

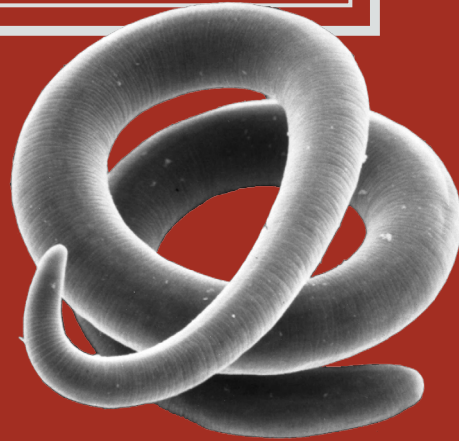
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Fifth Edition

Parasitic Diseases

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1. *Giardia lamblia* (Stiles 1915)

Introduction

Giardia lamblia is a flagellated protozoan that lacks a mitochondrion.¹ It is aerotolerant, but respire as an anaerobe, and lives in the small intestine. Other protozoa that share this metabolic strategy include *Entamoeba histolytica* (see page 84), and *Trichomonas vaginalis* (see page 46). It produces a cyst stage that is environmentally resistant. *Giardia* is acquired through the fecal-oral route, most commonly via contaminated drinking water.² *G. lamblia* is found throughout the world, and remains endemic in many regions. It is a common infection of children, especially those attending daycare centers.^{3,4} In 2002, The Centers for Disease Control and Prevention reported 21,300 cases of *Giardia* within the United States. It is highly likely that many more than that occurred there but went undiagnosed. Beavers are major reservoir hosts that are often responsible for contaminating public drinking water supplies. *Giardia* is the subject of much intensive research, including a complete sequence analysis of its genome.⁵ A survey of its genome has revealed the presence of genes for meiosis, although a sexual stage for this protozoan has not yet been described.⁶ An excellent review of the biology of *Giardia lamblia* was published by Adam.⁷

Historical Information

Antony Van Leeuwenhoek, the famous Dutch microscopist, in a letter written to Robert Hooke in 1681, described in detail the living trophozoite stage of *Giardia*, which he observed in a sample of his own stool: “. . . animalcules a-moving very prettily. Their bodies were somewhat longer than broad, and their belly, which was flatlike, furnisht with sundry little paws. . . yet for all that they made but slow progress.”⁸

Lambl described the main morphological fea-

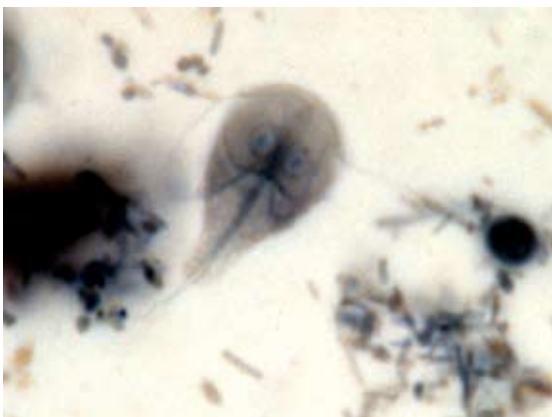


Figure 1.1. Trophozoite of *Giardia lamblia*. 15 μ m.

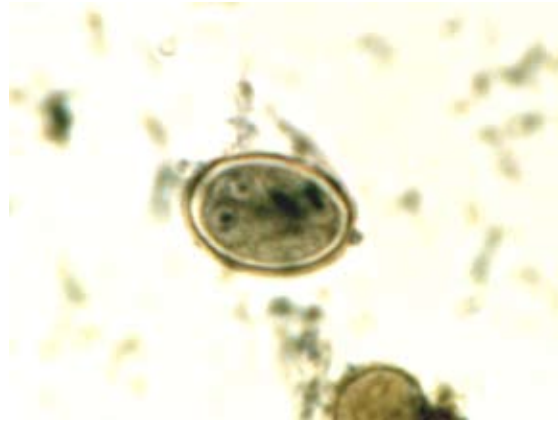


Figure 1.2. Cyst of *G. lamblia*. Two nuclei can be seen. 13 μ m.

tures of the trophozoite stage in 1859,⁹ that he obtained from the stools of various pediatric patients in Prague. His elegant scientific drawings remain impressive, even in today's world of sophisticated, technologically advanced light microscopy. Simon, in 1921,¹⁰ completed the description of its morphology.

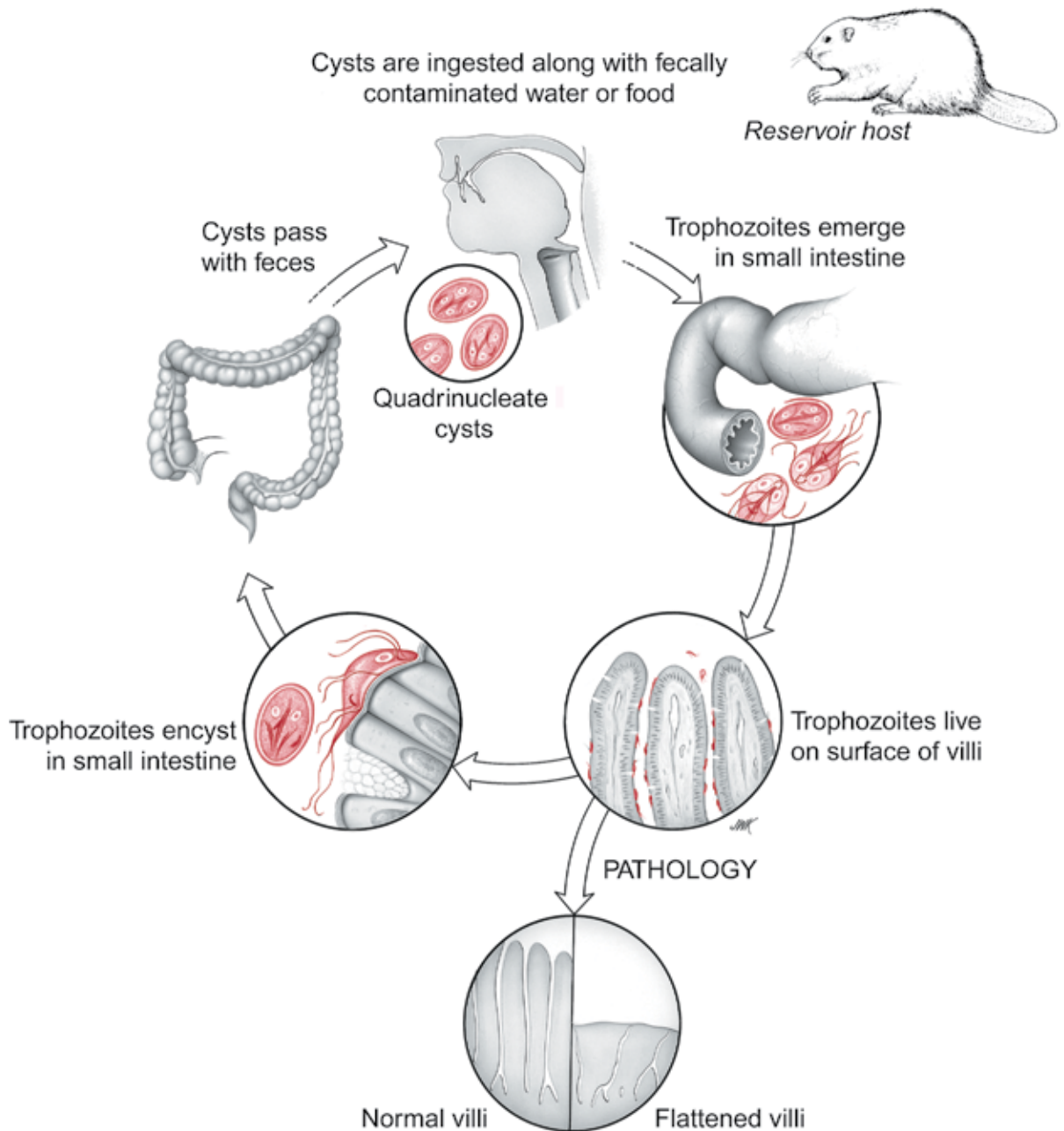
Life Cycle

Giardia lamblia exists in two forms: the trophozoite (Fig. 1.1) and the cyst (Fig. 1.2). The troph is pear-shaped and motile, measuring 10-20 μ m long and 7-10 μ m. in diameter. It possesses eight flagella and is binucleate. Both nuclei are transcriptionally active.¹¹ In addition, it contains two rigid structures, called median bodies, whose function is not known. *G. lamblia* has no mitochondria, peroxisomes, hydro-genosomes, or related subcellular organelles that might be associated with energy metabolism. Some strains of the parasite carry double-stranded RNA viruses, known as giardiaviruses,¹² whose function for the protozoan remains undefined. Apparently they are not linked with virulence of the infection. However, these viruses have facilitated the expression of foreign genes in *Giardia*, serving as shuttle vectors.¹³

Its anterior ventral region has a disc-like organelle that it uses for attachment to the surface of epithelial cells. The integrity of the disk is maintained by tubulin and giardins.¹⁴ The latter are members of the class III, low affinity, calcium binding annexins.¹⁵ Its surface is covered with cysteine-rich molecules.

Infection begins with ingestion of the quadri-nucleate cyst, which must then excyst in response to physiological stimuli from the new host. Excystation involves a complex sequence of cellular events and molecular responses¹⁶ to environmental cues received by the parasite. As the cyst passes through the stomach and into the small intestine, it is sequentially exposed to HCl¹⁷ and pancreatic enzymes.¹⁸

Giardia lamblia



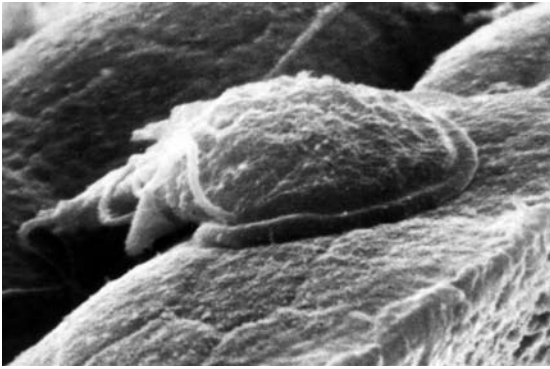


Figure 1.3. Scanning EM of a trophozoite of *G. muris* on epithelium of mouse small intestine. Courtesy R. Owen.

Excystation results in the emergence of two binucleate trophozoites that then attach to epithelial cells by their ventral disks (Fig. 1.3). The molecular mechanisms used to adhere to cells are not known, although carbohydrate binding lectins have been identified on the ventral disc's surface. Since the trophozoite can also adhere to an alcohol-cleaned glass surface, host molecules may not be necessary to the process. Once attached to epithelial cells, the binucleate organisms grow and divide by binary fission. Cysts are unable to replicate.

G. lamblia can be grown in vitro (Fig. 1.4). The nutritional needs of the trophozoite have yet to be fully determined, but some of its biochemical energy pathways are known.^{19, 20} Glucose and arginine²¹ appear to be its major sources of energy, and it may access a portion of its need for them through the breakdown of mucus.²² *Giardia* is unable to synthesize nucleic acid bases *de novo*, employing salvage pathways.²³ Lipids are absorbed directly, likely facilitated by bile and bile salts,²⁴ and perhaps by endocytosis of lipoproteins.²⁵ *G. lamblia* is not considered an invasive or tissue parasite, but its ability to adhere closely to the columnar cells at the level of the microvilli, and its penchant for secreting proteins at the site, results in antibody production and, eventually, to protective immunity. To exit the host and survive, trophozoites must encyst, though the precise conditions governing this process are not fully defined.²⁶ Encystation in vitro is inducible by exposure of the trophozoite stage to bile and elevated pH, possibly by sequestering cholesterol.²⁷ Trophs take up and release conjugated bile salts,^{28, 29} and these conditions may exist in its essential niche (Fig. 1.3). Apparently, a novel transglutaminase is also required for encystment.³⁰ Encysted parasites can endure for long periods of time outside the host if they remain moist. Both cysts and trophs pass out of the bowel with the fecal mass, but, as already stated, only the cyst stage survives. Cysts can withstand exposure to mild chemical treatments, such as chlorinated water. Even boiling water at high altitude may not kill cysts, and they do quite

well in cold water for weeks to months. Cysts can be killed by freezing or dessication. Production of cysts occurs throughout the infection, but the number produced each day varies greatly, depending upon a wide variety of conditions, including the development of acquired protective immunity.³¹ Protective immunity appears to be directed against both surface antigens³² and antigens that are secreted.³³

Cellular and Molecular Pathogenesis

Steatorrhea³⁴ and malabsorption with flattening of the villi³⁵ (Fig. 1.5), often accompanied by rapid weight loss, are the dominant pathological consequences of chronic infection. Despite the fact that there are numerous related species of *Giardia*,⁷ and that they can be manipulated in vivo and in vitro, surprisingly little is known regarding their biological effect(s) on the physiology and biochemistry of the small intestine. Hence, the molecular basis for these symptoms is as yet undefined.

Infection with *G. lamblia* induces numerous cellular³⁷ and humoral responses, some of which are protective in nature.³⁸ Particularly important is secretory IgA,³⁹ since it has been shown for nonsecretors that infection is easily established and not easily controlled. Physiological changes experienced during symptomatic infection could relate to these host-based responses, and might even be induced by mechanisms related to allergies,³⁷ such as those observed in wheat-gluten-sensitive individuals.³⁸

Antigenic variation of surface components of the trophozoite is typical in the early phase of infection,^{40, 41} and most likely aids the parasite in avoiding elimination by humoral responses (e.g., IgA antibodies)³⁹ directed at trophozoite surface proteins.⁴² Switching of cysteine-rich variant surface proteins (VSPs) also occurs when the parasite is about to excyst,⁴³

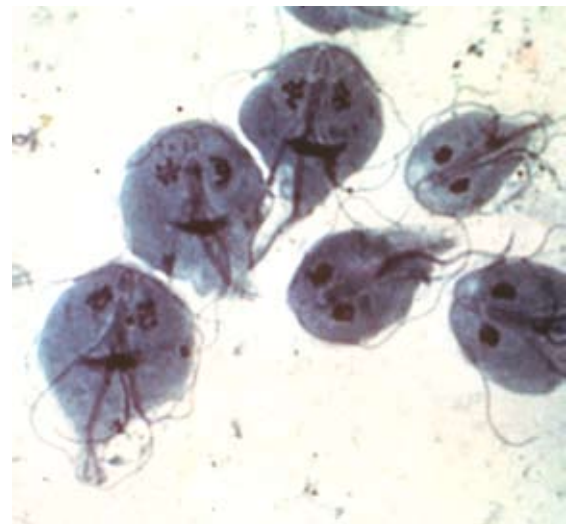


Figure 1.4. Trophozoites of *G. lamblia* in culture. Courtesy D. Lindmark.

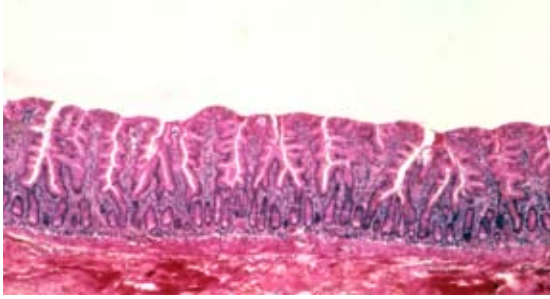


Figure 1.5. Flattened, fused villi of small intestine from a patient suffering from malabsorption syndrome due to *G. lamblia*.

allowing the parasite to evade immune elimination. Severe combined immune deficiency mice do not induce VSP switching, an indication that the overall process is under the control of B cell-mediated host responses. However, switching also occurs spontaneously or in response to physiological selection, but at a much slower pace than in immunocompetent hosts. Shuttle viral systems for transfecting *G. lamblia* have been developed.⁴⁴ Thus, genetic manipulation is now possible, which may lead to a more complete understanding of the molecular events governing pathogenesis.

Mother's milk is protective, because it contains antibodies of the IgA class.⁴⁵ Nonspecific defenses, such as lactoferrin or products of lipid hydrolysis of the milk in the normal digestive tract, may also play a role, as each is toxic to *Giardia*.^{46, 47, 48} Nitric oxide, released lumenally by intestinal epithelial cells in response to infection, inhibits parasite growth and differentiation, although *Giardia* might be able to disarm this potential defense mechanism by competitively consuming the arginine needed by the host cells for NO synthesis.⁴⁹ In summary, the duration and severity of infection depends upon both immune and nonimmune host defenses, as well as the parasite's ability to evade them.

Clinical Disease

An excellent review of the clinical literature is available.⁵⁰ About half of all those who encounter *G. lamblia* and become infected fail to progress to a state of ill health. They may remain asymptomatic for long periods of time, even though they are still infected, and could become chronic carriers referred to as *cyst passers*. Of those who go on to develop disease, the most prominent symptom is protracted diarrhea.^{22, 51} It can be mild and produce semisolid stools, or it can be acute with debilitating cramping when the stools become watery and voluminous. Untreated, this type of diarrhea may last weeks or months, although it usually varies in intensity. Children thus affected often fail to thrive.⁵² Chronic infections are characterized by steatorrhea accompanied

by malabsorption syndrome associated with rapid, substantial weight loss, general debility, and consequent fatigue.²² In addition, some people may complain of epigastric discomfort, anorexia, and even pain. Other symptoms may sometimes accompany giardiasis, such as allergic responses to certain food items,⁵³ but none of these have been proven to be caused by the parasite.

Certain patient groups are at greater risk for acquiring giardiasis and for developing chronic infection. In addition to those patients suffering from HIV/AIDS⁵⁴ and other immunocompromising conditions (e.g., hypogammaglobulinemia or cancer chemotherapies), cystic fibrosis patients⁵⁵ and children with underlying malnutrition⁵⁶ can have a protracted disease with more severe symptoms than other individuals generally contract.



Figure 1.6a. *G. lamblia* trophozoite in stool sample.

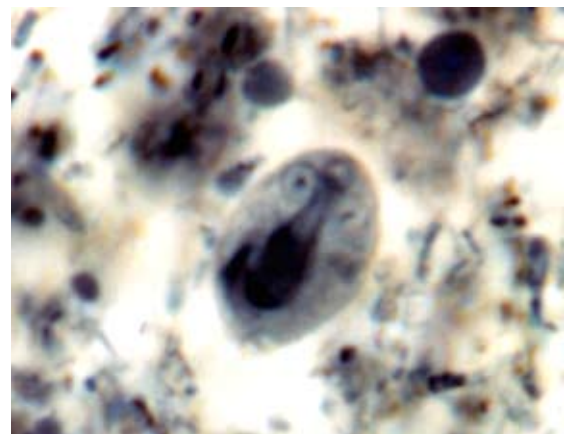


Figure 1.6b. *G. lamblia* cyst in stool sample.

Diagnosis

Definitive diagnosis depends upon: 1. direct observation of the parasites by microscopic examination of concentrated, stained stool sample in which either the trophozoite (Fig. 1.6a) or the cyst (Fig. 1.6b) is identified,⁵⁷ and 2. antigen-capture ELISA.⁵⁸ Both are comparable in specificity and sensitivity, as long as three or more stool samples per patient are sent to the diagnostic laboratory for microscopic examination. Antigen capture usually requires only one stool sample. While PCR is useful for detection of *Giardia* cysts in fresh water supplies,^{59, 60} its application to routine laboratory diagnosis of *G. lamblia* infection⁶¹ is not yet available due to cost constraints and lack of standardization. The string test⁶² is useful if capture ELISA is not available or when organisms have not been found upon repeated stool examination, despite a strong suspicion of *Giardia* infection on the part of the clinician.

Treatment

All symptomatic patients infected with *Giardia* should be treated; Metronidazole is the primary drug of choice.⁶³ Either drug controls clinical symptoms of giardiasis in 80% of symptomatic cases; repetition of therapy after 1-2 weeks is usually effective if failure to cure is encountered. A reasonable definition of cure for patients with infection caused by *Giardia lamblia* is long term disappearance of symp-

toms after therapy and failure to detect organisms in three consecutive stool specimens. Recurrence of symptoms should be treated in the same manner as the original infection. Apparently, resistant strains of *Giardia* have been recently described in a few HIV/AIDS patients.⁶⁴ In those cases, nitazoxanide was used successfully.⁶⁵ Pediatricians who do prefer not to prescribe metronidazole for younger children have the alternative of furazolidone. This nitrofurantoin is available in liquid suspension and is usually well tolerated. However, long courses of up to 10 days are frequently necessary to achieve high levels of cure. Albendazole may soon be considered an alternative drug, based on positive findings from clinical trials in Turkey.⁶⁶

Prevention and Control

Giardia lamblia is primarily a water-borne infection,^{2, 67} although food handlers and infected children in daycare centers no doubt play important roles in transmission. Prevention strategies include proper disposal of human wastes, filtration of drinking water supplies, maintenance of buffer zones around watersheds when filtration is not practiced (e.g., in New York City), and maintaining the highest standards of hygiene in daycare centers and mental institutions, although this last recommendation is admittedly the most difficult one to achieve. No *Giardia* vaccines are likely to emerge from the research laboratory within the next several years.

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