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Giardia: both a harmless commensal and a devastating pathogen

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The highly prevalent protozoan *Giardia lamblia* is an enteropathogen that can be asymptomatic in some individuals, while leading to persistent diarrhea and substantial morbidity in others. In this issue of the *JCI*, Bartelt et al. describe a mouse model of the disease and investigate the contribution of coincident malnutrition with the development of symptomatic infection. This work in part explains how *Giardia* infection can lead to growth retardation, and may offer insights that guide future therapeutic strategies.

Giardia lamblia (synonymous with *G. intestinalis* and *G. duodenalis*), referred to herein as *Giardia*, was first detected in 1681 by Antonie van Leeuwenhoek when looking at his own stools and was later described in 1859 by Lambl (1). Finding the organism as frequently in patients without symptoms as in those with diarrheal illness has led

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many over the years to conclude that the organism is not a pathogen. Giardia can be identified in stools of 2% to 5% of presumably healthy people living in industrialized countries like the United States and in 20% to 30% of people in developing regions (2). It is found in water sources and infects many animal species. The organism can be classified into at least 8 different genotypes called assemblages in humans and animals, with assemblages A and B being the most important in human infection. Each year in the United States, we identify approximately 20,000 people with Giardia infection, but the actual prevalence is estimated to be much higher.

The two faces of Giardia infection

In rural areas of the developing world, Giardia is ubiquitous and infects nearly all children, although most remain free of symptoms (3). In these endemic areas, infants experience an acute clinical disease only when first exposed to the protozoan, but quickly recover from infection without adverse long-term effects (4). Self-limiting diarrhea from a Giardia infection is common in young children newly attending day care centers (5, 6) and in international travelers (7) to endemic areas when first exposed to the protozoa. After initial exposure in otherwise healthy people, symptomatic infection occurs rarely. Risk factors for first symptomatic infection in young children were shown in one study carried out in rural Egypt to include young age, poverty, low education level, in-home storage of drinking water, and unhygienic treatment of girls related to gender discrimination (8). A proportion of infected people, mainly underweight children with preexistent mal-

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First exposure: self-limited illness that may include diarrhea, abdominal pain, bloating, nausea, vomiting, and minimal mucosal alterations

Ingestion of a Giardia strain



Malnourished young children with secondary immune defects and reduced gastric acidity People of any age with hypogammaglobulinemia or selective IgA deficiency

Giardia trophozoites in the small intestine attach to the epithelial surface and evade protective factors by antigenic variation. Chronic mucosal inflammation and cytokine release result in blunting of villi, disaccharidase deficiency, apoptosis of the epithelial barrier, and mucosal leak.

Failure to clear *Giardia* trophozoites in malnourished young children leads to worsening of malabsorption and malnutrition, resulting in growth retardation and cognitive impairment

Figure 1

Pathogenesis of Giardia infection.

nutrition, suffer from persistent infection with chronic diarrhea and dramatic health impairments (9), including worsening of nutrition (10), growth retardation, and cognitive impairment (11). In severe cases of giardiasis, during infection Giardia trophozoites attach to the epithelium of the proximal small bowel aided by their ventral adhesive discs, evade host defenses possibly by undergoing genetic variation (12), and produce local alterations of villus structure and cellular apoptosis. The most devastating effects of Giardia infection are related to damage of the absorptive small bowel mucosa, together with abnormal intestinal immunity that favors chronic infection (13, 14). While there is little evidence that preexistent malnutrition in young children makes them more susceptible to Giardia infection, once they are infected, persistent symptoms and health consequences are more likely to develop (15). Patients with hypogammaglobulinemia are particularly susceptible to chronic Giardia infection (16). However, Giardia is not a common opportunistic infection in patients with HIV infection or in those with cancer or cancer chemotherapy-induced immunosuppression, suggesting that not all forms of immunosuppression predispose to the infection. The likely explanation for increased symptomatic Giardia infection in infants with first exposure compared with older children and adults is the presence of an immature adaptive immune system in infants (17), particularly in those with preexistent nutritional deficits.

Long-term follow-up studies in children and adults with *Giardia* infection are needed to understand the relationship between infection and growth and learning defects, persistent abdominal symptoms (18), postinfectious functional bowel disease, and chronic fatigue (19). These chronic illnesses may result from low-level *Giardia* infections undetected by microscopic examination of stools (10), making their study and identification with previous *Giardia* infection more difficult.

What determines whether Giardia is a harmless commensal or a devastating pathogen? The difference may relate in part to the virulence of various Giardia strains, and more studies are needed to define these differences between Giardia strains and assemblages, many of which are derived from animal sources (20). In the rural developing world, a majority of young children are surrounded by animals that live in and roam about their homes and that may be sources of Giardia infection (21). A more likely explanation for the two faces of Giardia is the variation in host immune makeup and level of nutrition, although undoubtedly, future studies will reveal that host genetic factors also play an important role. Figure 1 outlines the host and microbial factors that are important in

the pathophysiology of asymptomatic and symptomatic giardiasis.

Modeling Giardia infection

In this issue of the *JCI*, Bartelt et al. (22) describe a novel animal model of giardiasis in which malnourished, weaned mice developed epithelial apoptosis and crypt hyperplasia associated with a Th2-mediated inflammatory response, persistent shedding of the infecting strain, and growth retardation secondary to Giardia infection. In this model, Giardia infection was associated with vitamin A and zinc deficiency and further impairment in nutrition. Vitamin A and zinc may be particularly relevant because reduced levels of each have been shown to contribute to the persistence of diarrhea. When vitamin A and zinc are administered with oral rehydration to children with diarrhea, the occurrence of persistent diarrhea is reduced (23).

In the study by Bartelt et al. in this issue of the JCI (22), infection by an assemblage B strain of Giardia led to decreased growth and mucosal histopathological changes similar to those seen in chronic human giardiasis (24). The model allows a characterization of mucosal histopathological response to Giardia infection mimicking that seen in humans, characterized by apoptosis of epithelium with intraepithelial eosinophils, decreased height of villi, alteration of crypt depth and cellularity, and a Th2-based immune response. The model should help us understand the microbial virulence factors and the host factors that work in concert to produce a chronic disease with potentially devastating growth and development parameters, and it suggests that malnutrition is fundamental to the development of host immune changes in chronic intestinal parasitic infection in children in the developing world. Using this new model, we may be able to define the microbe-host interactions of other pathogens including Cryptosporidium and possibly enteroaggregative E. coli known to be associated with growth and development parameters in young children.

Conclusions

More than 20 previous publications have described mouse or gerbil models of giardiasis, a few studies have developed a model of *Giardia* infection in rats, and one has been described in zebrafish (12, 25–47). These previous animal model studies of giardiasis have documented histopathological alterations associated with infection, host immune factors influencing susceptibility, reduced levels of serum zinc, mast cell degranulation, and release of cholecystokinin leading to the alteration of intestinal motility, and the amelioration of experimental infection by probiotics and antimicrobial agents. However, the model developed by Bartelt et al. (22) more closely resembles what is seen in the most severe pediatric Giardia infections in developing regions (20) compared with previous animal studies. The weaned mouse model of malnutrition-related giardiasis, mimicking the situation seen in malnourished infants and young children, should help us better understand real-life events relating to host defenses, Giardia strain virulence, and the role of intestinal immunity and intestinal microbiota in giardiasis. In addition, reversal of the damaging effects of the parasite can be studied in the model by administration of selective immune factors, probiotics, or antiparasitic drugs. There is reason to think that animal models with carefully controlled modifications of the study conditions will help us better understand how this protozoan can be both a harmless commensal and a highly pathogenic organism in vulnerable populations.

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