



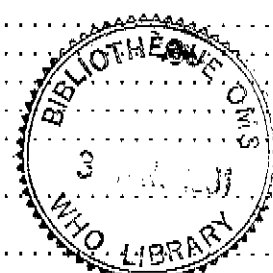
DIAGNOSIS AND MANAGEMENT OF PARASITIC DISEASES IN AIDS^a

by

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1. INTRODUCTION

The diagnosis and treatment of infections due to Entamoeba, Sporozoa (Toxoplasma, Isospora and Cryptosporidium), Microsporidia, and Strongyloides have been recognized by clinicians to be major challenges in managing patients with the acquired immunodeficiency syndrome (AIDS).^{1,2,3,4} Several similarities between these parasites influence the risk of both their development in persons infected with the human immunodeficiency virus (HIV) and of their causing complications in such persons:

- (a) all these parasites have a tissue "invasive" phase and/or an intracellular phase in man;
- (b) all have one or more internal reinfection cycles in the host;
- (c) taxonomically there continues to be controversy about the species of parasite affecting man.

Medical understanding of parasites of the phyla Sporozoa and Microsporidia is finite compared to the vast body of literature on their veterinary aspects.^{5,6} The clinicians and laboratory staff involved in the care of AIDS patients would be well advised to consult with veterinary and medical parasitologists on establishing reliable diagnostic procedures.

Pneumocystis carinii is one of the most important opportunistic infections in AIDS. Recently its classification as a parasite has been questioned due to the homology of its ribosomal RNA sequences with those of fungi. The extensive literature on its management may be consulted.³

In developing countries the parasitic infections of highest risk in AIDS patients are infrequently diagnosed in the general population and are not considered to be a public health priority. For example, cryptosporidiosis in Puerto Rico is infrequent in the general population and rare in association with HIV infection. Toxoplasmosis has been infrequently reported in AIDS patients in most sub-Saharan African countries and in some countries this association has not yet been observed.

Furthermore, the diagnostic techniques for parasitic diseases are being used by laboratory staff who are untrained and inexperienced in the diagnosis of protozoan infections of the gastrointestinal tract. Experts in this field are few and training courses and training facilities are lacking.

National quality control of parasitology laboratories plays an important role in maintaining high standards. In France, a national programme has been active since 1979 in which specimens are sent twice yearly to participating laboratories. In the most recent survey in which stool specimens and serum samples were sent to participating laboratories, 76% of 1144 sera responded correctly on Cryptosporidium and all of the specialized laboratories identified the Toxoplasma sera correctly, while out of some 1000 laboratories 67 had negative results on known positive sera.

Techniques such as those used in the above study require adequate supplies and equipment, including a light microscope. Even the simplest low-cost techniques must be properly managed so as to ensure proper updating and maintenance of the supplies. The concepts of supervision by trained staff and of quality control in specialized parasitology laboratories or general laboratories are recognized to be essential to achieving consistently reliable diagnoses.

^a For example the article by Hughes, W. T. Pneumocystis carinii pneumonitis. New England journal of medicine, 317: 1021-1023 (1987).

This document is intended for laboratory technicians and clinicians involved in diagnosis and management of opportunistic parasitic infections in AIDS. The present review of the diagnostic aspects focuses primarily on these infections in immunocompetent individuals. As clinical trials are completed and more experience on the management and treatment of these infections in AIDS is published, the information provided in this document will be modified.

2. DIAGNOSIS

The diagnosis of parasitic diseases requires repeated examination of blood, of lymphatic or cerebrospinal fluid (trypanosomiasis), and of excreta (intestinal parasites). Proper handling and disposal of specimens is an integral part of adequate laboratory procedures. Skin snips for diagnosis of onchocerciasis present a unique operational problem to avoid possible HIV transmission.

3. MANAGEMENT AND TREATMENT

The management and treatment of parasitic diseases in AIDS requires a thorough understanding of the "standard" drug dosage schedules and a recognition that these have been developed on the basis of clinical experience with:

- immunocompetent individuals;
- acute infections or infections of short duration;
- large-scale public health programmes rather than individuals;
- single infections, in the absence of concomitant HIV or other viral, mycotic or parasitic infections.

Although there are clinical trials currently under way, there are no established protocols for primary or secondary prophylactic chemotherapy of parasitic infections. Management of chronic recurrent diarrhoea in adults has not been a priority in the WHO Programme on Diarrhoeal Diseases Control and is not viewed as a general public health problem. In the WHO Model Prescribing Information series of publications, an issue on "Drugs used in parasitic diseases" will soon be published and, where relevant, all the citations in this document regarding dosages conform to those given in that issue.

The order in which infections are dealt with in this review is derived from the current assessment of their relative global frequency and clinical importance in AIDS as identified in the course of the Consultation on Opportunistic Infections in Developing Countries organized by the Biomedical Research unit of the WHO Global Programme on AIDS in Geneva in 1989.

4. MAJOR PARASITES

4.1 Toxoplasma

4.1.1 Diagnosis

The domestic cat is the definitive host and harbours the sexual stage which produces the oocysts. Infection occurs by the accidental ingestion of oocysts from cat faeces or by the ingestion of raw meat (usually lamb or pork) with tissue cysts containing bradyzoites. Congenital infections occur through the placenta during primary maternal infection. In man the proliferating tachyzoite and the dormant tissue cyst are the two forms of the parasite observed intracellularly. It has been suggested⁸ that differences in virulence and risk of development of encephalitis may vary according to the strain of Toxoplasma gondii.

The interpretation of serological results has been difficult in AIDS patients, since the infection is a reactivation rather than an acute infection. The loss of cell-mediated immunity results in a persistent acute infection or reactivation of latent foci. Thus active toxoplasmosis in AIDS is frequently observed in patients with low or negative serological titres. Interpretation of a positive titre may be further confounded by the background prevalence of positive serology in the general population ranging from 20-70% and usually increasing with age. Serological tests, at best, are limited to diagnosis of infection and not disease.

The Sabin-Feldman dye test is still the standard against which all other serological tests are evaluated. Rigorous evaluation and quality control in every laboratory which tests for Toxoplasma infection is a prerequisite rather than an option, since a wide range of tests and antigens are available. Several tests are usually performed rather than a single test. The combined results are then interpreted; i.e., high Sabin-Feldman or indirect fluorescent antibody test (IFAT) titres and positive complement fixation test (CFT) results are associated with acute infection. IgM IFAT and IgM enzyme-linked immunosorbent assay (ELISA) are useful in acute infections.⁹ Although monoclonal antibodies and DNA probes are available, they have not been evaluated in the diagnosis of toxoplasmosis associated with AIDS. Experimentally, Toxoplasma antigen can be detected in the urine by ELISA and Western immunoblots.¹⁰ Diagnostic techniques based on isolation of the organism by in vitro culture or direct specific staining are the most appropriate. Newer techniques such as detection of antigenaemia by immunological methods or polymerase chain reaction (PCR)¹¹ are not yet available for routine use. Direct staining with haematoxylin and eosin or Giemsa is appropriate for biopsy materials.

There is a spectrum of differential diagnosis in intracerebral abscesses as seen with Toxoplasma infection. Radiographic diagnosis (e.g. CAT scanning, NMR isotope imaging) and response to treatment are becoming established as the diagnostic procedure of choice.

Toxoplasmosis is the most common cause of focal intracerebral lesions in patients with AIDS. Despite its frequency and clinical importance, the cumulative experience of management and treatment of toxoplasmosis in AIDS has not achieved a general consensus. The initial manifestations of toxoplasmosis in AIDS patients are related to involvement of the central nervous system (CNS) but clinical signs referable to other organs such as the heart and lungs also occur. In contrast, there is a more frequent presentation of acute fever associated with lymphadenopathy (cervical, in particular) in immunocompetent individuals. Recent experimental evidence confirms the clinical observations which indicated that toxoplasmosis in AIDS is a reactivation rather than a new infection. Reactivation of toxoplasmosis has occurred experimentally after cytomegalovirus infection in mice.¹² Thus in patients with AIDS the diagnosis of toxoplasmosis should not terminate the diagnostic work-up.

4.1.2 Management and treatment

Inhibitors of dihydrofolate reductase such as trimethoprim and trimetrexate are efficient inhibitors of Toxoplasma.¹³ This organism has the necessary enzymes for de novo folate synthesis. Pyrimethamine is an inhibitor of folic acid synthesis that acts synergistically with sulfonamides, usually sulfadiazine. In AIDS patients a loading oral dose of pyrimethamine of 100-200 mg is given daily for 2-3 days. No consensus has been reached on the subsequent dosage schedules. The dose of pyrimethamine used by various investigators ranges from 25-100 mg daily in a single dose for 3-6 weeks. At the same time sulfadiazine or a trisulfapyrimidine preparation is given at 4-6 g daily in 3 or 4 divided doses. Thereafter, the patient must receive maintenance therapy for the remainder of his/her life. Though recommendations vary, the maximum maintenance dosage suggested is a 25-50 single daily dose of pyrimethamine and a daily dose of 2-4 g sulfadiazine.

Though the clinical implications are not yet clear, zidovudine (azidothymidine, AZT) used in the treatment of AIDS, antagonizes the toxoplasmodicidal activity of pyrimethamine

in vitro. In vivo, synergism of this drug and sulfadiazine against T. gondii was reversed and the therapeutic effect of pyrimethamine was antagonized by zidovudine.¹⁴

Clindamycin in combination with pyrimethamine may be used in patients with intolerance to sulfonamides and without sensitivity to macrolide antibiotics. The usual oral dosage schedule is 6 g daily in 3 divided doses for 3-6 weeks. Clindamycin has also been used alone as well as spiramycin in combination with pyrimethamine; however, the effectiveness of these regimens has not been confirmed in limited trials.

Other investigational drugs include: aprinocid (a purine analogue); piritrexim isethionate and trimetrexate (dihydrofolate reductase inhibitors); roxithromycin (macrolide antibiotic); and azithromycin.

Another potential therapeutic agent, gamma interferon, is a major moderator of resistance against Toxoplasma.¹⁵ In vitro, interferon-activated macrophages gain the capacity to kill or inhibit the replication of a diverse group of intracellular organisms including Toxoplasma.

4.2 Isospora and Cryptosporidium

4.2.1 Diagnosis

Like Toxoplasma, these organisms are classified as Sporozoa. All organisms in this phylum have an oocyst phase which is more resistant than in any other known protozoa. These parasites are frequent and widespread among different mammals, reptiles and amphibians. Medical diagnosis is based on the demonstration and identification of oocysts in human faeces.^{16,17,18,19} The difficulty of a correct diagnosis should not be underestimated and expert advice should be sought since there is little concordance between terminology used in standard modern textbooks on parasitology (as in Table 1) and descriptions in the literature. While the oocysts can be observed on a direct saline wet mount, flotation techniques, such as Sheather's sucrose¹⁹ or the zinc sulfate flotation techniques are the most sensitive. The modified Ritchie formol-ether concentration or other concentration techniques are less sensitive.

A wide range of staining techniques is used and each proponent claims superiority over the other.^{20,21} Currently the order of sensitivity and specificity can be ranked as: (1) monoclonal antibody, (2) auramine stain, (3) Garcia stain, (4) Heine, (5) Ziehl-Neelsen/Kinyoun. The Giemsa stain is not appropriate and so distorts the organism as to render it unrecognizable. The differential diagnosis of a faecal oocyst includes: Isospora, Cryptosporidium, Eimeria, Sarcocystis and Toxoplasma (Table 1). The differential diagnosis is best confirmed by phase contrast microscopy.

No standard serological tests are available for Cryptosporidium or Isospora infections. Specific IgA and IgM antibodies may be detected in the serum and breast milk of infected mothers.

4.2.2 Management and treatment

Although in immunocompetent persons these infections may be either asymptomatic or self-limited, in persons with HIV infection, diarrhoea associated with Cryptosporidium infection is clinically similar to the severe, protracted and debilitating diarrhoea due to Isospora infection. Treatment of coccidian infections of the gastrointestinal tract due to Isospora belli and Cryptosporidium is generally unsatisfactory. At least 20 different agents, alone or in combination, have been used. The management of the diarrhoea with extensive fluid loss, malabsorption, and weight loss is a challenge not unlike that of cholera. In some hospitals, the "cholera bed" has been reallocated to these patients whose gastrointestinal evacuations may reach 20-30 litres per day.

A commonly used regimen for treatment of Isospora infection is sulfamethoxazole, 800 mg, and trimethoprim, 160 mg, 4 times a day for 10 days followed by 2 times a day for

3 weeks.^{17,18} In spite of a dramatic initial clinical response associated with absence of the parasite at follow-up examination, recurrence was observed in about half of the patients between 2-20 weeks after completion of treatment. The recurrent episodes were clinically similar to the initial infection. Prophylaxis of recurrent disease is effective with either single doses of trimethoprim (160 mg)/sulfamethoxazole (800 mg) 3 times a week or weekly doses of pyrimethamine (25 mg)/sulfadoxine (500 mg).¹⁸

Treatment of cryptosporidiosis is unsatisfactory.¹⁹ In the immunocompetent individual, the infection, if not self-limited, requires only supportive management. Evaluations are currently being made of the efficacy of spiramycin (in a multicentre trial), alfadifluoromethylornithine (DFMO), oral bovine transfer factor, somatostatin, trimetrexate and recombinant interleukin-2.

4.3 Blastocystis hominis

4.3.1 Diagnosis

For decades this parasite has been considered to be a yeast commensal of the gastrointestinal tract. Although still shrouded in controversy,²² it is considered that, on the basis of symptoms and response to treatment in some immunocompromised patients, this parasite is the cause of chronic diarrhoea.^{23,24} On the biological side, it is now proposed that it be classified as a pathogenic sporozoa or Sarcodina,²⁵ but the issue has not yet been resolved.²⁶

The route of transmission is probably faecal-oral; however, aside from observations of familial outbreaks, this has not been confirmed.²⁷ Blastocystis hominis has been most frequently detected in liquid or watery stools. It appears that the organism is susceptible to osmotic or mechanical pressures which bias these findings. Stool concentration techniques may disrupt these organisms. Therefore, it is best observed directly without staining or with Gram's stain or a trichrome stain.

There is no consensus on the quantitative correlation between the intensity of Blastocystis infection and clinical disease. It is generally accepted that low density infections are not associated with diarrhoeal syndromes. Some reports indicate that five or more organisms per field with a 40X objective and 10X oculars (400X field) are associated with clinical disease in immunocompetent individuals.²² At least one report²² states that no serological antibody response is detectable by immunoblot against antigens isolated from the parasite infecting the patient.

4.3.2 Management and treatment

When Blastocystis hominis is the only parasite detected on the first stool examination, even if present in large numbers (>5/400X field), the examination should be repeated to rule out other etiological agents. The low pathogenicity and lack of effective treatment warrant such a conservative approach so as to avoid, as far as possible, a missed diagnosis of a treatable infection due to other causes. After the decision that treatment is necessary, metronidazole has been used at 2 g daily for 5 days. Diloxanide furoate and paromomycin are inactive against Blastocystis.

4.4 Microsporidia

4.4.1 Diagnosis

The 700 species of Microsporidia are obligate intracellular protozoa of hosts ranging from unicellular organisms to mammals.⁵ These parasites are uniquely characterized by their ability to infect cells by a polar tubule which "injects" nucleus and sporoplasm into the cytoplasm of the neighbouring cell. Mammals are possibly infected by the faecal/urine - oral route. The life cycle in man is unknown, but it may begin in the gastrointestinal tract.

Antemortem diagnosis of microsporidial infection is rare. There are no established techniques for detection or isolation of the organism in body fluids.²⁸ In routine autopsy examinations, these organisms may be overlooked because of their small size (1.5-2.5 microns by 2.5-4 microns), their inconsistent staining characteristics, and the lack of surrounding inflammatory response.^{29,30}

The immune response in the immunocompromised host may be absent.

Interpretation of serological results is further complicated by cross reactions with some insect microsporidia, by a lack of antigens derived from human isolates of Encephalitozoon species, by the generally low titres of specific antibody and by cross-reacting antibodies in patients with other parasitic infections. The first human infection of Encephalitozoon diagnosed antemortem was confirmed by a novel carbon particle immunoassay.³¹

4.4.2 Management and treatment

Treatment is unsatisfactory, or rather unknown. Sulfisoxazole alone or trimethoprim-sulfamethoxazole followed by sulfadiazine have apparently been used successfully. Fumagillin, an antibiotic, is effective in vitro but its toxicity in mammals precludes clinical trials.²⁸

4.5 Entamoeba

4.5.1 Diagnosis

There are few clinical reports on Entamoeba histolytica infection in AIDS even though the increased frequency of amoebiasis among homosexuals was recognized before the onset of the AIDS epidemic.³² Some investigators consider it to be of low pathogenicity in this high risk population.³³ Although Entamoeba histolytica is the most pathogenic of the Entamoeba, others such as E. hartmanni, E. polecki, and gastrointestinal protozoa such as Dientamoeba fragilis, Endolimax nana, Giardia intestinalis, Iodamoeba bütschlii, and Trichomonas hominis should not be ignored as possible causes of clinical disease.³⁴

It has been said that the diagnosis of Entamoeba histolytica is as reliable as the distance of the microscopist from the rectum of the patient; i.e., immediate examination of the stool specimen is imperative. The trophozoites of Entamoeba histolytica are found in liquid faeces while cysts are found in formed faeces. The trophozoites measure 7-40 microns. Those observed directly from the liver and the intestine are on the larger end of the spectrum whereas those from non-dysenteric stools or cultures are smaller.

The standard diagnostic technique is an appropriately buffered warm saline preparation^{35,36,37} which is used by all experienced microscopists. The iodine stained preparation cited in all manuals of medical parasitology is probably the most misused of all parasitological techniques. This is compounded by the diversity of instructions in parasitology and laboratory manuals. Dilute iodine solutions are necessary to identify properly Entamoebae, yet this is often ignored. The preparation of reagents is not well standardized and routine renewal, especially in developing countries, is the exception rather than the rule.

Iron-haematoxylin stains are the least used since their handling requires superior technical ability, but they are probably the best. The fixation of the material to the slide is the key to successful staining. Trichrome stains are generally variations of Gomori's original procedure and are also excellent although subject to fading in storage. If properly performed, Wright's stain may be used.³⁸

Many different culture media have been developed since Boeck and Drbohlav used a diphasic media to isolate Entamoeba histolytica.³⁹ Most recently, the defined TYI-S-33 media for cultivation of Entamoeba permits isolation of the parasite for identification.

The remarkable antigenicity of this parasite is shown by its surface which cannot be depleted of antigenic sites by Concanavalin A or by antibody exposure.⁴⁰ This is due to the fact that Concanavalin A antigen complexes are exocytosed and both capping and shedding occur due to antibody exposure. Serious efforts to diagnose invasive amoebic disease by serological tests for circulating humoral antibodies have resulted in a wide range of reliable tests with predictable sensitivity and specificity.⁴¹ These tests for the detection of invasive amoebiasis have a sensitivity in the order of 95% and a specificity of nearly 100%. Since recurrence of liver abscess is rare in immunocompetent patients, its early diagnosis and treatment is beneficial. New tests are being developed; their range goes from those relying on antigen detection, as in the case of invasive amoebiasis, to those using monoclonal antibodies⁴² and DNA probes.⁴³

Management and treatment

Although there is some controversy surrounding the pathogenicity of Entamoeba histolytica in the presence of HIV infection, the clinical improvement of gastrointestinal symptoms after specific treatment is well documented. Whether this is due to the direct effect of the drug on the organism or to the broader antimicrobial effect of drugs such as metronidazole remains open to speculation. Thus far in most clinical series of HIV infected patients, the associated E. histolytica infection is accompanied by diarrhoea rather than dysentery as is usually seen in acute infection in immunocompetent individuals.

A wide spectrum of drugs is available for treatment of amoebiasis. Metronidazole 30 mg/kg/day in 3 divided oral doses for 8-10 days has frequently been used in the past. In debilitated patients or in those with hepatic liver abscess, 1.5 g daily is used in 3 divided intravenous injections until the patient is able to take the drug orally. For non-invasive amoebiasis, diloxanide at a dosage of 500 mg three times a day for 10 days is now used to eliminate cysts from the stool. In the presence of HIV infection, paromomycin has been shown to be highly effective in eliminating the parasite and the gastrointestinal symptoms present before treatment.

Dehydroemetine, 1 mg/kg daily to a maximum of 60 mg over 4-6 days, is highly effective against amoebic liver abscess, but management of its toxicity requires careful supervision and experience with its use in immunocompetent patients.

Clinicians in endemic areas occasionally give these above-mentioned drugs in combination or in sequence. No recommendations are available on prophylactic regimens.

4.6 Strongyloides

4.6.1 Diagnosis

The number of reports of Strongyloides infections in AIDS patients has been fewer than in immunocompromised patients due to other causes.⁴⁴ There are three chronological clinical stages of infection with Strongyloides stercoralis: (1) cutaneous, (2) pulmonary, and (3) intestinal. The parasite is not usually identified in the first two stages and the larvae are difficult to find in the stool during the intestinal stage. The duodenal string test or duodenal drainage may be necessary to confirm the diagnosis.⁴⁵ Infections of 20-30 years' duration due to the various routes of auto-infection are well documented.⁴⁶ Infection may occur as a result of (1) ingestion of infective larvae via faecal contamination, (2) perianal penetration of the infective larvae, (3) penetration of the intestinal mucosa by the infective larvae, or (4) free-living adults which produce infective larvae which, in turn, penetrate the skin. Geographical differences include a Strongyloides fülleborni-like parasite which causes severe disease in Papua New Guinea and Africa.

4.6.2 Management and treatment

If any Strongyloides larvae are seen in the stool, treatment is imperative. Strongyloidiasis is rarely asymptomatic, and management problems of the disease include

cutaneous manifestations, severe haemorrhagic enteritis, pneumonitis, diarrhoea, malabsorption, oedema, liver enlargement, and paralytic ileus. Severe Strongyloides infections are frequently associated with gram negative septicaemia as a terminal event probably due to the penetration of the infective larvae through the intestinal wall.

Treatment with tiabendazole given at 25 mg/kg in 3 divided doses daily for 3 days is a standard; however, there are wide geographical differences in recommendations on the duration of treatment. Albendazole given at 400 mg daily for 3 days has been used more recently. Ivermectin, although still in clinical trials, shows promise in low single or repeated doses.

5. OTHER PARASITES

5.1 Giardia and other intestinal protozoa

Giardia intestinalis has been inconsistently reported to have clinical sequelae in HIV infected persons although its higher frequency in homosexual males is undisputed. There is no consensus on the nomenclature of this parasite. In the US Giardia lamblia is preferred, in Europe Lamblia intestinalis is used and a WHO Scientific Group has recommended Giardia intestinalis.⁴⁷ This protozoan has important mammalian reservoirs and like Entamoeba and Cryptosporidium may be transmitted through the community water supply.⁴⁸

Axenic culture was achieved in 1970 and in vitro culture in 1976 although serum is still used in the medium. In the small intestine, the Giardia trophozoite tends to adhere to the mucosal cell surface; the physiological consequences of this physical relationship are not well known. The mechanism of the associated decrease in IgA noted in some patients with giardiasis is not understood. The diagnostic techniques are similar to those used for other intestinal protozoa with the exception that duodenal aspiration is indicated if stool examinations are negative.

Several 5-nitroimidazole derivatives are effective against Giardia. Metronidazole, given orally in the range of 2 grams daily for 3 days, is the standard treatment. Tinidazole is given at 2 grams in a single oral dose. The treatment schedules for ornidazole and secnidazole have not been established.

Other intestinal protozoa have been variously cited as causes of T-lymphocyte activation, immunosuppression, or malabsorption in HIV infections. Although the prevalence of Endolimax nana, Entamoeba hartmanni, Entamoeba coli, and Iodamoeba bütschlii in AIDS patients has been observed to be higher than in "controls", their pathogenicity in HIV infections remains open to investigation.

Free-living amoebae, such as Acanthamoeba or Naegleria species causing either meningoencephalitis or keratitis, have not yet been reported in AIDS patients.

5.2 Leishmania

Visceral leishmaniasis has been associated with HIV infection⁴⁹ particularly in Spain and southern France where the disease is endemic^{50,51} and has previously been reported in immunosuppressed patients during anticancer therapy. The clinical presentation is prolonged fever and generalized adenopathy with hepatosplenomegaly.⁵² Leishmaniasis can be included in the differential diagnosis based on a patient's stay in an endemic area. The diagnosis must be confirmed by demonstration of intracellular Leishmania on bone marrow smears or even in monocytes of peripheral blood smears or splenic aspirates with Wright's, Giemsa or modified Field's stains.⁵³ Serological tests are not reliable. Treatment with sodium antimony gluconate is indicated. However, antimonials fail to eliminate all the parasites, clinical response is poor, and progression of the disease is the rule.⁵⁰

5.3 Trypanosoma

Trypanosoma cruzi infection either as a dissemination of an existing infection or via blood transfusion has rarely been reported. Diagnosis may be made by serological tests, isolation of the parasite on culture media, or direct observation of the parasite in peripheral blood or cerebrospinal fluid. Clinical suspicion based on prior exposure in an endemic area (Argentina through southern United States), presence of electrocardiographic abnormalities, or possible CNS involvement will guide the physician on whether to pursue this diagnosis.

African sleeping sickness due to Trypanosoma gambiense in its latent clinical phase may be reactivated in HIV infection. There are no known data on its importance in the AIDS epidemic, but the possibility of this diagnosis should be considered in all T. gambiense endemic areas in Africa for HIV infected patients with CNS manifestations. Diagnosis is facilitated by isolation of the parasite from the blood by microhaematocrit centrifugation or anion exchange columns or from the cerebrospinal fluid by a sensitive double centrifugation technique. The sensitivity and specificity of the serological screening techniques used in public health programmes have not been evaluated in HIV infection.

5.4 Schistosoma

Schistosomiasis due to Schistosoma mansoni has been observed in at least eight HIV infected persons at autopsy.^{54,55} In Puerto Rico, the rate of schistosomiasis amongst AIDS patients is higher than the expected rate in the general population. No hypothesis for this observation has been forthcoming. Antemortem diagnosis by stool examination or biopsy did not prompt specific treatment or alter the clinical management. It is of interest that Salmonella have been shown to persist in the gut of the adult schistosome or on the surface for long periods in the face of antibiotic treatment. The untreated syndrome of prolonged typhoid fever is usually fatal. Hepatitis B virus has been demonstrated in the gut or on the surface of the adult parasite and persists in the Kupffer cells of patients with hepatosplenic schistosomiasis. No information on the persistence of the HIV viruses in the parasite has been reported; however, schistosome DNA has been shown to hybridize with retrovirus sequences.⁵⁶

Other opportunistic infections were intercurrent and the primary causes of death. It has been noted that the usual periovular granuloma associated with schistosome eggs is diminished or absent. Treatment in HIV infected persons is probably unnecessary since the parasite does not multiply in man unless gram negative septicaemia is present.

6. AREAS OF FURTHER EXPLORATION

This section is intended to give some ideas for investigation rather than to evaluate needs and assign priorities for future research which was the mandate of the Consultation on Opportunistic Infections in Developing Countries organized by the WHO Global Programme on AIDS in September 1989 in Geneva.

Only recently has the involvement of the gastrointestinal tract in HIV infection become a focus of investigation.⁵⁷ In the absence of opportunistic enteropathogens, there appears to be direct damage to the mucosa as well as degeneration of the autonomic nerve. It has been suggested that parasitic infections may be an important risk factor in progression to small bowel dysfunction in HIV infection.⁵⁸

Our understanding of human infections due to Sporozoa should not be overestimated. Dogmatism in this area may prevent exploration of valid areas of inquiry. It is generally accepted that Toxoplasma infection is limited to the gastrointestinal tract in the feline species and that oocysts are excreted in the faeces. This is usually explained by the observation that cats eat rodents with the tachyzoite phase of Toxoplasma in the tissues. On the other hand, it is assumed that human infection occurs by ingestion of faeces containing the oocyst and that the proliferation of the tachyzoite

in tissues other than in the intestinal mucosa is the major manifestation of disease. However, in some countries where toxoplasmosis is putatively acquired by ingestion of uncooked meat containing the tachyzoite, the involvement (or lack of involvement) of the gastrointestinal tract has never been questioned.

The resolution of this question through: (1) correct identification of the oocysts in human faeces (perhaps using DNA probes) and (2) careful autopsy examination of the gastrointestinal tract in HIV infection, will contribute to the better management of Toxoplasma infection as a recurrent disease in HIV infected patients. If a gastrointestinal phase of toxoplasmosis is not feline specific and also occurs in man, the presence of Toxoplasma oocysts in the faeces may be a risk factor for recurrence after treatment of CNS or invasive manifestations. The need for a better understanding of the life cycles of Sporozoa may be extended to Isospora belli. Infections with this organism are difficult to treat and recurrences are frequent. Yet, no extraintestinal phase has been described.

The mechanism of change from dormancy to invasion (i.e. Entamoeba cysts to trophozoites; Toxoplasma cysts to invasive tachyzoites) is not understood. Endo-auto infection is known to occur with Entamoeba, Toxoplasma, Cryptosporidium and Strongyloides; thus the distribution of stages of other parasites in man may be found to follow a similar pattern. Most opportunistic parasitic infections seem to be recurrences of a dormant infection. The change from inactivity to overt disease may or may not influence the clinical course of AIDS or vice versa. Prospective protocols would promote our understanding in this area and contribute to better patient management, especially the question of prophylactic treatment which is now empirical at best.

It is not by chance that "shotgun" therapy has become the rule rather than the exception in the management of opportunistic parasitic infections in AIDS. In addition to the gaps in our knowledge of the biology and pathogenesis of these parasites, the mechanisms of action and synergism of most current antiparasitic drugs are not understood. The lack of consensus on drug regimens for treatment of Toxoplasma, Cryptosporidium and Microsporidia infections warrants controlled comparative clinical trials. Some national research institutions have initiated such trials.

Diagnostic techniques for application in developing countries need to be developed. These should be simple and reproducible with limited supplies and equipment. Standardized staining techniques for Entamoeba and other intestinal protozoa will increase the reliability of diagnosis and allow a better assessment of the true pathogenicity of these parasites in AIDS. A range of operational guidelines as to the minimal techniques, supplies and equipment for diagnosis of opportunistic parasitic infections associated with AIDS should be developed for and evaluated by laboratories at the lowest peripheral level in developing countries (simplified) to the tertiary care facilities in developed countries (complex).

Problems raised by parasitic infections associated with HIV infection have opened new areas of research. The correct diagnosis and proper management of these infections will be ongoing challenges.

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ODE TO PARASITES IN AIDS

A parasite by definition
lives in balance
with its host
and avoids attrition.

When the host immune state is faint
or compromised,
the parasite
meets no barriers or restraint.

Our knowledge is very small
of single cells
within and worms
outside the human cell wall.

Rather than arguing about taxonomy
good diagnosis,
treatment, and management
will help our patients' agony.

So if we understand,
that we know very little,
with an open mind
we may solve a parasite riddle.

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TABLE 1. IDENTIFICATION OF OOCYSTS OF HUMAN SPOROZOA¹

Genus	Size (microns)	Shape	Oocysts contain:
<u>Cryptosporidium</u>	4-6 in diameter	Round	0 sporocysts 4 sporozoites
<u>Eimeria</u>	23 long x 19 wide	Oval	4 sporocysts 8 sporozoites
<u>Isospora</u>	20-30 long x 10-19 wide	Oval	2 sporocysts 8 sporozoites
<u>Sarcocystis</u>	13 long x 10 wide	Oval	2 sporocysts 8 sporozoites
<u>Toxoplasma</u>	11-14 long x 9-11 wide	Oval	2 sporocysts 8 sporozoites

¹ Derived from Melhorn, H., ed. Parasitology in focus, Heidelberg, Springer Verlag, 1988, and other standard textbooks.