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| CORE TIP | Inflammatory bowel disease and celiac disease are immune-mediated pathologies that remain a treatment challenge for gastroenterologists. Despite the recent introduction of novel therapies, notably biological agents and newer management strategies, there are still many patients who do not respond, or have a poor response to current treatments. Helminth therapy seems a promising pathway to newer drugs, because it has been proven to alter intestinal permeability, altering the host’s immune response to a Type 2 cytokine-mediated response in animal models and pre-clinical studies. This editorial aims to stimulate further research in this field, hoping for better care for our patients. |
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EDITORIAL

Helminths as an alternative therapy for intestinal diseases

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**Abstract**

Animal models and clinical studies have shown that helminth infections exert immunomodulatory activity, altering intestinal permeability and providing a potential beneficial action on autoimmune and inflammatory disorders in human beings, such as inflammatory bowel disease (IBD) and celiac disease. This is consistent with the theory that intestinal microbiota is responsible for shaping human immunological responses. With the arrival of the immunobiologic era and the use of antibodies, we propose a distinctive pathway for treating patients with IBD and celiac disease. We have some evidence about the safety and tolerability of helminth use, but evidence about their impact on disease activity is lacking. Using worms to treat diseases could be a possible way to lower treatment costs, since the era of immunobiologic agents is responsible for a significant rise in expenses. Some questions remain to be investigated regarding the use of helminths in intestinal disease, such as the importance of the specific species of helminths used, appropriate dosing regimens, optimal timing of treatment, the role of host genetics, diet, environment, and the elucidation of the exact mechanisms of action. One promising approach is the use of helminth-derived anti-inflammatory molecules as drugs. Yet there are still many challenges with this method, especially with regard to safety. Studies on intestinal permeability point to *Strongyloides stercoralis* as a useful nematode for these purposes.

**Key words:** Helminths; Strongyloidiasis; Immunology; Inflammation; Inflammatory bowel diseases; Intestinal diseases; Intestinal permeability; Celiac disease

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**Core tip:** Inflammatory bowel disease and celiac disease are immune-mediated pathologies that remain a treatment challenge for gastroenterologists. Despite the recent introduction of novel therapies, notably biological agents and newer management strategies, there are still many patients who do not respond, or have a poor response to current treatments. Helminth therapy seems a promising pathway to newer drugs, because it has been proven to alter intestinal permeability, altering the host’s immune response to a Type 2 cytokine-mediated response in animal models and pre-clinical studies. This editorial aims to stimulate further research in this field, hoping for better care for our patients.

**INTRODUCTION**

The intestinal epithelium functions as an important part of the digestion and absorption of fluids and nutrients. It also plays an immunologic role because it protects the host from environmental pathogens and antigens[1]. When this barrier is altered, it leads to ease of antigen entry and subsequently to immune stimulation and inflammation[2].

Many intestinal diseases have immunogenic com­ponents that alter intestinal permeability. Some pathologic processes increase intestinal permeability, such as inflammatory bowel disease (IBD)[3-11], atopic eczema[12], celiac disease, dermatitis herpetiformis[13], cystic fibrosis[14,15], alcohol consumption[16], use of nonsteroidal anti-inflammatory drugs[17-20], and acute infectious diarrhea[12,21]. In contrast, some infections, such as those caused by *Blastocystis hominis*[22], can decrease intestinal permeability and alter the barrier function of the epithelium. These may thus provide an alternative pathway for treating patients by deviating the host’s immunologic response.

Intestinal permeability can be measured in many ways. One is *via* measuring urinary clearance of radioactive chromium-51 labeled ethylenedi­aminetetraacetic acid (51Cr-EDTA). When urinary clearance of 51Cr-EDTA is decreased, this indicates decreased intestinal permeability. Werneck-Silva *et al*[23] demonstrated that infection with *Strongyloides stercoralis* can diminish intestinal permeability compared to healthy volunteers (*P* = 0.0001). Intestinal infection with *S. stercoralis* led to abnormalities in mucus secretion and intestinal motility, as well as possible loss of macromolecules. *S. stercoralis* is a soil-transmitted helminth and is one of the most common parasites that affects patients living in tropical areas[24]. It infects 100 to 200 million people worldwide[25]. It predominantly compromises the mucosa of the duodenum and upper jejunum, although the whole intestinal wall or more extensive segments of the intestine can be involved, especially in immunocompromised patients[26-28].

**DISCUSSION**

***Hygiene hypothesis***

The hygiene hypothesis was initially described in the 1970s. It suggests that the higher incidence of allergic diseases in predominantly urban white communities, compared to those rural and indigenous, is due to the less frequent viral, bacterial and helminth infections[29]. A decade later, Strachan proposed that reduced exposure to infections in early childhood, owing to a combination of diminished family size, improved living standards and higher levels of personal hygiene, might result in an increased risk of allergic disease later in life[30]. In addition to allergic disease[31-33], it is believed that the recent increase in other autoimmune and inflammatory disorders, especially in developed countries, could be explained by a similar hypothesis. Many factors may be involved, such as changes in intestinal microbiota during childhood[34].

Helminth infections, in specific intestinal worms, are a particular area of research interest, since they can modulate the host response, inducing immunologic tolerance. Aoyama *et al*[35] have demonstrated an inverse relationship between autoimmune liver diseases, such as primary biliary cirrhosis, autoimmune hepatitis, and primary sclerosing cholangitis, and *S. stercoralis* infection. Recent studies point to the negative effects of deworming, since the helminths are able to not only downregulate specific immune responses, but also to modulate autoimmune and allergic inflammatory responses, contributing to metabolic homeostasis[36]. The study on the use of helminths and their products as anti-inflammatory treatments is a growing field.

***Helminth-induced immune responses***

Parasitic helminths evolved with the mammalian immune system, promoting their own survival by altering host immune responses[37]. The immune response induced by these worms is dependent on a Type 2 cytokine response, involving the secretion of interleukin (IL)-4, IL-5, IL-9 and IL-13, accompanied by the activation of intestinal mast cells[38], eosinophils, goblet cells, enterocyte proliferation and intestinal contractility[39]. Granuloma formation then occurs, isolating the eggs and larvae, and inducing tissue repair[40]. Other accessory pathways are activated, including the upregulation of regulatory T cell and IL-10 and/or transforming growth factor beta levels, leading to a predominantly anti-inflammatory response. It has been shown that IL-10- deficient-mice with helminth infections have higher mortality and/or morbidity[41].

The role of CD4+ T cells in expressing Th1, Th2 and Th17 cytokines in human infection with *S. stercoralis* is better explored by Anuradha *et al*[42], who demonstrated a decrease in functional Th1 and Th17 cells and an increase in functional Th2 cells, compared to uninfected individuals. The regulation of Th1, Th2 and Th17 cells was predominantly dependent on IL-10, while the regulation of Th2 but not Th1 or Th17 cells was also dependent on TGF. Anuradha *et al*[43] also examined the circulating levels of cytokines in infected individuals (*n* = 32) compared to those uninfected, discovering significantly lower circulating levels of pro-inflammatory cytokines (gamma interferon, tumor necrosis factor alpha and IL-1) and significantly higher levels of anti-inflammatory cytokines (IL-4, IL-5, IL-9, IL-10, IL-13, IL-27, IL-37, and TGF-). In addition, treatment of infection led to an opposite immunological response in the two studies. The question is whether these anti-inflammatory properties could be used in intestinal disorders with a predominant Type 1 cytokine response.

***Helminth therapy for intestinal inflammation***

The ability of helminth infections to alter and/or to suppress immune responses and intestinal inflammation could be useful in IBD[37]. To date, only two species of helminths have been used as clinical treatment: *Trichuris suis*, the pig whipworm, and *Necator americanus*, the human hookworm.

The first is acquired by ingestion of ova and colonization of the caecum and proximal colon of the human gut by worms, which only lasts a few weeks. The second infection develops after percutaneous administration of larvae that migrate to the small intestine, where they survive by feeding on blood from the mucosa. *T. suis*, due to the species-specificity and the lack of chronic infection, requires repeated treatments, although it poses lesser health issues. In the case of *N. americanus*, the long lasting infection means greater risk of anemia and gastrointestinal symptoms, which could be deleterious side effects[37]. To date, there are no studies of *S. stercoralis* for treating intestinal inflammation.

***Evidence of helminth therapy in inflammatory bowel disease***

Approximately 15 years ago, the first clinical studies of helminth therapy for intestinal disease in humans utilized embryonated viable eggs of *T. suis* in the treatment of ulcerative colitis (UC) and Crohn’s disease (CD). These studies showed safety, tolerance and a significant disease remission when oral administration of viable and embryonated eggs was performed repeatedly[44,45]. A placebo–controlled, double-blind, randomized trial in UC patients significantly improved the disease activity index and showed no side effects, although the remission rate was not different than placebo[46]. Another double-blind, placebo-controlled, randomized study (NCT01434693) reported that a single dose of *T. suis* ova (TSO) up to 7500 ova was well tolerated and did not result in short- or long-term treatment-related side effects in CD patients[47].

A brief review of Clinicaltrials.gov reveals three interventional studies of TSO in CD and two in UC. In CD, the studies were sponsored by Coronado Biosciences, which changed its name to Fortress Biotech, and by Dr. Falk Pharma GmbH. TRUST-1 (NCT01576471), a Phase 2 clinical trial evaluating 250 North American patients with moderate-to-severe disease did not improve the disease activity index or remission rates, although a nonsignificant improvement was noted in patients with a more severe disease score.

TRUST-2 (NCT01279577), a double-blind, placebo-controlled, randomized trial of 252 Eur­opean adults with mildly-to-moderately active ileo­colonic, uncomplicated CD, documented that the administration of fortnightly doses of 250, 2500, or 7500 TSO/15 mL suspension/day over 12 wk, with a four-week follow-up, was safe, with no serious adverse drug reactions. There was a dose-dependent immunological response, but no TSO dose showed a clinically relevant effect over placebo for the induction of clinical remission (CD Activity Index < 150) or response[48].

In UC, the first study was sponsored by the New York University School of Medicine, and the second by the National Institute of Allergy and Infectious Diseases. Both were terminated due to a small sample size and because it was not possible to draw meaningful conclusions. MUCUS (NCT01433471), a randomized, double-blind, placebo-controlled crossover study, was conceived to examine mucosal immunity after therapy with 2500 eggs by mouth every 2 wk for 12 wk. Primary outcomes were designed to better understand the mechanism of action of TSO on the intestinal mucosa and secondary outcomes were to bring about changes in the Mayo Score and in the Simple Clinical Colitis Activity Index.

A second, more controversial approach, was the use of *N. americanus*. Croese *et al*[49] showed that 7 of 9 patients with CD infected with 25-50 larvae followed over 20 wk experienced an improved CD activity index, while the other 2 worsened. There were no search results for interventional studies regarding the use of *Strongyloides, Ascaris, Ancylostoma, Wuchereria, Onchocerca, Toxocara* or *Enterobius* in CD or UC on Clinicaltrials.gov.

***Evidence of helminth therapy in celiac disease***

There are few studies examining the use of helminths in celiac disease, most of which with small samples. McSorley *et al*[50] and Daveson *et al*[51] examined 20 celiac patients followed by wheat challenge after 20 wk exposed to 5-10 larvae of *N. americanus*, compared to placebo, at Princess Alexandra Hospital, in Brisbane, Australia. The dose was well tolerated and analysis showed reduced gamma interferon and interleukin-17A in duodenal biopsies. No difference in symptoms was observed.

Another Australian clinical trial, NaCeD study (NCT016619330), evaluated the desensitization and gluten tolerance of 12 diet-managed celiac patients. They were previously infected with *N. americanus* and exposed to small incremental doses of gluten, in the form of pasta, over 12 wk. The mucosal histopathology before and after gluten challenge was examined. There were no significant differences in terms of duodenal villus height and crypt depth ratio and intraepithelial lymphocyte count.

Another clinical trial (NCT02754609) was registered in 2016 by James Cook University in Queensland, Australia, on Clinicaltrials.gov. This trial aims to be a phase 1b multicenter, multinational, randomized, double-blind, placebo-controlled clinical trial with a single-blind arm and an open label extension phase. The objective is to evaluate the safety and predictability of escalating gluten consumption to activate celiac disease. The cohort with diet-managed disease will be treated with placebo or with low- and medium-dose hookworm inocula. The primary outcome is to measure the difference in duodenal villus height and crypt depth ratio between baseline (week 2) and week 42.

There were no search results for interventional studies about *Trichuris, Strongyloides, Ascaris, Ancylostoma, Wuchereria, Onchocerca, Toxocara* or *Enterobius* use in the treatment of celiac disease on Clinicaltrials.gov.

***Other uses for helminth therapy***

There are other studies examining the role of helminth therapy in allergy, atopy and asthma, with conflicting results. The biggest problem seems to be that these studies proved that preventing allergic reactivity is possible, but only a handful have reported the ability to impact an already established process. In addition to allergy, a number of clinical trials are currently registered for the use of TSO in patients with multiple sclerosis[52], psoriasis, autism and rheumatoid arthritis[37], and for the use of *N. americanus* in patients with multiple sclerosis[35].

***Helminth products as possible new drugs***

Helminths are complex organisms that have a variety of immunomodulatory substances, such as lipids, carbohydrates and proteins, and jointly defined excretory-secretory products (ES). The identification of helminth products that can be used as biologicals in place of whole parasites is an engaging area of research. The ES-62 glycoprotein from the filarial nematode *Acanthocheilonema vitae* is one of the most studied compounds and is capable of promoting a Th2 response, inhibiting Th1 and Th17. Animal studies have demonstrated the ability of various ES products to inhibit intestinal inflammation in colitis models. These studies suggest a potential way for discovering new drugs for IBD. Concerns about antigenicity and safety need to be clarified prior to clinical testing[53].

Most published studies focus on the use of ne­matodes and their products in the treatment of intestinal disease. Unlike most studies, there is an ongoing multicenter phase 2 clinical trial, in the recruiting phase, sponsored by the University Hospital, Lille, France, named ACROHNEM (NCT02281916). It is designed to assess safety and tolerability of P28GST (protein 28 Kd glutathion S transferase), aiming to control inflammation in moderate CD, before or after intestinal resection surgery. P28GST is a parasite enzyme molecule from *Schistosoma* with potent immunogenic and anti-oxidant properties. Based on the experimental evidence of its anti-inflammatory properties, investigators hypothesized that the administration of P28GST could protect against recurrence after intestinal resection surgery in CD. To carry out this study, 24 moderate CD patients will be enrolled. Patients with moderate CD will be included after intestinal resection surgery. Drug therapy will consist of three injections of 100 µg of P28GST for 3 mo (one injection per month). The main objective of this study is to assess safety and tolerability in a 1-year follow-up. Secondary objectives are to control immunologic and inflammatory blood and tissue markers and evaluate clinical recurrence as assessed by CDAI (CD Activity Index).

**CONCLUSION**

The intestinal microbiota is responsible for shaping the human immune system, and the composition of the microbiome can alter and deviate specific host immune responses. Although much has been written about bacteria, we cannot forget that other organisms, such as the helminths, may possibly play an important role in maintaining a “healthy intestinal community”[54].

Mouse models[55] and human cross-sectional studies have shown that chronic helminth infections exert immunomodulatory activity and are able to regulate the host immune response, providing a potential beneficial action on autoimmune and inflammatory disorders in humans, such as IBD, celiac disease, asthma, atopy, allergy, multiple sclerosis, psoriasis, autism and rheumatoid arthritis[37].

We have some evidence about the safety and tolerance of helminth use, but evidence about the impact on various intestinal diseases is lacking. We need more clinical studies with larger samples, longer follow-ups and standardized doses of helminths and helminth products. Some questions remain to be investigated regarding the use of helminths in intestinal disease, such as the importance of the particular species of helminths used; appropriate dosing regimens (low or high); optimal timing of treatment (before the onset of disease, in acute or chronic disease, or at younger ages); the role of host genetics, diet and environment, and elucidation of the exact mechanisms of protective effect.

In regard to the species of helminth, we believe that the majority of the studies had negative results because of the use of *T. suis*. This pig whipworm induces a less intense and persistent inflammatory response, although Williams *et al*[56] verified that *T. suis* can mature to adult size and reproduce in humans. That is why we see *S. stercoralis* as a more potentially useful nematode, as it has proven to significantly diminish the intestinal permeability in humans[23], altering the interleukin profile in a more systemic way[42]. The prolonged interaction between *S. stercoralis* and its host induces a greater immunomodulatory action. Regarding the appropriate dose and duration of treatment, we have little comprehension of how much and how long is required to exert a significant and beneficial effect; therefore, safety concerns limit the dose that can be applied.

One important challenge is the high polymorphism of the human species, which reacts in a spectral manner to helminth infection. The genetic profile of each individual alters this response. In this context, the identification of helminth-derived anti-inflammatory molecular mediators may be a better and promising approach, since it replicates the benefits without the detriments[57]. There are many challenges with this method, such as the selection of a substance with a good safety profile and low antigenicity that is easily produced and that has a significant impact on clinical trials.

**REFERENCES**

1 **Kraehenbuhl JP**, Pringault E, Neutra MR. Review article: Intestinal epithelia and barrier functions. *Aliment Pharmacol Ther* 1997; **11** Suppl3: 3-8; discussion 8-9 [PMID: 9467973 DOI: 10.1111/j.1365-2036.1997.tb00803.x]

2 **Sartor RB**. Current concepts of the etiology and pathogenesis of ulcerative colitis and Crohn’s disease. *Gastroenterol Clin North Am* 1995; **24**: 475-507 [PMID: 8809232]

3 **Ainsworth M**, Eriksen J, Rasmussen JW, Schaffalitzky de Muckadell OB. Intestinal permeability of 51Cr-labelled ethylenediaminetetraacetic acid in patients with Crohn’s disease and their healthy relatives. *Scand J Gastroenterol* 1989; **24**: 993-998 [PMID: 2512633 DOI: 10.3109/00365528909089246]

4 **Bjarnason I**, O’Morain C, Levi AJ, Peters TJ. Absorption of 51chromium-labeled ethylenediaminetetraacetate in inflammatory bowel disease. *Gastroenterology* 1983; **85**: 318-322 [PMID: 6407889]

5 **Hollander D**, Vadheim CM, Brettholz E, Petersen GM, Delahunty T, Rotter JI. Increased intestinal permeability in patients with Crohn’s disease and their relatives. A possible etiologic factor. *Ann Intern Med* 1986; **105**: 883-885 [PMID: 3777713 DOI: 10.7326/0003-4819-105-6-883]

6 **Hollander D**. Crohn’s disease--a permeability disorder of the tight junction? *Gut* 1988; **29**: 1621-1624 [PMID: 3065154 DOI: 10.1136/gut.29.12.1621]

7 **Hollander D**. The intestinal permeability barrier. A hypothesis as to its regulation and involvement in Crohn’s disease. *Scand J Gastroenterol* 1992; **27**: 721-726 [PMID: 1411276 DOI: 10.3109/00365529209011172]

8 **Jenkins RT**, Jones DB, Goodacre RL, Collins SM, Coates G, Hunt RH, Bienenstock J. Reversibility of increased intestinal permeability to 51Cr-EDTA in patients with gastrointestinal inflammatory diseases. *Am J Gastroenterol* 1987; **82**: 1159-1164 [PMID: 3118697]

9 **Jenkins RT**, Ramage JK, Jones DB, Collins SM, Goodacre RL, Hunt RH. Small bowel and colonic permeability to 51Cr-EDTA in patients with active inflammatory bowel disease. *Clin Invest Med* 1988; **11**: 151-155 [PMID: 3135136]

10 **O'Morain CA**, Abelow AC, Chervu LR, Fleischner GM, Das KM. Chromium 51-ethylenediaminetetraacetate test: a useful test in the assessment of inflammatory bowel disease. *J Lab Clin Med* 1986; **108**: 430-435 [PMID: 3095471]

11 **Zuckerman MJ**, Watts MT. Intestinal permeability to 51Cr-ethylenediaminetetraacetate in patients with ulcerative colitis. *Am J Gastroenterol* 1993; **88**: 1978-1979 [PMID: 8237961]

12 **Forget P**, Sodoyez-Goffaux F, Zappitelli A. Permeability of the small intestine to [51Cr]EDTA in children with acute gastroenteritis or eczema. *J Pediatr Gastroenterol Nutr* 1985; **4**: 393-396 [PMID: 3926981 DOI: 10.1097/00005176-198506000-00012]

13 **Bjarnason I**, Marsh MN, Price A, Levi AJ, Peters TJ. Intestinal permeability in patients with coeliac disease and dermatitis herpetiformis. *Gut* 1985; **26**: 1214-1219 [PMID: 3934051 DOI: 10.1136/gut.26.11.1214]

14 **Escobar H**, Perdomo M, Vasconez F, Camarero C, del Olmo MT, Suárez L. Intestinal permeability to 51Cr-EDTA and orocecal transit time in cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1992; **14**: 204-207 [PMID: 1593376 DOI: 10.1097/00005176-199202000-00015]

15 **Leclercq-Foucart J**, Forget P, Sodoyez-Goffaux F, Zappitelli A. Intestinal permeability to [51Cr]EDTA in children with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1986; **5**: 384-387 [PMID: 3088249 DOI: 10.1097/00005176-198605000-00008]

16 **Bjarnason I**, Peters TJ, Wise RJ. The leaky gut of alcoholism: possible route of entry for toxic compounds. *Lancet* 1984; **1**: 179-182 [PMID: 6141332 DOI: 10.1016/S0140-6736(84)92109-3]

17 **Aabakken L**, Osnes M. 51Cr-ethylenediaminetetraacetic acid absorption test. Effects of naproxen, a non-steroidal, antiinflammatory drug. *Scand J Gastroenterol* 1990; **25**: 917-924 [PMID: 2120769 DOI: 10.3109/00365529008997613]

18 **Bjarnason I**, Williams P, So A, Zanelli GD, Levi AJ, Gumpel JM, Peters TJ, Ansell B. Intestinal permeability and inflammation in rheumatoid arthritis: effects of non-steroidal anti-inflammatory drugs. *Lancet* 1984; **2**: 1171-1174 [PMID: 6150232 DOI: 10.1016/S0140-6736(84)92739-9]

19 **Bjarnason I**, Williams P, Smethurst P, Peters TJ, Levi AJ. Effect of non-steroidal anti-inflammatory drugs and prostaglandins on the permeability of the human small intestine. *Gut* 1986; **27**: 1292-1297 [PMID: 3466837 DOI: 10.1136/gut.27.11.1292]

20 **Jenkins AP**, Trew DR, Crump BJ, Nukajam WS, Foley JA, Menzies IS, Creamer B. Do non-steroidal anti-inflammatory drugs increase colonic permeability? *Gut* 1991; **32**: 66-69 [PMID: 1899408 DOI: 10.1136/gut.32.1.66]

21 **Zuckerman MJ**, Watts MT, Bhatt BD, Ho H. Intestinal permeability to [51Cr]EDTA in infectious diarrhea. *Dig Dis Sci* 1993; **38**: 1651-1657 [PMID: 8359077 DOI: 10.1007/BF01303174]

22 **Zuckerman MJ**, Watts MT, Ho H, Meriano FV. Blastocystis hominis infection and intestinal injury. *Am J Med Sci* 1994; **308**: 96-101 [PMID: 8042662 DOI: 10.1097/00000441-199408000-00006]

23 **Werneck-Silva AL**, Sipahi AM, Damião AO, Buchpigue CA, Iriya K, Laudanna AA. Intestinal permeability in strongyloidiasis. *Braz J Med Biol Res* 2001; **34**: 353-357 [PMID: 11262586 DOI: 10.1590/S0100-879X2001000300009]

24 **de PAOLA**, DIAS LB, da SILVA J. Enteritis due to Strongyloides stercoralis. A report of 5 fatal cases. *Am J Dig Dis* 1962; **7**: 1086-1098 [PMID: 13941222]

25 **Viney ME**, Lok JB. Strongyloides spp. *WormBook* 2007: 1-15 [PMID: 18050491 DOI: 10.1895/wormbook.1.141.1]

26 **Cook GC**. Strongyloides stercoralis hyperinfection syndrome: how often is it missed? *Q J Med* 1987; **64**: 625-629 [PMID: 3328210]

27 **Purtilo DT**, Meyers WM, Connor DH. Fatal strongyloidiasis in immunosuppressed patients. *Am J Med* 1974; **56**: 488-493 [PMID: 4818417 DOI: 10.1016/0002-9343(74)90481-1]

28 **Igra-Siegman Y**, Kapila R, Sen P, Kaminski ZC, Louria DB. Syndrome of hyperinfection with Strongyloides stercoralis. *Rev Infect Dis* 1981; **3**: 397-407 [PMID: 7025145 DOI: 10.1093/clinids/3.3.397]

29 **Gerrard JW**, Geddes CA, Reggin PL, Gerrard CD, Horne S. Serum IgE levels in white and metis communities in Saskatchewan. *Ann Allergy* 1976; **37**: 91-100 [PMID: 987744]

30 **Strachan DP**. Hay fever, hygiene, and household size. *BMJ* 1989; **299**: 1259-1260 [PMID: 2513902 DOI: 10.1136/bmj.299.6710.1259]

31 **von Mutius E**, Vercelli D. Farm living: effects on childhood asthma and allergy. *Nat Rev Immunol* 2010; **10**: 861-868 [PMID: 21060319 DOI: 10.1038/nri2871]

32 **Asher MI**, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, Williams H; ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; **368**: 733-743 [PMID: 16935684 DOI: 10.1016/S0140-6736(06)69283-0]

33 **Nicolaou N**, Siddique N, Custovic A. Allergic disease in urban and rural populations: increasing prevalence with increasing urbanization. *Allergy* 2005; **60**: 1357-1360 [PMID: 16197466 DOI: 10.1111/j.1398-9995.2005.00961.x]

34 **Noverr MC**, Huffnagle GB. Does the microbiota regulate immune responses outside the gut? *Trends Microbiol* 2004; **12**: 562-568 [PMID: 15539116 DOI: 10.1016/j.tim.2004.10.008]

35 **Aoyama H**, Hirata T, Sakugawa H, Watanabe T, Miyagi S, Maeshiro T, Chinen T, Kawane M, Zaha O, Nakayoshi T, Kinjo F, Fujita J. An inverse relationship between autoimmune liver diseases and Strongyloides stercoralis infection. *Am J Trop Med Hyg* 2007; **76**: 972-976 [PMID: 17488925]

36 **Wammes LJ**, Mpairwe H, Elliott AM, Yazdanbakhsh M. Helminth therapy or elimination: epidemiological, immunological, and clinical considerations. *Lancet Infect Dis* 2014; **14**: 1150-1162 [PMID: 24981042 DOI: 10.1016/S1473-3099(14)70771-6]

37 **Helmby H**. Human helminth therapy to treat inflammatory disorders - where do we stand? *BMC Immunol* 2015; **16**: 12 [PMID: 25884706 DOI: 10.1186/s12865-015-0074-3]

38 **Vukman KV**, Lalor R, Aldridge A, O’Neill SM. Mast cells: new therapeutic target in helminth immune modulation. *Parasite Immunol* 2016; **38**: 45-52 [PMID: 26577605 DOI: 10.1111/pim.12295]

39 **Grencis RK**, Humphreys NE, Bancroft AJ. Immunity to gastrointestinal nematodes: mechanisms and myths. *Immunol Rev* 2014; **260**: 183-205 [PMID: 24942690 DOI: 10.1111/imr.12188]

40 **Allen JE**, Wynn TA. Evolution of Th2 immunity: a rapid repair response to tissue destructive pathogens. *PLoS Pathog* 2011; **7**: e1002003 [PMID: 21589896 DOI: 10.1371/journal.ppat.1002003]

41 **Schopf LR**, Hoffmann KF, Cheever AW, Urban JF Jr, Wynn TA. IL-10 is critical for host resistance and survival during gastrointestinal helminth infection. *J Immunol* 2002; **168**: 2383-2392 [PMID: 11859129 DOI: 10.4049/jimmunol.168.5.2383]

42 **Anuradha R**, Munisankar S, Dolla C, Kumaran P, Nutman TB, Babu S. Parasite Antigen-Specific Regulation of Th1, Th2, and Th17 Responses in Strongyloides stercoralis Infection. *J Immunol* 2015; **195**: 2241-2250 [PMID: 26202988 DOI: 10.4049/jimmunol.1500745]

43 **Anuradha R**, Munisankar S, Bhootra Y, Jagannathan J, Dolla C, Kumaran P, Shen K, Nutman TB, Babu S. Systemic Cytokine Profiles in Strongyloides stercoralis Infection and Alterations following Treatment. *Infect Immun* 2015; **84**: 425-431 [PMID: 26597982 DOI: 10.1128/IAI.01354-15]

44 **Summers RW**, Elliott DE, Qadir K, Urban JF Jr, Thompson R, Weinstock JV. Trichuris suis seems to be safe and possibly effective in the treatment of inflammatory bowel disease. *Am J Gastroenterol* 2003; **98**: 2034-2041 [PMID: 14499784 DOI: 10.1111/j.1572-0241.2003.07660.x]

45 **Summers RW**, Elliott DE, Urban JF Jr, Thompson R, Weinstock JV. Trichuris suis therapy in Crohn’s disease. *Gut* 2005; **54**: 87-90 [PMID: 15591509 DOI: 10.1136/gut.2004.041749]

46 **Summers RW**, Elliott DE, Urban JF Jr, Thompson RA, Weinstock JV. Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial. *Gastroenterology* 2005; **128**: 825-832 [PMID: 15825065 DOI: 10.1053/j.gastro.2005.01.005]

47 **Sandborn WJ**, Elliott DE, Weinstock J, Summers RW, Landry-Wheeler A, Silver N, Harnett MD, Hanauer SB. Randomised clinical trial: the safety and tolerability of Trichuris suis ova in patients with Crohn’s disease. *Aliment Pharmacol Ther* 2013; **38**: 255-263 [PMID: 23730956 DOI: 10.1111/apt.12366]

48 **Schölmerich J**, Fellermann K, Seibold FW, Rogler G, Langhorst J, Howaldt S, Novacek G, Petersen AM, Bachmann O, Matthes H, Hesselbarth N, Teich N, Wehkamp J, Klaus J, Ott C, Dilger K, Greinwald R, Mueller R; International TRUST-2 Study Group. A Randomised, Double-blind, Placebo-controlled Trial of Trichuris suis ova in Active Crohn’s Disease. *J Crohns Colitis* 2017; **11**: 390-399 [PMID: 27707789 DOI: 10.1093/ecco-jcc/jjw184]

49 **Croese J**, O’neil J, Masson J, Cooke S, Melrose W, Pritchard D, Speare R. A proof of concept study establishing Necator americanus in Crohn’s patients and reservoir donors. *Gut* 2006; **55**: 136-137 [PMID: 16344586 DOI: 10.1136/gut.2005.079129]

50 **McSorley HJ**, Gaze S, Daveson J, Jones D, Anderson RP, Clouston A, Ruyssers NE, Speare R, McCarthy JS, Engwerda CR, Croese J, Loukas A. Suppression of inflammatory immune responses in celiac disease by experimental hookworm infection. *PLoS One* 2011; **6**: e24092 [PMID: 21949691 DOI: 10.1371/journal.pone.0024092]

51 **Daveson AJ**, Jones DM, Gaze S, McSorley H, Clouston A, Pascoe A, Cooke S, Speare R, Macdonald GA, Anderson R, McCarthy JS, Loukas A, Croese J. Effect of hookworm infection on wheat challenge in celiac disease--a randomised double-blinded placebo controlled trial. *PLoS One* 2011; **6**: e17366 [PMID: 21408161 DOI: 10.1371/journal.pone.0017366]

52 **Benzel F**, Erdur H, Kohler S, Frentsch M, Thiel A, Harms L, Wandinger KP, Rosche B. Immune monitoring of Trichuris suis egg therapy in multiple sclerosis patients. *J Helminthol* 2012; **86**: 339-347 [PMID: 21838960 DOI: 10.1017/S0022149X11000460]

53 **Harnett W**. Secretory products of helminth parasites as immunomodulators. *Mol Biochem Parasitol* 2014; **195**: 130-136 [PMID: 24704440 DOI: 10.1016/j.molbiopara.2014.03.007]

54 **Round JL**, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol* 2009; **9**: 313-323 [PMID: 19343057 DOI: 10.1038/nri2515]

55 **Helmby H**. Helminths and our immune system: friend or foe? *Parasitol Int* 2009; **58**: 121-127 [PMID: 19223020 DOI: 10.1016/j.parint.2009.02.001]

56 **Williams AR**, Dige A, Rasmussen TK, Hvas CL, Dahlerup JF, Iversen L, Stensvold CR, Agnholt J, Nejsum P. Immune responses and parasitological observations induced during probiotic treatment with medicinal Trichuris suis ova in a healthy volunteer. *Immunol Lett* 2017; **188**: 32-37 [PMID: 28602842 DOI: 10.1016/j.imlet.2017.06.002]

57 **Maizels RM**. Parasitic helminth infections and the control of human allergic and autoimmune disorders. *Clin Microbiol Infect* 2016; **22**: 481-486 [PMID: 27172808 DOI: 10.1016/j.cmi.2016.04.024]

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