Giardiasis: A Common and Underrecognized Enteric Pathogen

David P. Sealy, MD, and Stanley H. Schuman, MD
Charleston, South Carolina

Until the early 1940s, Giardia lamblia was considered by virtually all to be a simple intestinal commensal that benignly fed on small amounts of ingested food, never to cause symptoms or invade tissue. In the past 35 years this organism has established itself, through epidemics in which other pathogens were ruled out, as a fairly common cause of human enteropathology. The most common forms of symptomatic giardial illness present initially to primary care physicians and invariably are diagnosed as "gastroenteritis" with a symptom complex of abdominal upset, diarrhea, cramping, flatulence, and belching. Unlike most enteritides, giardiasis may become chronic and cause severe weight loss, malabsorption, or generalized discomfort. Also, unlike most, the organism is quite sensitive to antimicrobials and may be simply eradicated. Therefore, it is crucial that the index of suspicion for this illness be raised among family physicians, since it may be treated at the primary care level instead of remaining unsuspected until eventually being referred for a major gastrointestinal evaluation.

While examining his own stools in 1681, during a bout of long-standing diarrhea, Antony Van Leeuwenhoek was doubtlessly the first to identify the organism eventually to be labeled Giardia lamblia.[1] In 1859, Vilem Dusan Fedorovich Lambl noted, once again, this organism in humans naming it Cercomonas intestinales. The genus eventually received its lasting name from Joseph Kuntsler as Giardia, though in 1888 an abortive attempt was made by Blanchard to honor Lambl by naming the organism Lamblia. This was unfortunately six years too late, although many in Europe still used the name Lamblia. Because of this confusion, in 1915, Charles Wardell Stiles

From the Department of Family Medicine, College of Medicine, Medical University of South Carolina, Charleston, South Carolina. Requests for reprints should be addressed to Dr. David P. Sealy, Department of Family Medicine, College of Medicine, Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29403.

0094-3509/81/01047-08$02.00

recommended Giardia lamblia and the name remained.[2] Until the early 1940s, this organism was generally considered by many to be nonpathogenic and a simple intestinal commensal. Others felt it to be pathogenic with large numbers of clinical cases. Many of these responded favorably to quinacrine therapy.[3] Since this time, the frequency and detection of giardial epidemics, invariably through water contamination, has begun to increase, as has concern over its pathogenesis, specific mode of transmission, and proper treatment. Recent large outbreaks in Rome, New York; Leningrad; Aspen, Colorado; Washington; and New Hampshire; and in day care centers, with the only common identifiable source for cysts being Giardia in stools, have confirmed the suspicion of many that giardiasis is pathogenic. Furthermore, infection can lead to severe and chronic illness if not treated, whether in epidemic or endemic settings.[4-7]

Epidemiology

Intestinal giardiasis is seen worldwide. It is the most common enteric pathogen in persons coming to the United States from overseas. Giardia is also the most common pathogenic intestinal parasite reported to the Center for Disease Control in Atlanta, Georgia; the rate of positive stools ranges from zero to ten percent for individual states, and averages 4.1 percent for the United States.[8] This represents a rising trend in stools found to be positive for Giardia (submitted by physicians and health departments to state laboratories). This rising trend has also been noted in Hampton County, South Carolina, currently being studied by the authors. There, the overall positivity rate has risen from 3.3 percent to 10 percent from 1971 to 1978, without the recognition of any epidemic. This has been reflected in most states throughout the country. Although epidemic giardiasis is increasingly recognized, endemic giardiasis accounts for the vast majority of stools found to be positive for cysts on a regular basis.

In virtually all epidemic studies the mode of transmission has been through water supplies that have been contaminated with the Giardia cyst. Most frequently this has involved cross-contamination of drinking water with sewage or with inadequate treatment of sewage. However, with recent outbreaks in daycare centers, household clustering of cases, and high rates among homosexual populations,[9] there is good reason to believe that direct transmission from person to person occurs. This may prove to be a major mode of transmission in endemic situations. Giardiasis transmission must include food handling and sexual activity as well as water-borne spread from human or small mammal reservoirs.

The Organism

This major intestinal flagellate exists in two forms (Figure 1). Unfortunately, the most spectacular form is rarely seen on standard stool preparations: the trophozoite. It is wonderfully identified by van Leeuwenhoek, who described the classic pear shape, with a broad anterior that comes to a blunt point posteriorly with two large nuclei appearing much like eyeballs, and with four pairs of flagellae that emerge from separate, yet consistent and symmetric locations within the body. The ventral surface consists of a large, round, attaching or sucking, disc that is concave and adheres well to the duodenal mucosa (Figure 2). In fresh preparations the trophozoite is unmistakable with its vigorous flagellar activity and slow progress, constantly rolling and flipping in the media. The most common form identified is the cyst, which is a robust encasement of the delicate trophozoite. It is ovoid, nonmotile, and has four nuclei, although rarely are more than two seen by standard light microscopy. The trophozoites range in size from 5-9 × 10-12 microns. The trophozoite form only rarely is seen past the proximal 25 percent of the gastrointestinal tract and then only when transit time is markedly increased and the stools are watery. The cysts are ingested and assisted in the excysting process by the acid environment. In the duodenum the excysting process is completed in the more alkaline environment[10] and the motile trophozoite goes about its work by attaching to the mucosa of the small bowel and

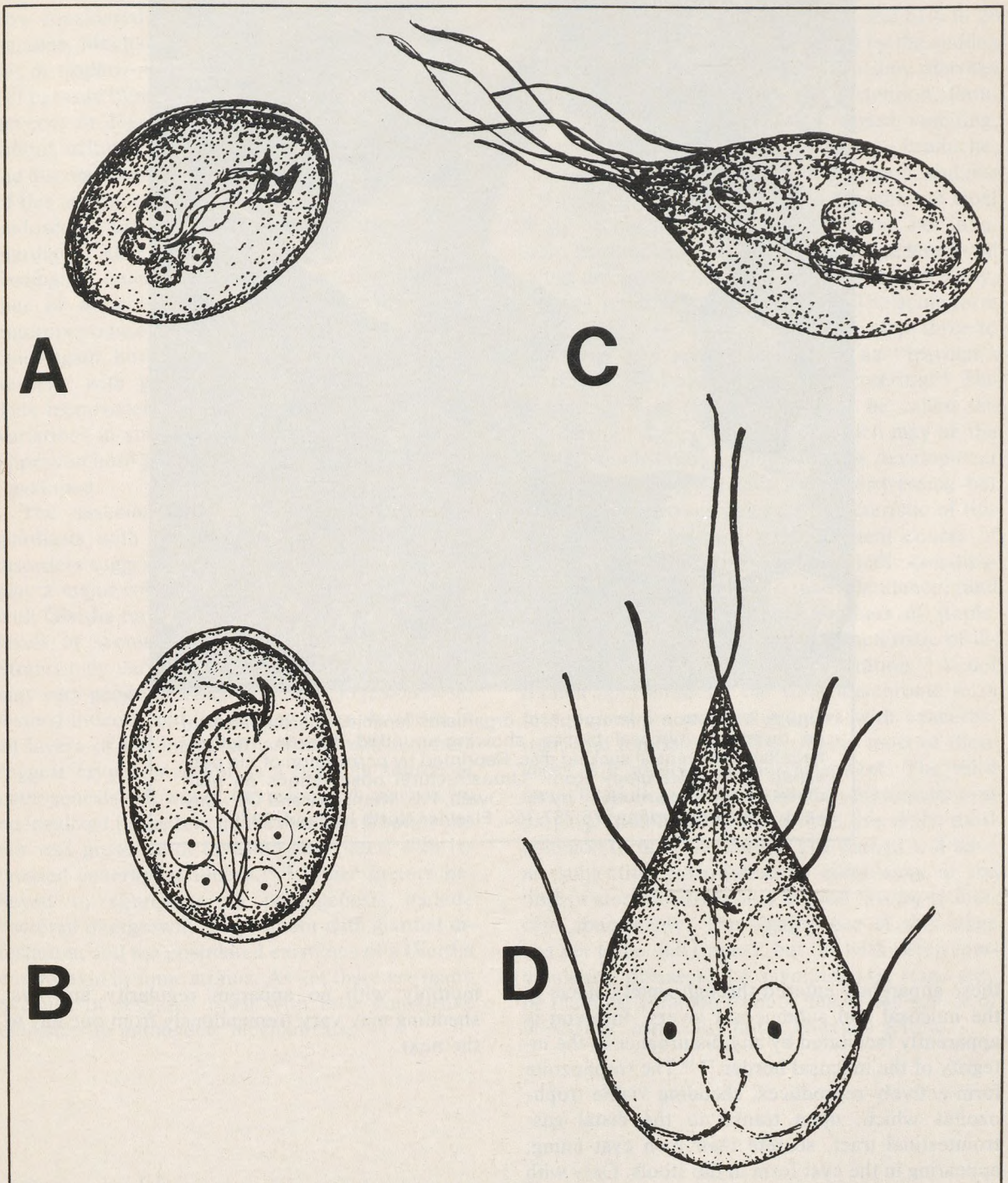

Figure 1. Drawing of organism, Giardia lamblia, in side view (A and C) and front view (B and D)

apparently feeding on debris in the unstirred layer. Although initially not thought to be invasive, duodenal biopsy evidence has shown rare trophozoites present down to the lamina propia;

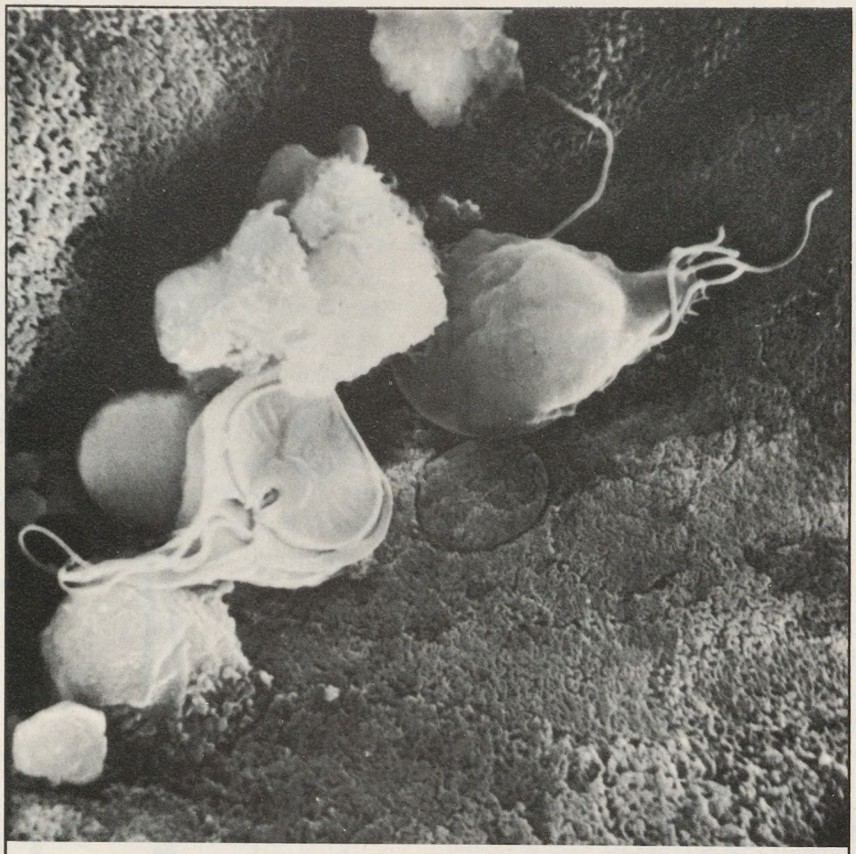

Figure 2. Electron micrograph of organisms (species Giardia lamblia) on duodenal mucosal biopsy, showing rounded dorsum, multiple flagellae, and ventral sucking disc. Reprinted by permission of the publisher, *Gastroenterology* from "Ultrastructural observations on giardiasis in a murine model," by R.L. Owen, P.C. Nemanic, and D.P. Stevens: *Gastroenterology* 76:757-769, Elsevier North Holland, 1979

these apparently entered through small defects in the mucosal and submucosal layers. Invasion is apparently facilitated by any disturbance in the integrity of the mucosal border.[11,12] The trophozoite form actively reproduces, shedding viable trophozoites which, upon transit to the distal gastrointestinal tract, secrete their own cyst lining, appearing in the cyst form in the stools. Only with marked increase in gastrointestinal transit time (ie, diarrhea, short bowel syndrome) will trophozoites appear consistently in stool. The number of cysts in the stool does not correlate well with the cyst burden in the proximal bowel since trophozoites multiply with no apparent regularity and cyst shedding may vary tremendously from one day to the next.

Pathogenesis

Mechanisms of pathogenesis still remain an enigma, though theories abound. At first thought to be a commensal, then graduated to the status of

"facultative pathogen" in the 1940s, Giardia is now considered to be directly pathogenic in many persons. Mechanical mucosal obstruction by masses of trophozoites has been suggested as causal, yet parasite burden does not correlate with disease severity or degree of malabsorption. Mucosal and villous irritation secondary to the powerful sucking disc has been blamed for symptoms. In support of this are the occasional findings of duodenitis on endoscopy or barium studies of patients with giardiasis. Also consistent with this have been the findings of mucosal damage and relative deficiencies of disaccharidase, peptide hydrolase, and enteropeptidase in the proximal bowel mucosa.[13] Once again, however, one would expect increased severity with greater numbers of trophozoites. This inconsistency has been blamed on possible variations in strains of Giardia which will remain unproven until good differentiation techniques are developed.

The association of increased prevalence of giardiasis with various hypogammaglobulinemic disorders suggests that immunologic defenses may play a major role in pathogenicity. Some patients with Giardia have been shown to have decreased levels of secretory IgA in the mucosal layer.[14] Strains may vary simply from multiple passage or may vary geographically. Recently, invasion of intestinal mucosa and the finding of trophozoites in all layers of the intestinal wall in small numbers suggest cryptic invasion as a possible source of pathogenesis. However, invasion was marked by no localized tissue reaction around the trophozoite nor was presence of invasion associated with increased severity of illness.[11,12] Other factors believed to contribute to pathogenesis include bacterial overgrowth concomitant with giardial infestation, and the postulated existence of a Giardia enterotoxin in some strains. As yet there are many avenues of research open with little conclusive evidence on pathogenic mechanisms.

Clinical Manifestations

Though symptoms range from severe malabsorption to mild discomfort, the clinical picture of giardiasis can be grouped into three broad categories. The first may be called the "acute" form which, after an incubation period of 4 to 20 days (average 9.1 days), is heralded by the sudden onset of explosive, watery, foul smelling diarrhea with abdominal discomfort and distention, flatulence, foul eructation, and often nausea, vomiting, fatigue, anorexia, and on occasion, headache, chills, and low grade fever. Mucus, blood, and pus are seldom seen in stools and, if present, are most likely secondary to diarrheal irritation, not invasion. Eosinophilia and an elevated white blood cell count are seldom seen but steatorrhea and bulky, floating stools may be present.[13,15] The acute form is often missed as it may attenuate after three to four days and simply be labeled as "traveler's diarrhea" or "acute viral gastroenteritis." The second type of presentation may be called the "subacute" or "chronic" form which may be the initial manifestation of illness or the development of the acute disease into a less distressing but nevertheless serious illness. Characteristic of this stage is the relentless or intermittent course of mushy stools, sometimes with periodic constipation, abdominal distention and flatulence, and slightly increased or normal numbers of stools. Anorexia and weight loss are characteristic of illness of greater than a ten-day duration.[15] If not treated appropriately, the subacute/chronic form may persist for months or years with exacerbations and remissions.[16] Eventually, most of these cases will resolve without treatment. The third form of the illness is marked by asymptomatic cyst passing. In non-epidemic settings this is the most common form of the illness. The patient will have no subjective gastrointestinal complaints at the time of stool positivity and no past history to indicate abnormality. The significance of this stage has yet to be determined, but, as with other communicable diseases, the asymptomatic stage may be the most common form of illness and source of infectivity, especially in the endemic setting.

Diagnosis

The mainstay for diagnosis of giardiasis has been the "wet mount" examination of stools. The preparation combines 0- to 12-hour-old stools with

saline and iodine to counterstain. It is still the simplest and only method used in many diagnostic laboratories.[17] Formalin-ether sedimentation and zinc-sulfate flotation have been used to concentrate cysts and have had minimal to moderate success. Detection varies with the skill of the examiner and the age of the specimen. The irregularity of the cyst excretion is a major reason for variable detection. One certain fact is that examination of multiple stools markedly increases the detection rate. Wolfe reports a sensitivity of 76 percent with one stool, 90 percent with two, and 97.6 percent with three stool specimens under direct and formal ether examination.[13] Others have not been so fortunate.[18] An overall rough estimate would indicate that anywhere from 25 percent to 50 percent of patients with giardiasis are missed on the first stool examination.

Dissatisfaction with stool examinations has stimulated the development of better tests for detection of the trophozoite. These tests center around obtaining tissue, mucous, or aspiration materials from the duodenum or proximal jejunum. If giardiasis is suspected and multiple stools are negative, one may try to increase diagnostic yield with duodenal aspiration, bowel biopsy, and mucous impression smears, or with string test capsules to collect mucous.[19,20] Duodenal aspiration is accomplished by passing a radio-opaque double lumen tube into the duodenum under fluoroscopy while draining the stomach with continuous nasogastric suction. Duodenal biopsy can be done during endoscopy or simply with a double lumen tube capable of sucking a small thickness of duodenum into a minute orifice in the outer lumen and cutting it off with a sliding blade across the orifice. Biopsies are generally without any major side effects and also allow mucous impression. These are simply the mucous layer immediately contiguous to the biopsied tissue section stripped away and free-mounted in one drop of saline. In their laboratory, Kamath and Murugasu have shown this to be 100-percent effective for detection of trophozoite.[19] The Enterotest is a small gelatine capsule on a string swallowed and allowed to pass into the duodenum (verified by bile stain on the string). The absorbent string is pulled back up, affording easy examination for trophozoites. This has been shown to be as effective as duodenal aspiration for detection of giardiasis.[20] With multiple negative examinations and a remaining high index of suspicion, a therapeutic trial of quinacrine has been recommended by some; treatment has no known effect on enterobacteria and therapeutic response suggests the presence of an unidentified giardial infection.[13] Indirect immunofluorescence for Giardia has yielded some success as has measurement of antigiardial antibodies in the serum, but both methods need further refinements before being applicable to the clinical setting.[21]

Treatment

Although for 40 years quinacrine has been used as the treatment of choice for giardiasis, other drugs have been advocated during the last seven to eight years. In almost all studies the antimalarial quinacrine has been shown to give parasitologic cures in 90 percent or more of patients with giardiasis. The standard dosage for adults is 100 mg three times a day for 5 to 7 days; for children aged 4 to 8 years, 50 mg three times a day; for ages 1 to 4, 50 mg twice a day. At this dosage level, side effects are minimal, consisting of gastrointestinal disturbances, headaches, and diuresis. Some have noted mild yellow discoloration of the skin and sclerae, and occasionally (one percent of cases) an acute toxic psychosis may develop which resolves with discontinuance of the drug. These are seen most often at 1 gm/day or greater doses formerly used for malaria. Effective in children but not as well tolerated, with unknown side effects during pregnancy, furazolidone is the only other FDA approved drug in the United States for treatment of giardiasis. Until recently, it was the only antigiardial drug in suspension form, making it useful for children. Dosages from 5 to 16 mg/kg/day up to 100 mg four times a day have been linked with 60 to 91 percent cure rates.[22] The toxicity of furazolidone is minimal. Most commonly seen are gastrointestinal disturbances, morbilliform rashes, hypersensitivity, eg, urticaria, and darkening of the urine, which is clinically insignificant apart from the hemolysis which may occur in glucose-6-phosphate dehydrogenase-deficient individuals. The last available drug in the United States, though not approved by the FDA for giar-

diasis, is metronidazole (Flagyl). In numerous studies it has had parasitologic cure rates of 70 to 100 percent depending upon dosage schedules and stage of disease during the treatment. At a dosage of 250 mg three times a day for 7 to 10 days, it appears to be slightly less effective than quinacrine, but somewhat better tolerated.[13,23,24] It may have slightly greater efficacy in more chronic infections.[23] Again, the side effects of metronidazole at the 250 mg three times a day dosage are minimal, consisting mainly of gastrointestinal disturbances, metallic taste, xerostomia, headaches, and urinary frequency. Also seen is an incompatibility with alcohol resembling the side effects of disulfiram. In fact, metronidazole has been used in rehabilitation programs for alcoholics, but has had questionable success.[25,26] At 2 gm/day levels, side effects are much more apparent. Also of recent concern have been the mutagenic effects seen in mice and bacteria. Although a recent large retrospective human study could not document cancer risks, serum levels equivalent to doses of 2 gm/day have been shown to be carcinogenic in mice and mutagenic in bacteria.[26-28] While metronidazole (Flagyl) is slightly less effective than quinacrine at lower doses, it is considered by some to be the drug of choice for giardiasis.

Two other nitroimidazole compounds—tinidazole and nimorazole—have been clinically tested in comparison with metronidazole. Tinidazole in a twice daily dose of 150 mg has been shown to be very effective with virtually no side effects. Parasitologic cures of 90 to 100 percent have been achieved in all studies after a seven-day course.[29,30] Nimorazole is slightly less effective than tinidazole and seems to have comparable side effects with metronidazole.[29,30] Since tinidazole is not FDA approved in the United States, further research needs to be done with this promising drug which has been effective in both epidemic and endemic giardiasis.

Discussion

Though not as prevalent as in some areas, Giardia lamblia is now the most commonly identified pathogenic intestinal parasite in the United States. Yet how often is Giardia overlooked by the majority of physicians to whom it will inevitably first present, those in primary care! Unlike many other forms of enteritis or colitis, giardiasis is very responsive to proper treatment and may become chronic if not properly treated. Giardiasis should be suspected in any diarrheal illness of longer than seven days, especially if foul belching and flatulence, abdominal cramping, and nausea and vomiting are present. Giardial stools are not dysenteric, and viral enteritis usually runs its course in less than seven days. If a stool specimen taken for other purposes discloses giardial cysts, it is recommended that the person be treated. This would serve the purpose of eliminating the possibility of person-to-person contamination and cure illness which at that point is present but not symptomatic. (Many stool specimens taken because parents say their children have worms or are restless at night are yielding Giardia in greater numbers than any other organism.) Once giardiasis is suspected, three stool specimens collected every other day should reveal the organism. The "Enterotest" gelatine capsule may be easily used in the office and provides a one-time immediate and quite gratifying diagnostic tool. The minimum recommended retention time for the string in the duodenum is four hours. The Giardia trophozoite is unique and easy to recognize.

Once a case is diagnosed, treatment may be either with quinacrine or with metronidazole. Both are recommended in seven-day, three times a day regimens. The choice of treatment involves balancing potential side effects and efficacy. Quinacrine is slightly more effective at accomplishing parasitologic cure but does carry a one percent incidence of a reversible toxic psychosis. Metronidazole (Flagyl) is slightly less efficacious but seems to be better tolerated. At the two gram single daily dosage for three days, metronidazole (Flagyl) is comparable to quinacrine. However, that dosage level is carcinogenic in rodents, and mutagenic in bacteria. For children unable to swallow tablets, furazolidone suspension at 6 to 10 mg/kg/day in four divided doses for seven days is recommended. If domestic tinidazole trials are consistent with foreign studies, it should replace quinacrine and metronidazole as the drug of choice.

In persons from non-endemic settings, attack rates of symptomatic giardiasis seem to be much

higher than those in endemic settings. This may be related to organism factors, immunologic factors, or both. Little information regarding the transmission, clinical spectrum of illness, epidemiology, and efficacy of treatment of giardiasis in the endemic setting is known. A substantial contribution to the understanding of the disease can be made by cooperative studies done by primary care physicians. Such endeavors, however, must start with an increased clinical index of suspicion and improved diagnosis in the less dramatic and in the nonepidemic setting of office practice.

Acknowledgement

The authors wish to acknowledge Fred E. Pittman, MD, Professor of Internal Medicine, Division of Gastroenterology, Medical University of South Carolina, for sharing information from his series of unpublished cases.

References

1. Dobell C: Antony von Leeuwenhoek and His "Little Animals." New York, Harcourt Brace, 1932, pp 223-225
2. Jacobowski W, Hoff JC (eds): Proceedings of the National Symposium on Waterborne Transmission of Giardiasis, Cincinnati, Ohio, September 18-20, 1978. Environmental Protection Agency (Washington, DC): publication No. EPA-600/9-79-001. Government Printing Office, 1979, pp 2-3
3. Hartman HR, Kyser FA: Giardiasis and its treatment. JAMA 116:2835, 1941
4. Brodsky RE, Spencer HC, Schultz MG: Giardiasis in American travellers to the Soviet Union. J Infect Dis 130:319, 1974
5. Moore GT, Crass WM, McGuire D, et al: Epidemic giardiasis at a ski resort. N Engl J Med 281:402, 1969
6. Shaw PK, Brodsky RE, Lyman DO: A community wide outbreak of giardiasis with evidence of transmission by a municipal water supply. Ann Intern Med 87:426, 1977
7. US Department of Health, Education, and Welfare, Center for Disease Control: Waterborne giardiasis outbreaks—Washington, New Hampshire: 1977. Morbid Mortal Week Rep 26:168, 1977
8. Intestinal Parasite Surveillance, Annual Summary. US Department of Health, Education, and Welfare, Center for Disease Control (Atlanta, Ga): publication No. (CDC) 79-8352, 1978
9. Schmerin MJ, Jones TC, Klein H: Giardiasis: Association with homosexuality. Ann Intern Med 88:801, 1978
10. Jacobowski W, Hoff JC (eds): Proceedings of the National Symposium on Waterborne Transmission of Giardiasis, Cincinnati, Ohio, September 18-20, 1978. Environmental Protection Agency (Washington, DC): publication No. EPA-600/9-79-001. Government Printing Office, 1979, pp 217-229
11. Brandborg LL, Tankersly CB, Gottlieg S, et al: Histological demonstration of mucosal invasion by Giardia lamblia in man. Gastroenterology 52:143, 1967
12. Owen RL, Nemanic RC, Stevens DP: Ultrastructural observations on giardiasis in a murine model. Gastroenterology 76:757, 1979
13. Wolfe MS: Giardiasis. N Engl J Med 298:319, 1978
14. Zinneman HH, Kaplan AP: The association of giardiasis with reduced intestinal secretory immunoglobulins. Am J Digest Dis 17:793, 1972
15. Jacobowski W, Hoff JC (eds): Proceedings of the National Symposium on Waterborne Transmission of Giardiasis, Cincinnati, Ohio, September 18-20, 1978. Environmental Protection Agency (Washington, DC): publication No. EPA-600/9-79-001. Government Printing Office, 1979, pp 39-47
16. Peterson H: Giardiasis. Scand J Gastroenterol 7(suppl):14, 1972
17. Jacobowski W, Hoff JC (eds): Proceedings of the National Symposium on Waterborne Transmission of Giardiasis, Cincinnati, Ohio, September 18-20, 1978. Environmental Protection Agency (Washington, DC): publication No. EPA-600/9-79-001. Government Printing Office, 1979, pp 94-95
18. Jeffry GM, Harrison AJ: A three-year epidemiologic study of intestinal parasites in a selected group of mental patients. Am J Hyg 71(1):1, 1963
19. Kamath KR, Murugasu R: A comparative study of four methods for detecting Giardia lamblia in children with diarrheal disease and malabsorption. Gastroenterology 66:16, 1974
20. Bezjak B: Evaluation of a new technique for sampling duodenal contents in parasitologic diagnosis. Am J Digest Dis 17:848, 1972
21. Jacobowski W, Hoff JC (eds): Proceedings of the National Symposium on Waterborne Transmission of Giardiasis, Cincinnati, Ohio, September 18-20, 1978. Environmental Protection Agency (Washington, DC): publication No. EPA-600/9-79-001. Government Printing Office, 1979, pp 53-63
22. Jokipii L, Jokipii AMM: Giardiasis in travellers: A prospective study. J Infect Dis 130:295, 1974
23. Wolfe MS: Giardiasis. JAMA 233:1362, 1975
24. Wolfe MS: Giardiasis. Pediatr Clin North Am 26:295, 1979
25. Penick SB, Carrier RN, Sheldon JB: Metronidazole in the treatment of alcoholism. Am J Psychiatry 125:1063, 1969
26. Beard CM, Noller KL: Lack of evidence for cancer due to use of metronidazole. N Engl J Med 301:519, 1979
27. Rustin M, Shubik P: Induction of lung tumors and malignant lymphomas in mice by metronidazole. J Natl Cancer Inst 48:721, 1972
28. Is Flagyl dangerous? Med Letter 17(13):53, 1975
29. Levi BC, deAvila CA, Neto VA: Efficacy of various drugs for the treatment of giardiasis. Am J Trop Med Hyg 26:564, 1977
30. Anderson T, Forssel J, Sterner G: Outbreak of giardiasis: Effect of a new antiflagellate drug, tinidazole. Br Med J 2:449, 1972