DOES THE FAILURE TO ACQUIRE HELMINTHIC PARASITES PREDISPOSE TO IBD?

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Running Heading: Helminthic parasites and IBD

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Abstract

Two polarized patterns (Th1 and Th2) of cytokines, secreted by stimulated lymphocytes, 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. This suggests that under exposure to an environmental agent may predispose 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. Helminthic parasites live within the human gut where they interact with the mucosal immune system. The host mounts mucosal Th2 inflammation that limits helminthic infection or expels worms. Helminthic parasites and their eggs probably are the most potent stimulators of mucosal Th2 responses. The Th2 inflammation provoked by parasitic worms can modulate the immune response to unrelated parasitic, bacterial, and viral infections. Many people now live in increasingly hygienic environments avoiding exposure to helminthic parasites. Perhaps failure to obtain these parasite infections and experience mucosal Th2 conditioning during childhood predisposes to Crohn's disease, which is an overly active Th1 inflammation

Keywords: Crohn's disease, ulcerative colitis, intestinal parasites, Th1/Th2 response

The frequency of Crohn's disease (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, ulcerative colitis is rare in underdeveloped countries. We propose that the absence of exposure to intestinal helminthic infections in childhood is an important environmental factor favoring the development of CD and perhaps ulcerative colitis (UC).

Genetic susceptibility in IBD: Epidemiological data suggest a genetic susceptibility to the development of CD and UC (Roth *et al.*, 1989a; Lashner *et al.*, 1986; Kyle, 1992; Orholm *et al.*, 1991; Meucci *et al.*, 1992). A definite positive family history can be elicited from about 20% of patients with CD or UC (Singer *et al.*, 1971; Roth *et al.*, 1989b). Although environmental factors alone can account for familial and regional aggregation (Hugot *et al.*, 1996), twin pair studies do suggest that there is genetic basis for familial predisposition (Tysk *et al.*, 1988). Yet, genomic scanning of IBD sibling-pair families and subsequent linkage analysis have yielded inconclusive results (Gusella and Podolsky, 1998).

Environmental influences in IBD: The incidence of CD in industrialized societies has increased from the 1950s until the mid 1980s, and now is from 1 to 8 per 100,000 persons per year (Rose *et al.*, 1988; Calkins, 1989; Ekbom *et al.*, 1990). This suggests that unknown changes in our environment have effected the frequency of CD.

IBD is more common in temperate climates. Occupation may be a risk factor, since both UC and CD are less frequent in people with blue collar jobs involving exposure to dirt and physical exercise (Sonnenberg, 1990). Hospital records of U.S. military veterans suggest that being raised in the rural south affords protection (Sonnenberg and Wasserman, 1991). Data from Europe also support the existence of a similar North-South gradient (Shivananda *et al.*, 1996). CD and UC are rare in Asia (Tan *et al.*, 1992), Africa (Hutt, 1979; Segal, 1984), and South America (Rolon, 1979). An exception is the white population of South Africa (Wright *et al.*, 1983). Infectious dysentery is common in these areas, making IBD more difficult to diagnose. However, misdiagnosis alone cannot explain the rarity of IBD in tropical third world countries. Physicians in these countries have the ability to recognize the unique features of CD and UC. Also, the descendants of immigrants from third world countries living in industrialized regions develop CD (Jayanthi *et al.*, 1992; Kurata *et al.*, 1992).

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. Decendents of Jewish immigrants to Israel and South Africa, countries with more Western style of living, have an intermediate rate of disease (Novis *et al.*, 1975). Epidemiologic studies of the Israeli population indicate a lower than expected prevalence of CD among immigrants from northern Europe and North America. The converse is true for immigrants from other Middle Eastern and Mediterranean countries. Thus, 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 (Fireman *et al*., 1989; Grossman *et al*., 1989). There remains an extremely low frequency of IBD in the Israeli Arab community (Niv *et al*., 1990; Shapira and Tamir, 1992; Odes *et al*., 1991; Odes *et al*., 1994).

It is not know what causes the geographic differences. These observations may suggest 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 the major environmental factor predisposing to IBD is underexposure during childhood to intestinal helminths, which promote strong T helper 2 (Th2) -type inflammation.

The regulation of T helper 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 IL2 and begin to proliferate. As the Th cell expands into a clone, members of the population secrete other cytokines such as IFNγ, LT, TNFα, IL4, IL6, IL9, IL10 or IL13. With prolonged antigen exposure the cytokine profile secreted by the Th cell clone can polarize to either the Th1 (IFNγ, LT, TNFα) or TH2 (IL4,IL5, IL6, IL9, IL10, IL13) pattern(Mosmann *et al*., 1986; Romagnani, 1994).

This polarization has important consequences. Th1 cells mediate delayed-type hypersensitivity reactions, macrophage activation, cellular cytotoxicity, and switch B cell immunoglobulin production to subclasses that fix complement (murine

IgG2a or human IgG1). Th2 cells mediate allergic responses, 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 IL4, IL13 and IL10 inhibit delayed-type hypersensitivity reactions, macrophage activation, and cytotoxicity. In general, the Th1 cytokines are pro-inflammatory while Th2 cytokines are anti-inflammatory.

In the last decade, much research has focused on what events result in the polarization of T cell cytokine responses. Antigen dose, accessory cell function, and co-stimulatory molecule display help select for Th1 or Th2 cells. However, the dominant effector shaping the Th1 or Th2 response is the cytokine profile present during antigen stimulation (Seder and Paul, 1994).

The presence of IL-12, IL-18 and IFNγ promotes expansion of Th1 cells. IL12 and IL18 released from macrophages augments Th1 cell development and stimulates secretion of IFNγ. IFNγ increases antigen presentation and IL12 production by macrophages (Kubin *et al.*, 1994). IFNγ increases Th1 cell high affinity IL12 receptor display (Gollob *et al.*, 1997). IFNγ inhibits the proliferation of Th2 but not Th1 cells (Gajewski and Fitch, 1988). Thus, the IL12/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 (Lichtman *et al.*, 1987; Swain *et al.*, 1990; Betz and Fox, 1990; Le Gros *et al.*, 1990). IL-4, signals through the “signal transducer and activator of transcription” 6 (STAT6), to augment it’s own

production in a positive feedback circuit (Lederer *et al.*, 1996). Yet, IL-4 inhibits release of IL-12 and other cytokines from macrophages (de Waal *et al.*, 1993), a characteristic shared with IL-13 and IL-10 (Moore *et al.*, 1993). IL-10 inhibits macrophage accessory cell function required by differentiated Th1 cells but not Th2 cells (Fiorentino *et al.*, 1991). IL-10 inhibits the up-regulation of the costimulatory molecule B7 (Ding *et al.*, 1993; Willems *et al.*, 1994)on macrophages and differentiated Th2 cells are not highly dependent on costimulation through B7/CD28 (McKnight *et al.*, 1994). Thus, IL-4, IL-13 and IL-10 inhibit Th1 cell development while fostering Th2 responses.

The immunopathology of CD and UC: While 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 luminal contents. This highly effective chronic inflammation is tightly controlled to limit tissue injury. IBD may result from inappropriately vigorous immune responses to luminal factors. CD appears to be an overly vigorous Th1-type inflammation that produces IFN-γ and TNFα (Fuss *et al.*, 1996). The nature of UC is less well defined.

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 recent discovery that some mice with genetically engineered gene deletions can 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 (Elson *et al.*, 1995; Berg *et al.*, 1996; Powrie *et al.*,

1996; Mizoguchi *et al.*, 1996; Ehrhardt *et al.*, 1997). Using some of the models, investigators have shown that a dysregulated immune system itself can mediate intestinal injury. The mucosal inflammation of several of these models generates large amounts of IFN-γ 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 (Berg *et al.*, 1996; Ehrhardt *et al.*, 1997). CD is a Th1 response. Thus, these models may have direct implications regarding the immunopathology of this human disease process.

The nature of helminthic infections: Helminths are elaborate multicellular worms with complex life cycles and development (Weinstock, 1996). The nematodes (non-segmented roundworms) and the platyhelminths (Flatworms) are the two groups of helminths that colonize the human intestines. Perhaps more than a third of the population of the world currently shelter one or more of these organisms. The life-time exposure rate, however, is actually much more. 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 helminthic infections because of their close contact with soil and suboptimal hygienic practices. Helminths incite an intestinal Th2 response, which can cause worm expulsion or limit the magnitude of infection (Herndon and Kayes,

1992; Korenaga *et al.*, 1996; Negrao-Correa *et al.*, 1996; Korenaga *et al.*, 1989; Ramaswamy *et al.*, 1996; Urban *et al.*, 1992; Urban *et al.*, 1993; Finkelman *et al.*, 1994; Urban *et al.*, 1995; Grencis, 1993; Else *et al.*, 1992; Else *et al.*, 1994; Bancroft *et al.*, 1994; Metwali *et al.*, 1996; Asano and Okamoto, 1992; Bortoletti *et al.*, 1992). Most children living in non-industrialized countries have these parasites. Many helminthic species survive for years within the gut, biliary tree or mesenteric veins making thousands of eggs daily. Thus, beginning in childhood, these worms and/or their ova release molecules that bathe the intestinal mucosal surface for years inciting Th2-type inflammation.

Nematodes that frequently inhabit the human gut are *Ascaris lumbricoides*, *Enterobius vermicularis* (pin worm*), Trichuris trichiura* (whipworm), *Ancylostoma duodenale* and *Necator americanus* (hookworms), and *Strongyloides stercoralis*. *Trichinella spiralis* infests the small intestine briefly.

The platyhelminths include the trematodes and cestodes. The most common adult trematodes that reside in the human intestines are *Fasciolopsis*, *Echinostoma* and *Heterophyes* species. Those that live in the biliary system include *Clonorchis sinensis*, *Opisthorchis viverrini* and *felineus*, and *Fasciola hepatica*. *Schistosoma* dwell in the venous system, but several species chronically affect the gut by the passage of eggs through the intestinal wall. Adult cestodes commonly infecting humans are *Diphyllobothrium* species (fish tapeworm), *Taenia*

saginata (beef tapeworm), *Taenia solium* (pork tapeworm) and *Hymenolepsis nana* (dwarf tapeworm).

There are limited epidemiologic data regarding the historical and current prevalence of helminthic parasites in the U.S. and worldwide. Yet, there are sufficient data to know that helminthic infections were extremely common particularly in children living in the Southeastern region of the United States (Blumenthal, 1977; Warren, 1974). Prior to the 1930's, it is probable that nearly all children harbored one or more of these organisms. In the 1940's, one in six Americans were infected with *Trichinella* (Zimmermann *et al*., 1968). This decreased to less than 5% by the 1960's (Zimmermann *et al*., 1968). In the late 1940's, at least 20% of randomly sampled children admitted to Charity Hospital of New Orleans harbored *T. trichiura* (Jung and Beaver, 1951). The prevalence of this organism remained high in African (Jeffrey *et al.*, 1963) and native Americans into the 1960's. In 1965, 92% of Children living on the Cherokee North Carolina Indian Reservation bore intestinal parasites as determined by a single stool examination (Healy *et al*., 1969). *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 (Fulmer and Huempfner, 1965).

The immune response to helminthic parasites promotes Th2 responses to unrelated antigens: It is already established that infestation with helminthic parasites, which all induce Th2-type inflammation, can modulate the Th1

immune response to unrelated concomitant parasitic, bacterial and viral infections. Patients infected with *S. mansoni* mount more of a Th2-like response to tetanus toxoid immunization than the usual Th1 or Th0 (Sabin *et al.*, 1996). Ethiopian immigrants with a high prevalence of helminthic infections have eosinophilia and a propensity to respond to PHA with Th2, rather than Th1 cytokines (Bentwich *et al.*, 1996).

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 IFN-γ, and no IL-4 or IL-5. However, mice infected with *S. mansoni* after the establishment of *Mycobacterium avium* infection form mycobacterial granulomas containing eosinophils. Also, splenocytes and granuloma cells from co-infected 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 IFN-γ (unpublished observation).

There are other examples. Infection of mice with *S. mansoni* delays clearance of vaccinia virus and alters responsiveness to sperm whale myoglobin (Kullberg *et al.*, 1992). Mice also develop a Th2 response when infected with the microfilariae, *Brugia malayi*, or immunized with a soluble filarial extract from this parasite. The ongoing Th2 response to this helminth antigen modulates the Th1 response to mycobacterial antigen (Pearlman *et al.*, 1993). 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 (Ledingham *et al.*, 1996).

Oral tolerance refers to the induction of systemic immune non-responsiveness to an antigen following its oral administration. Mice colonized with *H. polygyrus,* which elicits a mucosal Th2 response, have enhanced oral tolerance to Th1 antigens (Shi *et al.*, 1998).

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.

Summary: People in industrialized countries are living in increasingly hygienic environments and are acquiring helminths much less frequently. The decreasing frequency of helminthic infections appears to correlated with the increasing prevalence of CD. A case in point is the marked increase in the frequency of CD in young Asians and Africans after residing in Israel for greater than 10 years (Fireman *et al.*, 1989). Also, the frequency of helminthic colonization differs between the Jewish Israelis and Arabs. In 1969, stool examinations of hospitalized patients in Arab predominant East Jerusalem contained helminthic ova over 60% of the time. The frequency in Israeli predominant East Jerusalem was 10% or less (Jjumba-Mukasa and Gunders, 1971; Ben-Ari, 1962).

Thus, It is possible that the failure to acquire helminths and to experience mucosal Th2 conditioning predisposes to CD and UC **(Figure 1)**. Helminthic Th2 conditioning protects mice from TNBS-induced colitis (manuscript in preparation). Ongoing epidemiological surveys and animal investigation will further test the validity of this hypothesis.

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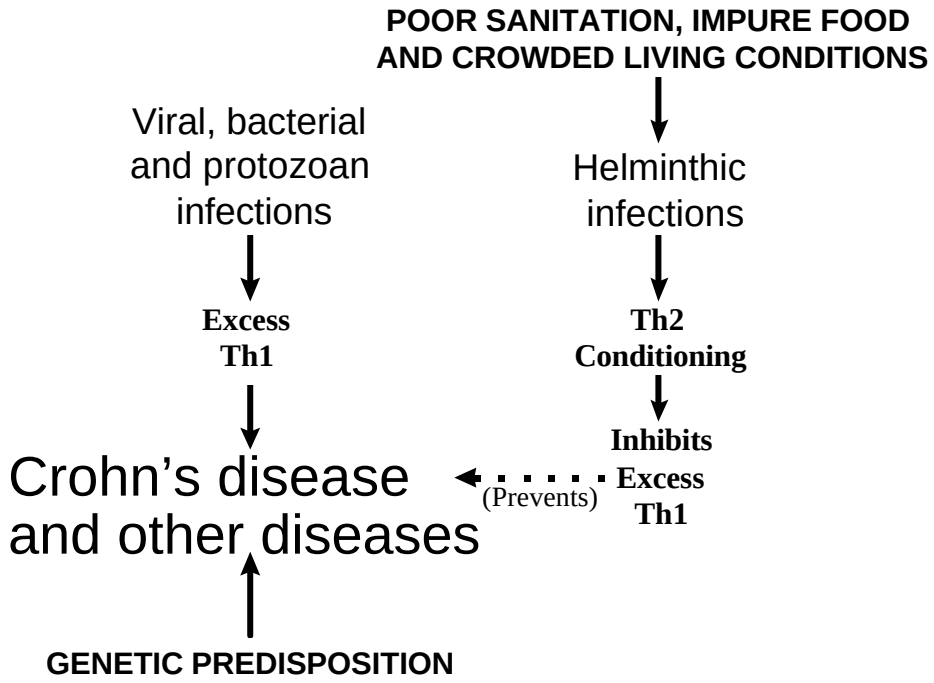
Figure 1:


POOR SANITATION, IMPURE FOOD
AND CROWDED LIVING CONDITIONS
Viral, bacterial and protozoan infections
Helminthic infections
Excess Th1
Th2 Conditioning
Inhibits Excess Th1
(Prevents)
Crohn's disease and other diseases
GENETIC PREDISPOSITION