

**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 Lamb (1). Finding the organism as frequently in patients without symptoms as in those with diarrheal illness has led 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 overweight children with preexistent mal-

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**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 enteric-aggregate *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 infec-

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**Figure 1**

Pathogenesis of *Giardia* infection.

Ingestion of a *Giardia* strain with human infectivity, usually of genetic assemblage A or B

Healthy children or adults

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

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.

Subsequent exposure: asymptomatic infection with short-term colonization

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


