Parasites and Malabsorption

THOMAS A. BRASITUS, M.D.
New York, New York

Intestinal parasites not only cause diarrheal illnesses but may also cause significant malabsorption in man. Separation of true malabsorption caused by a particular parasite from other factors that may coexist with and even mimic malabsorption, such as malnutrition may be very difficult. Despite these problems, it appears that giardiasis, coccidiasis, strongyloidiasis and capillariasis cause malabsorption of many important nutrients. D. latum interfere with vitamin B\textsubscript{12} absorption.

Intestinal parasitic infections in man are extremely common worldwide and have become more prevalent in the United States as foreign travel has increased. Parasites are commonly known to cause diarrheal illnesses, but it has not been appreciated that a number of them cause significant malabsorption.

In reviewing malabsorption secondary to intestinal parasites a number of problems arise. Appropriate socioeconomic and age-matched control populations are often lacking, and the effects of the parasite are often difficult to separate from those of malnutrition. Some of the studies originate in areas in which tropical sprue is endemic. In other areas, many apparently healthy patients have small intestinal mucosal histology which is considered abnormal by North American standards [1,2]. Malabsorption ascribed to a single parasite is often difficult since multiple parasitic infections are quite common. Despite these limitations it is clear that a number of parasites may cause malabsorption.

Intestinal parasites can be divided into two major groups: the Protozoa and Helminths. The latter can be subdivided into tapeworms, roundworms and flatworms. This paper will review their association with malabsorption in man.

PROTOZOA

Giardiasis. The flagellated protozoan Giardia lamblia was first described by van Leeuwenhoek of Delft in his own stools in 1681 [3]. It has a worldwide distribution with a prevalence varying from 2 to 50 per cent [4-7]. In the United States giardiasis is both endemic and imported with an over-all prevalence of 7.4 per cent as calculated from 24 published series [8]. There have been a number of epidemics of this infection in recent years [9-11]. The attack rate in American travelers to Leningrad over a four year period was calculated to be 23 per cent [10]. Of the servicemen hospitalized for chronic diarrhea in Vietnam, 36 per cent harbored this parasite [13].

G. lamblia resides in the upper part of the small intestine in man. The parasite has two forms, trophozoite and cyst. The trophozoites can be seen in diarrheal stool (Figure 1) but not in formed stool, whereas the infective stage of the parasite, the cyst, is usually found in formed stool. The cyst, which is quite resistant to chlorination [10,14], is usually

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York. Requests for reprints should be addressed to Dr. Thomas A. Brasitus, Division of Gastroenterology, College of Physicians & Surgeons, Black Building 1101, 630 West 168th Street, New York, New York 10032.
transmitted by fecally contaminated food or water [4,10,11] and perhaps by close interpersonal contact [15]. The diagnosis is best made by examining the duodenal aspirate if the stools are negative (Table I).

There appears to be an increased incidence of giardiasis in children [4,6], in patients with hypo or achlorhydria [16] and in certain immune deficiency states including acquired dysgammaglobulinemia [17-19] and, rarely, X-linked agammaglobulinemia [20].

Although most adults are asymptomatic, infection with this parasite can result in acute gastrointestinal distress as well as chronic diarrhea and malabsorption. The malabsorption can be severe enough to be clinically mistaken for celiac sprue [21,22].

Standard tests for malabsorption such as fecal fat and nitrogen, d-xylene absorption, serum folate and serum carotene are frequently abnormal [5,6,12,19]. Vitamin B₁₂ levels, although usually in the normal range, have occasionally been low in both normal [23] and immunodeficient patients [17] with giardiasis. Ament and Rubin suggested that the immunodeficiency state itself, bacterial overgrowth, or the parasite might all lead to low vitamin B₁₂ levels. Others [23] attributed abnormal Schilling tests to competition between the parasite and host enterocyte for the vitamin.

Roentgenograms of the small bowel may show thickening and distortion of mucosal folds suggestive of malabsorption [12]. Small intestinal biopsy findings have ranged from normal to complete villus atrophy [24]. A marked reversal of severe villus abnormalities

<table>
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<tr>
<th>Parasitic Disease</th>
<th>Diagnosis</th>
<th>Treatment for Adults</th>
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<tr>
<td>Giardiasis</td>
<td>Fresh stool for trophozoites or cysts</td>
<td>Quinacrine (Atabrine) hydrochloride 100 mg orally 3 times a day for seven days</td>
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<td></td>
<td>Duodenal aspiration for trophozoites</td>
<td>OR</td>
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<td></td>
<td>Stool examination after one or two days for mature oocysts</td>
<td>Metronidazole (Flagyl) 250 mg orally 3 times a day for 7-10 days [32]</td>
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<tr>
<td>Coccidiosis</td>
<td>Fresh stool for ova</td>
<td>75 mg pyrimethamine + 4 g sulfadiazine orally every day (21 days)</td>
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<td>Small bowel biopsy</td>
<td>THEN</td>
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<td></td>
<td>Duodenal aspirate</td>
<td>½ dosage for 28 days [39]</td>
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<tr>
<td>Capillariasis</td>
<td>Fresh stool for ova</td>
<td>Co-trimoxazole 2 tablets orally 4 times a day for 10 days and then 2 tablets orally 2 times a day for 3 weeks [84]</td>
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<tr>
<td>Strongyloidiasis</td>
<td>Fresh stool for larvae</td>
<td>Thiabendazole 25 μg/kg/day orally for several weeks [14]</td>
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<td></td>
<td>Duodenal aspirate</td>
<td>Quinacrine (Atabrine) hydrochloride 1 g in 40 cc of water down nasogastric tube which is in duodenum [87]</td>
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has been demonstrated in immunodeficient [23] and normal patients [24] harboring Giardia after metronidazole (Flagyl®) therapy.

Brandborg et al. [5] and others [25], using special stains, have demonstrated mucosal invasion by the parasite. Morecki and Parker [26] have shown Giardia within mucosal cells by electron microscopy. It appears that Giardia may invade the small intestinal mucosa and be responsible for the abnormal mucosal histology. The majority of biopsy specimens, however, even in patients with steatorrhea, do not appear sufficiently abnormal to adequately explain the malabsorption seen with the parasite. A number of other factors have been suggested in addition to direct mucosal injury by the parasite. Erlandsen and Chase [27] using electron microscopy have demonstrated direct attachment of G. muris' adhesive disc to the rodent microvillus membrane (see Figure 2). Giardia may, therefore, create a mechanical barrier to absorption. It may also directly compete with the host for nutrients [6,23] or alter intestinal motility as seen in other parasites [28]. It is also known that bacterial overgrowth may accompany giardiasis and may be partially responsible for the associated steatorrhea [29-31]. Recently, Tandon et al. [30] have shown that giardial infection is associated with high luminal free bile acid levels, even when not accompanied by bacterial overgrowth, suggesting that the parasite alone may be capable of bile salt deconjugation in vivo. Future studies will show whether any or all of these mechanisms play a role in the diarrhea and malabsorption seen with this parasite.

Successful treatment of Giardia with atabrine [32] or metronidazole (Flagyl®) [32] has usually cured the malabsorption (Table I). High doses for several weeks may be needed in immunologically deficient patients to eradicate the parasite. Broad-spectrum antibiotics may be useful in those patients in whom the parasite appears to have been eradicated but in whom steatorrhea persists [31].

Coccidiosis. Coccidia are ubiquitous intracytoplasmic protozoan parasites which are species specific and are invariably found in every animal examined including man [33,34]. The Isospora species beli, hominis and natelenis, are found in man. I. beli and I. hominis may be the same organism [35]. Coccidia are infrequently recognized as pathogens in man in the United States despite endemic areas in many parts of the world [36,37]. Their life cycle involves an asexual phase (Schizogony) and a sexual phase (Gametogony). This latter phase results in a nonsporulated oocyst which is eliminated in the feces and may become infectious if ingested [37]. Diagnosis by stool examination may be difficult since, despite severe diarrhea and steatorrhea, the oocysts may be rare [34]. Fecal specimens are best examined after one to two days at room temperature, which allow the oocyst to mature (Table I).

There is limited information on fecal fat excretion in these patients. Steatorrhea has been suggested in several
studies by either gross or microscopic examination [36,38]. Brandborg et al. [34] demonstrated abnormal fecal fat, d-xylose absorption and low serum carotene levels in several patients studied. Small bowel biopsy abnormalities varied from mild clubbing of villi to a flat mucosa. Almost every stage of the parasite's life cycle was demonstrated within the epithelium.

Trier et al. [39] have described a patient suffering from chronic coccidial infection. The patient had intermittent diarrhea for 20 years, probable malabsorption for more than seven years, and intestinal coccidial infection documented for at least 10 months. The intestinal mucosa was severely affected with shortened villi, hyperplasia of the lamina propria which gradually reverted to normal after treatment with pyrimethamine and sulfadiazine (Table 1). It is reasonable to ascribe the malabsorption seen with this parasite to small intestinal mucosal damage [34].

Cryptosporidia. These intracellular protozoan parasites are also considered to be coccidia. They belong to the family Cryptosporididae whereas Isospora belong to the family Eimeriidae [40]. The organism has been shown to produce a severe mucosal lesion in the small intestine and colon [40]. There is loss of villus height, elongation of crypts, and lymphocyte and polymorphonuclear infiltration in the lamina propria [41]. Cryptosporidia have been shown to cause marked diarrhea, but despite severe intestinal lesions, no malabsorption has been documented to date. This parasite may very likely be shown to cause malabsorption in the future, especially in immunosuppressed hosts.

Malaria. Gastrointestinal symptoms including nausea, vomiting and diarrhea may be clinically important manifestations of acute Falciparum malaria [42]. Plasmodium knowlesi infected monkeys appear to have decreased amino acid absorption [43]. There have been reports of abnormalities of d-xylose absorption [44,45,48], lactose absorption [44,46] and serum vitamin B12. Folate levels have been shown to be low but may reflect inadequate dietary folate, increased utilization of folate secondary to hemolysis, or fever and drug inhibition by the antimalarial chemotherapy [47]. Small intestinal biopsies have revealed congestion and edema of the lamina propria which have been interpreted as evidence that malaria may interfere with absorption by affecting the small intestinal microcirculation. These changes, however, are not dramatic and may even be artifactual. Over-all there is little evidence to suggest that malaria definitely causes malabsorption.

PARASITES AND MALABSORPTION: BRASITUS

Tapeworms. Diphyllobothrium latum: A number of tapeworms are parasites of the intestinal tract of man including D. latum [46]. Adult tapeworms are anchored to the intestine by a scolex and have egg-producing units called proglottides. The worm does not have an intestinal system but absorbs its nutrients through its intestinal tegument from the host's mucosa or intestinal contents [49].

Infection occurs from ingestion of raw infected fish [49] and although commonly seen in Scandinavia also occurs in the northern United States, Canada and Alaska. Although patients may be symptom-free, a number of patients have vitamin B12 deficiency, so called "tapeworm pernicious anemia" [49]. The mechanism for this vitamin B12 malabsorption is not clearly established [50], but in vitro studies have demonstrated that D. latum may take up free vitamin B12 [51] whereas vitamin B12 complexed to intrinsic factor is taken up more slowly [51]. Others have suggested that the parasite secretes a "releasing" factor capable of freeing vitamin B12 from intrinsic factor [52]. Mettrick and Podesta [53] have suggested that the worm alters the local pH of its microenvironment in the gut releasing the vitamin B12; thus allowing it to be taken up by the parasite. In addition to these studies, others have suggested that D. latum depresses gastric intrinsic factor secretion [50], although there is no evidence that intrinsic factor increases after eradication of the worm [50].

ROUNDWORMS

Strongyloidiasis. Strongyloides stercoralis is the species which produces disease in human subjects. Although it is the least common of the major intestinal nematodes, it deserves particular attention because it may produce overwhelming fatal infection [54-58]. It has a worldwide distribution [54,59] and is most often found in the rural south, but occasionally autochthonous cases have been reported in northern cities [54]. The prevalence is particularly high in Vietnam veterans [59], immunosuppressed patients [59], and in institutions for the mentally retarded [54].

Strongyloides are hatched in the host's small intestine and rhabditiform larvae are passed in the stool. These larvae may become free living adults that reproduce in the soil or may change into infectious filariform larvae and penetrate a host's skin. The larvae then migrate through the venous system to the lungs and from there be coughed up and swallowed and reach the small intestine [54,59]. This parasite is unique in that rhabditiform larvae may transform into filariform larvae within the distal small intestine or colon (internal autoinfection) or in the perianal area (external autoinfection) and thus repeat the cycle of infection [54,59]. In immunosuppressed patients, malnourished patients or occasionally normal hosts this process may cause an overwhelming fatal hyperinfective syndrome.

Although the majority of S. stercoralis carriers are asymptomatic, patients with high parasite loads may have steatorrhea, abnormal d-xylose absorption and low serum levels of vitamin B12 and folate [59,60]. There may be a severe hypoproteinemia [59] which cannot be explained on a nutritional basis alone and appear to be secondary to inflammation of the intestinal mucosa [59].
with a protein losing enteropathy. Roentgenologic evaluation may show nonspecific changes compatible with a malabsorption pattern or in severe cases may show "pipe-stemming" of the intestine mimicking regional enteritis, atypical lymphoma, or intestinal tuberculosis (Figure 3) [61,62,83]. After appropriate treatment this roentgenologic pattern has been shown to revert toward normal [60].

This parasitic infection has often been mistaken for tropical sprue. Small bowel biopsy specimens may show an increase in inflammatory cells (particularly eosinophils), in the lamina propria, dilated lacteals, loss of villus height and even ulceration [51]. It is very difficult to find these parasites in the biopsy specimen (Figure 4) but examination of duodenal fluid, as in the case of giardiasis, allows the diagnosis to be established in a very high percentage of patients with negative stool examinations [59].

Even asymptomatic patients harboring this parasite should be treated since they always are at risk of having the hyperinfection syndrome. A number of asymptomatic patients have died after immunosuppressive therapy induced this syndrome [54,56]. Thiabendazole, 25 mg/kg given orally twice a day for three days, has been highly effective in eradicating the parasite and diminishing symptoms in all but very severe cases (Table I) [59].

Ancylostomiasis. The two species of intestinal hookworm that infect man are Ancylostoma duodenale and Necator americanus [49,63]. The life cycle of both these species is similar to that of strongyloides [49]. Hookworms may remove as much as 0.67 ml of blood per worm per day [49].

There is considerable controversy as to whether hookworm infection can result in malabsorption. Despite numerous studies which purport to show steatorrhea, abnormal d-xylose absorption, abnormal small bowel biopsies, hypoproteinemia and low vitamin levels in this disease [64-69], many studies show poor correlation between worm load and malabsorption [63,66,70-72]. Intestinal pathology and malabsorption in these malnourished patients have been reversed solely by a nutritious diet [73]. Banwell et al. [70] have been unable to demonstrate that newly acquired hookworm infection contributed to preexisting malabsorption seen in patients with chronic pancreatic exocrine insufficiency.

The consensus is that hookworm disease does not cause malabsorption in man [49,69,70].

Capillariasis. Intestinal capillariasis is caused by Capillaria philippinensis which is only found in the Philippines [74]. Its only known host is man and its life cycle and means of transmission are completely unknown [74]. It has been suggested that consumption of uncooked intestine and other viscera may be epidemiologically important [75]. Whalen et al. [74] described an epidemic of over a thousand cases in 1967 with a mortality as high as 35 per cent in certain areas. These
patients had a severe sprue-like syndrome with diarrhea and severe malabsorption. Extensive laboratory investigations revealed significant steatorrhea and loss of minerals and protein in the stool. $^{51}$Cr-albumin studies revealed loss of protein into the gastrointestinal tract. Small bowel biopsy specimens were equally abnormal in control subjects and patients although the worm was seen only in the infected patients. The administration of thiabendazole, 25 mg/kg/day, rapidly eliminated C. philippinensis ova from the stool, decreased the diarrhea, and gradually reversed the abnormal laboratory values (Table I).

Watten et al. [76] showed differences in fecal fat loss, vitamin $B_{12}$ absorption and conjugated bile acid levels between asymptomatic and symptomatic patients who harbored the parasite. Isotopically labeled oleic acid was absorbed much better than triolein suggesting that infected patients may have impaired fat digestion as well as fat absorption.

The pathophysiology of the severe steatorrhea is still speculative. It may relate to an overwhelming number of parasites competing with the host for nutrients, a toxin elaborated by the parasite, a deficiency in digestive enzyme activity, or a decrease in bile acid conjugates [76]. Further studies are clearly needed in this area.

**Ascariasis.** Ascaris lumbricoides is a large round worm with widespread distribution. The life cycle involves swallowed eggs from contaminated food or drink, larvae developing in the proximal small intestine and penetrating the mucosa and reaching the portal venous system. The rest of the cycle is similar to that described for strongyloides and hookworm [49]. Although the adult worms may cause diarrhea and severe problems such as intestinal obstruction, perforation, appendicitis, pancreatitis and obstructive jaundice [49], it is not clear whether ascaris can cause intestinal malabsorption. Studies in children [77,78] have suggested that high worm burdens may lead to marked nutritional impairment although appropriate controls were not used. There appears to be little evidence at this time that ascarias can cause intestinal malabsorption.

**FLATWORMS**

**Schistosomiasis.** Schistosomiasis is believed to infect at least 150 million people. The lesions produced by Schistosoma japonicum, S. mansoni and S. haemato- bium are very similar [49]. Since the egg laying female of S. japonicum resides in the superior mesenteric venous system, it affects the small intestine more than S. mansoni which resides in the inferior mesenteric venous system.

The parasitic ova are the cause of overt disease which results in a granulomatous reaction by the host [49]. Fibrosis, polypoid lesions and even stenosis of the bowel may occur in the intestine as late manifestations of the granulomatous reaction [49]. Despite this there is little evidence that schistosomiasis causes malabsorption [48,79]. Domingo and Warren [79] have shown experimentally in mice, that S. mansoni which resides in the inferior mesenteric venous system.

The hypoalbuminemia seen in schistosomiasis has been attributed to liver disease or malnutrition. It has been shown that protein loss may occur with schistosomal polyposis of the colon [49]. El-Saardari et al. [80] have shown that excessive protein loss may correlate

Figure 4. Adult Strongyloides stercoralis present in the small intestinal mucosa. (Courtesy of Dr. Dickson D. Despommier.)
with increased portal pressure, and others [81] have demonstrated intestinal lymphangiectasis in advanced schistosomiasis. It appears that schistosomiasis may cause hypoalbuminemia for a variety of reasons, but that malabsorption is uncommon.

In summary, although many parasites have been said to cause malabsorption it appears that giardiasis, cocidiosis, strongyloidiasis and capillariais are the only parasitic diseases which cause malabsorption of many nutrients. D. latum appears to interfere with vitamin B_{12} absorption. In view of the increasing use of immunosuppressive therapy in a variety of disorders it is likely that intestinal parasites will be increasingly recognized as etiologic agents in intestinal malabsorption.

REFERENCES


