Giardiasis: Pathogenesis of Chronic Diarrhea and Impact on Child Growth and Development

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In a letter to the Royal Society (London) dated November 4, 1681, Antony van Leeuwenhoek gave what seems to be the first account of the human intestinal protozoan pathogen *Giardia lamblia* (1). Historically this is of great interest since he used his own stools as a source of the parasite, and his own invention, the microscope, to visualize it. Despite the three centuries that have now intervened, little is known of the mechanism by which *Giardia* colonizes the upper small intestine and causes diarrheal disease. Indeed, it is only during the past few decades that the organism has been elevated from its place as a commensal to that of an important pathogen.

*Giardia lamblia* is now considered the most common human enteric protozoan parasite and is found throughout temperate and tropical regions of the world (2,3). Prevalence of *Giardia* cyst excretion varies from 5 to 10% in the United States and Europe to much higher rates in the tropics (2). Increased prevalence is also found in residential institutions (4), day-care facilities (5), and in sexually active male homosexuals (6,7), when person-to-person spread by fecal-oral contact is the mode of transmission. In most countries *Giardia* is endemic, but water-borne epidemics have been reported with increasing frequency in Japan (8) and the United States (9). In all instances cyst-contaminated water was thought to be the cause of the epidemic, and in some of these cases clear evidence of fecal contamination of domestic water supplies with recovery of cysts from apparently treated water has been shown to be the basis of the outbreak (10). An interesting addition to our knowledge of the epidemiology of *Giardia* has been the observation that both wild and domestic animals, particularly the beaver and the dog (11), may harbor the parasite and therefore act as potential reservoirs of human infection.

**PATHOGENESIS OF DIARRHEA AND MALABSORPTION**

Many factors, some of which presumably related to the pathogen and others peculiar to the host, determine the outcome of an infection with *Giardia lamblia*. Our sparse knowledge to date, however, is dominated by predisposing factors in the host rather than specific virulent characteristics of the pathogen.
Colonization

Current evidence suggests that before the onset of symptomatic diarrheal disease the parasite must colonize the upper small intestine. This contention is supported by the observation that there is a delay, usually 7 to 15 days, between the ingestion of cyst-contaminated food or water and the development of diarrhea, although in some instances incubation periods as long as several weeks are reported (12–14). Important steps in the process of colonization are summarized in Table 1.

Cyst Ingestion

From the now classic transmission experiments of Rendtorff, it is evident that as few as 10 cysts are sufficient to initiate human disease (12). This represents an extremely small proportion of millions of cysts that a person with giardiasis can excrete each day in their feces (15). Hence the disease can be transmitted relatively easily by person-to-person contact in the same way that small inocula of *Shigella dysenteriae* (10¹–10² organisms) are sufficient to cause human dysentery. Variations in the length of the incubation period of *Giardia lamblia* infection may be partly related to the number of cysts ingested.

Excystation

Recent studies have clearly shown the importance of pH as the initial stimulus for the process of excystation (16). In these experiments, synthetic gastric juice was prepared to cover a wide pH range, but excystation and subsequent growth of trophozoites in axenic culture were found to occur maximally between pH 1.3 and 2.7. Trophozoites do not survive at this pH, so after this initial priming event in the stomach, cysts must rapidly enter the duodenum and upper jejunum where pH is higher and approaches physiological levels. Further *in vitro* studies

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mechanism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cyst ingestion</td>
<td>Food and water</td>
</tr>
<tr>
<td></td>
<td>Person-to-person contact</td>
</tr>
<tr>
<td>2. Excystation</td>
<td>Gastric and pancreatic secretions</td>
</tr>
<tr>
<td>3. Attachment</td>
<td>Hydrodynamic or mechanical forces</td>
</tr>
<tr>
<td></td>
<td>Surface membrane determinants (? lectin)</td>
</tr>
<tr>
<td></td>
<td>Low oxidation-reduction potential</td>
</tr>
<tr>
<td></td>
<td>Energy and nitrogen source</td>
</tr>
<tr>
<td></td>
<td>Preformed phospholipid</td>
</tr>
<tr>
<td>4. Multiplication</td>
<td>Bile</td>
</tr>
<tr>
<td>5. Encystation</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
have shown the excystation process can be enhanced if cysts are also exposed to a trypsin/tyrode solution.

Attachment

Adherence of bacteria, viruses, and protozoa to host tissues is now regarded as a crucial step in the pathogenesis of many infectious diseases (17). Without an effective attachment mechanism, it would be expected that the newly excysted trophozoites would be rapidly expelled from the gut lumen by intestinal peristalsis. At least three theories of attachment have been advanced, each concentrating either on the ventral disk (otherwise known as the adhesive or "sucking" disk) or the ventrolateral flange, a structure that skirts around the periphery of the disk (18,19) but separated from it by the marginal groove.

Holberton (18,20) in his hydrodynamic model of attachment for *Giardia muris*, the mouse pathogen, which is morphologically distinct from the human parasite *Giardia lamblia*, proposed that a suction force is maintained beneath the ventral disk by the vigorous beating of the ventral flagella. Some support of this theory is provided by scanning electron microscopic studies of infected mouse intestine, when mirror-image indentations, corresponding exactly to adhesive disk, can be seen on the villous surface (21,22). These lesions have, however, never been observed in similar studies involving human intestine.

An alternative theory proposes that the ventrolateral flange attaches the parasite to microvilli by a grasping or contractile mechanism (19,21,22). Scanning electron microscopic studies certainly reveal close apposition of this structure to the surface of the villus, with local distortion of the microvilli (21,22).

A third mechanically based theory suggests that a spiral conformation of the disk surface might permit attachment by a contractile, coiling movement associated with alterations in the diameter of the disk (23); contractile movements of the ventrolateral flange were also included as part of this attachment model.

At the time when these attachment theories were proposed, the nature of the structural components of the ventral disk and the ventrolateral flange were unknown, although electron microscopic studies did suggest that the ventrolateral flange had ultrastructural similarity to the paromyosin-containing filaments of invertebrate muscle proteins (19). Recent studies have confirmed that tubulin is the major protein of the disk's microtubular structure (24), and, in addition, contractile proteins actin, α-actinin, myosin, and tropomyosin have been identified in the peripheral region of the ventral disk, an area known as the lateral crest (25). These observations suggest an additional contractile role for the lateral crest of the disk, a function for which there is some supportive electron microscopic evidence (19,21,22). These recent findings are of great interest, although direct evidence for the participation of these contractile elements in the attachment process is still needed.

The presence of the ventral disk, the apparent attachment organelle, may have distracted investigators from considering other adherence mechanisms.
Recent observations on the interaction between *Giardia* and erythrocytes suggest that the parasite, like some bacteria, has lectin-like activity in its surface membrane (27). Whether this is biologically important in its association with intestinal cells and/or intestinal mucus remains to be established but, if confirmed, would represent an interesting, hitherto unknown, approach by which the parasite might evade expulsion from the host intestine.

**Multiplication**

Proliferation within the small intestine would appear to be the final goal of this luminal parasite. The growth requirements of *Giardia* are not well understood, but what is known has largely come from *in vitro* studies of trophozoite growth in axenic culture. Early *in vitro* experiments in rodents, however, indicate that bile is necessary for survival of *Giardia* (28) and that sodium glycocholate, but not sodium taurocholate, promotes growth *in vivo* (29). Recent growth studies *in vitro* have confirmed that mammalian bile promotes growth of *G. lamblia* with dramatic reduction in generation time (30).

In addition, mice fed a vitamin-B-deficient diet had reduced numbers of parasites in the intestine compared to animals receiving a complete diet (31,32), but similar effects were not apparent with vitamins A or C (32). Reducing the carbohydrate content of the diet also had a detrimental effect on parasite growth (32).

*In vitro* studies of trophozoites in axenic culture indicate that the organism has features consistent with a part-aerobic and part-anaerobic life-style. *Giardia* consumes oxygen but lacks mitochondria and cytochromes (19,33). The respiratory enzymes of *Giardia* are found in the particulate fraction of the cell (33), whereas those of another intestinal protozoan pathogen, *Entamoeba histolytica*, are found in the soluble fraction. Glucose is metabolized by the Embden-Meyerhof and pentose phosphate pathways but is not used as a precursor for lipid synthesis (34). Instead, under the facilitatory influence of bile salts, the organism appears to take up preformed lipids directly from the culture medium (35). This observation provides additional indirect evidence that *Giardia* is unable to synthesize membrane lipids *de novo* (34).

For growth *in vitro*, *Giardia* has an absolute requirement for a low oxidation/reduction potential, part of which is provided by the reducing agent L-cysteine (36,37). However, it is likely that L-cysteine also has an additional role as a growth promoter, since other reducing agents are considerably less effective in supporting trophozoite growth (36).

**Production of Intestinal Dysfunction**

A variety of mechanisms have been suggested to account for the morphologic and functional disturbances that occur in the intestine during infection with *Giardia* (Table 2). For some of these, there is now direct or indirect supportive
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TABLE 2. Diarrhea and malabsorption in giardiasis: proposed mechanisms

<table>
<thead>
<tr>
<th>Site of action</th>
<th>Mechanism</th>
<th>Clinical and/or experimental evidence (−/+</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal lumen</td>
<td>1. Competition for host nutrients</td>
<td>−</td>
<td>38–40,44</td>
</tr>
<tr>
<td></td>
<td>2. Physical barrier</td>
<td>−</td>
<td>38,41–43</td>
</tr>
<tr>
<td></td>
<td>3. Bacterial overgrowth</td>
<td>+</td>
<td>45–47</td>
</tr>
<tr>
<td></td>
<td>4. Inhibition of lipolysis</td>
<td>+</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>5. Toxin production</td>
<td>−</td>
<td>54</td>
</tr>
<tr>
<td>Intestinal mucosa</td>
<td>1. Invasion</td>
<td>+</td>
<td>43,49,58,59</td>
</tr>
<tr>
<td></td>
<td>2. Enterocyte damage</td>
<td>+</td>
<td>21,40,43,49–53</td>
</tr>
<tr>
<td></td>
<td>3. Increased enterocyte turnover</td>
<td>+</td>
<td>55,56</td>
</tr>
<tr>
<td>Pancreaticobiliary</td>
<td>1. Pancreatic insufficiency</td>
<td>+</td>
<td>80,81</td>
</tr>
<tr>
<td>system</td>
<td>2. Inflammation in gallbladder and bile ducts</td>
<td>+</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>3. Bile salt deconjugation by parasite</td>
<td>−</td>
<td>48</td>
</tr>
</tbody>
</table>

evidence in the literature, although many remain within the world of fantasy. These can be considered under two major headings, namely, factors that operate within the gut lumen and factors that directly affect the small intestinal mucosal cell (the enterocyte) and other cellular components of the gut mucosa.

Luminal Factors

Despite a lack of direct supportive evidence, it is a commonly held belief that intestinal malabsorption in giardiasis is at least partly a result of competition by *Giardia* for host nutrients (38–40) and physical barricade of the mucosa by vast numbers of adherent trophozoites (38,41–43). The vast functional reserve of the small intestine and the fact that usually only the proximal small intestine is heavily colonized make the second of these theories unlikely. The only direct experimental evidence available that examines possible competition for host nutrients is a study that failed to show significant uptake of vitamin B₁₂ by the parasite (44).

A possible role for bacteria in the pathogenesis of intestinal malabsorption during infection with *Giardia lamblia* was first suggested in 1968 (45), when symptoms improved after treatment with tetracycline, although the parasite was not eradicated. Since then two reports have confirmed significant bacterial overgrowth in the upper small intestine of patients with *Giardia* infection and malabsorption (46,47). In one of these studies, evidence of bile salt deconjugation was found in patients with bacterial overgrowth (47), suggesting that these bacteria were directly contributing to intestinal fat malabsorption. However, in this same study, free bile acids were also found in subjects without bacterial overgrowth, indicating that *Giardia* itself might be responsible. A recent study in *vitro*, using
trophozoites from axenic culture, addressed this issue but was unable to demonstrate bile salt deconjugation by the parasite (48). However, sonicates of the same axenically grown trophozoites inhibited lipolysis (by pancreatic lipase) of the triglyceride tributyrilglycerol, suggesting yet another possible mechanism of fat malabsorption in giardiasis (48).

Mucosal Factors

In addition to the lumenal events that might interfere with normal intestinal function, there is clear evidence of structural damage and functional derangement of the enterocyte. By light microscopy, the full spectrum of changes from normality through partial to subtotal villous atrophy have been reported in human *Giardia* infection (40,49–52). Usually the changes in villous morphology are not severe, but the degree of mucosal damage does correlate with the extent of the functional impairment (53). Even when villous morphology appears normal by light microscopy, damage to the microvilli can be seen by transmission electron microscopy (43). Destruction of the microvilli results in impaired function of the digestive–absorptive complex of the brush border membrane through reduction in surface area and brush border enzymes such as the disaccharidases. The ways by which the parasite damages the enterocyte are not clearly understood. Electron microscopic studies have suggested that microvilli are damaged during the attachment process (21), perhaps as a result of the postulated suction pressure under the ventral disk (29) or the contractile events in the disk periphery and ventrolateral flange (21–23). The proposition that *Giardia* secretes or releases noxious substances (“cytotoxins”) in the vicinity of the intestinal cell (54) has not as yet been demonstrated experimentally.

A contributory factor to the enterocyte dysfunction in giardiasis is the increase in gut epithelial cell turnover, indicated by increased epithelial mitotic index (55,56). Intestinal villi, under these circumstances, become populated by a relatively immature population of cells with reduced digestive and absorptive function. However, reduction in disaccharidase activity antecedes changes in villous architecture, suggesting that direct damage to the microvillus membrane is the prime offender (57).

Several reports indicate that, on occasion, trophozoites actually invade the small intestinal mucosa (43,49,58). The presence of parasites in the submucosa of mice was reported as early as 1929 (59); since then sporadic accounts have confirmed that trophozoites can penetrate through all layers of the intestinal wall and may rarely enter the lymphatic and circulatory systems (60). Although it is generally considered that mucosal invasion is not a major pathogenetic mechanism in the production of intestinal disease, it has been suggested that this event may occur more commonly than the above sparse reports would suggest, since it is now clear that active phagocytosis of trophozoites by rabbit peritoneal macrophages (61) and human peripheral blood monocytes (62) does occur in vitro. Hence, the intramucosal life of *Giardia* trophozoites might be extremely brief as a result of rapid intervention by tissue macrophages.
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There is also evidence that the parasite can not only occupy intercellular domains in the mucosa but is on occasion found within the enterocyte (43). *In vitro* studies with human fibroblasts have confirmed the parasite's ability to enter and destroy cells in tissue culture (63). Whether direct invasion of gut epithelial cells followed by cell killing is an important step in the establishment of intestinal disease during infection with *Giardia* remains to be determined, although available evidence at present would suggest that it is not.

Although several mechanisms for the production of diarrhea have been discussed, such as (a) direct enterocyte damage leading to impaired absorption of nutrients, water, and electrolytes, (b) deconjugation of bile salts resulting in fat malabsorption and secondary mucosal injury from increased intraluminal concentrations of free bile acids, and (c) osmotic diarrhea from disaccharidase deficiency, particularly lactase deficiency, the question of whether infection with *Giardia* actually causes intestinal secretion has not seriously been addressed. Clinical observations, however, do favor an initial secretory episode, as the illness often begins with acute watery diarrhea. Intestinal symptoms may then subside, the stools developing the characteristics of malabsorption (steatorrhea) rather than the high-volume watery stool of an intestinal secretory state. In a patient with severe giardiasis, a stool output of 4 liters a day was clearly documented, confirming the presence of a secretory diarrhea (64). However, although no other pathogens were isolated, one can never be entirely certain that this was caused solely by *Giardia*.

Finally, it seems increasingly likely that the intestinal mucosal inflammatory response to infection with *Giardia* may play an important role in the pathogenesis of this disease (53,56). Even before there is evidence of morphological damage to the enterocyte, the number of intraepithelial lymphocytes is already increasing (56), presumably in response to *Giardia*-related antigen(s). The extent of the lymphocytic infiltration correlates with the degree of dysfunction as judged by tests of intestinal absorption (53). Further evidence that immunopathogenetic mechanisms may be involved in producing mucosal damage is the observation that despite delayed clearance of *Giardia muris* from the intestine of experimentally infected nude (hypothymic) mice compared to immunologically intact animals, the mucosal lesion in the nude mice is less severe (65). A similar mechanism has been invoked to explain the small intestinal injury in celiac disease, where the antigen is thought to be a gluten peptide, β-gliadin.

Mast cells and local anaphylaxis may also be involved in the intestinal inflammatory response in *Giardia* infection. Mast-cell-deficient mice are more susceptible to *G. muris* infection (66), and the histamine/serotonin antagonist, cyproheptadine causes prolongation of the infection (67). Whether mast cells can be implicated in the mucosal damage in *Giardia* infection remains to be established.

The inflammatory process in giardiasis may not be restricted to the small intestine, as several reports describe colitis or proctitis in humans and animals (68–71) associated with *Giardia* infection. In none of these accounts can *Giardia* be directly implicated as the causal agent, although in some instances improve-
ment in the large bowel lesion coincided exactly with antigiardial therapy (68-70).

An intriguing observation in the mouse pathogen *Giardia muris* is the presence of endosymbionts. Bacteria-like structures were first observed within *Giardia* from meadow mice in 1917 (72), since when several reports have confirmed this finding (73-76). As yet, such structures have not been observed in *Giardia lamblia*, but the potential importance of *Giardia*-associated microorganisms in the pathogenesis of giardiasis requires further attention. The potential for transferring enterotoxigenic bacteria, drug resistance, and other plasmid-associated phenomena, together with the known ability of endosymbionts to change metabolic requirements (77) and surface membrane characteristics (78) of their hosts, lead us into a labyrinth of possible disease-producing processes, some of which may open new channels for therapeutic intervention. However, as yet there is no evidence that enterotoxigenic organisms are associated with *Giardia* infection. In addition, Smith et al. (78a) failed to demonstrate enterotoxin production in established animal models by four strains of *G. lamblia*.

**Pancreatic and Biliary Function**

Rarely, *Giardia* infection spreads from the duodenum into the pancreaticobiliary system. On occasions, this has been reported to cause overt cholecystitis and cholangitis (79) and has led to the term “hepatobiliary *Giardia* syndrome.” Functional impairment of the pancreas has been described in children with this condition (80,81), and potentially this could contribute further to malabsorption through other factors such as intestinal mucosal damage and bacterial overgrowth. However, the prevalence of extraintestinal giardiasis is unknown, and its physiological and nutritional significance remains to be determined.

**NUTRITIONAL DEFICITS**

The fact that *Giardia* can cause a florid malabsorption syndrome with wasting, hypoalbuminemia, steatorrhea, and failure to thrive is now undisputed (39,43,55,82-84). One should, at the same time, not lose sight of the fact that many *Giardia* infections (possibly as many as 50%) occur without causing any structural or functional deficit in their hosts. Malabsorption and/or deficiency of a variety of specific nutrients has been reported in *G. lamblia* infection, and these have been summarized in Table 3. Fat malabsorption leading to steatorrhea has been reported by many investigators (39,41,46,50,52,54,65-87,109-111) as occurring in as many as 100% of patients studied. Prevalence of this abnormality is difficult to determine, since selection criteria must have varied widely. Important mechanisms of fat malabsorption probably include (a) mucosal damage with reduction of surface area, (b) bacterial overgrowth, (c) possible inhibition of lipolysis by an as yet undefined mechanism, and (d) disturbance of pancreaticobiliary function.
Much of the information regarding defects in carbohydrate absorption in giardiasis arises from the D(-)xylose absorption test, which is reported to be abnormal in a substantial proportion of patients (38,39,50,52,54,85,87,110,111). However, the validity of this test as an indicator of absorptive potential for the biologically relevant hexoses glucose and galactose is now questioned. In addition, D(-)xylose can be metabolized by some intestinal bacteria (88), making interpretation of this absorption test in the presence of bacterial overgrowth virtually impossible. Disaccharidase deficiency in giardiasis has been demonstrated by abnormal plasma glucose curves after a lactose load (89,90) and by a reversible fall in lactase, sucrase, and maltase activity in jejunal mucosa of infected patients (39,91,92).

Absorption of vitamins A, B\textsubscript{12}, and folic acid may be abnormal in giardiasis. There is no evidence that the parasite actively competes with the host for any of these nutrients. Impaired absorption of vitamin A and folic acid is likely, therefore, to be related to the morphological disturbance in the proximal small intestinal mucosa. However, vitamin B\textsubscript{12} is absorbed in the distal ileum, a region of the intestine not generally regarded as being Giardia’s preferred habitat.

Whether associated bacterial overgrowth can be implicated as the cause of vitamin B\textsubscript{12} malabsorption remains to be established.

Fecal nutrient loss in giardiasis has not been systematically investigated. However, small intestinal cell turnover is clearly accelerated in acute and chronic infection in the mouse model (93), suggesting that mucosal exfoliation is increased. Marked intestinal protein loss has been demonstrated in isolated case reports (94,95), although its impact in Giardia infection overall has not been determined.

A potentially important aspect of the nutritional demands of Giardia infection is total energy expenditure during infection. Energy balance during infectious

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### TABLE 3. Intestinal malabsorption in giardiasis

<table>
<thead>
<tr>
<th>Study (ref.)</th>
<th>No. of subjects</th>
<th>D(-)Xylose</th>
<th>Lactose</th>
<th>Fat</th>
<th>Vitamin B\textsubscript{12}</th>
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<tbody>
<tr>
<td>Veghelyi (41)</td>
<td>14</td>
<td>—</td>
<td>—</td>
<td>71</td>
<td>—</td>
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<tr>
<td>Cantor et al. (109)</td>
<td>20</td>
<td>—</td>
<td>—</td>
<td>25</td>
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<td>Hoskins et al. (39)</td>
<td>6</td>
<td>50</td>
<td>100</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>Alp and Hislop (54)</td>
<td>5</td>
<td>20</td>
<td>20</td>
<td>100</td>
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<td>Barbieri et al. (38)</td>
<td>11</td>
<td>27</td>
<td>—</td>
<td>82</td>
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<tr>
<td>Ament and Rubin (90)</td>
<td>7</td>
<td>—</td>
<td>—</td>
<td>66</td>
<td>100</td>
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<tr>
<td>Cowen and Campbell (91)</td>
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<td>—</td>
<td>66</td>
<td>100</td>
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<td>Tewari and Tandon (87)</td>
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<td>23</td>
<td>—</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>Rabassa et al. (110)</td>
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<td>62</td>
<td>27</td>
<td>34</td>
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<td>—</td>
<td>50</td>
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Adapted from Dedieu and Gibon (112), with permission.
disease is probably one of the major determinants governing the outcome of a given infection with respect to its effect on body mass. We presume that as the energy deficit increases, the effect on body mass becomes more severe. As yet such information is not available in giardiasis.

**EFFECT ON GROWTH AND DEVELOPMENT**

Although our knowledge of the impact of *Giardia* infection on growth is by no means complete, evidence in animals and humans suggests that infection with this parasite can indeed lead to growth retardation. This is a critical issue, since *Giardia* is endemic in most countries of the world, with high prevalence in developing societies. Before aggressive eradication programs are begun, its impact on child health at a community level should be determined. Mata’s study (L. J. Mata, personal communication) in Guatemala indicated that all children had had at least one *Giardia* infection by the age of 3. Peak prevalence probably occurs during the first 5 years of life and thereafter gradually declines (96). Thus it is the preschool years when the child is at greatest risk, a time when other infections of the intestinal and respiratory tracts are also taking their toll, when breast feeding ceases, and when other food supplies are scarce.

**Animal Studies**

Weight gain in mice infected experimentally with *G. muris* was significantly less than in uninfected control animals (97). This apparent inhibition of growth was related to the magnitude of the initial inoculum of cysts given to the animals; the deleterious effects on body weight were more marked in animals receiving 10,000 cysts than in those receiving 100 cysts. Interruption in growth, again as determined by body weight, is also reported in experimental *G. lamblia*-infected weanling rats (98). Since food intake in both of these studies was not determined, it cannot be stated with certainty whether effects on body weight were the result of reduced appetite, intestinal malabsorption associated with negative energy and nitrogen balances, or a combination of the two. Experimental *G. lamblia* infection in mongrel dogs, however, failed to influence body weight (99), although death in naturally infected puppies has been reported (100). Recently, *Giardia* infection in budgerigars has been observed; infected birds were described as “going light,” and some of them died (101).

**Human Data**

Veghelyi, in 1938 (102), reported clinical data on 92 children who were infected with *G. lamblia* and had no evidence of other diseases. Of these, 12 children (13%) had significant impairment of linear growth, and more than half were underweight for their age.

The majority of infected children were between 6 and 13 years old. Subsequently, several studies have confirmed that *Giardia* infection in children may
lead to suboptimal weight gain and failure of linear growth (92,103–106). Kay et al. found that 31% of 154 children with giardiasis presented with either growth failure or weight loss (92). The vast majority of these children were under 5 years of age. After eradication of the parasite, 24 children were followed as outpatients, and 9 of them demonstrated “catch-up” growth. This observation suggests that Giardia did have a significant negative effect on host nutritional status, sufficient to affect growth.

Community-based studies in the developing world on the impact of Giardia on growth and development are sadly lacking. However, it is evident from the work of Mata et al. (107) in the village of Santa Maria Cauqué in highland Guatemala that the prevalence of Giardia stool isolations increases progressively during the first 3 years of life up to a peak prevalence of 22%. Mata’s data also showed that 40% of these episodes were associated with diarrhea, a proportion of which clearly occurred at the beginning of or during a period of growth stagnation (L. J. Mata, personal communication).

Gupta, also working in Guatemala (108), has attempted to demonstrate the nutritional impact of Giardia and Ascaris by randomly allocating 159 children 2 to 5 years of age to twice-monthly treatment with one of the following four treatment regimens: piperazine, metronidazole, piperazine plus metronidazole, or placebo. During the year of the study, growth and parasite load were determined at regular intervals. In the groups receiving metronidazole, a significant increase in height (average 1 cm) was observed, associated with a concomitant fall in the prevalence of Giardia in the stools. Treatment with piperazine had no effect on growth or Ascaris load. Although it is difficult to assess the nutritional impact of Giardia in these children with any certainty, since metronidazole therapy is not monospecific, this study does support the view that this parasite interferes with growth, not just in isolated cases but to a degree that is measurable at a community level. However, caution must be exercised as the growth increment seen in the metronidazole groups, although significantly greater than controls, was small, and its biologic significance remains to be determined.

SUMMARY

Giardia lamblia is a common parasite endemic throughout the world and pathogenic to humans. Expression of disease is variable, and neither the virulence characteristics of the parasite nor the determinants of the host’s response have been clearly defined. Since a method for cultivating the parasite in vitro has been devised, information on its metabolism and colonization requirements has been forthcoming. A proportion of infected individuals suffer from an acute diarrheal illness, and some of these progress to a chronic malabsorption syndrome associated with morphologic damage to the small intestinal mucosae. The mechanisms by which Giardia causes chronic diarrhea are poorly understood, although some evidence indicates that overgrowth of intestinal bacteria may be involved, at least in part. Malabsorption of fat, carbohydrate, and some vitamins is well documented in giardiasis, which in some children is followed by weight loss,
wasting, and growth arrest. Preliminary reports indicate that *Giardia* infection in children, particularly those under 5 years old, may significantly interfere with growth and normal development. This issue requires further investigation at a community level so that appropriate strategies can be devised to deal with this parasite in the developing world.

REFERENCES


GIARDIASIS


