Does the failure to acquire helminthic parasites predispose to Crohn's disease?

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ABSTRACT **Two polarized patterns (Th1 and Th2) of cytokines regulate inflammatory responses. Each cytokine pattern inhibits production of the opposing pattern. Lymphocytes from inflamed intestine due to Crohn's disease secrete a Th1 pattern of cytokines. Crohn's disease is most prevalent in highly industrialized countries with temperate climates. It occurs rarely in tropical third world countries with poor sanitation. We propose that exposure to an environmental agent predisposes individuals to Crohn's disease. Parasitic worms (helminths) are common in tropical climates and in populations subject to crowding and poor sanitation. Children are most subject to helminthic colonization. Many helminths live within or migrate through the human gut where they interact with the mucosal immune system. The host mounts a mucosal response that includes Th2 cytokine production limiting helminthic colonization. Helminths and their eggs probably are the most potent stimulators of mucosal Th2 responses. The Th2 response provoked by parasitic worms can modulate immune reactions to unrelated parasitic, bacterial, and viral infections. Many people in developed countries now live in increasingly hygienic environments, avoiding exposure to helminths. Perhaps failure to acquire these parasites and experience mucosal Th2 conditioning predisposes to Crohn's disease, which is an overly active Th1 inflammation.—Elliott, D. E., Urban, J. F., Jr., Argo, C. K., Weinstock, J. V. *FASEB J.* 14, 1848–1855 (2000)**

Key Words: ulcerative colitis · helminths · Th1/Th2 response · CD

CROHN'S DISEASE (CD) is an idiopathic, chronic intestinal inflammation marked by periods of remission and relapse. CD can affect any part of the gut from mouth to rectum producing aphthous ulceration, transmural inflammation, granulomas, strictures, and fistulae (1). The frequency of CD has increased substantially over the last 40 years. It is most prevalent in temperate regions that are highly industrialized. This suggests that there is some critical environmental factor responsible for the change in frequency. Also, CD is rare in lesser developed countries (LDC). We propose that the absence of exposure to intestinal helminths is an important environmental factor favoring the development of CD and perhaps ulcerative colitis (UC).

GENETIC SUSCEPTIBILITY IN INFLAMMATORY BOWEL DISEASE (IBD)

Epidemiological data suggest a genetic susceptibility to the development of CD and UC (2–6). A definite positive family history is elicited from ~20% of patients with CD or UC (2, 7). Twin pair studies suggest a genetic basis for familial predisposition (8). Yet genomic scanning of IBD sibling-pair families and subsequent linkage analysis have yielded inconclusive results (9, 10). This suggests that several genes may impact the risk for or severity of IBD depending on the patient population.

ENVIRONMENTAL INFLUENCES IN IBD

The incidence of CD in industrialized societies increased from the 1950s until the mid-1980s, and is now 8 per 100,000 persons per year in some locales (**Table 1**). This change in one generation is much too rapid to be solely gene-based. Instead, alterations in our environment must have increased dramatically the risk for CD in genetically predisposed individuals.

The prevalence of IBD varies according to occupation and geography. Both UC and CD are less frequent in people with blue collar jobs involving exposure to dirt and physical exercise (24). IBD is most common in temperate climates. Hospital records of U.S. military veterans suggest that being raised in the rural South

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TABLE 1. *Trends in the average annual incidence (new cases) of Crohn's disease in the same locales over time*

Locale	Annual incidence of Crohn's disease (per 100,000)						Reference
	1930s	1940s	1950s	1960s	1970s	1980s	
Olmsted Co., Minnesota, USA		0.8	2.5	4.5	6.8		(11)
Cardiff, Wales	0.25	0.7	1.5	3.2	4.9	7.1	(12, 13)
Derby, England			0.7	2.0	4.7	6.7	(14)
Notingham, England			0.7	1.9	3.6		(15)
N./N.E. Isles, Scotland			1.7	4.0	6.0	8.2	(3)
Stockholm Co., Sweden			1.4	3.0	4.6	4.7	(16)
Örebro and Central, Sweden			1.5	3.3	5.1	6.7	(17, 18)
Malmö, Sweden			2.8	4.4	6.2		(19)
Copenhagen Co., Denmark				0.7	2.5	4.1	(20)
Kinneret, Israel				1.0	1.3	3.0	(21)
Beer Sheva, Israel				0.6	1.2	2.1	(22, 23)

affords protection (25). Data from Europe also support the existence of a similar North-South gradient (26). CD and UC are rare in Asia (27), Africa (28, 29), and South America (30). An exception is the white population of South Africa (31).

Infectious dysentery is common in LDC, making IBD more difficult to diagnose. However, misdiagnosis alone cannot explain the rarity of IBD in the tropics. Physicians in these countries can recognize the unique features of CD and UC. A lack of genetic risk does not explain the rarity of IBD in tropical LDC because the descendants of immigrants living in industrialized regions develop CD (32, 33).

There is a higher prevalence of IBD among Jews living in the northern hemisphere. It appears that Jews living near the equator have substantially lower rates. Descendants of Jewish immigrants to Israel and South Africa, countries with a more Western style of living, have an intermediate rate of disease (34). The various Jewish ethnic groups living in Israel do not develop CD and UC according to their country of origin, but rather conform to the prevalence expected in Israel (35, 36). There remains an extremely low frequency of IBD in the Israeli Arab community (37–40).

It is not known what causes the geographic differences, but the data suggest that an environmental exposure unique to temperate countries and highly industrialized societies predisposes to the development of IBD. An alternative explanation is that it is unhealthy to be raised in an 'overclean' environment. We propose that a major environmental factor predisposing to IBD is underexposure to intestinal helminths, which promote strong T helper 2 (Th2) -type inflammation.

THE REGULATION OF T HELPER (TH) CELL RESPONSES

T lymphocytes, along with other cell types, secrete cytokines, small soluble proteins that have autocrine and paracrine effects on T cell function. A naïve Th cell, first presented with a specific antigen, will secrete interleukin 2 (IL-2) and begin to proliferate. As the Th cell expands into a clone, members of the population secrete other cytokines such as interferon γ (IFNγ), LT, tumor necrosis factor α (TNF-α), IL-4, IL-5, IL-10, or IL-13. With prolonged antigen exposure, the cytokine profile secreted by the T cells can polarize to either the Th1 (IFNγ, LT, TNF-α) or Th2 (IL-4, IL-5, IL-10, IL-13) pattern (41, 42).

This polarization has important consequences. Th1 cytokines mediate delayed-type hypersensitivity reactions, macrophage activation, cellular cytotoxicity, and switch B cell immunoglobulin (Ig) production to subclasses that fix complement (murine IgG2a or human IgG1). Th2 cytokines mediate eosinophilia, B cell proliferation, and switch B immunoglobulin production to IgA, IgE, and IgG subclasses that do not fix complement (murine IgG1 or human IgG4). The Th2 cytokines IL-4, IL-13, and IL-10 inhibit delayed-type hypersensitivity reactions, macrophage activation, and cytotoxicity.

In the last decade, much research has focused on what events result in the polarization of cytokine responses. Antigen dose, accessory cell function, and costimulatory molecule display help select for Th1 or Th2 cells. However, the dominant effector shaping the Th1- or Th2-type response is the cytokine profile present during antigen stimulation (43).

The presence of IL-12, IL-18, and IFNγ promotes expansion of Th1 cells. IL-12 and IL-18 released from macrophages augments Th1 cell development and stimulates secretion of IFNγ. IFNγ increases antigen presentation and IL-12 production by macrophages (44). IFNγ increases Th1 cell high-affinity IL-12 receptor display (45). IFNγ inhibits the proliferation of Th2, but not Th1 cells (46). Thus, the

IL-12/IFNγ positive feedback circuit augments Th1 while inhibiting Th2 cell development.

The presence of IL-4 and IL-10 promotes expansion of Th2 cells. IL-4 is an autocrine growth and differentiation factor for Th2 cells (47–50). IL-4 signals through the 'signal transducer and activator of transcription' 6 (STAT6) to augment its own production in a positive feedback circuit (51). Yet IL-4 inhibits release of IL-12 and other cytokines from macrophages (52), a characteristic shared with IL-13 and IL-10 (53). IL-10 inhibits macrophage accessory cell function required by differentiated Th1 cells, but not Th2 cells (54). Thus, IL-4, IL-13, and IL-10 inhibit Th1 cell development while fostering Th2 responses.

THE IMMUNOPATHOLOGY OF CD AND UC

Although the cause of IBD remains undetermined, it is presumed to result from dysregulation of the intestinal mucosal immune system. Inflammatory cells in the mucosa normally protect us from potentially harmful intestinal contents. This highly effective chronic inflammation is tightly controlled to limit tissue injury.

It is unlikely that IBD results from chronic infection with a specific persistent pathogenic organism. Effective treatment of CD often requires medications that suppress cellular immunity. CD will usually remain in remission after immunosuppressive medications are withdrawn (1). Persistent infections typically worsen with such treatment. Animal models of IBD show that normal intestinal flora induces intestinal inflammation in animals with a dysregulated immune system.

IBD most likely results from inappropriately vigorous immune responses to normal intestinal contents. CD appears to be an overly vigorous Th1-type inflammation that produces IFNγ and TNF-α (55). The cytokine profile of UC is not as polarized, but does show elevated IFNγ production in some studies (56).

ANIMAL MODELS OF IBD

Although there are no actual animal models of human IBD, there are several animal models of chronic intestinal inflammation. An important advance is the discovery that some mice with genetically engineered gene deletions develop chronic bowel inflammation similar to IBD. These include mutant mice bearing targeted deletions for IL-2, IL-10, MHC class II, or TCR genes, among others (57–60). Using some of the models, investigators have shown that a dysregulated immune system itself mediates intestinal injury. The mucosal inflammation of several of these models generates large amounts of IFNγ and TNF-α suggesting that excess production of Th1-type cytokines is one common mechanism underlying the pathogenesis of disease. Also, blocking Th1 circuitry prevents the inflammation (58, 59, 61). CD appears to be a dysregulated Th1 response. Thus, these models may have direct implications regarding the immunopathology of this human disease process.

THE NATURE OF HELMINTHS

Helminths are elaborate multicellular worms with complex life cycles and development (62, 63). The nematodes (nonsegmented roundworms) and the platyhelminths (flatworms) are the two groups of helminths that colonize the human intestines. More than a third of the population of the world currently shelter one or more of these organisms (**Table 2**). The lifetime exposure rate, however, is actually much greater. The prevalence of helminths is highest in warm climates and in populations subject to crowding, poor sanitation, and impure food supply. IBD is rare in these same regions.

The host acquires various helminthic species through contact with soil, food, or water contaminated with the infective form of the parasite. Children most frequently harbor helminths because of their close contact with soil and suboptimal hygienic practices. Helminths incite an intestinal Th2 response, which can cause worm expulsion or limit colonization (64–75). Most children living in LDC have these parasites. Many helminthic species survive for years within the gut, biliary tree, or mesenteric veins. Thus, beginning in childhood, these worms and/or their ova release molecules that bathe the intestinal mucosal surface for years, inciting Th2-type cytokines.

There are limited epidemiologic data regarding the historical and current prevalence of helminths in the U.S. and worldwide. Yet there are sufficient data to know that helminths were once extremely common, particularly among children living in the

TABLE 2. *Helminths that colonize the human gastrointestinal system*

Nematodes (roundworms):
Enterobius vermicularis (pinworm), *Trichuris trichiura* (whipworm), *Ancylostoma duodenale* and *Necator americanus* (hookworms), *Ascaris lumbricoides, Strongyloides stercoralis,* and *Trichinella spiralis*
Platyhelminths (flatworms):
Trematodes (flukes):
Fasciolopsis sp., Echinostoma sp., Heterophyes sp., Clonorchis sinensis, Opisthorchis viverrini, O. felineus, Fasciola hepatica, Schistosoma mansoni, and *S. japonicum*
Cestodes (tapeworms):
Diphyllobothrium sp., Taenia saginata, T. solium

Southeastern region of the United States (76). Prior to the 1930s, it is probable that nearly all children harbored one or more of these organisms. In the 1940s, one in six Americans showed signs of previous *Trichinella* exposure upon routine autopsy. This decreased to less than 5% by the 1960s, with only 0.5% showing signs of recent infection (77). Hookworm infection was common in the southern U.S. the first quarter of the 20th century, but had declined substantially by the 1950s (78). In the late 1940s, at least 20% of randomly sampled children admitted to Charity Hospital of New Orleans harbored *Trichocephalus trichiura* (79). The prevalence of this organism remained high in African (80) and native Americans into the 1960s. In 1965, 92% of children living on the Cherokee North Carolina Indian Reservation bore intestinal parasites determined by a single stool examination (81). Ascaris (50%) and *Trichuris* (38%) were detected most frequently. Similarly, a survey of intestinal helminths among school children in three eastern Kentucky counties revealed high prevalence rates for both of these parasites (82).

The prevalence of helminths in the U.S. has been declining for the past 60 years (83). The exception is new immigrants to the U.S. from LDC (84, 85) and some populations in under-served areas (81). IBD remains rare in these groups.

Another example is the inverse difference in frequency of CD and helminthic colonization between the Jewish and Arab Israelis. In 1969, stool examinations of hospitalized patients in Arab-predominant East Jerusalem contained helminthic ova over 60% of the time. The frequency in Jewish Israeli-predominant West Jerusalem was 10% or less (86). CD is much more common in Jewish Israelis than the Israeli Arab community (37–40).

THE IMMUNE RESPONSE TO HELMINTHS PROMOTES TH2 RESPONSES TO UNRELATED ANTIGENS

It is established that infestation with helminths, which all induce Th2-type inflammation, can modulate the Th1 immune response to unrelated concomitant parasitic, bacterial, and viral infections. Patients infected with *Schistosomiasis mansoni* mount more of a Th2-like response to tetanus toxoid immunization than the usual Th1 or Th0 (87). Ethiopian immigrants with a high prevalence of helminths have eosinophilia and a propensity to respond to PHA with Th2, rather than Th1 cytokines (88).

Animal experimentation supports this contention. Mice infected with *Mycobacterium avium* develop chronic Th1-type granulomatous inflammation in the lungs and liver. Splenocytes and granuloma cells from these infected animals normally produce IgG2a and IFNγ, and no IL-4 or IL-5. However, mice infected with *S. mansoni* after the establishment of *M. avium* infection form mycobacterial granulomas containing eosinophils. Also, splenocytes and granuloma cells from coinfected mice secrete more IgG1 and much less IgG2a. The cytokines released from these cells both constitutively or after mycobacterial antigen stimulation include IL-4 and IL-5 and much less than normal quantities of IFNγ (R. E. Sacco and J. V. Weinstock, unpublished observation).

There are other examples. Infection of mice with *S. mansoni* delays clearance of vaccinia virus and alters responsiveness to sperm whale myoglobin (89). Mice also develop a Th2 response when infected with the microfilariae *Brugia malayi* or are immunized with a soluble filarial extract from this parasite. The ongoing Th2 response to this helminth antigen modulates the Th1 response to mycobacterial antigen (90). Moreover, *Nippostrongylus brasiliensis,* a murine intestinal nematode, stimulates Th2 activity. *Nippostrongylus* delays kidney graft rejection in rats. Cross-regulatory suppression of Th1 activity probably is the mechanism (91).

Oral tolerance refers to the induction of systemic immune nonresponsiveness to an antigen after its oral administration. Mice colonized with *Heligmosomoides polygyrus,* which elicits a mucosal Th2 response, have enhanced oral tolerance to Th1 antigens (92).

These findings have important implications. Persons harboring helminths possibly are more apt to mount a diminished Th1 response when challenged with other antigens. This may prevent an overly exuberant Th1 inflammation at mucosal surfaces like that seen in CD.

EXPERIMENTAL EVIDENCE THAT EXPOSURE TO HELMINTHS LIMITS TH1-TYPE INTESTINAL INFLAMMATION

We tested the hypothesis that exposure to intestinal helminths limits Th1-mediated colitis by using murine models of Th1 intestinal inflammation. Mice rectally challenged with trinitrobenzenesulfonic acid and ethanol develop colitis, which is prevented by inhibiting Th1 cytokine circuitry (93). Mice preexposed to *S. mansoni* had diminished Th1 and augmented Th2 responses, and were protected from developing colitis in this model (94)

We also treated IL-10-deficient mice with intestinal helminths. Mice with disrupted IL-10 genes develop severe colitis due to excessive Th1 responses to colonic contents (58). For these experiments, IL-10-deficient mice (C57BL/6-*Il10*^{tm1Cgn}, Jackson Laboratories, Bar Harbor, Maine) were inoculated *per os*

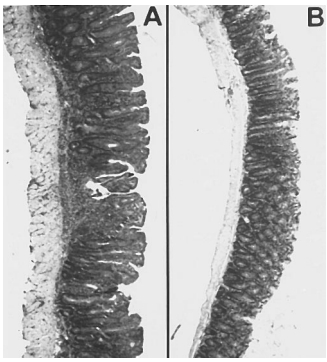

Figure 1. Exposure to *Heligmosomoides polygyrus* reduces intestinal inflammation in IL-10-deficient mice. *A*) Representative field from a sham-exposed, IL-10−/− mouse. *B*) Representative field from an littermate IL-10−/− mouse previously exposed to *H. polygyrus.*

with 200 *H. polygyrus* third stage larvae, which develop into fecund adult worms in the jejunum (95). Control IL-10 −/− received gavage lacking parasites. Thirty five days after inoculation, the mice had persistent colonization with mature worms and were 10 wk of age. At this time, colons were removed, fixed, and sectioned for histiologic examination. The sections were coded and examined by two investigators blinded to the treatment groups. Each group contained at least 5 animals and the experiment was repeated three times. Inflammation was graded on a four point scale; 0 = no inflammation, 1 = low level inflammation, 2 = intermediate level, 3 = high level inflammation with wall thickening, and 4 = transmural infiltration, loss of goblet cells, and wall thickening (93)

As shown in **Fig. 1**, sham-exposed IL-10 −/− mice spontaneously develop severe colitis (average score 3.67±0.17). However, animals exposed to *H. polygyrus* had significantly less intestinal inflammation (2.2±0.44, $P<0.01$ by Student's *t* test).

Exposure to a different helminth, *Trichuris muris,* also reduced colitis in IL-10-deficient mice. In these experiments, C57BL/6-*Il10*^{tm1Cgn} were inoculated with 5000 *T. muris* eggs. Colons were removed from the mice 59 days after initial inoculation, when the animals were 14 wk of age. Colon histology was evaluated by two investigators blinded to the treatment groups. Sham-exposed IL-10 −/− mice developed severe colitis (3.03±0.3) whereas mice exposed to *T. muris* had attenuated intestinal inflammation (2.2±0.1, $P<0.05$). *T. muris* also protected normal Balb/c mice from TNBS colitis (94).

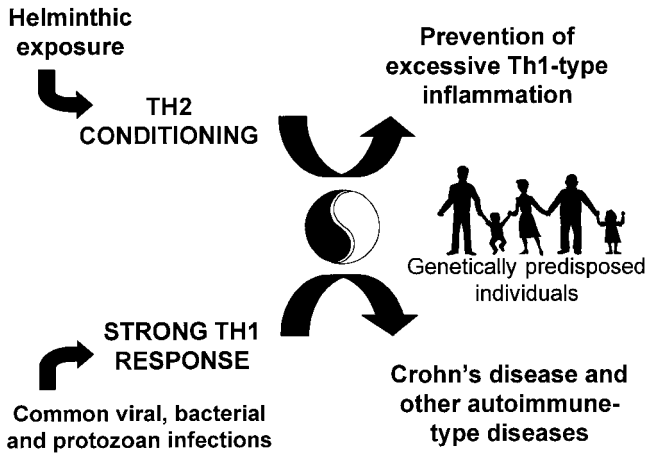

Figure 2. Exposure to helminths promotes Th2-type immune responses that may prevent development of the excessive Th1-type inflammatory reactions that cause autoimmune disease in genetically predisposed people.

TABLE 3. *The hygiene hypothesis*

1. Organisms that live in our intestines are important for toning and shaping not only our local intestinal immune system, but also our systemic immune responses.
2. The progressively hygienic lifestyles of people living in industrialized societies have removed us from the natural surroundings that drove adaptation of our immune systems, and now provide an intestinal environment far different from that of our ancestors.
3. This difference is leading to the emergence of various autoimmune and other types of immunological diseases.
4. Loss of helminthic colonization and the unique influence of these animals on our immune response are major factors contributing to development of these diseases.

SUMMARY

People in developed countries are living in increasingly hygienic environments and are acquiring helminths much less frequently. The decreasing frequency of helminthic colonization appears to correlate with the increasing prevalence of CD. Helminths induce strong Th2 immune responses that can inhibit or deviate Th1 responses to other antigens. A dysregulated Th1 mucosal immune response likely causes CD. It is possible that the failure to acquire helminths and to experience mucosal Th2 conditioning predisposes to CD and possibly UC (**Fig. 2**).

Other Th1-driven inflammatory diseases exist that share the distinctive epidemiology of IBD. For example, multiple sclerosis (MS) is rare in tropical countries and more common in industrialized, temperate regions. MS results from an exuberant Th1 immune response probably directed against a peptide sequence shared by a virus (or bacteria) and cells that make myelin. Initial exposure to viruses or bacteria usually occurs at mucosal surfaces. Mucosal Th2 conditioning may prevent dysregulated Th1 responses to such shared peptide sequences.

Assuming this hypothesis is correct, we do not advocate a return to less hygienic conditions. Certainly, some helminths can cause or contribute to severe disease (96). Yet most people harbor relatively few intestinal helminths and have no symptoms attributable to these organisms (97). Perhaps by eradicating helminths from our envi-

ronment, we have inadvertently allowed increased expression of diseases due to dysregulated inflammation (**Table 3**). FJ

This work was supported by National Institutes of Health grants AM38327 and DK02428, by the Crohn's and Colitis Foundation of American, and by the Thomas Irwin Memorial Fund.

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Received for publication October 7, 1999.
Revised for publication January 3, 2000.