnenberg, 1998). This protection could possibly be due to increased helminth exposure in these environments. MS is exceedingly rare where *T. trichiura* carriage rates are greater than 10%, creating a strong dichotomy ($P < 0.0001$) between areas where *T. trichiura* and MS are prevalent (Fleming and Cook, 2006).

Immune-mediated diseases arose in those populations where exposure to helminths declined (Elliott et al., 2000) and remain rare in locales where helminth colonization is prevalent. However, the rise of IBD, asthma, MS and T1D could be due to another environmental change that occurred alongside the loss of helminth exposure. A major reason to focus on the loss of helminths is that worm exposure protects animals in experimental models of these diseases.

4. Animal models of helminthic protection from immune-mediated disease

Animal models of human disease provide insight into the mechanisms that drive illness and help identify therapeutic interventions. Animal models of immune-mediated disease share certain features: (i) immune dysregulation produces excessive inflammation, (ii) excessive inflammation results in organ dysfunction, and (iii) suppressing immune cell function or restoring immune regulatory pathways reduces inflammation and organ damage. The effect of helminth exposure has been tested in animal models of IBD, asthma, MS, and T1D (Table 2).

Helminth exposure can prevent or reverse colitis in animal models of IBD. Mice and rats develop colitis when rectally exposed to trinitrobenzenesulfonic (TNBS) acid in 50% ethanol. TNBS colitis is suppressed by inhibiting inflammatory cytokines (TNFα, IL12) or promoting production of immune regulatory cytokines (IL10, TGFβ). Exposure to helminths prevents TNBS-type colitis (Khan

Table 2
Animal modules of human disease that show improvement with helminths

Animal model	Human disease	Model-associated immune character[a]	Helminth studied[b]	Helminth-associated immune change[a]
Trinitrobenzenesulfonic and dinitrobenzene sulfonic acid-induced colitis	Crohn's disease	↑IFNγ, ↑IL12, ↑TNFα, ↓IL4, ↓IL10	*Schistosoma mansoni*	↓IFNγ, ↓IL12, ↑IL4, ↑IL10
			Heligmosomoides polygyrus	↓IFNγ, ↓IL12, ↑ IL4, ↑IL10, ↑TGFβ
			Trichinella spiralis	↓IFNγ, ↓IL12, ↑ IL4, ↑IL10
			Hymenolepis diminuta	↓IFNγ, ↓IL12, ↑ IL4, ↑IL10
IL10 −/− colitis	Crohn's disease	↑IFNγ, ↑ IL12, No IL10	*H. polygyrus*	↓IFNγ, ↓IL12, ↑IL4
			S. mansoni	↓IFNγ, ↓IL12, ↑IL13
			Trichuris muris	
Reactive-airway disease	Asthma	↑IL4, ↑IL5, ↑IL13	*S. mansoni*	↓IL5, ↑IL10
			H. polygyrus	↓IL5, ↑IL10, ↑TGFβ
Autoimmune encephalitis (EAE)	Multiple sclerosis	↑IFNγ, ↑IL12, ↑IL6, ↑IL17	*S. mansoni*	↓IFNγ, ↓IL12, ↓TNFα, ↑IL10, ↑IL4, ↑TGFβ
Non-obese diabetes mouse	Type 1 diabetes	↑IFNγ, ↑IL12,	*S. mansoni*	↑IL4, ↑IL10
			T. spiralis	
			H. polygyrus	

[a] Most of these studies measure the p40 component of IL12 which is shared with IL23. Therefore, an increase or decrease in IL12 may include a change in IL23.
[b] Reference provided in text.

et al., 2002; Elliott et al., 2003; Moreels et al., 2004; Hunter et al., 2005). Mice exposed to *S. mansoni* eggs, *T. spiralis*, *Hymenolepis diminuta* or *Heligmosomoides polygyrus* make less IL12 and IFNγ, but more IL4 and immunoregulatory IL10 (Khan et al., 2002; Elliott et al., 2003; Hunter et al., 2005). Protection from colitis in these models requires intact host IL4 circuitry and IL10 signalling (Elliott et al., 2003; Hunter et al., 2005).

IL10-deficient mice develop severe chronic Th1-driven colitis in response to normal gut flora (Sellon et al., 1998). Colonization with *Trichuris muris* or *H. polygyrus* exposure inhibits development of colitis in IL10 −/− mice (Elliott et al., 2000). Furthermore, colitis improves in IL10 −/− mice given *H. polygyrus* after inflammation is previously established (Elliott et al., 2004). Improvement is associated with inhibition of gut-associated immune cell production of IFNγ and the p40 component of IL12. Colonization of IL10 −/− mice with *H. polygyrus* augments mesenteric lymph node T cell regulatory function and expression of FoxP3 mRNA which codes for a transcription factor expressed by T cells that inhibits autoimmune inflammation (Elliott et al., 2004).

Recently, we have identified additional regulatory circuits induced by helminths. Colonization with *H. polygyrus* induces a novel population of T cells in the lamina propria that express the receptor for bacterial lipopolysaccharide (tol-like receptor 4, TLR4) and produce immune regulatory TGFβ when stimulated with lipopolysaccharide (Ince et al., 2006). Helminths also induce a population of lamina propria CD8+ T cells that inhibit the proliferation of other T cells (Metwali et al., 2006). Thus, colonization with helminths induces several immune regulatory circuits in the gut that impede excessive intestinal inflammation.

The temporal and geographic prevalence pattern of asthma is similar to those for IBD, MS and T1D. Unlike IBD, MS and T1D, which are considered to develop from dysregulated Th1 responses, asthma is thought to result from an excessive Th2 response. Helminths induce Th2 responses and so would be predicted to worsen asthma. However, helminths also induce regulatory cytokines (IL10 and TGFβ) and T cells that can prevent airway inflammation in response to allergens.

Reactive airway disease improves with helminth exposure in murine models of asthma. Mice properly sensitised to an antigen (ovalbumin or dust mite protein) develop airway inflammation upon subsequent aerosol challenge with that antigen. Colonization of mice with male *S. mansoni* protects against airway hyperreactivity (Mangan et al., 2006) but this protective effect is lost with patent (male and female) infection producing Schistosome eggs. The male worm-only colonized mice developed a modified immune response in the lung with decreased allergen-specific IL5 and increased IL10 production compared with uninfected mice. Patent intestinal colonisation with *H. polygyrus* before or during antigen sensitisation inhibits subsequent airway inflammation (Wilson et al.,

2005; Kitagaki et al., 2006) and reactivity(Kitagaki et al., 2006). Helminth exposure is associated with a drop in allergen-specific IL5 production, similar to that seen in people with *S. mansoni* infections (Araujo et al., 2004). The pattern of regulatory cytokines induced by *H. polygyrus* differs by mouse strain showing parasite enhanced IL10 in C57BL/6 and TGFβ in BALB/c mice (Wilson et al., 2005). Protection requires intact IL10 signalling in C57BL/6 (Kitagaki et al., 2006) but not BALB/c (Wilson et al., 2005) mice. *Heligmosomoides polygyrus* exposure increases the percentage of mesenteric and thoracic lymph node CD4+ T cells that express CD25+ and FoxP3+ markers for T cells that inhibit inflammation. Passive transfer of mesenteric lymph node cells or splenocytes from colonized mice inhibits airway inflammation in worm-free mice showing regulatory cell activity (Wilson et al., 2005; Kitagaki et al., 2006).

Helminth exposure inhibits immune-mediated CNS inflammation in mouse models of MS. Mice immunised with myelin-associated proteins develop autoimmune encephalitis (EAE). Exposure of mice to viable *S. mansoni* or dead (freeze-thawed) *S. mansoni* eggs protects mice from EAE (La Flamme et al., 2003; Sewell et al., 2003). Schistosome exposure reduces Th1-type cytokines (IL12p40, IFNγ and TNFα) and promotes regulatory and Th2-type cytokine (TGFβ, IL10, IL4) expression in splenocytes and CNS cells. As seen in TNBS-colitis, protection against EAE by *S. mansoni* egg exposure requires intact IL4 signalling (Sewell et al., 2003).

Helminth exposure prevents onset of autoimmune diabetes in the non-obese diabetes (NOD) murine model of T1D. Female NOD mice spontaneously develop diabetes due to a Th1-type immune-mediated destruction of insulin-secreting pancreatic β-cells. NOD mice with *Schistosomiasis mansoni* or exposed to *S. mansoni* eggs or antigens are protected from developing diabetes (Cooke et al., 1999; Zaccone et al., 2003). Schistosome egg or antigen exposure induces immune regulatory IL10 and Th2-type responses that may help prevent insulinitis. Helminth exposure also augments natural killer (NK) T cell activity, which is abnormally depressed in NOD mice (Zaccone et al., 2003). Colonization with other helminths (*T. spiralis*, *H. polygyrus*) also inhibits diabetes in NOD mice (Zaccone et al., 2006).

IBD, asthma, MS and T1D are rare in areas where helminth infection is common. In animal models helminth exposure provides protection from developing these types of diseases. These models demonstrate that helminth colonization induces multiple immune regulatory circuits that abrogate excessive inflammation. Similar immune regulatory circuits have been shown in helminth-infected people (van den Biggelaar et al., 2000; Doetze et al., 2000). Thus, epidemiological and animal model evidence suggests that loss of helminth exposure increases the risk of developing immune-mediated disease. In addition, animal models suggest that exposure to helminths can treat established disease (Elliott et al., 2004).

5. Clinical studies of helminths as therapy for immune-mediated disease

Epidemiological associations, case control studies and experiments using animal models, suggest that helminth exposure may prevent or treat immune-mediated illnesses. Clinical studies testing the therapeutic potential of helminths are warranted. There are many species of helminths. Some have enough disease-causing capacity that their therapeutic application is impractical. Others, with negligible or no pathogenic capacity, are beginning to be studied clinically. Most of the trials to date have used *Trichuris suis*, the porcine whipworm. *Trichuris suis* is closely related to *T. trichiura* (human whipworm) and can briefly colonize people (Beer, 1976). *Trichuris* spp. have many features that make them good candidates for clinical use. They are geohelminths acquired by ingesting embryonated ova. The larvae and adults remain confined to the intestines. They do not multiply within their host. Freshly deposited ova require several weeks of incubation in moist soil to embryonate and become infective. Thus, modern hygienic practices block transmission to close contacts. *Trichuris suis* has additional characteristics that make it an attractive candidate. *Trichuris suis* can be obtained in large numbers with absolute purity from pigs raised in a specific pathogen-free environment. Adult worms are collected from the colon, washed and cultured in vitro for several days where they continue to deposit ova. These ova are collected, washed extensively and incubated for several months to allow embryonation. This removes the risk of contaminating the *T. suis* ova with other infectious agents. While *T. suis* is present in many pig herds and farmers must be exposed to this organism, *T. suis* has not been documented to cause human disease. This suggests that any risk from using this "non-human" helminth is likely to be small.

Initially, the effect of *T. suis* colonization was studied in a small open-label trial of seven patients with IBD (four Crohn's disease, three ulcerative colitis). "Open-label" means that the patients and their care givers knew that they had received helminths. The patients ingested 2500 embryonated ova and were then observed. All showed improvement in their symptoms (Summers et al., 2003). A second study tested repeated dosing with *T. suis* in 29 patients with active Crohn's disease (Hubbard et al., 1974; Summers et al., 2005a). The patients received 2500 *T. suis* ova every 3 weeks for 24 weeks. At week 24, 79% had responded with a significant reduction in symptoms. A third study was a double blind placebo-controlled trial of *T. suis* in 54 patients with active ulcerative colitis (Summers et al., 2005b). In this type of trial neither the patient nor the care-givers know if the patient receives helminth or placebo. This removes bias. The patients received either a placebo or 2500 *T. suis* ova every 2 weeks for 12 weeks. A significant percentage (43.3%) of the patients given *T. suis* improved compared with those given placebo (16.7%, $P < 0.04$). The study also included a 12 week crossover

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limb where patients originally on placebo where switched to *T. suis* and those on *T. suis* were switched to placebo, while maintaining the double blind. In the crossover limb, 56.3% of the patients given *T. suis* improved compared with 13.3% of patients given placebo ($P = 0.02$) (Elliott et al., 2005).

Colonization with hookworm (*Necator americanus*) is also being investigated for therapeutic use. Hookworms have pathogenic potential (Hotez et al., 2004) but in low numbers, *N. americanus* is likely to be relatively safe (Pritchard and Brown, 2001) but can cause gastrointestinal symptoms (Maxwell et al., 1987). People are colonized by applying infective larvae to the skin. Larvae are cultured from the feces of human "reservoir donors" who carry patent infection and are extensively screened to reduce the risk of co-transmitting other infections. A small open-label trial tested *N. americanus* in nine patients with Crohn's disease (Croese et al., 2006). Two of these patients had moderately active disease when they received 50 larvae. Both showed improvement in their symptom scores. The other seven patients in the initial trial had inactive or very mild disease which did not significantly change with helminth exposure. Clinical trials of *N. americanus* in asthma have been organised (Falcone and Pritchard, 2005).

6. Discussion

We have reviewed findings showing that: (i) the prevalence of immune-mediated disease increases in areas that practice meticulous attention to hygienic lifestyles, (ii) these lifestyles preclude natural exposure to helminths, (iii) helminths can prevent immune-mediated disease by altering immune responses, and (iv) exposure to helminths may treat some immune-mediated diseases. These observations strongly suggest that the loss of colonization with helminths permits development of immune-mediated disease. If this is indeed true, several questions need answers.

Question 1. How do helminths "regulate" the immune system? Humans and helminths co-evolved. We are learning how the immune system changes in response to helminth colonization and we are beginning to discover the factors secreted by helminths that can influence immune cell function. It is likely that several immune-regulatory mechanisms are exploited by individual helminths. Otherwise, a helminth could not reliably evade our immune system to reproduce. It is equally likely that each helminth species utilises a different mix of pathways to regulate the immune system. This would develop out of the need to establish a unique niche for each species in a given host. Thus, immune regulatory interactions between helminth and host are probably complex.

Question 2. Which immune-mediated diseases are influenced by helminths? There are over 40 different immune-mediated diseases which together affect more than 10% of the population in highly developed countries. If atherosclerosis is included (Doria et al., 2005) this percentage goes much higher. Each immune-mediated disease is unique. However, asthma, which is a Th2-type disease, and Crohn's disease, which is a Th1-type disease, both appear to be suppressed by helminths. As we learn more about the specific immune dysregulation that occurs in each disease and the different immune regulatory pathways helminths exploit, we should be able to predict which diseases would be suppressed by helminths.

Question 3. Can helminths be used therapeutically to treat or prevent immune-mediated disease? *Trichuris suis* appears to be safe and effective in early studies of IBD and it has unique characteristics that make it a good candidate for clinical use. Plans are in development to test *T. suis* in other immune-mediated diseases. In addition, other helminths with suitable characteristics (Table 3) could be tested.

Many helminths can cause disease. Should we discard some of these organisms as being too pathogenic to have therapeutic potential? Perhaps, but most of the medications currently used to treat immune-mediated disease have a "narrow therapeutic window" or significant adverse effect profile. Giving too little medication has no beneficial effect, giving too much can be fatal. Even in proper dosage, immuno-suppressive medications can cause dangerous adverse reactions. Physicians must balance the benefits and risks of any therapy.

Question 4. Can factors isolated from helminths treat immune-mediated disease? Helminths release many factors that alter immune cell function (Maizels and Yazdanbakhsh, 2003). Once we have a good mechanistic understanding of how helminths alter immunity, we may be able to apply identified factors individually or in combination to treat disease. Living helminths may be more than the "sum of their parts", able to vary factors quickly to counter changing immune conditions. However, isolated factors or engineered worm products may be more effective than living helminths for selected diseases or may augment responses maintained by living helminths.

Over the next few years, investigators will begin to answer these questions. The concept of some helminths may change from that of a strict parasite – harmful to the host, to a mutualist – providing benefit to the host as governors of immune-mediated inflammation.

Table 3
Ideal characteristics for a therapeutic helminth

- Has little or no pathogenic potential
- Does not multiply in the host
- Cannot be directly spread to close contacts
- Produces a self-limited colonisation in humans
- Produces an asymptomatic colonisation in humans
- Does not alter behaviour in patients with depressed immunity
- Is not affected by most commonly used medications
- Can be eradicated with an anti-helminthic drug
- Can be isolated free of other potential pathogens
- Can be isolated or produced in large numbers
- Can be made stable for transport and storage
- Is easy to administer

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