MEDICAL GRAND ROUNDS

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RECENT ADVANCES IN THE PATHOGENESIS, DIAGNOSIS AND TREATMENT OF GASTROINTESTINAL PARASITIC INFECTION

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Worms

I. GENERAL ASPECTS

The study of parasitic diseases has taken a backseat in medical practice and in research in modern times. The reason for this low level of interest among both those in practice and in academic medicine are numerous— 1) The prevalence of parasitic infestation is assumed to be low in the developed countries and cities of the world and the United States,and the underdeveloped areas of the United States (the rural South) and the world are the areas with high prevalence rates and low physician numbers. Neither medical schools nor private physicians nor the pharmaceutical industry have considered parasitic diseases an area in which an adequate return on investment could be attained. 2) There exists a psychological block by most individuals in the medical profession present early in training which inhibits the acquisition of knowledge about parasitic infections. Such an inhibition probably arises from consideration of the organisms themselves and of the symptomatology with which patients present. 3) Shortage of research workers concerned with parasitic diseases has led to a delay in the application of scientific progress obtained in other fields which is then applied to the field of parasitology and to progress which makes the field attractive to new investigators. Examples of this limiting research capability can be seen in two ways— 1) In no instance has the complete life cycle of any of the important helminths that infect man been reproduced under laboratory conditions and 2) Adequate animal models of infection have yet to be developed in the laboratory.[1] The failure to have these techniques prevents the study of the pathophysiology of infections with these agents. It also inhibits drug development and an understanding of the mechanisms of acquired resistance.

In spite of these negative factors, significant advances have been made in the study of parasitic infections. A number of pathophysiological mechanisms have been elucidated. Immunological responses have been examined intensively for understanding of host response and for usefulness as diagnostic tests. At the present time, effective agents are available for the treatment of virtually all of the organisms which reside within the gastrointestinal tract. The purpose of this presentation is to review this recent progress in various aspects of parasitic infections of humans.

II. PREVALENCE

Published surveys of prevalence rates of parasitic manifestations have been infrequent in the last few years in the United States. Surveys of inhabitants of southern states have indicated a high prevalence rate (Table 1). These studies indicate that Ascaris and hookworm infection continue to be the prevalent intestinal parasites whereas Trichuris and Strongyloides are relatively infrequent.[2-4] The prevalence rates for Enterobius (pinworm infection) are not valid since two of the studies were performed on stool samples only. The 36% prevalence rate in the study from Tennessee is a more likely true figure.[4] Protozoan infestation was not commonplace in these surveys. One of the last surveys for E. histolytica was in 1963 in Arkansas which revealed prevalence rates of 3.4%.[5] Infection with Giardia has been noted in 1-3% of persons sampled in the United States.[6, 7]

TABLE 1

SURVEYS OF PARASITIC INFESTATION IN THE UNITED STATES

Organism	McCreary County Kentucky (2)	South Carolina (3)	Williamson County Tennessee (4)
Date	1968	1969	1969
	Prevalence (% Positive)		
Ascaris	7.7	13	10.9
Hookworm	14.8	3	0
Trichuris	4.8	2	-
Enterobius	0.5	0.3	36
Strongyloides	0	-	0.9
Entamoeba histolytica	0	0.01	-
Giardia lamblia	-	0.1	-

Recent autopsy studies have shown that the prevalence of trichinosis has decreased from 16% in 1940 to 4.2% in recent years.[8] No available data is at hand on the prevalence of tapeworm infection in humans in the United States; however, infection rates are thought to be quite low.

Studies of service men returning from Viet Nam indicate that parasitic infestation is commonplace in this group. In one study of 97 asymptomatic American soldiers, 14 (14%) had hookworm ova in the purged stool, 4% had E. histolytica and 1 had Strongyloides larvae.[9] Another study of 57 patients revealed that 13 (23%) had hookworm and 3 (5%) had Ascaris, but no Strongyloides larvae were identified.[10] In a series of patients evaluated for malaria, 40% of those having eosinophilia of more than 5% had either Strongyloidiasis or hookworm or both.[11]

Another major potential endemic focus of parasitic infestation is that of mental hospitals and institutions. Scattered reports indicate significant infection does occur in institutions. One report concerned the acquisition of Strongyloides by 38% of the inmates in a children's mental institution in Illinois with one serious illness.[12] Serious amoebic disease has been noted in the state mental hospital in Arkansas by Juniper. Although he does not give prevalence rates, the mortality rate is significantly higher for inmates with amoebic infection in the state hospital (52%) whereas the mortality rate in the University and VA Hospital was 4%.[13] An epidemic of diarrhea occurred in a children's ward of a mental institution which was due to E. histolytica.[14] A survey of the children in the ward revealed prevalence rates of 14% for E. histolytica, 2% for Giardia lamblia, 7% hookworm, 38% Trichuris, and 5% Hymenolepis nana.

A survey has been made of the stools examined at Parkland Memorial Hospital for ova and parasites to determine the prevalence among employees and patients on whom stools were submitted. During the two year period of 1970-1972, 13 of the 207 samples submitted by personnel (primarily in the dietetics department) were positive for parasites (6.4%) and 29 of 756 patients with stool samples submitted were positive (3.9%). 10% of the specimens submitted were unsatisfactory. Pathogenic entamoeba were present in half of the samples which were positive from personnel (Table 2). No nematodes or cestode ova were demonstrated in stools from personnel. Giardia lamblia was the predominant organism present in patients. Stool samples were positive for nematodes in 8 (1%) and for cestodes in 4 (.05%) of patients examined in this time period.

TABLE 2

PARASITIC INFECTION IN PERSONNEL AND PATIENTS AT PARKLAND MEMORIAL HOSPITAL, JAN. 1970 - JAN. 1972

	Personnel	Patients
E. histolytica	3	2
Giardia lamblia	4	9
Non-pathogenic Entamoebae	7	11
Hookworm	0	1
Strongyloides	0	3
Trichuris	0	4
Taenia	0	1
H. nana	0	3
Total	14	34
Double Infection	1	3

III. PATHOPHYSIOLOGICAL MECHANISMS

A. Malabsorption and Malnutrition

Malabsorption has been clearly demonstrated in patients infected with Giardia lamblia, Strongyloides stercoralis, Capillaria philippinensis and Coccidia.[15] Many other parasites may cause diarrhea without producing significant malabsorption. Steatorrhea was documented in an outbreak of epidemic diarrhea due to Giardia lamblia in one individual by stool fat and abnormal dxylose excretion studies.[16] Steatorrhea and diarrhea disappeared with treatment. Intestinal mucosal biopsies performed in patients with Giardia infections having steatorrhea reveal a normal mucosa with no inflammatory response or epithelial cell damage.[17] Organisms were present within the mucosa in the majority of these patients. Mucosal biopsies in patients with Strongyloidiasis and malabsorption have revealed blunting of the

villi with a chronic inflammatory infiltrate and eosinophils within the lamina propria.[18] Patients with intestinal Capillariasis have been shown to have a severe protein-losing enteropathy and malabsorption syndrome.[19] The worms were seen to penetrate the jejunal mucosa in biopsy specimens, but no differences were noted in histological features in control and infected patients. Although it is postulated that mucosal damage accounts for the malabsorption states in these parasitic diseases, differences in mucosal biopsies from patients with malabsorption and controls without malabsorption are not striking. The cause of malabsorption in parasitic diseases requires further study.

Whether malabsorption occurs or not with hookworm infection remains controversial. A study of patients in Puerto Rico demonstrated histological and radiological abnormalities of the small intestine which were associated with abnormal biochemical tests compatible with malabsorption.[20] Treatment of the hookworm infection lead to improvement in the fecal fat excretion. Other studies however have not demonstrated this association.[21, 22] In most of these other studies, malabsorption abnormalities are attributed to other nutritional deficiencies.

Malnutrition has been noted as a prominent feature of illness with the nematodes, particularly with Ascaris, hookworm, and less commonly with Strongyloides infection. The factors secondary to parasitic infection which are responsible for malnutrition have not been adequately evaluated. An additional difficulty in the evaluation of malnutrition due to parasites in endemic areas is the fact that malnutrition is a common problem in these areas. At least one experimental study in man has demonstrated that infection with Ascaris does lead to a loss in protein which amounts to approximately 10% of the ingested protein per day.[23] It is postulated that with heavy infections, the worms could deprive the host of a critical amount of protein. Hypoalbuminemia is a feature of hookworm infection and is associated with a decreased exchangeable albumin pool.[24] These patients have protein-losing enteropathy which could account for the low albumins.

Although vitamin deficiencies could be present in populations with worm infestation because of low intake, at least two deficiencies have been noted with worm infections. In Ascaris infection and with Giardia infections, Vitamin A deficiency has been noted.[23, 25] Following the treatment of each condition, symptoms of night blindness rapidly improved. In addition, in Giardiasis, low serum Vitamin A levels respond with a rise to normal levels with therapy, whereas treatment with Vitamin A alone does not produce a rise. Vitamin C deficiency has been commonly associated with Ascaris infection.[23] Experimental studies have shown that infected children excrete a significantly lower quantity of ingested Vitamin C than do the non-infected children.

It has also been postulated that the more malnourished the individual the more likely a severe degree of intestinal parasitic infection will be. However, recent experimental studies in humans have demonstrated that nutritional

repletion does not influence the degree of hookworm infection.[26] The hookworm ova excretion did not change nor did the quantity of blood lost in the stool in 12 patients following addition of an adequate diet to infected patients.

B. Anemia

A hypochromic and microcytic anemia is a feature of infection with hookworm.[24] This anemia which is secondary to iron deficiency develops as a result of the fecal loss of blood. The loss of blood is proportional to the number of worms present and in general requires a count of greater than 5,000 eggs per gram of feces for anemia to develop.[27] At this level, blood loss is approximately 10.5-22.3 ml/day and iron loss 3.5 to 7.4 mg/day. The anemia responds to treatment with iron alone; however, if the patients are not wormed, the hemoglobin generally drops after iron treatment is stopped. Successful treatment of the hookworm infection is associated with remission of the anemia. Infection with hookworm has also been associated with folic acid deficiency.[28] This anemia may be noted during the recovery following treatment of the iron deficiency anemia and more likely relates to deficiencies of folic acid in the diet than to parasitic infection.

Infection with Diphyllobothrium latum has been noted to be associated with a megaloblastic anemia.[29] This has been seen predominantly in northern Europe. Although the tapeworm is quite common in Southern Canada and Northern United States, (Great Lake Region), there has been little association with infection and anemia in the North American continent.[30] The anemia develops secondary to the avidity of the worm for Vitamin B_{12}, for studies have shown 44% of the injected B_{12} was absorbed by the worm.[31] An extensive study of 29 patients with fish tapeworm pernicious anemia showed megaloblastic erythropoiesis, impaired urinary excretion of B_{12} (Schilling test), and low B_{12} serum levels.[29] Most of the patients with anemia were over 60 years of age and had gastric achlorhydria, whereas most of the tapeworm carriers without anemia had free hydrochloric acid in their stomachs. The megaloblastic anemia results from the presence of the parasite, decrease intrinsic factor activity, and possibly insufficient dietary supply of Vitamin B_{12}. Expulsion of the worm leads to improvement in neurological signs, hematological improvement, and a rise in B_{12} levels.

C. Other

Parasitic infections have been claimed to be responsible for a number of other clinical syndromes. In one study, patients with bronchial asthma were frequently infected with Ascaris, Strongyloides, and hookworm, whereas a smaller control group had no parasitic infection.[32] This study has been criticized since: 1) bronchial asthma is not common in other parts of the world where Ascariasis is common[33, 34] and 2) other studies do not show any difference in parasitic infestation in asthmatic patients vs. controls.[35] Hypersensitivity to parasites, in particular to Ascaris, has been noted particularly in veterinarians, parasitologists, and technicians in parasitology laboratories.[23, 30, 36] However, it is not likely that in large populations that it is a cause of bronchial asthma.

It has also been postulated that toxocaral larvae which invade the brain is a common cause of epilepsy.[37] This is primarily based upon skin test data in which skin test to toxocaral antigen is positive 3 1/2 times as frequently in patients with epilepsy as in those who are healthy controls. It has even been postulated that the larvae might be a factor in poliomyelitis subsequent to carrying the virus to the brain. However these data are exceedingly preliminary, and have not been repeated in other clinics.

Another myth that has been profounded recently in the literature concerns the relationship of parasitic infections to "autoimmune disease". Observations in Nigeria reveal a very low prevalence of rheumatoid arthritis and the arthritis runs a benign course and patients rarely have vascular involvement.[38] The group in Nigeria has examined other "autoimmune" processes and has found these to be extremely unusual causes of admission to the hospital. They have postulated that a presence of multiple parasitic infections from childhood is one of the environmental factors protecting the population of tropical Africa from this group of conditions. Again, these are single observations concerning disease processes about which multi-factorial factors may be at play. It is more likely the observations are fortuitous albeit interesting.

IV. HOST FACTORS

Eosinophilia is a feature of the host response to infection with helminths such as: Ascaris, hookworm, Strongyloides and Trichinella. Virtually all patients with these infections will develop eosinophilia soon after tissue migration of larvae which is generally through the lung. The eosinophil count may persist for months even after expulsion of the worms from the gastrointestinal tract.[39] The level of eosinophils will diminish if a bacterial infection develops.[40]

Eosinophilia has been studied recently using the intravenous injection of Trichinella larvae into rats.[41] The development of eosinophilia requires a local cellular reaction following entrapment. Homogenized parasites were not arrested in the lung and did not elicit an eosinophil response. The eosinophil response is independent of the antibody response to the larvae. The induction of the eosinophilia is mediated through lymphocytes.[42] Procedures known to deplete or diminish the pool of circulating lymphocytes resulted in a highly significant reduction in the eosinophilic response. The eosinophilic response could be restored by reconstituting irradiated animals with circulating lymphocytes and bone marrow cells. The eosinophilia has also been shown to develop earlier and to have an augmented response upon secondary challenge.[43] This is analagous to the increase in the antibody following the second administration of antigens. These studies indicate that eosinophilia shares common features with recognized immune responses and can be classified as an immune response.

Lymphocytes obtained from delayed-hypersensitive guinea pigs have been shown to produce a substance which interacts with immune complexes to release a factor chemotactic for eosinophils.[44] A factor selectively chemotactic for

eosinophils has also been elaborated following the antigenic challenge of human lung passively sensitized with serum from a ragweed sensitive donor.[45] IgE mediated the elaboration of this factor. The presence of such a chemotactic factor in both in vivo and in vitro situations suggest that it plays a role in the accumulation of eosinophils in lymphoid tissue and at sites of immunologic reaction. Little is known of the role of eosinophils in spite of their association with clinical states. Since it is known that eosinophils are highly phagocytic for antigen and for antigen-antibody complexes,[46, 47] it has been suggested that they play a possible regulatory role in the immune response at local sites.[44]

Separate lines of investigation have prompted the suggestion that mast cell activity within the gastrointestinal tract plays a role in the expulsion of parasites.[48] A close relationship has been noted between the rise in numbers of granulated mast cells in the intestinal wall and the onset of the expulsion of worms. The administration of reserpine (which prevents the storage of active amines in mast cell granules)and a mast cell lytic agent are associated with a delay in expulsion of worms.[48, 49] It is not presently known whether the relation between mast cell activity and expulsion of the parasites is mediated through the pharmacological or immunological mechanisms.

Both cellular immunity and antibody are a feature of the host response to parasitic infections of the gastrointestinal tracts. Significant protection against the infection has been demonstrated in passively immunized animals by transfer of syngeneic immune cells.[50, 51] The immune lymphoid cells accumulate in the infected small intestine as early as 6 hours after transfer whereas non-immune cells do not accumulate.[52] Contact between these cells and parasite occur in the epithelium of the bowel.[53] Protective antibodies to protozoa and helminths have generally been associated with IgG although IgM antibody has been demonstrated.[54] Little evidence has been accumulated that IgA antibody develops with gastrointestinal tract infection. In fact, no increase in IgA producing plasma cells nor IgA antibody occurred with Trichinella spiralis infection.[55]

Elevated IgE levels have been reported in patients with Ascariasis, capillariasis, Trichinosis and Visceral Larva Migrans.[56-59] Studies of patients with Visceral Larva migrans show that all patients with high levels had antibodies to toxacara antigen as determined by passive cutaneous anaphylaxis test in monkeys.[59] IgE levels in trichinosis by day 27 are elevated after infection but returned to normal six months after infection. Increased levels of IgE occur in parasitic infections with a tissue invasion. Considerable work remains to be done in assessing the immunological response to parasites. In particular, the predominant significance of the immunological response has been to provide tools for diagnosis as in delayed hypersensitivity tests for toxacara and serological tests for amebiasis, toxoplasmosis and trichinosis.[60]

V. CLINICAL FEATURES AND DIAGNOSIS

The identification of ova and parasites are performed best on specimens submitted immediately after collection to the laboratory. The preferred method for those physicians with access to a hospital laboratory is to schedule the procedure with the parasitology section of the microbiology laboratory, administer 1/2 oz. epsom salts, and have the patient deliver the purged stool to the laboratory.(61) Material obtained by sigmoidoscopy should be aspirated with a pipette or onto a spoon rather than obtained with a cotton swab (which entraps organisms in the meshes of cotton) and submit immediately to the laboratory. Identification of E. histolytica from extraintestinal sites such as abscesses is less frequently successful than is identification from intestinal infections. Amoebae may only be present at the periphery of the abscess, so it is important to examine material at end of aspiration for active and motile trophozoites. The identification of parasites in the stool can be interfered with by a number of substances (Table 4).

TABLE 4

SUBSTANCES THAT INTERFERE WITH PARASITOLOGIC EXAMINATION OF FECES

Antidiarrheal Preparations
- Bismuth
- Koalin (Kaopectate)

Antacids, Laxatives
- Oils
- Magnesium hydroxide

Biologically Active Drugs
- Sulfonamides, antibiotics
- Antiprotozoal drugs
- Antihelmintic agents

Radiographic Procedures
- Barium sulfate

Enemas
- Water
- Soap Solution
- Irritants
- Hypertonic salt solutions

A. Protozoa

1. Entamoeba histolytica

Man is the principal host as well as source of infection for the organism producing amebiasis. Cysts are passed in the feces and infection is acquired by ingesting contaminated food or drink. Transmission can occur through polluted water supply, handling of food by infected food handlers and by poor personal hygiene such as occur in inmates of psychiatric hospitals or other institutions. The quantity of chlorine usually employed in water purification for pathogenic bacteria is ineffective in killing cysts of E. histolytica, consequently, water borne outbreaks such as that studied by Dr. LeMaistre and associates in 1955 do occur.(62)

In this particular outbreak, the mode of transmission was through a chlorinated private water supply of the plant which had been intermittently contaminated with sewage containing E. histolytica. A ratio of 4 symptomatic cases occurred for every 100 carriers. Infection can either be autoinfection or from another host.

Neal postulates that the ameba are normally avirulent in the intestinal lumen and with stimulus they change to the invasive form.[63] A great deal of evidence indicates that bacteria are greatly responsible for this virulence. It is possible that the bacteria provide a suitable environment such as the proper low redox potential to support the metabolic integrity of the amoeba.[63, 64] Experiments have shown that amoebae develop increase virulence and become invasive by contact with living bacteria.[65] Certain "suitable" bacterial strains are postulated to contain a virulence factor that can be transferred to the amoebae.[65] Structural observations of amoebae in human colon have demonstrated a "fuzzy coat" which is not seen in amoebae grown in vitro.[66] It is possible that surface membrane plays a significant role in the pathogenesis of amebiasis.

The most common clinical state is the asymptomatic carrier. Patients who present acute amebic colitis may present with a history of recurrent episodes of diarrhea over a period of several months.[67] The episodes of diarrhea frequently are self-limiting and last from five to ten days. Almost without exception, patients present with bloody diarrhea and cramping abdominal pain (Table 5).[67, 68]

TABLE 5

ABNORMALITIES OF ACUTE AMEBIC DYSENTERY

	Ref 67	Ref 68
Number of Cases	55	50
History:		
Bloody diarrhea	100%	100%
Abdominal cramps	46%	100%
Physical		
Fever	38%	38%
Hepatomegaly	24%	22%
Hepatic tenderness	—	52%
Sigmoidoscopic ulcers	86%	74%
Laboratory		
Leucocytosis	38%	24%
Abnormal Liver Function Test	48%	4%
Ova in stool	20%	24%
Positive rectal swab	80%	68%

Weight loss is frequently present. Physical findings are not particularly helpful. In general the fever when present rarely exceeds 101°. Rectal ulcerations are usually visible at time of sigmoidoscopy. The most reliable test in diagnosing these individuals was to demonstrate E. histolytica trophozoites from scrappings of the ulcer.[67, 68] Juniper has emphasized that acute amoebic colitis presents frequently in association with other disease processes such as carcinoma of the colon, bacterial dysentery, or chronic debilitating diseases.[67] Hence, other laboratory tests such as stool cultures for bacteria and barium enema should be performed later, even though amoebic colitis is the correct initial diagnosis.

The diagnosis is based upon demonstration of the parasite in stool, preferably a purged stool.[69] Individuals who are asymptomatic carriers may have E. histolytica in stool intermittently. In studies to compare normal stool versus purged stool, approximately one third of normally passed stools will be positive the first day, 56% by 3 days, and 75% at 6 days.[70] A single purged specimen is positive in 89%.

Amoebic liver abscess continues to be seen in the United States although invasive amoebic colitis has decreased considerably in the last few years. Juniper considers this phenomenon as due to the frequent non-specific use of antibiotics which mask the intestinal manifestations of amebiasis but do not cure the infection.[13] Consequently many individuals present with amoebic liver abscess with no history of diarrhea and with no E. histolytica demonstrable in the stool. Amebic liver abcesses in adults occur predominantly in males, whereas in children both sexes are seen with equal frequency.[64, 71] Patients with amoebic liver abscesses present with fever, weight loss and right upper quadrant abdominal lower chest pain or shoulder pain, (Table 6). Hepatic involvement is suggested in most of the individuals by tenderness to percussion over the liver or by enlargement of the liver.[68, 71] Most of the patients have anemia, leucocytosis, and some have evidence of liver function abnormality. Rarely are the individuals jaundiced. The important distinguishing sign between amoebic abscess and acute pyogenic abscesses are: history of diarrhea and abnormal chest finding in those with amebic liver abscess and hyperbilirubinemia in those patients with pyogenic liver abscess.[71] Chest findings which are common include right pleural effusion, dullness or rales over right base,or an elevated immobile right diaphragm.

TABLE 6

FINDINGS OF AMEBIC LIVER ABSCESSES AND PYOGENIC LIVER ABSCESSES

	Amebic Liver Abscess		Pyogenic Liver Abscess
	Ref 68	Ref 71	Ref 71
	Per Cent		
History			
Fever	94	67	72
Weight Loss	76	100	100
Pain	76	74	50
Diarrhea	48	48	8*
Physical			
Hepatic tenderness	76	74	67
Hepatomegaly	70	74	67
Chest Findings	35	87	20*
Jaundice	12	0	28
Laboratory			
Leucocytosis	100	74	75
Anemia	76	94	67
Liver Function Abnormality	60	30	50
Hyperbilirubinemia (>1.0)	12	10	67*

* Statistically significant at $p < 0.05$

CASE REPORT #1

A 21 year old [redacted] male was transferred from the [redacted] to the [redacted] with a one month history of right shoulder pain which increased with coughing, right anterior chest pain and fever. He had diarrhea three times in Viet Nam: the last occasion was three months prior to admission. On admission his temperature was 101°. He appeared acutely ill. He had dullness and decreased breath sounds over the right lower lung field without rales. The liver was palpable 1 fingerbreadth below the right costal margin and was non-tender. Chest x-ray showed blunting of the right costal margin and elevation of the right diaphragm. A liver scan showed a large single filling defect in the anterior portion of the right lower lobe. Approximately 5 hours after admission, he had the acute onset of right upper quadrant, abdominal and right chest pain. Soon, he began to cough up brownish material, which he said tasted like "fresh liver". The pleural effusion increased over the next 24 hours and an abscess was noted with an air fluid level. He was begun on Emetine, 30 mg IM every 12 hours and Chloroquine 500 mg/day. Two days later Metronidazole (Flagyl) 750 mg tid was added. His liver function studies had been normal on admission, but two days after admission his SGOT was 73, (normal 40), alkaline

phos. was 24 (normal 15), and albumin was 2.5 with a total protein of 7.6 g %. He was mildly anemic (hemoglobin 10.7, hematocrit 32) and his white count was 14,100 with 85% neutrophils, 13% lymphocytes and 2% eosinophils. His temperature responded and his pleural effusion cleared both on x-ray and on physical examination. At time of discharge 21 days after admission, the hematocrit was 39.

Diagnosis of amebic liver abscess is generally based upon clinical suspicion. Liver scan with both anterior and lateral scans will be positive in 90%.[68] Chemotherapy is usually instituted without positive identification. Needle aspiration is rarely indicated except when there is danger of the abscess rupturing into the pericardium or peritineum, obvious bulging of an abscess between the ribs, or following inadequate response to chemotherapy.[68] Open surgical drainage is only indicated when there is an inadequate response to chemotherapy and aspiration, or when secondary bacterial infection is thought to have developed.[68] Rupture of abscess generally occurs into the right lung or the right pleural cavity. Significant mortality rate occurs upon rupture into the peritoneal cavity or into the pericardial sac. This situation is an acute medical emergency and requires instant drainage of the abscess. Clinical response is usually rapid to chemotherapy, generally with defervescence and improvement in pain within 2 to 3 days. However, the abscess can persist as determined by repeat liver scans up to 5 to 6 months after therapy. Persistance of the abscess cavity is no indication of relapse however.

Serological tests for intestinal and hepatic amebiasis have been utilized within the last few years. Two reliable tests are presently available, the gel diffusion precipitin test and indirect hemaglutination.[61] Preparations of amebic antigens free of bacterial and other antigens are possibly due to the development of axenic techniques for culturing E. histolytica.[72] These tests are highly sensitive for invasive amebiasis. False positive reactions are rare in asymptomatic individuals and only a small percentage of asymptomatic carriers of E. histolytica have positive tests (Table 7). All the patients in this study with acute amebic dysentery and acute hepatic abscess had a positive indirect hemagluttination test and most had a positive agar gel diffusion test. The indirect hemagluttination test tended to remain elevated following recovery from hepatic abscess whereas the agar gel diffusion test became negative. Serology would appear to be a very promising procedure for invasive disease, such as liver abscess.

TABLE 7

SEROLOGICAL TESTS FOR ANTIBODIES TO ENTAMOEBA HISTOLYTICA ANTIGENS (Ref 72)

	Indirect Hemagglutination %	Agar Gel Diffusion %
Carriers E. histolytica, positive	16	1
Amebic dysentery, acute	100	82
Abscess, hepatic, acute	100	100
Abscess, hepatic, old	86	14

2. Giardia lamblia

Until recently, little information was available about the mode of spread of Giardia lamblia. A point source outbreak of protracted intermittent diarrhea has been reported in association with Giardia lamblia.(16) Environmental studies carried out after the epidemic suggested water borne spread of the organisms through contamination of well water by sewage leakage. This indicates that as with E. histolytica, Giardia is resistant to chlorine. Two common source outbreaks of Giardiasis in tourists visiting the Soviet Union have been reported recently.(73) Environmental studies suggested that water was the most likely vehicle and Leningrad the most likely site of infection. No evidence of secondary spread was noted after the tourists returned to the United States.

The clinical features of documented Giardia lamblia infection include diarrhea as the most common symptom with fatigue, nausea, anorexia, abdominal cramps, flatulence and less commonly vomiting and fever. The illness may be protracted and last up to 10 weeks in certain individuals. Recurrence of diarrhea with periods of normalcy in between occur in one-quarter of the cases. Steatorrhea has been documented in individuals with Giardia infection.(16) A number of patients with immunoglobulin deficiency and Sprue have been reported with Giardia lamblia in the stools.(74) Invasion of the intestinal mucosa has been demonstrated in patients with diarrhea and trophozoites.(17)

3. Other protozoan

Two other protozoan which have been associated with intestinal disease are Dientamoeba fragilis and Balantidium coli. Recurring episodes of lower abdominal discomfort and flatulence associated with frequent loose stools have been described in individuals harboring D. fragilis.(75) It has not been demonstrated to invade tissues. The mode of spread has not been established. Infection with Balantidium coli may follow a history of contact with pigs. Man is only an occasional host. The organism can penetrate the mucosa producing necrosis and ulceration, similar to amebic dysentery.(76)

B. Nematodes

1. Ascaris lumbricoides

Infection with Ascaris lumbricoides develops following ingestion of eggs present in dirt, on contaminated vegetables or from soiled hands.(23) The eggs hatch in the stomach or small intestine, the larvae penetrate the intestinal wall, and eventually migrate to the lungs. After this migration, the larvae are swallowed and mature into adults in the small intestine. The adult lies free in the small intestine. The female deposits up to 240,000 eggs a day which require development for 2 weeks in the soil to become infective again. They do resist freezing and drying and may remain viable for years. A survey in Kentucky

revealed infestation rates twice as high in individuals who used spring or creek water for drinking water than the rates in those using city water, and rates three times as high in those who did not have indoor toilets.[2] In South Carolina the heaviest rates were in the coastal counties where the mild temperature and moist soil provided a favorable environment for survival and proliferation of nematodes in the soil.[3] A recent report indicates Ascaris infection is a "rancorous" complication of eating organically grown food.[77]

TABLE 8

CHARACTERISTICS OF INTESTINAL PARASITES

Parasite	Route of Entry	Vehicle	Site of Adult	Tissue Reaction	Eosinophilia (lung migration)	Other Sites
Protozoan						
Entamoeba histolytica	Oral	food, water	large intestine	ulceration	No	liver, brain pleura
Giardia lamblia	Oral	food, water	small intestine	mucosal changes malabsorption	No	Not described
Nematodes						
Ascaris lumbricoides	Oral	food drink	small intestine	granulomatous with migration	Yes	lung, bile duct, peritoneum
Necator americanus	Skin	soil	small intestine	mucosal changes	Yes	"ground itch", "fox hole cough"
Strongyloides stercoralis	Skin	soil	small intestine	mucosal changes malabsorption	Yes	pruritis
Trichuris trichuria	Oral	hands	large intestine	None	No	None
Enterobius vermicularis	Oral	fingers food	small, large intestine	pruritis ani	No	none
Trichinella spiralis	Oral	uncooked meat	muscle	inflammation necrosis	Yes	Heart CNS
Visceral larva migrans	Oral	fingers	liver	granulomatous	Yes	lung, eye CNS

Symptoms in man can result from: 1) manifestation of the allergic reaction to the migrating larvae or adult, 2) infection within the gastrointestinal tract, and 3) complications secondary to the migration of adults from gastrointestinal tract.[23] The predominant features of illness associated with migration of the larvae through the lung include an irritating, non-productive cough, malaise, chest pain, and hemoptosis.[78, 79] Approximately 15% of the patients have a pruritic eruption within 5 days of the onset of pulmonary symptoms. Physical findings are minimal, and chest x-ray reveals pulmonary infiltrates. Eosinophilia is present (30-70%) and reaches a peak when symptoms are subsiding.

The features of infection within the gastrointestinal tract include vague symptoms such as anorexia, irritability, mild abdominal distress and evidence of malnutrition. These symptoms are more frequently present in areas of the world where malnutrition is a problem. Minimal symptoms are present with even heavy infection where dietary deficiencies are not present. Intraluminal Ascaris may lead to mechanical obstruction within the small bowel if a small bolus of worms develops.[80] Hence, Ascaris infection must be considered in the differential diagnosis of intestinal obstruction in children over two years of age. The most common serious complication of Ascaris infection is the migration of adult worms in the biliary ducts.[81] Biliary obstruction ensues and suppurative cholangitis and liver abscesses may develop. Such migration has been noted to occur when the infected individual has other febrile illness, undergoes anesthesia, or receives treatment for a combined hookworm infection.

CASE REPORT # 2

A 20 year old returnee from [redacted] presented to the [redacted] with a history of having passed a worm one hour prior to admission. The worm was identified as Ascaris lumbricoides. He had no previous history of passage of worms and was completely asymptomatic. Physical examination was in normal limits. The patient had a normal hematocrit and all laboratory studies were normal. Four consecutive stools for ova and parasites were negative, an upper GI study was within normal limits. The patient was treated with piperazine, 3.5 grams per day for 2 days and discharged.

Diagnosis of Ascaris infection of the intestine is made by the direct examination of a fecal smear for eggs. The most reliable diagnostic criterion for Ascaris pneumonia is to find the typical third stage larvae in the sputum or gastric aspirate.[78] Diagnosis can also be made in some individuals following expulsion of the worm from the stomach or in the stool. In patients with acute intestinal obstruction, the diagnosis can be made radiographically.[80] The adult worm may appear as linear tissue densities contrasted with intestinal gas content. In barium studies, the parasite can be visualized by the barium coating its walls. Correct identification of larvae in histological sections can be made from a key prepared by Nichols.[82]

2. Hookworm (Necator americanus)

Hookworm infection follows the penetration of skin by larvae which are present in the soil. A local reaction to this penetration "ground itch" is noted in retrospect by some patients.(39) The larvae progress to the lung, eventually rupture through the aveolar capillaries and are swallowed. The adult is present in the small intestine and attaches to the small bowel mucosa by the cutting plates or teeth.

Hookworm infection is asymptomatic in many patients unless it leads to the iron deficiency anemia or is associated with malnutrition. Hookworm infection can produce an acute syndrome consisting of abdominal pain, anorexia, nausea, diarrhea, and weight loss of 10-40 pounds.(39, 83) This was particularly noted in American soldiers in the South Pacific and southeast Asia in World War II.(39, 83) One quarter of these gave a history of the "ground itch" and three-quarters gave a history of a respiratory symptom: this primarily consisted of a deep chest cold with cough without coryza, which came to be termed "fox hole cough", well remembered because at night it gave away the soldiers' position to the enemy. The abdominal complaints were primarily an intermittent cramp-like pain in the epigastric region usually occurring after eating, more intense at night but not relieved by food or alkalies. Bowel movements alternated from soft, mushy movements to constipation. The onset of symptoms averaged 143 days after exposure. A large proportion of patients in both studies were admitted with a diagnosis of psychoneurosis. Most of the patients had a eosinophil count which ranged from 9 to 70%.

CASE REPORT # 3

This 23 year old [redacted] male developed "foot itch" within one month of entering [redacted]. He was hospitalized and given treatment for hookworm infections on two occasions. He has presented on numerous occasions to the [redacted] with periumbilical cramping pain, loose bowel movements, nausea, and vomiting. On each occasion that he has been examined, he has had hookworm eggs. Most recently stools have demonstrated many eggs. The white blood cell count was 9,700 with 11% eosinophils and an hematocrit of 48. Treatment with tetrachlorethylene produced little relief in symptoms and no change in number of eggs in stools. Recent treatment with thiabendazole has produced a clinical remission. The last stool examination revealed very few hookworm eggs present. Upper GI series is normal.

The diagnosis is made by finding the characteristic ova in stools. Diagnosis in one group of soldiers require repeated examinations and the use of concentration methods increased the reliability from 21 to 86%.(39) Hookworm infection should be considered in individuals in endemic areas who present with eosinophilia or with iron deficiency anemia.(24)

3. Strongyloides stercoralis

Strongyloides stercoralis enters the body by the skin and passes through the lung in a similar fashion to hookworm. Infrequently, symptoms may be a skin eruption with pruiritis or a cough and hemoptysis due to lung migration. Patients with infection in the intestinal tract which is primarily in the duodenum may be asymptomatic or have vague abdominal complaints. Abdominal pain when present may be cramp-like, present at any time of the day and is frequently associated with weakness, irritability and nervousness.(83) Symptomatic patients generally present with diarrhea (which may be episodic) and steatorrhea may develop.(84, 85) Small bowel obstruction and intestinal ileus may develop in rare instances.(84) Recently cases have been reported in which abdominal symptoms with distention and diarrhea, hypoproteinemia, and hypokalemia develop shortly after individuals are given steroids.(18, 86) Auto infection does occur in which larvae may invade multiple organs of the body including the appendix, lungs, liver and brain.(85) Eosinophilia is generally present.

Diagnosis is made by examination of direct smear or concentrated material for larvae. A number of studies indicate that infection is present without larvae being demonstrated in stool. Consequently, duodenal aspiration, for examination of the larvae is frequently necessary to prove the infection.(83) As with other parasites, a purged stool may yield better results.

4. Trichuris trichuria (whipworm)

Whipworm infection is acquired following ingestion of contaminated dirt or food. Its life cycle is similar to Ascaris and involves a considerable time in the egg outside the host.(4) The worm resides in the superficial mucosa of the cecum feeding on intestinal juices and rarely producing any mucosal damage.(86a) It is not associated with tissue invasion and consequently eosinophilia is not a feature of infection. Most infections are asymptomatic but infection producing ulceration of the mucosa, dysentery, and anemia have been reported. In heavy infections, prolapse of the rectum may occur. Diagnosis depends upon the recovery from the stool of eggs.

5. Enterobius vermicularis (pinworm)

Pinworm infection due to Enterobius vermicularis is ubiquitous and knows no socio-economic boundaries.(4) The worms live unattached in the lumen of the lower small intestine and the large intestine. The gravid adult female migrates to the perianal area at night and releases eggs. The primary symptom of infection is perianal pruiritis, probably as a result of sensitization to the worm products.(87) Re-infection of small children commonly occurs from contamination following scratching or from the persistence of eggs on clothing and sheets. Generally, the entire family with preschool children or early school age children will be infected. Diagnosis may be made in two ways: 1) by utilizing

the scotch tape swab technique in the perianal region and examining for eggs or 2) by visualization of the adult worms at night after the child has fallen asleep.

6. Trichinella spiralis

Trichinosis develops as a result of the ingestion of the larvae of T. spiralis, generally in uncooked food products. In the last five years, 95% of the trichinosis cases reported have resulted from the ingestion of commercially prepared pork products.(88) The most common product is uncooked sausage.(89) Post mortem examinations have revealed that the prevalence of trichinae in muscle has dropped from 16% to 4% in years 1966-1970.(88) Trichinosis following ingestion of bear meat has been reported recently.(90, 91) The organisms have been found in muscles of approximately 60 different species of mammals distributed throughout the world.(92) Following ingestion, the cysts which contain larvae open in the intestinal tract. Within five to seven days the females are fertilized and invade the intestinal mucosa and produce larvae which circulate in the blood stream. These finally reach skeletal muscles, particularly those low in glycogen, generally within 8-9 days following the infecting meal.

The clinical manifestations include a flu-like illness which persists for two to six weeks with fever, malaise, fatigue, periorbital edema, myalgia, conjunctivitis, and occasionally myocardial involvement.(91, 92) Gastrointestinal symptoms include abdominal cramps and diarrhea and occur early, but are generally only present in about one third of the patients.(91) The periorbital edema generally begins the stage of muscular invasion. Other symptoms include disagreeable taste, profuse sweating and a sensation of ants crawling beneath the skin.(92) Most fatal infections are the result of myocarditis. Other complications include central nervous system manifestations, and include hemiplegia, polyneuritis, psychosis, and cerebellar syndromes.(93)

The clinical diagnosis is based upon clinical symptoms in an individual with eosinophilia. Diagnosis is based upon the demonstration of larvae obtained from muscle at biopsy. The preferred muscles for biopsy are the deltoid biceps gastrocnemius or intercostal muscle near the diaphragmatic insertion. Demonstration of larvae in biopsy material is performed by compressing freshly excised muscle between glass slides. Serological tests are a value in confirming the diagnosis.(60, 94) The bentonite flocculation and the complement fixation test are positive in only 20-30% of patients after one week of illness but reach a peak of 80-90% of the patients by the fourth to fifth week. Skin tests have not been as reliable, especially when the commercially available antigen has been used. In individual patients skin tests, as with other disorders, skin test is not as reliable as serological tests.

7. Visceral larvae migrans

Visceral larvae migrans is a syndrome generally in young children which develop following infection with Toxocara canis and T. cati, nematodes common to dogs and cats.(95, 96) The infective eggs hatch in the upper intestinal

tract and the larvae enter the portal system and reach the liver. Some migrate to the lung and may be disseminated throughout the systemic circulation. Four common ways in which eggs may be ingested by children include: 1) direct contamination of the hands, 2) handling puppies that are between the age of three weeks and six months, 3) indirect contact with objects contaminated with eggs, and 4) ingestion of soil containing infective eggs. A recent contribution to the significance of Toxocara cati in cats is that cats infested with T. cati can transmit toxoplasma gondii.[97]

Visceral larvae migrans is a disease of world wide distribution but is principally recognized in children one to four years of age.[95, 96] The syndrome is characterized by fever, cough, irritability, and loss of weight. Most of the patients present with hepatomegaly. Laboratory abnormalities include eosinophilia, mild liver function abnormalities, and hypergammaglobinemia. Rare complications include myocarditis, cerebral involvement with an encephalitis picture and ocular involvement which is in the posterior segment and resembles a retinoblastoma. Diagnosis is based upon recovery of toxocara larvae from sections of liver biopsy. Skin tests and antibody tests are available, but these are primarily useful in surveys. Cross reactivity with other Ascaris organisms is common with the serological tests.

D. Cestodes

1. Diphyllobothrium latum

Infection in humans follows the ingestion of larvae from poorly cooked fish, imperfectly pickled fish, or a sampling of "gefullte" fish during preparation. The infection is world wide, wherever fresh water fish are eaten.[30] Infection is asymptomatic in most individuals, and when present are due to B_{12} deficiency. Diagnosis is based upon direct fecal examination for the ovum.

2. Taenia saginata (beef tapeworm)

Human become infected by eating raw or poorly cooked beef which contain infective larvae or cysticerci imbedded muscles. The infection is generally an asymptomatic one, although non-specific abdominal symptoms may be present. Diagnosis depends upon the detection of eggs in stool or in perianal area with scotch tape test and by finding typical proglottids in stool.

3. Taenia solium (pork tapeworm)

Tapeworm infection develops in humans following the ingestion of raw or poorly cooked pork that contains the larva or cysticerci. Infections are generally asymptomatic. If infection occurs following the ingestion of tapeworm

eggs present in food or water, cysticercosis or infection with the larval stage develops. Manifestations depend upon the site of the larvae which may lodge in muscles, subcutaneous tissue, brain or eye. Diagnosis as with that of T. saginata is made by direct examination of stool for ova or proglottids.

4. Hymenolepis nana (dwarf tapeworm)

Infection with H. nana follows the ingestion of food or water containing eggs. H. nana is the only human tapeworm which can be spread by person to person contact.[99] The crysticercoid attaches to the mucosa of the small intestine but tissue invasion does not occur. Rarely, individuals develop abdominal pain and diarrhea. Diagnosis depends upon identification of ova in direct fecal smears.

IV. THERAPY

A. Specific Treatment

Effective therapy is presently available for the majority of these intestinal parasites. Certain recent additions to anti-parasitic chemotherapy have significantly improved cure rates and have less toxicity than previously available drugs. The following table is an adaptation from Table 8 of The Guide to Antimicrobial Therapy, 1971 prepared by the Infectious Disease Service.

The biochemical mechanisms of antihelminthics have been discussed in a recent review article.[118]

TABLE 9

CURRENTLY USED ANTI-PARASITIC DRUGS

Protozoa	Drug of Choice	Usual Dosage	Route	Cure Rates	Ref.
Entamoeba histolytica					
intestinal, non-dysenteric	Diiodohydroxyquin (Diodoquin)	650 mg tid 21d	po	80-90%	100
	or				
	Bismuth glycolyarsanilate (Milibis)	500 mg tid 7 d	po	80-90%	
intestinal, dysenteric	Emetine HCl	1 mg/kg/day 5-10 d	IM	>95%	101
	and				
	Tetracycline	500 mg qid, 10 d	po		
	or				
	Metronidazole (Flagyl)	800 mg tid 10 d	po	85%	102
extraintestinal	Metronidazole	800 mg tid 10 d	po	>95%	102, 103
Giardia lamblia	Quinacrine hydrochloride (Atabrine)	100 mg tid 5 d	po (after meals)	75%	16
	or				
	Metronidazole	250 mg tid 5-10 d		>80%	104
Dientamoeba fragilis	Diiodohydroxyquin	650 mg tid 10 d	po	>80%	18
Balantidium coli	Tetracycline	500 mg tid 7 d	po	>80%	105
Nematodes					
Ascaris lumbricoides	Piperazine citrate (Antepar)	75 mg/kg qid for two days (maximum 3.5 g)	po	80%	106

Hookworms (Necator americanus)	Tetrachlorethylene or	0.12 ml/kg	po	80%	107
	Thiabendazole (Mintezol)	25 mg/kg for 3 d	po	70%	108
Strongyloides stercoralis	Thiabendazole	25 mg/kg bid for 2 d	po	90%	109
Enterobius vermicularis	Pyrivinium pamoate (Povan) or	5 mg/kg x 1	po	95%	110
	Pyrantel pamoate (Antiminth)	10 mg/kg x 1	po	95%	111
Trichuris trichuria	Thiabendazole Hexaresorcinol enema	25 mg/kg bid 2 d	po	30-70%	112
Trichinella spiralis	Thiabendazole	25 mg/kg bid 5-7 d	po	50%	112, 113
Visceral larva migrans	Thiabendazole	25 mg/kg bid	po	?	114
Cestodes					
Diphyllobothrium latum	Quinacrine HCL (Atabrine) or	0.1 g every 10 min to total 0.8 g	po	80%	115
	Niclosamide (Yomesan)*	1.0 g, 1.0 g 1 hr later	po	85%	116
Taenia saginata	Same as D. latum			70%	117
Taenia solium	Same as D. latum			70%	117
Hymenolepis nana	Quinacrine HCl (Atabrine)	0.1 g every 10 min to total 0.5 g repeat x 1	po	70%	115

* Obtained from Parasitic Disease Drug Service, Epidemiology Program, Center for Disease Control, Atlanta, Georgia 30333. Tel. 404 633 3311

B. Prevention and Control

1. Protozoa
   a. Entamoeba histolytica
      1) careful plumbing inspection to eliminate back siphonage or cross connections
      2) water treatment requires slow filtration since chlorination does not kill cysts
      3) screen food handlers and prevent cyst carriers from handling food until free of cysts
      4) avoid raw vegetables which might have been fertilized with fecal excreta.

   b. Giardia lamblia (same as E. histolytica)

2. Nematodes
   a. Ascaris lumbricoides

      Prevent soil contamination by providing for adequate toilet facilities, educational programs to encourage their use. In some cases, mass treatment of infected school children necessary.

   b. Hookworm

      Provide adequate toilet facilities, treatment of soil to reduce contamination, encourage wearing of shoes.

   c. Strongyloides stercoralis: (same as hookworm)

   d. Trichuris (same as Ascaris)

   e. Enterobius

      Treat infected family members, clean personal hygiene

   f. Trichinella spiralis
      1) public education to emphasize thorough cooking of pork products (internal temperature of 137°F)
      2) storage of raw pork in freezer(5°F) for 20 days if less than 6 inches thick, and for 30 days if more than 6 inches
      3) forbid use of raw garbage
      4) require routine post-slaughter inspection of carcasses

   g. Visceral larva migrans
      1) regular deworming of dogs and cats
      2) discourage playing with puppies
      3) clean yard of excreta until animal is worm-free
      4) prevent pica

3. Cestodes

Do not eat raw meats, no matter how tempting.

4. General

Careful screening of patients and personnel in institutions with pre-admission stool examination for all mental hospitals. Screen food handlers.

I wish to thank Ms Barbara Gaylor for her diligence and patience in preparing this protocol.

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