Parasitic Diseases of the GI Tract in the United States

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ALTHOUGH parasitic infections that are seen in the United States frequently have been acquired outside the continental limits of the country, the physician should realize that parasites are not always imported. The North American economy does maintain a modest domestic supply of parasites pathogenic for man. The United States citizen can acquire amebiasis, giardiasis, pinworms and strongyloidiasis, for example, without so much as a passport application! In various areas of this country additional intestinal helminths are still being transmitted.

The purpose of this review is to consider the clinical significance of parasitic infections of the GI tract that are likely to be encountered by physicians in the United States. Emphasis will be on the practical aspects and on the more common entities, but a section will be devoted to several newly recognized parasitic diseases as well. After some general considerations of the entire subject, each of the various parasitic infections will be discussed from the viewpoint of the parasite's life cycle that may have clinical implications, epidemiologic features, clinical aspects, diagnostic procedures and treatment.

General Considerations

Although the importance of returning military personnel for certain parasitic diseases such as malaria is dominant, the contribution of the civilian sector to imported disease in general probably is numerically greater. Some appreciation of the numbers of people on the move both out of and into this country each year is provided in Table 1. Europe received the largest group of American travelers but holds few hazards insofar as parasitic infections are concerned. It is noteworthy that this number was easily exceeded by the number of travelers to Mexico and the West Indies combined. A total of somewhere between a half million and 1 million Americans annually visit the more tropical regions of Asia, Latin America and Africa, where opportunities for exposure to parasitic infections are maximal.

When the 1 to 2 million annual load of foreign visitors to this country are added to the pool, the total foreign traveler "at risk" group becomes a respectable 5 million or so. Of course, the proportion of this group whose socioeconomic status, living habits, occupation, etc. actually expose them to parasitic infections probably is small. Yet, because of the ease and rapidity of global travel and the fact that it is constantly increasing, the practicing physician must continue to widen his diagnostic horizons.

Will various parasites that are brought back to the continental United States become locally established if not here already, or augment the transmission potential of those already present? This same question was raised during and after World War II when military personnel returned from Africa, Asia and the Western Pacific regions. But there was no evidence that an increase in existing parasite transmission occurred or that new parasites were introduced and transmitted to any significant degree. Unusual circumstances can and do permit occasional focal outbreaks of certain parasitic infections such as malaria (1), but environmental conditions simply do not favor continued and expanding transmission of most parasites. The reason for this is that the majority of parasitic infections, especially the intestinal worms and protozoa, are dependent on lower levels of sanitation and hygienic practices than those that generally

TABLE 1.—FOREIGN TRAVEL FROM AND TO THE UNITED STATES*

GEOGRAPHIC AREA	U.S. CITIZEN DEPARTURES IN MILLIONS AND PER CENT TOTAL				FOREIGN VISITOR ARRIVALS† IN MILLIONS AND PER CENT TOTAL			
	1969		1970		1969		1970	
	Number	%	Number	%	Number	%	Number	%
Europe	2.326	34	2.827	38	0.887	30	0.982	30
Mexico	1.700	25	1.800	24	1.033	35	1.086	33
West Indies	1.535	23	1.532	20	0.355	12	0.373	11
Far East and Asia	0.374	6	0.476	6	0.257	9	0.357	11
Central and South America	0.263	4	0.309	4	0.388	13	0.430	13
Africa	0.024	<1	0.028	<1	0.023	1	0.028	1
Other	0.566	8	0.560	7	—	—	—	—
TOTAL‡	6.788		7.532		2.943		3.256	

*Statistics available from U.S. Travel Service, U.S. Department of Commerce, Washington, D. C.
†According to country of permanent residence.
‡Does not include Canada, which was visited by about 20 million U.S. citizens in 1969 and 1970, and which contributed about 9.5 million visitors to the U.S. in those years.

prevail in the United States. In fact, it is precisely in those areas in which the standard of living, education and sanitary practices are low, in combination with favorable climatologic features, that parasitic infections have persisted to this day. It should be remembered that the diseases now considered "tropical," such as cholera, yellow fever, the dysenteries and hookworm disease, were previously present in the United States and the disappearance of these entities occurred without the benefit of specific control measures but coincident with an across-the-board improvement in social conditions.

It is both interesting and ironic that here in the United States we may currently be in the process of a backward swing of the sanitary-environmental pendulum. The influence of various factors such as increasing population density, increasing costs and deterioration of public services and increasing environmental pollution may all combine to produce setbacks in the control of infectious and parasitic diseases. A sobering discussion of this trend with particular respect to vector-borne disease has appeared recently (2). A recent water-borne outbreak of giardiasis at a ski resort (3) is an example of the type of event that might be seen more frequently in the future. Presently, however, such episodes still represent exceptions to an over-all favorable picture.

Before individual parasitic entities are discussed, it would be useful to clarify certain parasitologic terminology and concepts that apply to clinical situations. First, the classification of parasitic infections by organ involvement, as the GI tract in this review, is not entirely logical and therefore must be arbitrary. For example, in intestinal schistosomiasis, gastrointestinal manifestations may be completely absent. But, since the adult worms tend to localize in the vessels of the GI tract and it and the liver are the sites of primary pathologic changes, this entity has been included. Although in trichinosis the larvae are ingested and adult worms develop and stay some period in the gut, systemic signs and symptoms predominate; consequently, this entity is not considered. Also, many parasitic infections may be associated with GI symptoms and pathology, such as diarrhea in *falciparum* malaria or in kala-azar; but, since these manifestations are incidental to the site of primary tissue or organ involvement, those entities are not covered in this review.

A second important clinical consideration is the distinction

between parasitic *infection* and *disease* due to the infection. When an individual is infected by a parasite, this is by no means synonymous with disease. With many parasites, particularly the helminths, a quantitative assessment of the intensity of infection or worm burden is needed before disease can be attributed to the parasite. Except for unusual psychologic considerations, light infections with certain parasites need not be treated, and, indeed, persistent and vigorous attempts to eradicate some infections may result in unnecessary discomfort or side reactions to the patient.

In the same vein, it is useful for the physician to have some concept of potential morbidity of a parasitic infection. Extraintestinal amebiasis probably kills more people in the United States than does *falciparum* malaria. Yet, the mere presence of *E. histolytica* in the feces is no cause for panic; many such individuals have few or no relevant symptoms. Infection with most of the intestinal worms is more of a nuisance than a matter of clinical significance, but under certain conditions some can produce serious disease.

Finally, infection with gastrointestinal parasites may be acquired under quite different circumstances. This will be elaborated on for each entity to be discussed, but the matter deserves emphasis here. The intestinal protozoa and certain of the intestinal worms are acquired by oral ingestion of infective stages of the parasite (cyst, embryonated egg or suitable stage in poorly cooked food). Infection with certain worms is initiated by contact with contaminated soil to permit penetration of skin by infective larvae. Skin penetration by infective stages in water applies to still another parasite. Obviously, these may be important points to establish in eliciting a medical history from someone in whom parasitic infection is suspected.

Amebiasis

CLINICAL IMPLICATIONS OF PARASITE LIFE CYCLE.—The life cycle of *Entamoeba histolytica* is straightforward in that human infection is acquired by ingestion of the resistant cystic stages through some type of fecal contamination. The organisms multiply as trophozoites in the bowel lumen or on the mucosa, although under normal conditions of intestinal function and motility the organisms have again encysted by the time they

are excreted in the feces. The circumstances are still not known under which this benign commensal existence of *E. histolytica* changes to invasion of the mucosal barrier and consequent intestinal pathology or more distant spread of the trophozoites via lymphatic or blood vessels to produce extra-intestinal amebiasis. Incidentally, only trophozoites, never cysts, are found in the invaded tissues.

The fact that the asymptomatic infected individual is excreting cysts of *E. histolytica* has led many to erroneous conclusions concerning therapy for the cyst-passer in contrast to the symptomatic patient who shows trophozoites in the feces. Therapy is never directed at the cystic stage of the organism in the infected individual, whether symptomatic or not. Therapy is directed at the actively feeding and multiplying trophozoite form located at some higher level in the large intestine. Therefore, treatment of the so-called cyst-passer basically is the same as treatment of one with symptomatic intestinal amebiasis, except that the latter situation may demand more rapid therapeutic action.

EPIDEMIOLOGIC FEATURES.—Although no very recent data are available on prevalence of infection with *E. histolytica* in this country, it probably can be assumed from past studies (4) to be somewhere around 5% over-all, with fluctuations to much higher levels in selected local areas. Such a large reservoir of infection suggests that most local strains of *E. histolytica* have no or low pathogenicity. However, there is no uniform reporting of disease caused by this parasite, so it is not possible to assess accurately the magnitude of amebiasis morbidity. Elsdon-Dew (5) has used reports of amebic liver abscess, a fairly distinct clinical or pathologic entity, rather than reports of amebic dysentery, as a crude but more reliable index for geographic distribution of amebic disease. The relative importance of imported vs. indigenous strains of *E. histolytica* as a cause of morbidity also is not clear, although there is no question that infections acquired in the United States can result in serious or fatal disease. On the other hand, disease-producing strains of amebae are clearly more common in certain geographic regions such as Mexico, parts of South Africa and India than in Puerto Rico, for example (5).

It is now clear that lack of pathogenicity of *E. histolytica*-like

amebae can be related to certain morphologic, physiologic and biochemical properties. Organisms that are smaller but otherwise virtually identical morphologically with classic *E. histolytica,* and to which some still refer as small race *E. histolytica,* now are regarded by most as a distinct and nonpathogenic species, *Entamoeba hartmanni* (5). In addition, certain strains that appear to be large race *E. histolytica* have been shown to have optimum growth temperatures of about 26° C, and these also are nonpathogenic (6). Recent studies have shown that the low-temperature strains can be differentiated from the classic type *E. histolytica* on the basis of genome size (DNA per cell) and nucleic acid base ratio and homology (7).

Several of these epidemiologic features of amebiasis may be illustrated by my own experience with 10 cases of extra-intestinal disease that came to my attention in various hospitals of the Boston area over a period of 4 years (1965–1969). Although the experience from such a relatively small group of cases may be atypical and biased in the direction of selecting severe amebic disease with extra-intestinal complications, an analysis of this series illuminates very well many important features of the subject. Pertinent features of these 10 cases, plus 1 case encountered earlier, are summarized in Table 2. One of the most striking aspects of this series was the fact that 4 of the 11 patients with complicated amebiasis died, a mortality of 36%; and this in a supposedly enlightened medical community. A second point, apropos of the origin of infection, is that most infections were acquired outside the United States, with at least 3 and perhaps as many as 5 originating in Mexico. Yet, at least 1 and probably 2 of the cases had had no recent travel outside the country. Other aspects of amebiasis illustrated by this series will be referred to later.

Patient R. M. (patient 7 in Table 2), who previously had worked as an orderly in a mental hospital, represents another epidemiologic guidepost for amebic infections in this country. The level of sanitation that prevails in many mental hospitals and institutions for mentally retarded is one that facilitates transmission of fecal pathogens as a consequence of understaffing and the nature of the patients. Infection rates for *E. histolytica* in such institutions generally are much higher than in the surrounding community.

TABLE 2.—CASES OF EXTRA-INTESTINAL AMEBIASIS SEEN DURING 1965–1969 IN BOSTON, MASSACHUSETTS

	AGE, SEX AND OCCUPATION	PROBABLE ORIGIN OF INFECTION	MODE OF ONSET	ORGAN INVOLVEMENT	OUTCOME
1.	34-year-old male clinical psychologist (seen in 1959)	Mexico (?Turkey, Spain)	*Acute*—with chills, fever, myalgia and, later, RUQ plus shoulder pain	Rt. lobe liver 2–3 abscesses	*Cure*—Rx with drugs and closed aspiration
2.	24-year-old male migrant worker	Mexico	*Acute*—nephrectomy for "pyelo"; postop peritonitis	Rt. lobe liver abscess; perfor. bowel, peritonitis	*Died*—6 weeks after onset
3.	61-year-old businessman	Mexico	*Acute*—FUO with shaking chills, in 10 days localization of signs to abdomen	Perfor. bowel with subphrenic and subhepatic abscesses	*Died*—Dx too late, fluid and electrolyte loss
4.	46-year-old businessman*	U.S.A. ?? Far East 22 years before	*Gradual*—disappearing epigastric mass, later chest pain, hemoptysis, etc.	Bilat. pulmonary from left lobe liver abscess	*Cure*—but draining liver abscess for 5–6 weeks before specific Dx and Rx
5.	50-year-old businessman	Virgin Islands	*Gradual*—but 3 separate episodes of FUO, started on Rx for tuberculosis	Right lobe liver abscess	*Cure*—open surgical drainage
6.	31-year-old male college professor	Mexico	*Acute*—epigastric pain, fever, myalgia	Left lobe liver abscess	*Cure*—chemo Rx first, later, surgical drainage
7.	33-year-old male mental hosp. orderly	U.S.A. ?mental hosp.	*Gradual*—RUQ pain, later, fever	Rt. lobe liver abscess, brain abscess	*Died*—open drainage of abscess but no specific Dx—4 month course
8.	20-year-old male student	Venezuela	*Gradual*—development of symptoms over several weeks	Rt. lobe liver abscess	*Cure*—no aspiration, chemo Rx
9.	26-year-old male African student	Africa (Liberia)	*Subacute*—over several weeks with chills, fever, sweats, low chest or epigastric pain	Left lobe liver abscess	*Cure*—closed aspiration and chemo Rx
10.	47-year-old wife of business exec.	Mexico ??Puerto Rico	*Gradual*—intermittent diarrhea for months	Entire colon with perforation and peritonitis	*Died*—steroid Rx and total colectomy for ulcerative colitis
11.	21-year-old female "hippie"	Nepal or India	*Acute*—shoulder and chest pain, fever, chills and fatigue	Rt. lobe liver abscess	*Cure*—chemo Rx but ruptured liver from cardiac massage during arrest at x-ray

*Case records of M.G.H., New England J. Med. 281:1004, 1969.

When, on the other hand, the level of sanitation is reasonably good in a home environment, there seems to be little or no risk of transmission of amebic infection within the family. This was one of the conclusions of a careful study carried out during investigation of an outbreak of amebiasis in an urban U.S. environment (8). This seems to fit with the concept that amebic infections generally require relatively heavy and perhaps chronic exposure to the organism. In most cases, it is unlikely that casual and isolated ingestion of a few cysts will result in infection.

CLINICAL FEATURES.—With the exception of amebic granuloma, intestinal amebiasis presents no differently than gastro-

enteritis or dysentery due to other causes. However, the spectrum of signs and symptoms can vary greatly, from intermittently occurring loose stools that last only for a few days associated with some abdominal discomfort all the way to fulminant or frank dysentery. The most common differential diagnosis will involve ulcerative colitis or, less frequently, regional ileitis. An amebic granuloma is an uncommon proliferative and chronic inflammatory tissue response of the intestinal wall to invasion of *E. histolytica.* The reason why this type of tissue reaction occurs in some infected individuals rather than the usual ulcerative lesion is not known. The result is a thickened, tumor-like lesion of the large bowel, frequently in the cecum, that may come to clinical notice in the manner of a neoplasm.

Intestinal amebiasis may go on to serious extra-intestinal complications either from perforation of the bowel or from metastasis of organisms from the bowel to other organs, especially the liver, via the portal blood or lymphatics. A perforating lesion of the bowel is almost always preceded by a clinically manifest infection with *E. histolytica* in which intestinal signs and/or symptoms have been present. In contrast, amebic liver abscess may develop in an infected individual who has had few or no intestinal symptoms. Furthermore, it is not unusual for the patient with hepatic amebiasis to have a negative stool examination for amebae. There are additional atypical features of amebic liver abscess that can make the diagnosis particularly difficult if the entity is not considered in differential diagnosis. Initial symptoms and signs may not be strongly referable to the right upper quadrant but suggest diaphragmatic or pulmonary disease, or a prominent initial manifestation may be fever of unknown origin. Also, the onset of illness may be acute rather than protracted or gradual, as might be expected for the type of pathologic process. Some of these points are brought out in the small series of cases summarized in Table 2. In this group, 5 of the 11 patients had sudden onset of illness, often with chills and/or fever, and the clinical picture initially was one of an acute infection with general systemic involvement.

DIAGNOSTIC PROCEDURES.—Although serologic tests are very useful in certain situations, the only specific laboratory procedure for diagnosis of amebiasis is still the time-honored,

tedious and difficult one of demonstrating the organism microscopically. Unfortunately, few laboratories in even the best medical centers have adequately trained and experienced personnel to reliably examine a stool for *E. histolytica* and other intestinal protozoa. In addition to the examination of a direct smear of feces, a suitable concentration procedure (such as the formalin-ether technic) should be used and it is preferable that a permanently stained smear should be made also. In order to differentiate small race *E. histolytica* from certain nonpathogenic amebae with reasonable certainty or to identify nonpathogenic amebae as to species, some variety of permanent, stained smear is necessary. There are exhortations in the past literature for some multiple number of fecal examinations before results can be called negative, but economics and common sense dictate that one or two *reliable* examinations are better than multiple tests by inexperienced technicians. In patients suspected of having intestinal amebiasis and in whom stool examinations are negative or equivocal for *E. histolytica,* sigmoidoscopy can be a useful diagnostic procedure. Not only can the mucosa be evaluated for lesions, but, if present, the lesions can be aspirated and examined for amebic trophozoites, or the lesion can be biopsied and sectioned to search for amebae. It is important that the contents of ulcerative lesions be aspirated or scooped out to examine for amebae instead of taken up with a cotton swab, since the organisms will be soaked up in the cotton and not be transferred to a slide.

As was mentioned earlier, even reliable stool examinations may be negative for amebae in patients with hepatic amebiasis. In addition, depending on local prevalence of amebic infection, presence of the organism in the feces would not necessarily establish etiology of the liver abscess. In such situations, the hemagglutination (HA), complement-fixation (CF) or various precipitin tests using axenically* grown amebae as antigen are very useful in diagnosis. There has now been sufficient experience to indicate that one of the above tests, especially the HA or CF, done in a laboratory with experienced personnel, will be positive in 95% of cases of extra-intestinal amebiasis. The type of test used and the local experience will determine what

*Grown without bacterial associates.

serum dilution is considered positive. Since a much lower percentage of cases (around 50%) with intestinal amebiasis will have a positive HA or CF test, this serologic method is not very useful in diagnosis of intestinal disease.

Skin test reactions, of both the immediate and delayed type, and elicitable by antigens similar to those used in the HA or CF test have been described in amebiasis patients. If proper concentrations of antigens are used, it appears that specific skin test reactions are demonstrable in many amebiasis cases. Although preliminary results are promising, the diagnostic usefulness and reliability of the skin test remain to be determined.

In patients with amebic liver abscess, use of radioisotope scanning technics has proved very useful to demonstrate the presence or absence of abscesses and their size and location in the event that aspiration is necessary. If abscess contents are aspirated, the material should be cultured for bacteria, with anaerobic technics as well, if possible. Although amebic abscesses may become secondarily infected, the presence of bacteria in the first aspirate of an abscess should make one seriously question amebic etiology. Also, abscess material should be examined microscopically for motile trophozoites and, if present, stained for confirmation. In this regard, abscess contents from the wall of the lesion, obtained at the very end of the procedure or even by irrigating the cavity with a small amount of sterile saline, may be more likely to contain amebae than the material in the center of the abscess. If facilities for actual culture of amebae are available with a suitable bacterial associate, this certainly should be attempted. It has been reported that needle biopsy of the edge of an abscess, preparatory to aspiration of abscess contents, may demonstrate the organisms histologically in the biopsied tissue (9). When aspiration and/or biopsy is performed, specific anti-amebic therapy should be initiated just before or immediately thereafter if the diagnosis of amebiasis is seriously entertained.

The changing pattern in etiology of liver abscess in this country, as shown in Table 3, reflects the decline in amebiasis as a cause. The data cited demonstrate also that even many years ago amebiasis was not common in certain areas of the country, such as Boston, where only 10% of liver abscesses could be attributed to amebiasis. But in some southern cities,

TABLE 3.—CHANGING PATTERN IN ETIOLOGY OF LIVER ABSCESS IN THE UNITED STATES

GEOGRAPHIC AREA	% ATTRIBUTED TO AMEBIASIS IN TIME PERIOD INDICATED	
Boston, Mass.*	10% during 1900–1930	3% during 1930–1960
Dallas, Texas†	55% in 1940s	21% in 1950s
New Orleans, La.‡	63% during 1930–1940	No data available

*Sherman, J. D., and Robbins, S. L.: Am. J. Med. 28:943, 1960.
†May, R. P., *et al.*: Arch. Int. Med. 119:69, 1967.
‡Ochsner, A., and De Bakey, M.: Surgery 13:460 and 612, 1943.

even as late as the 1940s, 50–60% of liver abscesses were amebic in origin. No recent statistics are available from New Orleans, but the frequency of amebic liver abscess has declined significantly in Dallas and Boston. It is interesting to be reminded of the fact that even in recent years about 90% of liver abscesses in Mexico were found to be amebic and that 4–12% of deaths in general hospitals were due to amebiasis (10).

TREATMENT.—Within the past few years, several new drugs have been found to be quite effective in the treatment of amebiasis, especially the extra-intestinal form. A recent authoritative review on the subject by Powell (11) can be consulted for details. Although it is tempting to now use a single drug, metronidazole, for treatment of all forms of amebiasis, it would be prudent to await further experience with the drug in evaluating its efficacy for intestinal amebiasis. South African workers had advised that 800 mg. of metronidazole three times daily for 5 days will cure more than 90% of cases of amebic dysentery, and half that dose for a similar period will suffice for patients with hepatic amebiasis. However, since the development of amebic liver abscess within 3 months after treatment of intestinal amebiasis with the drug has been reported recently (12), the definitive place of metronidazole in therapy of intestinal amebiasis is still somewhat uncertain. Furthermore, it seems that some protozoa can develop a change in their susceptibility to

metronidazole (13). However, it is comforting to know that at least three different classes of drugs are effective in the treatment of amebic liver abscess or other forms of extra-intestinal amebiasis. The adult dose of metronidazole for hepatic amebiasis is 400 mg. three times daily for 5 days; the lack of toxicity, the ease of administration and the effectiveness of the drug make it a strong contender as a first-choice medication.

Although chloroquine alone has been used for successful treatment of hepatic amebiasis, it generally is given in addition to emetine or dehydroemetine for maximum benefit. The dose of chloroquine for adults is 0.6 Gm. (base) for 2 days and then 0.3 Gm. (base) daily for 2 weeks.

The third, but somewhat more toxic, drug that can be recommended is emetine hydrochloride, or its less toxic relative, dehydroemetine. The latter is administered I.M. in a dose of 1–1.5 mg./kg. daily for 10 days, with a total dose not to exceed 1.0 Gm. Even though emetine can be used alone, chloroquine often is given simultaneously, or after the course of emetine.

Aspiration or surgical drainage of an accessible amebic abscess is still indicated to effect the most rapid therapeutic response. Specific anti-amebic therapy should be started just before or immediately after aspiration or open drainage has been performed.

For the treatment of intestinal amebiasis, the antibiotics tetracycline and erythromycin have a fairly high order of effectiveness even when used alone. Their primary action against *E. histolytica* probably is indirect by affecting bacterial associates of the parasite. In adults, the dosage of either drug is 0.5 Gm. three times a day for 7–10 days. Diodoquin, an iodinated hydroxyquinoline, which is poorly absorbable and acts directly on amebae, also can be used alone in treatment of intestinal amebiasis at an adult dosage of 0.65 Gm. three times daily for 15–20 days. Commonly, an antibiotic is given concurrently with Diodoquin. If actual dysentery is present, it is wise also to give a course of chloroquine to avert possible hepatic involvement and to be sure that organisms invading the bowel wall and inaccessible to locally acting drugs will be destroyed.

Giardiasis

CLINICAL IMPLICATIONS OF PARASITE LIFE CYCLE.—Like the amebae, *Giardia lamblia* is a protozoan with a resistant cystic stage that constitutes the infective form and is passed in the feces. The organisms normally localize in the upper portion of the small intestine as motile trophozoites applied to the intestinal epithelium. Their presence in large numbers, therefore, might be expected to result in impairment of normal physiologic processes of the small bowel. This, in fact, does happen, but the exact mechanism for malabsorption that is seen in giardiasis is not known. The significance of the reported tissue invasion by giardia trophozoites (14) and the contribution of this to the pathologic process are difficult to evaluate, since such few organisms were demonstrable below the mucosal barrier.

EPIDEMIOLOGIC FEATURES.—Although a history of recent travel abroad often can be elicited from patients found to have symptomatic giardiasis, foreign exposure certainly is not required. A recent outbreak of giardiasis was reported from a Colorado ski resort, presumably from fecal contamination of the water supply (3). Another interesting epidemiologic relationship has been found between the clinical syndrome of malabsorption associated with lymphoid nodular hyperplasia and infection with *G. lamblia* (15). A striking majority of cases reported in the literature with this variety of malabsorption also have been found to have giardia infection, probably a consequence of the immunoglobulin deficiency (IgA) characteristically present in this disorder.

CLINICAL FEATURES.—The main manifestation of symptomatic giardiasis is a mild to moderate diarrhea, with bulky, foul-smelling and light-colored stools. Systemic symptoms are few and ill defined—perhaps some vague abdominal discomfort and fatigue. Occasionally, the diarrhea may be more severe and give the clinical picture of dysentery but without blood or exudate in the stool. Weight loss, weakness and other findings of malabsorption can develop if the process continues. However, many individuals are found, especially in areas with poor sanitation, with *G. lamblia* in the feces and without illness. Whether such infected individuals would ever develop evidence of disease if simply observed for a long period and what

factor(s) are needed to convert infection into disease are not known. Since there is no test for pathogenicity of *G. lamblia,* there is no way to investigate this factor in different strains to explain the lack of disease in some infected individuals.

DIAGNOSTIC FEATURES.—The organism must be demonstrated microscopically either in the feces or in duodenal fluids obtained by aspiration in order to establish the diagnosis of infection with *G. lamblia.* There are no serologic tests for giardiasis. As with the amebae, the motile trophozoites generally are found only in liquid or mushy stools. Concentration technics are useful in finding cysts of *G. lamblia* when they are not present in large numbers. If positive, the duodenal aspirate also will have motile trophozoites, so the specimen should be examined without much delay.

TREATMENT.—Two different drugs, quinacrine (Atabrine) and metronidazole, are about equally effective in the treatment of giardiasis. Quinacrine can be given in doses of 100 mg. three times daily for 5–7 days for patients 8–10 years or older, but the dose should be reduced appropriately for age and weight in younger children. Metronidazole is used in a dose of 250 mg. three times daily for 5 days in patients older than 8 years of age.

Schistosomiasis (S. Mansoni)

CLINICAL IMPLICATIONS OF PARASITE LIFE CYCLE.—Since this review focuses on parasites of the gastrointestinal tract, both *Schistosoma mansoni* and *Schistosoma japonicum* should be considered. However, since *S. japonicum* infections are seen so infrequently in this country, the discussion will center on *S. mansoni,* which affects principally the large bowel, liver and portal system.

In this instance, the parasite that infects man is a small worm that penetrates the skin as a cercaria after it has developed in a suitable snail and has been shed into the water. A local skin reaction may be noted within minutes to a few hours after cercarial penetration, but this is not a regular event, and hence is not a useful point for inquiry in the clinical history. If there has been exposure to large numbers of cercariae, the first signs and symptoms of illness may begin within 3 or 4 weeks as the parasites are developing and before eggs laid by the female

worm have appeared in the feces. It is not until at least 6–8 weeks after exposure, when the adult worms have migrated to the terminal venules of the large intestine and eggs deposited intravascularly are extruded into the intestinal mucosa by an inflammatory tissue reaction, that symptoms referable to the colon are noted. Many of the eggs that are not trapped in the tissues are swept back in the portal circulation and deposited in the liver, where a heavy infection and time may combine to produce a periportal fibrosis, presinusoidal portal obstruction, portal hypertension, esophageal varices, etc. If sufficient schistosomal eggs are shunted from the portal stream to the lungs, cor pulmonale can occur. Shunting of eggs to the central nervous system via collateral circulation of the hemorrhoidal-vertebral system may account for some cases of spinal schistosomiasis. But actual migration of female worms to aberrant sites may account for the majority of instances of neurologic involvement, as well as the finding of eggs in unexpected locations. Although the life expectancy of the *average* schistosome, i.e., the duration or persistence of its egg-laying life, is now believed to be something of the order of 3–5 years, some may survive for 20 years or more.

EPIDEMIOLOGIC FEATURES.—The geographic distribution of intestinal schistosomiasis is not only widespread on a global basis but often so spotty within a given country that only the specialist can keep this information in mind. *S. japonicum* infections of man are confined primarily to mainland China and certain islands of the Philippines. They are disappearing in the few foci where they existed in Japan, but have been found in Laos and Thailand. The extent of human infection in the latter two countries is not entirely clear at present, but it does not appear to be widespread. Evidence of schistosomiasis has been sought in U.S. military personnel in Southeast Asia but only a few suspected cases have been found, so this should not be a problem in returning servicemen.

Most schistosomiasis seen in this country is found in Puerto Ricans, returning Peace Corps volunteers and a few tourists, and in foreign students. Urinary schistosomiasis, caused by *S. haematobium,* originates from the Middle East and many different regions of Africa. However, regions of the world in which *S. mansoni,* the intestinal variety, may be acquired are more

diverse and include the Western Hemisphere. In addition to scattered areas of Africa, Manson's schistosomiasis is found widely distributed in Brazil, a few foci in Venezuela and in selected islands of the Caribbean such as Puerto Rico, St. Lucia, Martinique and Guadeloupe.

The circumstances under which schistosomal infections are acquired always involve contact with fresh water harboring infected snails, but the exact manner in which this comes about can be variable. For indigenous populations in endemic areas, the activity generally involves children swimming and bathing, women washing clothes and men in agricultural work. The life style of Peace Corps volunteers or field anthropologists, patterned after that of local inhabitants both at work and at play, provides more chance for acquiring schistosomiasis than the activities of the average tourist. Infection may be acquired from less obvious exposure, such as a rustic shower bath or a homemade swimming pool, if the water comes from a body of water exposed to fecal pollution containing appropriate snail hosts.

CLINICAL FEATURES.—The clinical syndrome resulting from heavy exposure to cercariae and which begins before eggs are found in the feces can be both puzzling and striking (16). It is characterized by chills, fever, urticarial skin eruptions, hepatosplenomegaly, lymphadenopathy and muscle aches and pains—in short, signs and symptoms of a systemic illness that could resemble various acute infectious diseases. A brisk eosinophilia is present and can be a helpful clue to the nature of the illness. In a less severe but yet moderately heavy infection, the first clinical manifestations might be a schistosomal dysentery with crampy abdominal pain and diarrheal stools containing blood and/or mucus. Some components of the acute schistosomiasis picture described above might be present also.

However, the most common clinical setting in which schistosomiasis is found is one of no or a few nonspecific symptoms in which infection is discovered accidentally or secondary to investigation of some other finding, such as unexplained eosinophilia. Almost always such infections are light, and further study produces normal tests of liver function and no evidence of portal hypertension. Only rarely are cases of hepatosplenic schistosomiasis encountered in this country and they would be found in expatriates from endemic areas. Even in the variety of severe

intestinal schistosomiasis with portal hypertension, the nature of the liver lesion with presinusoidal obstruction is such that liver function is well preserved unless repeated episodes of bleeding from esophageal varices with shock have occurred or some other type of liver disease is superimposed. The cardiopulmonary complication of intestinal schistosomiasis, or cor pulmonale, would be expected only in those with heavy, long-standing infection. A much less common variant of pulmonary involvement has been described (17) and is characterized by cyanosis and clubbing of the digits. The pathogenesis of this entity probably is based on some type of vascular shunting and may be more reversible with treatment than schistosomal cor pulmonale.

The neurologic complications of Manson's schistosomiasis almost always are limited to involvement of the spinal cord, whereas CNS complications of *S. japonicum* are likely to involve the brain. This may be explained by the greater egg output of the *S. japonicum* female worm and their tissue localization in the small bowel being less likely to permit access of eggs or worms to the vertebral venous system.

DIAGNOSTIC PROCEDURES.—The finding of schistosomal eggs in the feces or in the tissues is the only definitive method of diagnosis. Since excretion of eggs in the feces is modest in numbers and also may be irregularly present, a suitable concentration procedure, such as the formalin-ether technic, is an essential part of a stool examination. If several fecal examinations are negative, rectal biopsy of suspicious lesions or from at least two or three sites of normal mucosa during sigmoidoscopy may reveal eggs in crush preparations and/or serial tissue sections of the biopsy. Examination of the fresh crush preparations requires an experienced observer, but it permits examination of the entire specimen, and the material still can be fixed and sectioned for a pathologist's evaluation. Biopsy of the liver is a much less efficient method for recovery of schistosomal eggs, but it may be a useful procedure in cases in which other types of liver pathology are suspected. In any case, when schistosomal eggs are found in feces or in tissue specimens, an attempt to evaluate their viability should be made, since the presence of a viable-appearing miracidium inside the egg will indicate an active infection with living worms.

The various immunologic tests for schistosomiasis may be useful in certain circumstances but they are not completely specific. The immediate skin test reaction, for example, will give positive reactions in individuals who have had swimmer's itch, indicating sensitivity to cercariae of nonhuman schistosomes (18). The hemagglutination and complement-fixation tests have greater degrees of specificity but a positive reaction may reflect a cross reaction to infection with some other helminth. Other special tests, such as the circum-ovum precipitin test, can be done only in research laboratories and have not been standardized.

TREATMENT.—In the United States, the only approved drugs for treatment of schistosomiasis are the antimonials stibophen (Fuadin) and antimony dimercaptosuccinate (Astiban). Several interesting and reasonably effective oral medications, niridazole (Ambilhar) and hycanthone, which were developed recently, are still being evaluated elsewhere. Use of niridazole has been associated with mental changes, including seizures, in some patients, and a controversy still exists over the possible human hazards of certain properties of hycanthone. The advantage of antimony dimercaptosuccinate (Astiban) over stibophen (Fuadin) is that a course of treatment equal in effectiveness to that of stibophen can be given more rapidly, such as one dose every third day, for a total of five doses within a 2-week period. The recommended total dose of antimony dimercaptosuccinate is 40 mg./kg. for adults and 50 mg./kg. for children in five I.M. injections given at a frequency of once or twice a week. With stibophen, the drug is administered I.M. as a 6.3% solution every other day in 5 ml. amounts for an adult, and the total dose for maximum therapeutic effect should be at least 75 ml.

A legitimate question that can be asked is whether the usual case of schistosomiasis mansoni seen in this country should be treated. It can be argued that the drugs used in treatment are toxic and that light infections probably will do no harm to the host. Although our current concepts of pathogenesis indicate that schistosomal disease requires a fairly heavy worm burden, the critical level below which the infection may be benign is not known, nor is the duration of the time course of infection before disease is produced known. It also must be admitted that

the currently available method for assessing worm burden, quantitative egg counts of urine or feces, is still cumbersome and not too precise. Ideally, every patient should have at least two or three and preferably more egg counts to evaluate the intensity of the infection and some estimate as to the activity of the infection from the percentage of viable eggs being excreted. Other crude indices of activity of infection include the presence or absence of fever, sedimentation rate, degree of eosinophilia, and tests of liver function.

Experience with *S. haematobium* infections indicates that early bladder lesions, at least, are reversible with antischistosomal therapy as shown by x-ray studies (19). There are no suitable methods to seek similar evidence with early *S. mansoni* lesions. Some of the reports of CNS schistosomiasis suggest that specific treatment may hasten the resolution of already established anatomic lesions (20). But these observations are still indirect arguments in support of the concept of treatment of all active schistosomal infections. Only a long-term controlled study can provide an answer as to the benefit or lack thereof in the treatment of mild schistosomiasis.

Strongyloidiasis

CLINICAL IMPLICATIONS OF PARASITE LIFE CYCLE.—The causative organism, *Strongyloides stercoralis,* is a nematode that is similar to the hookworm but has several important differences that influence its epidemiology and the pathology produced by it. As with the hookworm, the infective stage is caused by a larva that penetrates the skin and migrates through the lungs, whereas adult worms normally are found in the small bowel. But unlike the hookworm, the adult female *Strongyloides* burrows into the submucosa to deposit its eggs. These hatch in the tissues and the resulting rhabditiform larvae migrate back to the lumen of the gut and are passed in the feces. Under certain conditions that are not understood, the rhabditiform larvae may transform to infective filariform larvae before they exit the host and reinvade the same host at a lower level of the bowel or the perianal region. This process is termed internal auto-infection and permits the parasite to multiply in the host.

Other features of the life cycle of *Strongyloides* have considerable epidemiologic significance. The time required for the development of the infective-stage larva is short and the environmental conditions for this development are not nearly as exacting as for hookworm larvae. In addition, *S. stercoralis* is equipped with an alternative mechanism for survival. On passage from the host, the rhabditiform larvae may initiate a free-living cycle with development of adults that, in turn, produce more rhabditiform larvae, etc., all taking place on the soil without need for a host. The free-living larvae are capable of switching back to a parasitic existence by transformation into filariform larvae that initiate a new parasitic cycle.

EPIDEMIOLOGIC FEATURES.—Some of the characteristics of *Strongyloides* just discussed help explain certain epidemiologic features of the infection in man. The capability for a free-living cycle reduces the need for a constant supply of human reservoir hosts to account for new infections. The process of auto-infection also may serve to perpetuate the duration of infection in some individuals and thereby amplify the potential for transmission.

The rapid transformation to infective stages of larvae passed in the feces provides insight into why *Strongyloides* frequently is found infecting inmates of institutions for the mentally retarded or mentally ill. The condition of the patients and the frequent understaffing of custodial personnel make it difficult to maintain optimum levels of hygiene. The report of an epidemic of strongyloidiasis in such an institution illustrates the problem (21).

CLINICAL FEATURES.—At the time that many individuals are found to be infected with *S. stercoralis* they are without symptoms, but the primary clinical manifestation is that of a malabsorption syndrome (22). Abdominal pain, resembling that of peptic ulcer in nature and location but not in relation to eating, may be present in cases of strongyloidiasis. Symptoms of abdominal discomfort are understandable in view of the submucosal inflammatory reaction and edema in the affected regions of the small intestine consequent to the presence of female worms, eggs and larvae of the parasite. At times, diarrhea may be severe and blood may be present in the stool.

A significant degree of peripheral eosinophilia is present in

approximately half of the cases. Some patients may have urticarial-type skin lesions, especially in the area of the buttocks and upper thighs in those cases with auto-infection. In some instances of auto-infection, more generalized systemic evidence of infection, including pulmonary involvement, is present. The cases with auto-infection often are patients with other underlying or debilitating disease; fatal outcome with *Strongyloides* prominently present has been reported in patients receiving corticosteroids (23).

DIAGNOSTIC PROCEDURES.—Diagnosis is established only by demonstration of motile larvae by microscopic examination of feces or fecal culture, or of duodenal aspirate. Since the numbers of larvae in the feces generally are very scanty, the chances of finding them on even multiple direct fecal smears are slim. The formalin-ether concentration procedure is better, but larvae are killed by the formalin and are no longer motile. Even more efficient technics should be used. Duodenal aspiration is useful. The Harada-Mori test-tube cultivation procedure (24) is simple to perform, requires no special equipment and the amount of feces that can be smeared on each strip of filter paper for one culture is about 1 Gm. One disadvantage of the Harada-Mori culture is that the larvae found in the water reservoir will have to be differentiated from hookworm larvae. The Baermann extraction technic (25) probably is the most efficient but is a somewhat cumbersome method for detecting nematode larvae in the feces, since it can sample at least 10 Gm. of fecal material at one time.

TREATMENT.—Recent availability of thiabendazole has provided a very effective treatment for strongyloidiasis. The dosage for treatment of adult patients is 25 mg./kg. twice daily for 2 days. When used in the amounts recommended, the untoward side-effects of thiabendazole thus far reported have not been too serious.

Tapeworm Infections

Since the principal tapeworm infections in which man is the definitive host—i.e., when the adult worm is present—have features in common, they will be considered together. The parasites concerned are *Taenia saginata,* the beef tapeworm;

Taenia solium, the pork tapeworm; and *Diphyllobothrium latum,* the fish tapeworm.

CLINICAL IMPLICATIONS OF PARASITE LIFE CYCLE.—Human infections in the instance of each parasite are acquired by eating raw or poorly cooked meat of the appropriate intermediate host—beef, pork or fish—that contains the larval form of the parasite. To complete the life cycle, these animals, in turn, become infected because of human fecal pollution, which deposits the tapeworm eggs on soil for ingestion by cows and pigs, or in water. In the latter case of *D. latum,* the parasite cycle is somewhat more complicated because the parasite must undergo development in a fresh water copepod before it reaches the fish.

The pork tapeworm, *T. solium,* deserves further consideration because the eggs of this parasite also are capable of infecting man with the cysticercoid larval stage. In contrast, human ingestion of the eggs of *T. saginata* or *D. latum* is harmless because the larval stages cannot develop in man. Human cysticercosis, or larval infection with *T. solium,* may occur in the same individual who harbors the adult tapeworm, or in those free of the worm, depending on the recipient of fecal pollution.

EPIDEMIOLOGIC FEATURES.—Currently there is very little transmission of beef tapeworm infection, and *T. solium* is virtually non-existent in this country. The fish tapeworm was fairly common in the lakes of the north central states and Canada in past years, but there is no recent information on its prevalence. Most tapeworm infections seen in this country are in individuals who have acquired their infection elsewhere, and the majority involve the beef tapeworm, *T. saginata.* Jewish housewives have been one category of patients with an occupational predilection for fish tapeworm because the preparation of gefüllte fish requires tasting the mixture of uncooked fresh fish to check proper seasoning. Another ethnic group in whom the fish tapeworm is more likely to be encountered is composed of the Scandinavians, especially in Finland, which probably has the largest endemic focus of the infection. Immigrants from Scandinavia probably introduced *D. latum* to Minnesota, Wisconsin, Michigan and Canada in this hemisphere.

Incidentally, the adult *D. latum* can develop in certain mam-

mals other than man, so, theoretically at least, a nonhuman reservoir for this parasite may exist.

CLINICAL FEATURES.—It is doubtful whether specific clinical symptomatology can be attributed directly to the presence of these tapeworms, but after the diagnosis becomes known, patients often develop a wide variety of complaints. A well-known, indirect complication of infection with fish tapeworm, of course, is a macrocytic anemia indistinguishable from true pernicious anemia. This comes about in a minority of infected patients because the worm has a high requirement for vitamin B_{12} and depletes the host's supplies of B_{12}. Apparently this is more likely to happen if the worm is situated in the upper portion of the small bowel and is better able to compete with the host for the vitamin.

Clinical manifestations of human cysticercosis are secondary to mechanical effects of the larval cysticercus, as it grows or as it degenerates and excites a cellular reaction. Degenerated and calcified cysticerci in skeletal muscle that have elicited no symptoms may be incidental findings in x-rays taken for other purposes. Cysticerci also may lodge in the brain and produce pressure effects similar to those of a tumor. A cysticercus in a silent area of the CNS may produce symptoms for the first time after it loses viability, degenerates and elicits an inflammatory reaction. In one South African study population, more epilepsy was attributed to cysticercosis than to any other identifiable cause (26).

DIAGNOSTIC PROCEDURES.—Patients become aware of their tapeworm most commonly by noting single motile proglottids (segments of the worm) in their feces. Sometimes the diagnosis becomes known by the more dramatic experience of finding one of the highly contractile, worm-like proglottids in bed on arising! The terminal segments break off the long strobila from time to time and are sufficiently motile to wriggle out of the anus. Because the eggs are enclosed within the gravid segments, fecal examination frequently is negative for eggs unless the segments have ruptured. Gravid proglottids occasionally do rupture during defecation, so eggs may be distributed in a burst over the perianal area. The "Scotch tape" method of examination for pinworm eggs, in which the perianal skin is dabbed repeatedly with the sticky side of the tape and applied to a

glass slide for microscopic examination, is a useful diagnostic procedure for *T. saginata* eggs (27).

The differentiation of *T. saginata* from *T. solium* is an important issue to establish, since the patient with pork tapeworm is a potential source of cysticercosis to himself and to others. The presence of *Taenia* eggs alone is of no help in differential diagnosis, since they are identical for both species. If the scolex (head) of the worm is available, a specific identification may be made. Differential diagnosis usually must be made from proglottids passed in the feces. If a small amount of India ink is injected into the base of the proglottid with a No. 27 needle and 0.25-ml. syringe, the uterine branches can be outlined and counted after the segment is pressed firmly between two glass slides. *T. solium* segments have no more than 10–12 main lateral branches of the uterus whereas *T. saginata* segments usually have more than 15.

In the case of *D. latum* infections, typical, large eggs with a delicate operculum are discharged into the intestinal lumen from the gravid proglottid in large numbers, so there generally is no problem in finding the eggs on microscopic examination of the feces. The proglottids of the fish tapeworm also are quite different from *Taenia* segments, so their identification is not too difficult.

The diagnosis of human cysticercosis usually requires a tissue specimen and even then may be difficult to establish. Serial sections of an excised cystic structure approximately 1 cm. in diameter hopefully will disclose the characteristic circle of hooklets on the scolex. A hemagglutination test using antigen prepared from pig cysticerci has been used elsewhere and is available at the Center for Disease Control in Atlanta (formerly known as the National Communicable Disease Center), but its reliability has not been critically assessed.

Peripheral blood eosinophilia does not occur to a significant extent in humans harboring an adult tapeworm. Occasionally, an eosinophilic response in the cerebrospinal fluid is found with CNS cysticercosis.

TREATMENT.—The best standard medication for many years, yet often disappointing in its efficacy, has been quinacrine (Atabrine), but a more convenient drug, niclosamide, recently has become available on an investigational basis. Quinacrine

is given in an adult dose of 200 mg. at 5–10-minute intervals for four doses (total dose 0.8 Gm.) after food has been withheld overnight, and this is followed by a magnesium sulfate purge 2–4 hours later. Sodium bicarbonate, 600 mg. with each dose of quinacrine, may be given to reduce its tendency to gastric irritation. The efficacy of quinacrine can be increased by administering the drug via a tube that is in the duodenum. In this case, the entire dose of 0.8 or even 1.0 Gm. can be crushed in about 100 ml. of water at body temperature and poured down the tube. Thirty minutes later, 1½–2 ounces of magnesium sulfate can be given in the same manner.

Niclosamide is reportedly at least equal to quinacrine in effectiveness (28) and requires no special preparation of the patient either before or after it is given. The dose for adults is a single one of 2.0 Gm. Niclosamide is not recommended as yet for *T. solium* infections because the drug produces disintegration of worm segments, and the eggs that are released might theoretically be able to infect the same host and produce cysticercosis.

Treatment of symptomatic human cysticercosis is surgical removal of the lesion. When the CNS is involved, skillful neurosurgery is required, but surprisingly good results have been reported (29).

Ascariasis

CLINICAL IMPLICATIONS OF PARASITE LIFE CYCLE.—Human infection with *Ascaris lumbricoides* results from the ingestion of embryonated eggs that contaminate food, fingers or the air. The eggs are very resistant to environmental influences but are not infective when passed in the feces, requiring 2–3 weeks of development. Since the larvae migrate through the lungs after being ingested and are 0.5–1.0 mm. in length at this time, infection with a large number may result in a pneumonitis within 1–2 weeks after exposure. After migrating up the trachea, the larvae are swallowed and return to the small intestine, where they develop into adult male and female worms a total of 8–12 weeks after the original ingestion of eggs. Therefore, eggs would not appear in the feces of an infected individual before a period of 2 months after exposure. Normally, the worms remain in the

bowel without producing signs or symptoms of illness, but large numbers of worms may become tangled up and produce intestinal obstruction. Also, if disturbed by fever or other conditions, they may begin to migrate. Thus, even a single worm may enter and block the bile or pancreatic ducts, perforate the bowel and cause peritonitis, or actually reach the parenchyma of the liver via the biliary passages and produce a liver abscess. Spontaneous passage of the worms and cure of infection usually occurs within a year.

EPIDEMIOLOGIC FEATURES.—The tremendous resistance of ascaris eggs permits their survival under conditions of extreme dryness, near freezing temperatures and viability in the soil for a year or longer. In arid climates, active winds may produce a virtual aerosol of infective eggs that are ingested with dust (30).

In areas in which infection is endemic, defecation around the house is a major epidemiologic factor, and children are the ones principally infected. The use of human feces as fertilizer is still practiced in many regions of the world, including some countries of Europe, so that poorly washed and uncooked vegetables and fruits may be a source of infection. *Ascaris* infections seen in tourists generally are light, involving only a few worms.

CLINICAL FEATURES.—For reasons explained above, the clinical syndromes that require heavy *Ascaris* infections, such as *Ascaris* pneumonia or intestinal obstruction, seldom are seen in tourists who have acquired their infections elsewhere. However, fairly heavy infections with *Ascaris* are still seen in children in certain areas of the southern United States. The clinical picture of *Ascaris* pneumonitis is one of cough, fever, eosinophilia and x-ray evidence of diffuse mottling of the lungs that clears within a few days to a week. Despite a recent controversial report, there is no evidence that the usual case of asthma is associated with ascariasis (31).

The clinical pictures resulting from intestinal obstruction by ascaris, or from migration of adult worms to produce perforation of the bowel, biliary tract obstruction or liver abscess are all consistent with similar pathology produced by other causes.

DIAGNOSTIC PROCEDURES.—For diagnosis of ascariasis, one ordinarily thinks of a stool examination to detect the characteristic eggs that are produced in large quantity by the female worm and therefore are not difficult to find. However, in certain

instances there may be no eggs in the stool or they may be relatively scanty. In the patient with *Ascaris* pneumonitis, the feces are negative for eggs because the process is produced by larvae that will require nearly 2 months longer to become adults and produce eggs. In this situation, the sputum will show eosinophils and might reveal larvae, but the larvae can be demonstrated more effectively by examining the sediment of an early-morning gastric aspiration. Another circumstance in which no or only a few eggs are present in the feces is when only one or very few worms are present. A male worm can escape detection because it produces no eggs, and a single female worm will produce unfertilized eggs that may not be abundant and are atypical in appearance. This might be one of the few situations in which a stool concentration procedure would be useful in the diagnosis of *Ascaris* infection.

A history of vomiting or passing an obvious worm tentatively may establish a diagnosis of *Ascaris* infection, since the adult worms are approximately 21–30 cm. long, but beware of accepting structures that come from either orifice as worms without examining them! Larval migration in the early stage of infection initiates a peripheral blood eosinophilia that can persist for several months. But this, in itself, is not very helpful in diagnosis, and later, when adult worms are present in the intestinal lumen, the eosinophilia subsides.

TREATMENT.—The most effective, least expensive, and safest treatment for ascariasis is piperazine, which may be administered as piperazine citrate syrup. The syrup contains about 100 mg. of the drug per ml., so the adult dose is 3–4 Gm. in a single dose or 30–40 ml. of the syrup.

Ascaris pneumonitis must be treated nonspecifically and symptomatically, since I am unaware of anthelmintics that can affect migrating *Ascaris* larvae. A method of medical treatment for intestinal obstruction caused by *Ascaris* has been reported (32), and is worth keeping in mind should surgical facilities be unavailable. It consists basically of intestinal decompression by tube and administration of piperazine via the same tube, which is then clamped off for several hours thereafter. The necessity for specific treatment and its efficacy is difficult to evaluate in this situation, since the obstruction may resolve spontaneously.

CLINICAL IMPLICATIONS OF PARASITE LIFE CYCLE.—The whipworm, *Trichuris trichiura,* is acquired by ingestion of embryonated eggs, which, like *Ascaris* eggs, are not infective when passed in the feces but require at least 10 days under optimum conditions for development. However, unlike certain other intestinal nematodes, *Trichuris* has a direct cycle of development that does not require migration through the lungs. After hatching from the eggs, the larvae remain in the intestine, where they develop into adults and attach themselves by embedding their thread-like anterior portion into the superficial mucosa of the large intestine from the cecum to the rectum.

EPIDEMIOLOGIC FEATURES.—*Trichuris* infections are found wherever human fecal pollution of the soil occurs and where standards of hygiene are poor. The distribution of *Trichuris* frequently coincides with *Ascaris* and hookworm infections, but the environmental conditions required for *Trichuris* are somewhat intermediate to those of the other two intestinal nematodes. For example, the whipworm will flourish in climates conducive to hookworm but does not require the loose, sandy soil that is best for hookworm larvae. On the other hand, *Trichuris* eggs are not nearly as resistant as those of *Ascaris* and require considerable moisture and shade.

CLINICAL FEATURES.—The likelihood that clinical manifestations will be associated with *Trichuris* infection has clearly been related to intensity of infection (33). Another important factor determining whether infection results in disease is the age of the patient, but this may simply be another reflection of a greater worm burden in the young child. Thus, light whipworm infections are asymptomatic, whereas heavy infection in the young child may be manifested by mucoid diarrhea or even dysentery, with bloody stools, abdominal pain, anemia, dehydration and weakness. In severe infections, rectal prolapse can occur, and in the heavily infected young child the disease may be fatal. All of the pathology seems to be related to the diarrheal disease and is localized to the large bowel.

DIAGNOSTIC PROCEDURES.—Diagnosis of *Trichuris* infections is accomplished quite simply by finding in the feces characteristic double-shelled, barrel-shaped eggs with mucoid plugs on

both ends. Light infections may require concentration procedures in order to detect eggs, but if this is required the infection certainly is not producing disease. Generally, at least 25,000 eggs per Gm. of feces are found in clinically significant infections, and these can be detected readily by a simple saline smear of the feces, even by a novice in parasitology. The quantification of numbers of eggs in the feces, either by the direct smear method of Beaver or the Stoll dilution technic (24) is very useful in clinical evaluation of infections and in following response to therapy.

TREATMENT.—It is fortunate that clinically significant infections with *Trichuris trichiura* are not encountered frequently in this country, because effective treatment is not easy to apply. None of the currently available and approved anthelmintics are effective for this infection. The most effective therapy is the rather messy and involved procedure of administering hexylresorcinol enemas. First, the bowel must be cleansed with saline enemas. Since hexylresorcinol can be very irritating to the external skin, the buttocks and thighs are coated with petrolatum for protection. Up to 500 ml. of a freshly prepared 0.2% aqueous suspension of hexylresorcinol is instilled and hopefully retained for as long as 30 minutes before expulsion. If possible, the site attained by the enema (hopefully to the cecum) can be visualized fluoroscopically by mixing enough barium in the enema to be seen. This type of retention enema may be repeated 3 or 4 times at several-day intervals. It is heroic therapy—but it really works if done properly!

Hookworm Infections

CLINICAL IMPLICATIONS OF PARASITE LIFE CYCLE.—Hookworm infections of man, which can be caused by two different species, *Necator americanus* and *Ancylostoma duodenale,* are acquired by contact with soil that has been polluted by human feces. The following discussion will consider the two species and their associated infections jointly but, as will be noted, there are some differences between human *Necator* and *Ancylostoma* infections with epidemiologic and clinical implications. Hookworm eggs require proper conditions of humidity and temperature for the development of larvae, which hatch within 24–28

hours after being passed in the feces. Similar environmental conditions, plus a reasonably well-drained and particulate soil type, are needed for the larvae to complete their development in about 4 or 5 days and to survive. Human infection occurs when the larvae come into contact with skin that permits their penetration, such as the areas between the fingers or toes or the dorsum of the foot. More recent re-evaluation of the life cycle of different species of hookworms, especially by Japanese workers (34), has indicated that human infection by ingestion of infective larvae may occur more commonly than has been thought. This is particularly the case with *A. duodenale,* from which patent infections may be attained more readily after inoculation of larvae into the stomach than after percutaneous exposure. Furthermore, from studies in experimental animals, it seems that the larvae do not necessarily migrate through the lungs after oral infection with *A. duodenale.* Apparently, pulmonary migration of larvae always takes place with *N. americanus,* regardless of the route of inoculation (35).

Whichever route of larval migration takes place, after the worms arrive in the upper small intestine, they attach themselves to the intestinal mucosa, begin sucking blood, grow to adults and the female worm begins putting out eggs. Adult worms of *A. duodenale* exhibit other differences from *Necator.* They are more effective blood-suckers than *N. americanus,* averaging nearly 0.2 ml. of blood per worm per day, about five times that extracted by *Necator.* In addition, *A. duodenale* tend to be more aggressive and may invade part way into the submucosa of the bowel. With either species, at least 5 weeks are required after exposure before eggs appear in the feces.

It should be mentioned that other species of animal hookworms may invade the human host with a variable outcome. For example, *Ancylostoma braziliense,* a hookworm of cats and dogs, does not develop normally in the human host but the larvae that invade can migrate in the skin and remain viable for weeks, producing a dermatitis in the sensitized individual. A closely related species, *A. ceylonicum,* has been found capable of developing to maturity in human volunteers, with eggs appearing in the feces as early as 21 days after exposure to larvae (36).

EPIDEMIOLOGIC FEATURES.—A tropical or subtropical cli-

mate, with adequate rainfall, shade and well-drained, sandy soil are factors that contribute to the development and survival of hookworm larvae. Of course, a reservoir of human infection with defecation on the ground is a necessary prerequisite to continued transmission. The situations that lead to heavy infections are those in which people frequent the same contaminated area repeatedly, such as agricultural workers on plantations. Such conditions were common in the southern United States until the past several decades, but heavy infections with hookworm (i.e., with 10,000 or more eggs per Gm. of feces or 100 or more worms) probably are encountered rarely now in the indigenous population of this country. Infections acquired elsewhere by tourists likewise would be light.

The species of hookworm present in North America, and in virtually all of South and Central America as well, is *N. americanus. Necator* is found in Africa and Asia also but it overlaps considerably in distribution with *Ancylostoma* in other areas of the world.

"Creeping eruption" (the larval migrans resulting from exposure to *A. braziliense*) can occur in children who play in areas in which infected dogs and cats have defecated and also in adults whose occupation requires crawling or lying on the ground in similar areas. It is seen, for example, during the summer months in bathers on certain beaches or in workmen who must crawl under houses, and is most common in the southern United States.

CLINICAL FEATURES.—Skin lesions of a maculopapular variety with rather severe pruritus, and lasting for several days, may be noted at the site of larval penetration. Although a larval pneumonitis during the migration phase after large exposure is theoretically possible, this does not come to clinical recognition very often. There is an interesting and sometimes striking clinical syndrome, hardly noted in the literature, that may occur in the evolution of hookworm infection before egg laying begins. Basically, this consists of a gastroenteritis with varying degrees of abdominal distress, which occurs shortly before the worms have reached maturity. Such a syndrome was described during World War II (38) and also was noted in experimental *A. ceylonicum* infections (36). I had a vigorous personal introduc-

tion to this syndrome in the course of a self-induced infection with only 50 larvae.

Most clinical interest concerning hookworm is correctly related to hookworm disease, i.e., the sequelae of chronic blood loss associated with heavy infection. The important distinction between simple infection with relatively few worms and actual disease resulting from a sizable worm burden can be quantified quite convincingly with this parasite (38). Depending on the infecting species, each adult hookworm extracts an average of 0.03–0.15 ml. of blood per day from the victim, who can recover or reabsorb less than half of the iron and probably much less of the protein present in this amount of blood. With worm loads of 300 or more, the patient loses at least 10 ml. of blood daily. If dietary and tissue stores of iron are inadequate to keep pace with this loss, the result is inevitable. The patient with hookworm disease presents with signs and symptoms that simply reflect a chronic blood loss.

Creeping eruption caused by the cat and dog hookworm can cause considerable discomfort from the intense itching that lasts for weeks. The lesions are elevated, erythematous and develop in a serpiginous fashion with some areas that become vesicular; pyogenic infection may develop secondarily.

DIAGNOSTIC PROCEDURES.—Hookworm eggs are not difficult to identify in the feces to establish the diagnosis. As with the whipworm, the concentration of eggs in the stool should be sufficient to detect in a simple fecal smear if the infection is heavy enough to be clinically significant. To resolve any doubts concerning the intensity of infection, a quantitative estimate of the number of eggs per Gm. of feces can be made by Beaver's direct smear method or Stoll's dilution technic (24). Only if egg counts exceed 5,000 per Gm., which would be roughly equivalent to 5 or more eggs per low-power microscopic field of a standard smear, would the infection be likely to be of clinical significance. Since the principal finding in hookworm disease that has been present for a reasonable time is anemia, it would be useful to check the hemoglobin level and reticulocyte count. As is the case with *Ascaris* infections, an eosinophilic response of peripheral blood is stimulated during larval migration early in infection but subsides within a few months.

If a fecal specimen containing hookworm eggs is allowed to

stand at room temperature for many hours, the eggs may hatch and the motile larvae present be mistaken for *Strongyloides* larvae. An experienced observer is needed to differentiate larvae of the two species.

TREATMENT.—Hookworm disease requires treatment of the iron-deficiency anemia that is present, but only anti-worm measures are indicated for treatment of simple hookworm infection. It was shown long ago that a perfectly adequate reticulocyte response and return to normal hemoglobin levels would follow administration of iron in patients with hookworm anemia (39). Of course, the worms should not be ignored indefinitely, but they can be attended to later with either tetrachloroethylene or bephenium hydroxynaphthoate. The former is more effective in the treatment of infections caused by *Necator,* and is used in a dose of 0.10 ml./kg. with a maximum of 5 ml. For *A. duodenale,* bephenium is the preferred drug in a single dose of 5 Gm. of the salt. It is doubtful if light, asymptomatic hookworm infections need be treated at all. Certainly there is no rationale for repeated courses of medication to achieve complete cure of hookworm.

Enterobiasis (Pinworm Infection)

CLINICAL IMPLICATIONS OF PARASITE LIFE CYCLE.—*Enterobius vermicularis,* the pinworm, is another nematode with a simple, direct life cycle in which infection is acquired by ingestion of embryonated eggs that hatch into larvae that grow to adults without leaving the lumen of the bowel. The fertilized female worm remains in the cecum or colon until it becomes full of eggs and then migrates out the anus to discharge its eggs on the perianal skin. The parasites generally do not disintegrate or liberate their eggs while in the colon, so that usually eggs are not detected in a fecal examination. The parasite cycle from ingestion of eggs to the time that mature worms develop requires 2–3 weeks. Incidentally, pinworm eggs are infective within a few hours after being deposited and can remain infective and viable for 7–10 days. Since the eggs do not require a long period or special conditions for development, the host can reinfect himself. Another mechanism, called retrofection, can occur whereby eggs hatch in the moist anal region and the

larvae re-enter the rectum and go on to develop to maturity. With either mechanism, the infection in a single host is amplified.

On rare occasions, the gravid female worm is adventurous or confused enough to migrate to unusual sites in the human host. By making a wrong turn, it may enter the vaginal cavity of a female host and arrive as far afield as the abdominal cavity via the fallopian tubes. This does not happen often but, in view of the ubiquitous distribution of the pinworm, such an occurrence can be expected from time to time (40).

EPIDEMIOLOGIC FEATURES.—Enterobiasis undoubtedly is the most common helminthic infection of man in this country, and perhaps on a global basis as well. It most commonly comes to notice in children, but its presence usually passes unnoticed unless the infection is heavy enough to produce symptoms, or if it happens to occur in the offspring of a sharp-eyed mother with a preoccupation for early-morning inspection of children's bottoms.

Pinworm eggs tend to be disseminated widely in the environment of the infected individual because the gravid female worm often ruptures after migrating to the outside. Since the eggs are relatively resistant, remain viable for up to 10 days and may be transported in the air with dust particles, ingestion of at least a few eggs can occur very readily without obvious fecal contamination and in a most innocent manner. For example, viable eggs have been demonstrated in the dust on window sills and door casings. It is therefore understandable that pinworm infection often becomes a family affair, including Mom and Dad, after an index case has been introduced into the household.

Several aspects of enterobiasis with important epidemiologic implications, namely immunity or resistance to infection, have not been explained. Whether reduced prevalence and/or intensity of infection in older children or adults is due to less intense exposure or to actual acquired immunity is not clear. An apparently clear-cut innate or natural resistance to infection with *Enterobius* in black populations in comparison with Caucasians of similar socioeconomic status has been noted (41).

CLINICAL FEATURES.—Since virtually everyone becomes infected with *E. vermicularis* at one time or another, the majority of infections must be asymptomatic. Anal pruritus, which may

be very severe at times, is the most conspicuous symptom. It is seen mainly in children and presumably is a specific allergic reaction elicited by the worms or eggs on the perianal skin. A great many nonspecific symptoms have been indiscriminately attributed to pinworms, but restlessness and irritability seem to be justifiable manifestations.

A puzzling clinical picture may ensue in those rare instances in which a migrating female worm and her discharged eggs are trapped in or around the adnexal tissues. The symptoms may resemble salpingitis or endometriosis, a palpable mass may be found on pelvic examination and if surgery is done, the granulomatous and eosinophil infiltrated tissue reaction with occasional necrotic foci that is found may be difficult enough for a pathologist, let alone a surgeon, to interpret. It is likely that this type of granulomatous lesion due to pinworms and their eggs occurs more commonly in the peritoneal cavity than has been appreciated, but if it does not produce symptoms it will go unnoticed.

DIAGNOSTIC PROCEDURES.—Since pinworms migrate to the perianal skin to deposit their eggs, the Scotch tape sampling procedure is the most effective method for their recovery. The usual stool examination for ova and parasites of an individual known to be infected generally is negative for *Enterobius* eggs. A slight modification of the Scotch tape procedure, which is said to displace air bubbles and otherwise provide better visualization of the eggs, is to place the sticky side of the tape down in a drop of toluene on a microscope slide rather than on a dry slide (42). The best time of day for sampling the perianal skin in order to detect pinworm eggs is early in the morning on arising, and decidedly not after a bath or shower has washed away the eggs. It often is impractical for the physician to carry out the Scotch tape swabbing himself at the optimum time with outpatients, but parents can be instructed how to obtain the specimens and bring them to the office for later examination.

Correct diagnosis of the pelvic or abdominal granulomata that result from migrant pinworms can be a problem if the possibility is not considered. I know of such pathology being diagnosed as neoplastic peritoneal implants at surgery and being misinterpreted as tuberculous or schistosomal lesions on histologic examination. Serial section of different parts of the tissue

specimen may be required to find portions of the worm or eggs in order to make a correct diagnosis.

TREATMENT.—The largest experience in treatment of pinworm infections has been with two drugs, piperazine citrate (Antepar) and pyrvinium pamoate (Povan). There are certain advantages to the use of each drug but they are of nearly equal effectiveness. The recommended dose of piperazine is 65 mg./kg. in a single daily dose not exceeding 2 Gm. a day, and given for 6 consecutive days. Pyrvinium can be given in a single-dose treatment at a dosage of 5 mg./kg. (pyrvinium base), but this drug may result in some gastrointestinal side-effects at times and the drug will stain clothing red on contact.

In most cases, however, the therapy that must be given in the largest doses is reassurance of the parent or the patient himself, depending on the patient's age. If the physician can convey the impression in a calm and philosophic manner that pinworm infection is very common, that it occurs in even the best of families, that it is not synonymous with gross fecal contamination and need not be absolutely eradicated in order to control symptoms, the situation can be managed with a minimum of anxiety. Although prevention of infection ultimately is related to high standards of personal hygiene and general cleanliness of the household, recommendations in this regard ought to be reasonable, such as a daily morning bath with particular attention to washing the perianal area and genitalia, frequent laundering of pajamas, sheets and underwear, proper handwashing, etc.

Newly Recognized Parasitic Diseases of the GI Tract

An interesting report by Brandborg *et al.* (43) has focused new interest on protozoan parasites known as coccidia as a cause of intestinal disease in man. In all 6 cases of malabsorption syndrome reported by these authors, intracellular coccidia, believed to be *Isospora belli,* were demonstrable in epithelial cells of the small intestine obtained by biopsy. The significance of this report is not in calling attention to human *Isospora* infection, which has been known, or even to coccidiosis as a cause of human disease, which has been described (44). The importance of the report comes instead from several apparently

new dimensions to human coccidiosis that enlarge the possibilities for recognition and diagnosis of the disease. In several of the cases, the duration of disease apparently was months to a year or longer. Four of the 6 patients described had no demonstrable parasites in the stool, several in repeated tests, yet organisms were found in the biopsy or in duodenal contents. Finally, this type of organism, which can be difficult to recognize in tissues if it is not being specifically sought, probably has not been generally considered in the etiology of most small bowel disorders seen in this country. Although in 3 of the reported cases the patients probably acquired their infections outside the United States, at least 1 and perhaps 2 additional cases were indigenous.

The coccidia are a very large group of parasites with an apparently high degree of specificity for their vertebrate hosts, which include man, cats, dogs, cows, birds, etc. Infection is initiated by ingestion of an infective oocyst that has been passed in the feces of a previous host, and the sporozoites, which are liberated from the oocyst, invade epithelial cells of the intestine. They then undergo a complex cycle of intracellular development, ultimately resulting in immature or unsporulated oocysts, which are extruded into the lumen of the intestine and passed in the feces. In view of recent findings with another parasite, *Toxoplasma gondii,* which is now considered to be a coccidian parasite of cats (45), perhaps the matter of host specificity of this group of parasites should be re-evaluated.

Attention also should be called to another parasite of worldwide distribution that has rather recently been shown to be associated with acute abdominal syndromes and the finding of eosinophilic granuloma of the stomach or small intestine. The cause was first recognized in Holland (46) and was attributed to local tissue sensitization to a nematode parasite present in the flesh of uncooked fish. These parasites, now recognized as various species of *Anisakis,* normally parasitize large marine mammals, but earlier larval stages are found in the viscera or flesh of a wide variety of fish eaten by man, such as salmon, cod and herring, especially in the western portion of the North Pacific and in the North Atlantic oceans (47). When fish are caught at sea and refrigerated without being eviscerated immediately, the larval worm, if in the viscera, will burrow into

the muscular portion of the fish. Since they are only about 1 or 2 cm. in length, they may be ingested unwittingly if the fish is eaten raw. Presumably, repeated exposure to the larvae is needed before a severe eosinophilic reaction develops to a subsequent exposure. Definitive diagnosis can be made only by identification of the worm in the midst of an intensive, eosinophilic granulomatous reaction involving the stomach or small intestine. Patients affected with this disorder frequently have been operated on for other suspected diagnoses. If the true cause of the syndrome is known, surgical intervention is not necessary, and even if it is recognized at surgery, no further manipulation is recommended. The pathologic process is reversible, and the patient is thereafter best managed by appropriate supportive therapy. This clinical syndrome, which can be termed anisakiasis, has been recognized in England and Japan as well as Holland, but no reports of its occurrence in North America have yet appeared.

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