Leading article—Tropical infection of the gastrointestinal tract and liver series

Parasitic infections of the small intestine

The tropics support a diverse group of protozoal and helminthic pathogens that inhabit the small bowel of humans. Warm temperatures permit ova to survive for prolonged periods of time and support the maturation of ova and larvae into infectious forms. Poor sanitation and hygiene, low standards of education, and close contact between persons living at a subsistence level with the environment favour the spread of intestinal parasites. Human infection typically follows ingestion of contaminated food or water, or invasion of larva through exposed skin.

Parasites can be divided into two main groups, protozoa and helminths. Protozoa are single celled organisms, which can multiply in their hosts. Infection with even one protozoan can result in severe, life threatening disease. In general protozoal infections are not associated with eosinophilia. In contrast helminths are multicellular, multi-system organisms, often with complex life cycles. They are composed of the roundworms (nematodes) and the flatworms (platyhelminths), which include flukes (trematodes) and the tapeworms (cestodes). Most of them must develop in soil or in intermediate hosts before they become infectious for humans; few are capable of autoinfection.

The morphology, life cycle, metabolism, and susceptibility to chemotherapeutic agents are often similar for members of the helminthic genera. In some instances ova are ingested, excyst in the small intestine, and develop to adulthood, and adults reside there for the rest of their lives. In others helminths follow a complex path through the body before coming to reside in the small intestine as adults. Eosinophilia is common when larvae migrate through tissue, but it is often not seen when adult helminths are present only in the gastrointestinal tract.

The manifestations of helminthic infections depend on the pathogenicity of the parasite, the host immune response, and the worm burden. People with a limited number of adult helminths are often asymptomatic, although on occasion even a single worm can produce life threatening pathology as for example, when an adult *Ascaris lumbricoides* obstructs the pancreatic duct. Some human parasites, like the beef tapeworm *Taenia saginata*, are well adapted to their human host and produce minimal evidence of disease despite their large size. Other helminths cause significant tissue damage by direct toxic effects or by eliciting damaging immune responses. In general, the greater the parasite burden, the higher the likelihood of disease.

The signs and symptoms of protozoal and helminthic infections of the gastrointestinal tract are variable. Abdominal pain, diarrhoea, and weight loss may be seen.

The clinical presentation is complicated by the fact that people living in the tropics may be infected with multiple parasitic species as well as enteropathogenic bacteria and viruses. In general the diagnosis of intestinal parasite infection is made by identifying cysts, ova or larvae in the stool. In several instances sensitive and specific assays have been developed to detect parasite antigens in the stool. Effective chemotherapy is available for most but not all of the protozoal and helminthic pathogens that inhabit the bowel. Attempts to develop effective forms of immunoprophylaxis have not yet yielded successful vaccines.

The Table lists the parasites that produce pathology in the small intestine.

**Protozoa that produce pathology in the small intestine**

The previous decade has been a period of dynamic change in the understanding of protozoal infections of the small intestine.

<table>
<thead>
<tr>
<th><em>Protozoa</em></th>
<th>Phylum sarcomastigophora (flagellates)</th>
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<tbody>
<tr>
<td><em>Giardia lamblia</em></td>
<td></td>
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<tr>
<td><em>Cryptosporidium parvum</em></td>
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<tr>
<td><em>Isospora belli</em></td>
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<tr>
<td><em>Sarcocystis species</em></td>
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<tr>
<td><em>Coccidial like bodies</em> (CYclospora species)*</td>
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<tr>
<td><em>Phylum Microspora</em></td>
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<tr>
<td><em>Entamoeba histolytica</em></td>
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<tr>
<th><em>Helminths</em></th>
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</thead>
<tbody>
<tr>
<td><em>Nematodes (roundworms)</em></td>
<td>Infection confined to the gastrointestinal tract</td>
</tr>
<tr>
<td><em>Trichuris trichiura</em></td>
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<tr>
<td><em>Capillaria philippinensis</em></td>
<td></td>
</tr>
<tr>
<td><em>Dicrocoelium species</em></td>
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<tr>
<td>*Infection begins in the gastrointestinal tract; larvae invade other organs, adults reside in the gastrointestinal tract</td>
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<tr>
<td><em>Ascaris lumbricoides</em></td>
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<tr>
<td><em>Trichinella spiralis</em></td>
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<tr>
<td><em>Nematodes of animals that can infect the human small intestine</em> (coccidian like)</td>
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<tr>
<td><em>Angiostrongylus cantonensis</em></td>
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| *Cestodes (tapeworms)*             |                                                                                                         |
| *Taenia saginata*                  |                                                                                                         |
| *Taenia solium*                    |                                                                                                         |
| *Hymenolepis nana*                 |                                                                                                         |
| *Trematodes (flukes)*              |                                                                                                         |
| *Schistosoma mansoni*              |                                                                                                         |
| *Schistosoma japonicum*            |                                                                                                         |
| *Intestinal flukes (Fasciolopsis buski, Heterophyes heiligers, Metagonimus yokogawai, Echinostoma species)* | |

*One group of investigators has recently identified coccidian like (cynomastigophora like) bodies as a *Clostridium species*.**
intestine. Novel organisms, a microsporidia species and coccidial like (cyanobacterium like) bodies, which may be a *Cyclospora* species, have been recognised as human enteric pathogens. Two previously recognised but rarely described protozoa, *Cryptosporidium parvum* and *Isospora belli*, have now gained recognition as important causes of diarrhoea worldwide. The emergence of recognition of *C parvum*, *I belli*, and microsporidia has been fuelled by the human immunodeficiency virus pandemic as these organisms can cause severe disease in patients with the acquired immunodeficiency syndrome (AIDS). New understanding of disease caused by *Giardia lamblia* has arisen from recent epidemiological studies, which call into question its role as a pathogen among some indigenous populations in the tropics. Other enteric protozoa, including *Entamoeba histolytica*, which is one of the most prevalent and dangerous of the enteric parasites, and the less important pathogens *Dientamoeba fragilis*, *Balantidium coli*, *Entamoeba polecki*, and *Blastoctyssis hominis* are thought to primarily affect the large intestine and are discussed elsewhere in this series.

*Giardia lamblia* is prevalent throughout the world. In industrialised countries it is among the most commonly isolated intestinal parasites, occurring primarily in waterborne outbreaks. In developing countries, it is one of the first enteric parasites to infect infants, reaching prevalences of 15–20% among children under 10 years of age. The pathogenicity of *G lamblia* varies among epidemiological settings. While it is a well reported cause of illness among travellers from areas of low prevalence and during waterborne outbreaks in non-endemic areas, its role as a pathogen in highly endemic tropical areas has been questioned. Several studies have failed to show an association between infection with *G lamblia* and symptomatic illness in that setting. In addition, even after successful treatment, most patients residing in highly endemic areas will be reinfected within a few months. These findings have led many to advise against routine treatment of asymptomatic patients in tropical settings. Still, others argue that *G lamblia* infection may contribute to malnutrition and growth retardation among young children, though the complexity of the interaction between host, parasite, and environment makes this difficult to prove. Studies on this issue have yielded conflicting results.

The diagnosis of giardiasis is usually made by identification of cysts or trophozoites in stool or duodenal specimens. Recently developed commercially available enzyme linked immunosorbent assay (ELISA) and fluorescent labelled monoclonal antibody tests for identifying *G lamblia* in stool are more sensitive than routine microscopy. Treatment for giardiasis includes metronidazole, tinidazole, quinacrine, and furazolidone.

*Cryptosporidium* species belong to a group of intestinal coccidia that are characterised by a sexual cycle of reproduction that occurs within epithelial cells of the small intestine, ultimately resulting in oocysts, which are excreted in the faeces. Although these organisms have been recognised since the early 1900s, they were not identified as a human pathogen until 1976. In recent years there has been emerging recognition of *Cryptosporidium parvum* as an important cause of diarrhoeal illness worldwide. Although it can affect normal hosts, its most notable impact has been among patients with AIDS, in whom it can cause severe illness.

Cryptosporidiosis has been reported on six continents and is most prevalent in less developed regions. Stool surveys among patients with diarrhoea in North America and the United Kingdom have shown prevalences of 1–4%. In contrast, reports of prevalence in Africa, Central and South America, Asia, and Australia range from 3 to 20%. In many of these studies *Cryptosporidium* was considered to be the most significant enteropathogen causing diarrhoeal illness. Seroprevalence studies show that infection with *Cryptosporidium* may be even more common than predicted by stool surveys. In the USA and UK, seroprevalence ranges from 25–35% while in developing countries as many as 64% of residents have antibodies against *Cryptosporidium*. An estimated 250–500 million cases of cryptosporidiosis occur annually among people in Asia, Africa, and Latin America. Recent studies in the US have found prevalences of 15–16% among AIDS patients with diarrhoea. In developing countries, prevalences of 22–41% have been reported in that setting.

The infection is spread by two main mechanisms, waterborne and person to person. In the tropics infection is more common in warm and rainy months of the year. *Cryptosporidium* can infect people of all ages but is most common in those under two years. Breast feeding seems to be protective. *Cryptosporidium* has also been recognised as a cause of travellers' diarrhoea.

The clinical presentation of cryptosporidiosis is dependent upon the underlying immune state. In immunocompetent persons, the illness begins after an incubation period of about two weeks. The spectrum of illness ranges from vague epigastric pain, dyspepsia, and mild diarrhoea to severe cholera like diarrhoea (up to 20 litres a day) associated with cramping epigastric pain, weight loss, anorexia, malaise, and flatulence. The illness is self limited, usually resolving in less than two weeks, although it may persist for up to four weeks. In immunocompromised patients, particularly those with AIDS, cryptosporidial infection typically begins with mild diarrhoea and progresses to voluminous watery diarrhoea with severe malabsorption. Unlike immunocompetent patients, patients with AIDS cannot clear the organism, and it often persists for the remainder of the patient's life. A recently identified complication of cryptosporidiosis in patients with AIDS is biliary tract involvement leading to stricture of the distal bile duct similar to sclerosing cholangitis.

The diagnosis of cryptosporidiosis is usually based on the identification of oocysts in stool specimens by modified acid fast stain. The oocysts appear as red, oval or crescentic shaped organisms 4–6 microns in diameter. Concentration techniques may aid in the diagnosis when low numbers of organisms are present. A fluorescein labelled monoclonal antibody test that identifies *Cryptosporidium* antigen in stool specimens is commercially available. It is more sensitive than conventional staining.

The optimal treatment for cryptosporidiosis has yet to be defined. Most ongoing work in this area has been directed towards the treatment of cryptosporidiosis in patients with AIDS. A small number have been successfully treated with hyperimmune bovine colostrum. Although it is hypothesised that IgG and IgA may be the active components, the mechanism of action is unknown. Although many drugs have been tested, recent interest has focused on two oral anti-biotics that have shown promise: azithromycin and paromomycin. Both drugs are currently being evaluated in randomised controlled trials. Initial studies suggested that octreotide given subcutaneously, a somatostatin analogue, might be useful in treating cryptosporidium associated diarrhoea in patients with AIDS. A prospective, multicenter trial showed, however, that it had only modest effect.

*Iospora belli* is another intestinal coccidian, which is known to be an important enteric pathogen in tropical and subtropical climates. It is endemic in South America, Africa, and South East Asia. It can cause disease in immunocompetent hosts and has been recognised as a cause of diarrhoea in travellers. Its highest prevalence, however, is in immunocompromised patients and it is an important cause of diarrhoea in patients with AIDS. This
experience is contrasted with the US where the organism is found in 0-2% of AIDS patients.49

Clinically, isosporiasis presents as a syndrome almost indistinguishable from cryptosporidiosis. It is a self limited diarrhoeal illness in normal hosts, although it may persist for several weeks' duration. In immunocompromised patients with AIDS it can produce severe, chronic diarrhoea associated with malabsorption and weight loss. The diagnosis is made either by identifying oocysts in the stool using a modified acid fast stain or by a small bowel biopsy. After acid fast staining, oocysts are red, ellipsoidal, large (23-33 microns), and contain 1-2 sporoblasts.

Isosporiasis responds rapidly to trimethoprim/sulphamethoxazole (TMP/SMX). Metronidazole or pyrimethamine are alternatives in patients with sulphonamide allergy. Unfortunately, relapses are common after treatment in patients with AIDS (up to 50%). A randomised control trial has shown that recurrences can be prevented with maintenance TMP/SMX given three times weekly or with sulfadoxine/pyrimethamine once weekly.48

Sarcocystis species, closely related to the genus Isospora, have also been implicated as human enteric pathogens. Although usually an infection of skeletal muscle, intestinal infection has been reported. Gastrointestinal symptoms such as nausea, vomiting, and diarrhoea have been described after voluntary ingestion of meat containing Sarcocystis.45 In a small series, eosinophilic necrotising enteritis was associated with the presence of Sarcocystis sporocysts in resected specimens of small bowel.50

Microsporida are obligate intracellular protozoa that have a wide host range, which includes invertebrates as well as vertebrates. Recent studies have implicated a newly recognised microsporidia, Enterocytozoon bieneusi as a cause of diarrhoea and malabsorption in patients with AIDS.33-36 Prevalence studies using small bowel biopsies have found the organism in 23-50% of American and European AIDS patients with chronic diarrhoea for which no other cause can be identified.50,51 Although seroprevalence surveys are not available from tropical regions, studies of other microsporida genera suggest that E bieneusi is probably common in tropical areas as well.37 One study conducted in Zambia and Uganda showed a prevalence of 6-5% among AIDS patients with unexplained diarrhoea.52

The pathological findings with microsporidiosis are similar to those in cryptosporidiosis. Infection is confined to small bowel enterocytes resulting in villous atrophy and sloughing of some epithelial cells.53 Although characteristic spores can be identified in a modified trichrome or Geimsa stained stool and duodenal aspirates,34-36 the diagnosis is usually made by electron microscopy of small bowel biopsy specimens. Effective treatment has not been established, but success with metronidazole or albendazole have been reported in small, uncontrolled series.54 Coccidian-like (Cyanobacterium like) bodies (CLB) were first described in the stools of North American travellers returning from Haiti and Mexico with diarrhoea.44 Now thought to be an important human enteric pathogen, these organisms have been reported in stools from patients in the USA, Caribbean, Central and South America, South East Asia, and Australasia. CLB have been implicated as the cause of large outbreaks of diarrhoea in Chicago and Nepal.55 Recently, investigators studying CLB isolated in Peru proposed that they are coccidians of the genus Cyclospora.33 The investigators hypothesised that CLB reported by others may be organisms from that genus. The illness, which occurs in both normal and immunocompromised hosts, is characterised by severe, intermittent watery diarrhoea and fatigue, which can persist for weeks before spontaneous recovery. CLB are described as spherical cysts 8-10 microns in diameter that stain red by modified acid fast stain and are autofluorescent under ultraviolet light.56 The exact incidence of disease associated with this organism is not known. There is no known treatment at this time.

Pathogenic nematodes (roundworms) found in the small intestine

Ascaris lumbricoides, the hookworms Necator americanus and Ancylostoma duodenale, and Trichuris trichiura, which resides predominantly in the colon, are among the most prevalent parasites of humans. In many developing areas of the tropics most residents are heavily infected with more than one of these parasites. In the case of Ascaris and Trichuris infection occurs when ova are ingested in faecally contaminated food and water. In the case of hookworm, infectious filariform larvae invade the skin through bare feet or other exposed skin. A purpuric, papular or vesicular eruption may be seen at the site of entry. After going through a series of developmental stages, which in the case of Ascaris and the hookworms pass through the lung occasionally resulting in pulmonary symptoms, infiltrates and eosinophilia, these nematodes reside as adults in the intestinal tract. They produce a prodigious number of ova, which are disseminated in the environment in stool.

People who are infested with intestinal helminths often complain of abdominal discomfort and may have diarrhoea, but they are also often coincidentally infected with enteropathogenic bacteria or viruses, or both and it is difficult to determine the degree to which the parasites are responsible for their symptoms. When present in large numbers, clumps of Ascaris lumbricoides can produce obstruction of the small intestine, with findings suggestive of an acute abdomen. It is estimated that this occurs in 1 in 1000 subjects in endemic areas.44 Individual ascarids, which can grow to more than 30 cm in length, migrate into the common bile duct or pancreatic duct on occasion producing ascending cholangitis or pancreatitis.57 Hookworms, which usually reside in the small intestine, can produce abdominal pain and bloody diarrhoea when subjects are infected for the first time, but are commonly associated with iron deficiency anaemia, which may be severe when the worm burden is high and iron intake is limited.58,59 Trichuris trichiura is associated with blood loss from the colon, chronic diarrhoea, and occasionally rectal prolapse.70-72 Mass treatment programmes in areas where all three of these parasites are endemic, suggest that they produce malnutrition and adversely affect growth in children who are heavily infected.74

The diagnosis of Ascaris, hookworm, or Trichuris infection is typically made by finding ova in the stool. These parasites are susceptible to a number of anthelmintic agents. Mebendazole and albendazole are active against all three.33 Albendazole, which has not yet been licensed in the United States, has the advantage of being effective when given as a single dose and has been successfully used in mass treatment programmes.74

Strongyloides stercoralis, another small bowel pathogen, is also endemic in many tropical areas. Similar to hookworm, larvae invade through the skin and may elicit pulmonary infiltrates with eosinophilia as they migrate through the lungs or a pruritic skin lesion known as larva currens.54 Strongyloides adults in the intestine can produce abdominal discomfort, diarrhoea, and eosinophilia55 Strongyloides differ from the intestinal nematodes previously discussed in that autoinfection can occur. Disseminated hyperinfection may occur in subjects with compromised T cell immunity associated with steroid use, neoplasm, malnutrition, or infrequently AIDS.64-66 The diagnosis is made by identifying rhabditiform or filariform larvae in the stool.71 Thiabendazole is effective in treating strongyloidiasis, but is commonly associated with nausea, vomiting, and other side effects.
effects. Ivermectin, which is much better tolerated, is promising in preliminary studies.

Trichinella species, another nematode capable of causing pathology in the small intestine, are prevalent worldwide, including the tropics. The intestinal phase of trichinosis occurs in the first week after ingestion of meat infected with Trichinella cysts when larvae penetrate the small bowel epithelium and develop into the adult stage. This phase is associated with nausea, abdominal pain, and diarrhea and is quickly followed by periorbital oedema and muscle pain as newborn larvae penetrate into muscle cells. A less common syndrome of chronic diarrhea has been described in Inuit Indians in North America infected with T. natra. This unusual presentation is felt to be the result of secondary infection in previously infected subjects.

A number of other pathogenic intestinal roundworms that inhabit the small bowel are found in the tropics. Trichostrongylus species are important pathogens of cattle, and are found in humans in cattle raising areas. Human infection is usually mild or asymptomatic. Capillaria philippinensis, which is endemic in scattered areas of Southeast Asia and the Philippines, can result in malabsorption, chronic diarrhea, wasting, and death. Humans typically become infected when they ingest contaminated fish. Angiostrongylus costaricensis occurs in scattered areas of Latin America. Humans become infected when they ingest food contaminated by infected land snails. The parasite causes acute inflammatory lesions of the small intestine colon and may be confused with bacterial infections, acute appendicitis, Meckel's diverticulum or neoplasm. Many cases come to surgical exploration and resection. Anisakiasis occurs when inadequately cooked fish contaminated with anisakine larvae is ingested. Acute inflammatory lesions may be found in the stomach or small intestine at the sites where larvae attempt to invade.98 99

Pathogenic trematodes (flukes) found in the small intestine
A number of flukes, or trematodes, are pathogens of humans. They have complex life cycles involving snails. They gain access to their human hosts either by entering the skin, as is the case for Schistosoma species, or when they are consumed in uncooked, contaminated food. Schistosomiasis is the most prevalent and important of the helminthic infections. Schisto-

somansoni endemic throughout Africa and is found in many areas of Latin America and the Middle East. Schisto-
somajaponicum is found in Asia. Adult schistosomes reside in venules in the mesenteric plexus where they release their ova. Intestinal disease is characterised by mucosal inflammation, hyper trophy, and ulceration. Those infected may complain of abdominal pain, diarrhea, and bloated stools. Intestinal polyps and strictures may result later in disease.96 Eggs that are swept back to the liver elicit granulomatous inflammatory responses. Fibrosis of varying severity results and can lead to presinusoidal portal hypertension and hepatosplenomegaly.97 The diagnosis is usually made by finding the ova in stool or biopsy specimens, but it may be suggested by the identification of anti-schistosomal antibodies. Diffuse or patchy mucosal hyperaemia and friability may be seen at colonoscopy.98 Praziqantel has been effective in the treatment of all forms of schistosomiasis. Oxamniquein can be used to treat Schistosoma mansoni.99

Several flukes live within the gastrointestinal tract. Fasciolopsis buski, which is acquired when people ingest contaminated raw water plants such as the water chestnut, results in inflammation of the small intestine and epigastric pain, nausea, and diarrhea of varying severity. Similar symptoms may be seen with two other intestinal flukes, Heterophyes heterophyes and Metagonimus yokogawai, which are acquired when contaminated fresh water fish are con-
sumed,100 101 or Echinostoma species, which are ingested in raw, infected snails, amphibians or fish.99

Pathogenic tapeworms (cestodes) found in the small intestine
Tapeworms have complex life cycles. Adults live in the intestinal tract of their definitive host while larvae are found encysted in intermediate hosts such as cattle or pigs. Despite reaching extraordinary lengths in humans, adult Taenia saginata and Taenia solium tapeworms cause minimal disease. When ova of Taenia solium, the pork tapeworm, are ingested by humans, however, they can protrude in the brain, causing lesions in the brain. Cysticercosis is a condition known as cysticercosis.99 Neurocysticercosis is an important cause of morbidity and death in Latin America and in some areas of Asia and Africa. In the case of the dwarf tapeworm, Hymenolepis nana, humans serve as both the intermediate and definitive host and autoinfection is prominent. Infection is thought to occur in 20 million people worldwide. Light infections are typically asymptomatic, but heavy infections can produce loss of appetite, abdominal discomfort, diarrhea, and anorexia.99 Niclosamide and praziquantel are active against adult tapeworms in the intestinal tract; praziquantel or albendazole can be used in the treatment of neurocysticercosis.

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