Gut, 1973, **14**, 145-168

Progress report

Intestinal parasites

This review is a sequel to the previous reviews which have appeared in *Gastroenterology*[1,2]. It attempts to fulfil the same objectives, namely, to mention research advances likely to be of interest in the biomedical field, to provide material for a search of the literature and to offer some guide to current therapy. Because of the volume of papers published our approach is necessarily eclectic and we have selected contributions that seem important to us. Also two important books of general relevance to the subject should be mentioned. A valuable manual on the pathology of protozoal and helminthic diseases has appeared[3]. Maegraith and Gilles[4] have compiled a sound text book on the management of tropical diseases with a helpful section on drug pharmacology.

Biomedical Advances in the Protozoa

AMOEBIASIS

It is now recognized that besides true *Entamoeba histolytica* an the small non-pathogenic species *E. hartmanni* there is a third group of amoebae with quadrinucleate cysts that infect man[5]. These are not pathogenic and were originally detected by their ability to grow at room temperature; they are now referred to as *E. histolytica*-like amoebae; they differ from *E. histolytica* in many biological and biochemical characteristics[6]. Within the true *E. histolytica* group some rather minor strain differences have been found by immunoelectrophoresis[7], DNA base composition and genome size[8], and also by immunofluorescence after cross absorption with antisera between two strains[9]. For the first time genetic heterogeneity has been demonstrated, using trophozoite size as a genetic marker, within the population of long established strains[10]. If this is confirmed it will be necessary to use clone-derived strains for precise characterization. Transfer of genetic markers by 'mating' has been described[11] with the production of hybrids between classical and *E. histolytica*-like strains; these were unstable, however, and soon reverted back to one parental type. The virulence of a strain in weanling rats is now regarded as a somewhat unstable characteristic[12] and may even differ in repeated isolates from the same patient[13]; a close correlation with the clinical state of the patient is not always obtained[14]. In a stimulating review Biagi and Beltran[15] discuss their work showing that dietary cholesterol and the administration of testosterone, progesterone, and cortisone all enhance the virulence of amoebiasis in experimental animals. The literature on cholesterol and amoebiasis is quite extensive and often conflicting; there is another report[16] on enhancement *in vitro* of virulence with cholesterol.

Our knowledge of the role of bacteria in pathogenesis has been extended in a study[17] showing that axenic amoebae, unless recently axenized, do not produce liver abscess in hamsters. Reassociation with bacteria for 12 hours led to abscess formation but reassociation for one hour or bacteria alone did

not. Neither killed bacteria nor bacterial extracts restored virulence. It is suggested that living bacteria transfer an episomal virulence factor to the amoebae following ingestion. The finding that amoebae grown monoxenically with crithidia produce liver abscesses in hamsters[18] requires confirmation. Feeding cultures of *Bacillus subtilis* or *Clostridium perfringens* but not *Escherichia coli* to rats enhanced tissue invasion by intracaecally inoculated amoebae[19]. In culture a cell-free filtrate from a *Bacteroides* culture promoted amoebic growth more than did killed bacteria[20]; the same worker had previously shown that the relevant factor was non-dialysible and partly heat labile[21].

In Malaysia amoebic dysentery was found to be associated with infection with *Edwardsiella tarda*[22], a potentially pathogenic species of Enterobacteriaceae. Further study of interactions *in vivo* between bacterial and amoebic infections are indicated.

The ultrastructure of trophozoites grown axenically[23,24,25] monoxenically with a bacterial[24,25], or crithidial associate[25], polyxenically with a mixed bacterial flora [26,27,25], or obtained direct from patients with amoebic colitis[28] and hamsters with liver abscess[25,29] have been compared and found to be similar in most respects. Spherical intranuclear bodies that probably contain acid phosphatase have been interpreted as lysosomal structures or possibly virus particles. Cytoplasmic cylindrical structures, 120 mμ long and arranged in a rosette pattern to form a spherical complex measuring 1000 mμ in diameter, have been described; although they contain no acid phosphatase a digestive function has been suggested. Eaton's group[30], using amoebae added to tissue culture monolayers, have shown that direct cell-to-cell contact is necessary for amoebae to exert their cytopathic effect, so confirming the previous work using human leucocytes[31]. They have described and dramatically illustrated by scanning electron micrographs cup-like structures with a central vermiform trigger; these are interpreted as 'surface active lysosomes' capable of damaging other cells, possibly by membrane depolarization, on contact with the trigger. Similar structures have now been described in trophozoites from human colon[32].

The cytochemistry of axenic and monoxenic amoebae has been compared[33]. The separate pathways of aerobic and anaerobic fermentation of glucose have been studied in detail[34]; *E. histolytica* should be regarded as microaerophilic. Earlier work on amoebal enzymes has been reviewed[35]. So far such studies have not explained differences in virulence between strains

Immunology in relation to amoebiasis has been fully reviewed[36]. For diagnostic purposes an indirect fluorescent antibody test has been found useful[37]. In one study a complement-fixation test (CFT) using a relatively crude antigen from a polyxenic bacterial culture has compared favourably with more sophisticated techniques[38]. A simple latex agglutination test[39] taking only minutes to perform is promising, and a commercial kit is available. The immobilization test is relatively insensitive for diagnostic purposes but by tagging antibody with fluorescein it has been possible to demonstrate that when a proportion of the amoebae remobilize they ingest and apparently digest their own antibody[40]. An intradermal test correlated reasonably well with the sensitive indirect haemagglutination test (IHA)[41]. Persons with active infection usually give an immediate response, sometimes followed by a delayed reaction; their sera give passive cutaneous anaphylaxis in guinea pigs. A delayed reaction occurs quite frequently in cyst passers and may

represent past tissue invasion. Good results have been obtained with an intradermal test among Saskatchewan Indians[42]; a positive result may persist for 30 months. One difficulty is that a few normal subjects may react even to axenic antigen and others may be sensitized by it[43]. For seroepidemiological purposes[44] it is important to know how long antibody persists after treatment. Indirect haemagglutination test titres, which sometimes correlate poorly with the severity of disease, may remain raised for three years or more. The gel diffusion test becomes negative more rapidly and the CFT occupies an intermediate position[45]. By microimmunoelectrophoresis using axenic antigen up to 14 precipitin arcs may be shown[46]; the number falls progressively after treatment. By means of the IHA the practical value of seroepidemiology has been demonstrated in six different communities[47].

The importance of invasive amoebiasis in non-tropical countries is emphasized by the outbreak in an Indian reserve in Saskatchewan[48]; 32% of the population were infected and 8% had amoebic dysentery and there were six reported deaths. The relationship of acute invasive amoebiasis with late pregnancy and the puerperium has been noted.[49,50,51,52]. Exacerbation or precipitation of amoebic dysentery by systemic corticosteroids[49,53,54] or antimetabolite drugs[49] is important and the correct diagnosis is likely to be missed; steroid therapy for supposed ulcerative colitis may be disastrous and not often recorded. Cutaneous amoebiasis of the perianal region or vulva may mimic carcinoma[55]; three cases of amoebiasis of the uterine cervix closely resembled tumours[56]. Invasive amoebiasis in children may be commoner than is supposed. Forty cases in infants aged less than 3 months have been reported from Mexico[57]. Series of 73 cases of amoebic peritonitis[58] and 56 cases with multiple liver abscess[59] have been described from Bombay, India. The appearances of amoebic proctitis have been recorded by photography[60], classified, and correlated with the histological features[61]. The results illustrate the broad spectrum of host response to amoebic invasion. Diagnosis depends upon the demonstration of the parasites, preferably in living material; macroscopic appearances and the tissue response seen on histology are not pathognomonic. Patients with amoebic liver abscess may have an impaired intestinal absorption of vitamin B_{12}[62] and a raised serum mucoprotein level[63]; the latter falls steadily after treatment.

A new effective and relatively simple culture technique has been described by Robinson[64], and his results show a strong correlation between the presence of *E. histolytica* and other intestinal amoebae. A full account has been given of the improved method of growing *E. histolytica* with *Trypanosoma cruzi* or *Crithidia* spp[65]; this technique is useful for research purposes and is an essential step in the axenization of a strain. A successful method for cryopreservation of axenic amoebae has also been described[66]. Axenic cultures may contain viral contaminants[67] and this problem has created difficulties in large-scale manufacture of antigen. Amoebae may be identified in tissue sections, including old stained preparations, using an indirect fluorescent antibody technique; by this means even a retrospective diagnosis can be made[68].

Human infection with *E. polecki* is common in parts of New Guinea where pigs and man live in close association[69]; this pig parasite has a uninucleate cyst but otherwise resembles *E. histolytica* closely; culture is difficult[70].

Mixed infections with *Dientamoeba fragilis* and *E. histolytica* are common in Israel where both have even been found in scrapings from the gallbladder wall or in duodenal juice following cholecystokinin[71].

GIARDIASIS

Contrary to an earlier report, ultrastructural studies of jejunal biopsies from three children showed no evidence of mucosal or tissue invasion[72]. By light microscopy five symptomatic patients, all with steatorrhoea, showed partial or severe subtotal villous atrophy; one showed low mucosal lactase[73]. Secondary vitamin A deficiency is suggested by lower serum carotene levels in children with *G. intestinalis* infection[74].

Of great interest is the relationship between *Giardia* infection and immunoglobin deficiency syndromes other than those of the familial X-linked type. Patients with these syndromes commonly have malabsorption, no plasma cells in the lamina propria, and abnormal mucosal histology, sometimes with nodular lymphoid hyperplasia of the small bowel and rectum. In one series seven out of eight carefully studied patients were found to have giardiasis, which sometimes was detectable only on biopsy. All showed dramatic symptomatic, functional, and histological improvement with metronidazole therapy[75]. Another group of five patients with acquired hypogammaglobulinaemia in adult life all had giardiasis but the effect of treatment was not studied[76]. Four out of five patients with non-selective immunoglobin deficiency had giardiasis and responded to therapy[77]. It appears that lack of secretory immunoglobulin, mainly IgA, in such patients may lead to bacterial colonization of the jejunum and increased susceptibility to *Giardia* infection. The bacteria may cause steatorrhoea by deconjugating bile acids but it is now clear that opportunistic *Giardia* infections greatly aggravate the condition and should be treated.

Symptomatic giardiasis is being increasingly recognized among travellers[78, 79]. In a report from California, USA, over 80% of infected persons gave a history of persistent diarrhoea following overseas travel[80]. An outbreak attributed to sewage contamination of piped water occurred at a ski resort in Colorado and produced over 100 symptomatic infections[81]. During a 10-year study in India 23% of 300 patients with non-dysenteric diarrhoea were found to be infected with *Giardia* compared with 4-6% of 700 patients without diarrhoea[82]. Milk intolerance was common in those with giardiasis. Giardiasis was discussed at a recent symposium in India[83] and a 248-page monograph written in Rumanian has been devoted to it[84].

It is now clear that compared with *E. histolytica* infections a higher proportion of those infected with *G. intestinalis* have symptoms. Recognition of this fact has been delayed because symptoms are often mild and transient and the infection is never fatal. Diagnosis is not always easy but an ingenious method of sampling the upper small bowel with a recoverable nylon yarn swallowed in a weighted capsule has been devised and found useful[85]. *Giardia* spp. from several mammalian hosts can now be cultivated axenically[86].

COCCIDIOSIS

The recent demonstration[87,88] that *Toxoplasma gondii* is a coccidian parasite is one of the most important parasitological discoveries of the decade. So far oocyst formation has been found only in the cat[89]. The cat is infected by two species of *Isospora*, namely, *I. felis* and *I. bigemina*, the newly described intestinal phase of *Toxoplasma* closely resembles the 'small form' of *I. bigemina* and the two may be identical[90]. No known species of *Isospora* form tissue cysts and it is not proposed to place *Toxoplasma* in that genus.

Hoare[91] has discussed the nomenclatural changes necessary for the stages of *Toxoplasma* life cycle in the light of its coccidian nature. It is possible that *I. belli* infections in man give antibodies crossreacting with *Toxoplasma*. Human volunteers fed on raw beef and pork infected with cysts of *Sarcocystis* spp. have later passed *Isospora* oocysts in their stools; similar results were obtained by feeding *Sarcocystis* spp. to dogs and cats.[92] Further studies are necessary before definite statements can be made about any possible tissue phase of *I. belli*.

The life cycle of *I. belli* was conjectural until the paper of Brandborg *et al*[93] describing six patients, three of whom died, with diarrhoeal illnesses lasting up to 15 years. The parasite was seen in intestinal biopsy specimens in all the patients although oocysts were found in the stool of only two. Both the asexual schizogonic and the sexual phases were demonstrated by Giemsa colophonium staining. The steatorrhoea was probably explained by the mucosal damage seen in the biopsy specimens. This finding suggests that schizogony can continue in the small bowel epithelium for some time; previously the infection was regarded as self-limiting. The literature has been reviewed by Jarpa Gana[94] who also describes a personal series of 57 patients most of whom had symptoms with diarrhoea, weight loss, and fever lasting from six weeks to six months.

Further high prevalence rates have been reported from various parts of the world, including Rumania[95], Holland[96], and Chile[97]. This parasite deserves more attention from both clinicians and parasitologists.

Chemotherapy of Protozoal Infections

AMOEBIASIS

One of the major developments in therapy in recent years has taken place in amoebiasis. Metronidazole (Flagyl), a 5-nitroimidazole which can only be given by mouth, has now assumed a position as the drug of choice in many forms of the disease[98]. The drug is rapidly absorbed from the gut, blood levels reach a maximum within two hours, and up to 70% is excreted unchanged in the urine[99]. Identified metabolites are an acid oxidation product and also a glucuronic acid conjugate which undergoes enterohepatic recycling. It appears that some of the drug is secreted directly into the colonic lumen also. Side effects include nausea, diarrhoea, metallic taste, dizziness, and discoloration of the urine. Most authorities recommend avoidance of alcohol during therapy because of the disulphiram-like activity of this drug[100].

Metronidazole, 800 mg thrice daily for five to 10 days, is a suitable regimen in amoebic dysentery or liver abscess. Lower doses, though yielding improvement within 48 hours and clinical cure[101,102], are associated with some parasitological relapses. A second course of therapy may be needed in a minority of patients[103]. Experience with metronidazole in non-dysenteric intestinal amoebiasis[104] suggests that it is less effective, giving a cure rate of 65 to 83% compared with that of 90% in dysentery[98]. Diloxanide furoate continues to be the drug of choice for this form of the disease and cure rates of 95% have been reported[105].

In the United States, where diloxanide is not available, diiodohydroxyquin (Diodoquin) is still widely used in the treatment of asymptomatic intestinal amoebiasis[106]. It is chemically similar to iodochlorohydroxyquin (Enterovioform) and there are recent reports[107,108,109] associating the latter drug with

subacute myelo-optic neuropathy. This syndrome, consisting of muscle pain, weakness, optic atrophy, and ataxia, has been reported, especially from Japan, with a few cases in northern Europe[110] and probable cases in Britain[111] and the United States[112]. The occurrence of this syndrome in dogs fed clioquinol (iodochlorohydroxyquin)[113] argues strongly against the suggestion that a virus is responsible for this syndrome.

When because of contraindications or unavailability neither emetine nor metronidazole are being used in amoebic dysentery chloroquine should be given to prevent the development of liver abscess. This practice is supported by the report from Durban[114] in which 25 cases of liver abscess developed in 509 patients treated with broad-spectrum antibiotics or luminal amoebicides but in none of 125 patients receiving chloroquine as an additional drug.

In children metronidazole in a five to seven day course is as effective as a course of 20 to 25 days of combined therapy (tetracycline, chloroquine, diiodohydroxyquin[115] or dehydroemetine, tetracycline, diloxanide furoate)[116]. When oral therapy is not feasible, as in peritonitis, one of the other regimens should be employed.

Relatively small doses of metronidazole are usually effective in treating amoebic liver abscess. A single dose of 2·0 g or 2·4 g as a single or divided dose cured 105 male Africans with amoebic abscess[117]. Failure occurred when 600 mg was given as a single dose. Two hundred mg of metronidazole given thrice daily for one week produced a rapid clinical response in 25 patients with hepatomegaly and *E. histolytica* in the stool, seven of whom had proved hepatic abscess[118]. However, a few had persistent cysts in the stool after treatment. Weber[119] has reported five cases of amoebic abscess occurring one to three months after apparent successful metronidazole therapy of amoebic colitis.

Emetine, dehydroemetine, and chloroquine, though excellent drugs for the treatment of amoebic liver abscess, have largely been replaced by the less toxic metronidazole. But, several clinicians believe that emetine, because of its rapid action, still has a place in the treatment of severely ill patients with either liver abscess or dysentery. Electrocardiographic changes and serum transaminase elevations continue to be reported[120,121] in 40-54% of patients receiving emetine, though similar changes have also occurred with choroquine and metronidazole to a lesser degree[122].

Severe muscle weakness is a rare side effect of emetine; although usually attributed to myositis, a neuromuscular blockade may also be partly responsible[123].

In children severely ill with amoebic abscess, Scragg and Powell[124] use emetine or dehydroemetine (2 mg/kg/day subcutaneously for 10 days) in addition to metronidazole (50 mg/kg/day for 10 days) or niridazole (25 mg/kg/day for 10 days). Interestingly, niridazole is well tolerated at this dose level by children whereas it has no place in the treatment of the adult because of the occurrence of neuropsychiatric and cardiotoxic side effects[125].

Surgical intervention without preoperative antiamoebic therapy may be accomplished with safety when necessary[126]. Grant *et al*[127] have reviewed the anterior transperitoneal approach for pyogenic and amoebic abscesses. Pastore[128] described a case in which a peritoneal dialysis cannula with low suction was used to drain a large abscess thereby avoiding multiple aspirations or open surgical drainage.

Doshi[129], reviewing amoebic granuloma (amoeboma) from 1916 to the

present, urged multiple stool examinations and biopsy, when possible, for diagnosis. Multiple lesions are frequent and a therapeutic test with emetine may be helpful as surgical interference is hazardous. Cases of amoeboma have been reported responding to metronidazole[130] or dehydroemetine[131]. For amoebic peritonitis parenteral emetine is required. Pleuropulmonary amoebiasis is usually treated with emetine and chloroquine with needle aspiration of the chest or intercostal drainage together with aspiration of the liver abscess that is usually present[132,133]. Amoebic pericarditis usually results from either rupture of, or fistulous connexion from, an hepatic abscess. Treatment includes drainage from above and below the diaphragm together with emetine and chloroquine or perhaps metronidazole alone[134].

There is some evidence that certain strains of *Trichomonas vaginalis* are becoming resistant to metronidazole[135]; possibly other protozoa will develop the same resistance The search for new amoebicidal agents continues. Among the 5-nitroimidazoles a series of compounds have been tested in man, including MK-910[136,137], BT-985[138], and RO7-02-07[139]. None has proved consistently more effective than metronidazole. Teclozan (WIN-13,146, Falmonox)[140] and also a long-release preparation of erythromycin stearate[141] have been shown to be effective in intestinal amoebiasis but further clinical trials are needed.

The evaluation of effectiveness of drugs in amoebiasis would be greatly enhanced if the criteria, classification, follow up, and definitions advocated by Powell[142] and a WHO Report[5] were to be followed. Powell[143,144] and Sodeman[145] have reviewed the development of current therapy including efficacy, sites of action, and limitations of drugs.

BALANTIDIASIS

At present tetracyclines remain the drugs of choice[142]. Tetracycline and diiodohydroxyquin successfully rid a symptomatic patient returned from Vietnam of this infection[146]. Metronidazole, though promising by *in-vitro* testing, cured only two of five patients in Micronesia[147]. Paromomycin (humatin) has been found effective in experimental animals[148] and erythromycin stearate curative according to a single case report[149].

GIARDIASIS

Patients in an outbreak of epidemic giardiasis were successfully treated with mepacrine (quinacrine)[81]. Some relapses occurred but these responded to a second or third course of the drug. Bassily *et al*[150] compared mepacrine, metronidazole and furazolidone, and a placebo in the treatment of giardiasis. Mepacrine and metronidazole were equally effective and considerably better than furazolidone. Metronidazole was the best tolerated and was considered the drug of choice. Khambatta[151] reported few adverse effects and an 85% cure rate with single doses of 1·6 g of metronidazole daily for two days. Nitrimidazine (Naxogin)[152] and tinidazole,[153] both 5-nitroimidazole derivatives, are also effective in giardiasis but offer no definite advantages over metronidazole at this time.

Biomedical Advances in the Helminths

TREMATODES

Jordan and Webbe's book[154] provides a useful introduction to the confusing subject of schistosomiasis. An excellent monograph[155] on schistosomiasis

mansoni has appeared from Brazil and also a recent symposium on the same subject.[156] Much information is now available on the dangerous *S. japonicum* species. The research and control programmes in mainland China since 1949 have been reported[157]. Half a million cases in the Philippines are estimated to cost 12 million dollars a year in treatment and man days lost from work[158]. The dog is an excellent reservoir host with the shortest prepatent period and largest egg output. A species like *S. japonicum* has been described from northern Thailand[159]. Ingenious methods of possible biological control measures for schistosomiasis continue to be reported. These include snail-eating fish which themselves provide a good source of protein[160] and also plants[161] and fish[162] which eat cercariae. Perhaps more promising are the molluscicidal properties of certain plants[163,164]. The histochemistry of the cercarial acetabular glands[165] and the favourable effect of short-chain fatty acids and some amino acids on cercarial penetration have been studied[166].

Experimental evidence confirms the clinical impression that *S. japonicum* adults do not move much in the portal circulation[167,168] thereby causing local egg granulomas with intestinal obstruction much more frequently than *S. mansoni* where the eggs are more scattered[169]. *S. mansoni* involvement of the small intestine occurs relatively often[170,171].

Various workers have again described acute schistosomiasis (Katayama syndrome) in man[172,173]. Neves calls this the toxaemic form of the disease and recognizes many clinical types in Brazilian patients[174]. Serum IgG and IgM levels are raised during this acute phase and several precipitin lines are demonstrable by immunodiffusion[175,176]. In a supplement to the *Central African Medical Journal* work at the Blair Laboratory, Salisbury, shows how much can be learned from the intensive study of a single patient—Foster Mavida[177].

Schistosome adults continue to be reported from unusual sites and a good review of bilharziasis of the central nervous system has appeared[178]. *Schistosoma intercalatum*, a West African species producing significant intestinal disease in man, has been recently discussed by Wright *et al*[179]; the eggs of this species somewhat resemble those of *S. haematobium*.

Two interesting disease problems associated with hepatosplenic *S. mansoni*, which occur particularly in Brazil, are the renal lesions and the prolonged *Salmonella* bacteraemia. Andrade's necropsy studies[180] suggest that all grades of chronic diffuse glomerulonephritis may occur. Other workers have described proliferative membranous glomerulonephritis with a thickened basement membrane and have confirmed the presence of IgG and complement but detected no schistosome antigen[181,182]. It has been suggested that this may be an immune complex disease. The finding of specific circulating schistosome antigen in heavily infected hamsters is of interest[183]. Recently antibodies to DNA have been demonstrated in hamsters with *S. mansoni* and human subjects infected with *S. japonicum*[184].

The susceptibility of hosts with hepatosplenic *S. mansoni* infection to protracted *Salmonella* bacteraemia has been well documented[185,186]. The serum of such patients appears to have reduced activity against *Salmonella*[187] and leucocyte migration is inhibited[188] but neither fact provides a definite explanation. The observation that when various Gram-negative bacteria are injected into animals parasitized by schistosomes the bacteria can penetrate the schistosomes, multiply in their caeca and kill them could have some relevance, but it is still too early to say[189].

Smithers and his group have made important contributions to our understanding of the immunology of schistosomiasis. Rhesus monkeys immunized against mouse tissue destroy *S. mansoni* adults transferred from mice to the portal circulation of these monkeys and this is antibody mediated[190,191]. The breakdown of the schistosome integument during this immune reaction has been studied and the rate of acquisition of host antigens during schistosomulum development in the host assessed[192]. It is postulated that there is a host-like antigen in the worm's integument which acts as a disguise protecting the worm against the host's normal immune responses. More recently it has been shown that the protecting antigen is probably associated with the host's red cell wall and schistosomulae can acquire human blood group antigen on cultivation *in vitro*[193]. It appears that although host antigen is closely associated with the integument of the worm it can be exchanged for that of a new host within a week.

It is suggested by the above workers that the excretory and secretory products of the adult worms play an important role in stimulation of the host's immunity. Studies of heterologous immunity in laboratory animals have shown that partial protection against *S. mansoni* can be achieved by previous infection with *S. bovis*, *S. mattheei*, or *S. mansoni*[194,195]. Warren has reviewed his work on the immunopathology of schistosomiasis[196]. The cell-mediated hypersensitivity reaction of the egg granuloma follows a distinct sequence. The three major species of human schistosome have been compared in the mouse as regards their capacity to produce granulomas. The physiochemical properties of the soluble egg antigen, which is probably a phospholipid, has been studied and its granuloma-producing effects demonstrated when coated onto bentonite particles[197]. Further studies have appeared on the pathology of both *S. mansoni* and *S. japonicum* in the chimpanzee[198,199]. Laparoscopy has shown that even in early human *S. mansoni* infections granulomas were visible on the small and large intestines and the liver[200].

Michael's elegant *in-vitro* work has given us some insight into schistosome mating[201]. In another interesting study she shows that the guinea pig appears to lack one or more substances necessary for the production by *S. mansoni* of eggs capable of maturation[202]. Ultrastructure studies have revealed interesting properties of the schistosome integument[203,204]. Further attempts to maintain *S. mansoni* adults in a continuous flow apparatus have been recorded[205]. We still lack knowledge of the habits of the adult worms particularly in relation to the determinants of sexual maturation, egg laying, and migration in the portal system.

Outbreaks of fascioliasis continue to occur in Europe, including England[206, 207]. Serodiagnosis is more specific using subcuticular antigen which only cross-reacts with *Fasciola gigantica*[208].

Clonorchiasis remains important in Korea[209]; the prevalence in Hong Kong is 25% which is the same figure as in 1944. Most of these infections are probably from mainland China[210]. Ouchterlony gel diffusion has been used to study the antigens of *Clonorchis*[211]. Human opisthorchiasis remains an important problem in Thailand (*O. viverrini*)[212] and the Ukraine (*O. felineus*)[213]. It is estimated that 10 million people are infected with *Fasciolopsis buski* in the Far East[214].

CESTODES

Diphyllobothrium latum, *D. dentriticum*, *D. lanceolatum*, *D. ursi*, and *D.*

dalliae have all been obtained from man in Alaska after treatment with mepacrine[215]. A monograph on the morphology and pathogenicity of *Cysticercus cellulosae* and *Cysticercus bovis* has appeared[216] and the epidemiology and other aspects of beef tapeworm infection have been reviewed[217]. Sexual characteristics other than the number of uterine branches, which may be unreliable, can be used to distinguish *Taenia saginata* and *T. solium*[218].

There are estimated to be 600-800 new cases of hydatid disease annually in Chile[219] and the case histories of 144 infected Chilean children are documented[220]. The current prevalence and distribution of hydatidosis with special reference to the Americas has been reviewed[221]. Libyan Arabs may become infected by the hot wind from the desert bringing dust containing hydatid ova from the faeces of dogs and jackals[222].

Of 223 patients with hydatid cysts, 57 had an eosinophilia of over 5%. Non-specific reactions to Casoni antigen have been reported in Puerto Ricans with *S. mansoni*[224]. The indirect fluorescent antibody test appears to give satisfactory results[225]. Evidence increases to suggest a scolex antigen is most satisfactory and such a preserved antigen has been prepared[226]. It has been noted that hydatid cysts of bone yield lower antibody levels than those in soft tissues [227]. The cultivation *in vitro* of *Echinococcus granulosus* and three other species from onchosphere to cystic larva has been achieved[228]. Self insemination of adult *E. granulosus* has been observed in sections of intestine from infected dogs[229]. Selective angiography is valuable in the diagnosis of hydatid disease of the liver[230].

NEMATODES

A thiomersal-iodine-formalin direct smear is a simple method for evaluating *Ascaris*, *Necator*, and *Trichuris* infections, and is as reliable as others, including Kato's thick smear technique[231]. Concentration techniques detect very light infections (500 eggs/g stool). Forty per cent of introduced nematode larvae were recovered from herbage by a concentration method[232]. Skin tests for nematodes should be interpreted with caution as cross reactions and false positives may occur[233]. *Ascaris* infections in children can lead to marked nutritional impairment when a high parasite load is associated with a low protein intake[234]. A retrospective study of the American Armed Forces Institute of Pathology material revealed 35 fatal *Ascaris* infections[235]. It contains some unique case material and useful information on the appearance of *Ascaris* ova and larvae in tissue sections. A stone in the common bile duct containing *Ascaris* ova was found in a 12-year-old boy in the United States[236]. An eosinophilic granuloma of the pancreas caused by *Ascaris* eggs has been described[237]. Three self infections in Russian volunteers, each with 150 eggs, that had been in the soil for 10 years produced Loeffler's syndromes[238]. The daily egg output is estimated to vary between 73 000 and 227 000 per female worm[239].

The sex ratio of worms in the intestine is near unity. Smith believes the environment in the gut near the mucosa is not anaerobic, and has shown *in vitro* that adult *Ascaris* require oxygen for normal metabolism[240]. A detailed antigenic analysis of the developmental stages of *Ascaris suum* has been undertaken[241,242]. There is some evidence of sharing of host components between host and parasite[243], and animals may be protected using antigenic extracts of adults or larvae[244].

Strongyloides stercoralis producing severe disease in immunosuppressed patients (hyperinfection syndrome) has again been described[245], and an eosinophilic granuloma with small bowel obstruction diagnosed in a 6-month-old Australian aborigine[246]. In six patients with the hyperinfection syndrome DNA losses from the small intestine were much higher than in patients with hookworm or controls and fell to normal after treatment[247]. The 'string test' referred to under giardiasis[85] has been found very useful in obtaining *Strongyloides* larvae from the jejunum.

In a volunteer repeatedly exposed to *Necator americanus* there was no evidence of protective immunity on the basis of repeated egg counts[248]. The fluorescent antibody titre rose two weeks after each larval exposure, peaked at three months, and then declined; CFT and haemagglutination titres were also followed. No correlation between FAT titres and worm load could be found in Nigerians with hookworm; serological cross reactions with other Strongyloidea were noted. In a field study of *Ancylostoma duodenale* infection in Korea no evidence of protective immunity was observed[249].

A recent study establishes that a small proportion of patients heavily infected with hookworm have evidence of malabsorption[250]. The interesting effect of garlic inhibiting the development of eggs in culture should be followed up[251]. The effects of temperature, humidity, faecal and urine contamination, and various salad dressings on larval development have been studied[252]. *Trichuris trichiura* occurs frequently in mental institutions in England[253]. Malnutrition may be the principal cause of increased pathogenicity of *Trichuris trichiura* leading to rectal prolapse[254]. It appears probable that the mode of transmission of *Capillaria philippinensis* is by the ingestion of three species of mainly marine fish which have been shown to contain infective larvae. An autoinfective cycle has been shown to occur in experimental animals and man but it is still uncertain as to whether interhuman transmission occurs[255]. A 10 000-year-old human *Enterobius vermicularis* infection has been described on the basis of a radiocarbon dating of a coprolite in western Utah[256]. A study of threadworm re-infection rates in families after treatment suggests that extrafamilial contacts are more important than is generally realized[257], and three patients with bowel wall fibrosis or peritonitis associated with adult worms penetrating previously diseased bowel have been reported[258].

Beaver[259] has summarized his views on the nature of visceral larva migrans, a subject to which he has made such important contributions. It is probably less confusing in our opinion to abandon this term and use when possible the name of the worm responsible. Many aspects of toxocariasis have been described by Woodruff[260]. The fluorescent antibody titres, reagin levels and IgE have been estimated in experimental infections[261]. A modified haemagglutination method has also been used[262]. There have been further reports of mature worms in man[263,264]. Anisakiasis is on the increase in the Netherlands[265]. There may be three species involved[266]. Monkeys can be experimentally infected but do not appear to develop intestinal granulomas as in man[267,268]. Serodiagnosis continues to improve[269,270]. Of 34 helminthic pseudotumours of the ileum and large bowel, three were found to contain *Oesophagostomum apiostomum* and one *Ternidens deminutus*[271]. An African boy seems to have ingested *O. dentatum* larvae on vegetation contaminated with pig manure[272]. In infections like these obscure eosinophilia is often a feature and the important work of Beeson's group showing that immuno-

logically competent lymphocytes play a role in the induction of eosinophilia should be noted here[273,274]. It is of significance in so many helminthiases.

Chemotherapy of Helminthic Infections

A quantitative approach to the evaluation of new schistosomicidal drugs is important[154,155,275]. The percentage reduction in egg count is probably a more reliable parameter than cure rate. Davis[276] had discussed the principles governing drug trials and the search continues for an ideal schistosomicidal drug. As yet none exists and there is certainly no drug suitable for mass treatment that is both effective and not toxic.

A comparison of the chemotherapeutic potencies of four antimonial compounds showed that antimony potassium tartrate was the most potent drug, followed by antimony lithium thiomalate, then stibophen, and lastly stibocaptate[277]. There was close correlation between the toxicity of these drugs and their relative activities *in vivo*. Four other schistosomicidal drugs—mirasan, lucanthone, hycanthone, and niridazole—were compared under standard conditions in mice infected with an East African strain of *S. mansoni*. It appears that the first three drugs, mirasan, lucanthone, and hycanthone, affect primarily male worms whereas niridazole affects primarily female worms. Hycanthone and lucanthone appeared to act more slowly than mirasan and niridazole. Niridazole left the greatest proportion of worm pairs after treatment compared to other drugs[278].

Trivalent antimonials are still the most potent drugs for the treatment of *Schistosoma japonicum* infection. Their principal drawback is the high incidence of moderate to severe side effects, especially when the quantity of antimony administered is increased to obtain maximum therapeutic effect.

An intensive regimen of sodium antimony tartrate injections in which a total dose of 12 mg/kg body weight (not exceeding 700 mg given twice a day for three days) has been used for more than half a million cases of schistosomiasis in Kiangsu, Chekiang, and Yunnan provinces and in Shanghai. Satisfactory therapeutic results as well as good tolerance were achieved, and eggs disappeared from the stools of 80% of those treated[157]. Three different schedules of stibophen treatment were given to 216 patients with *S. japonicum* infections and it was shown that a course of 15 injections gave a cure rate of 49% and a reduction in egg count of 96%, six months after treatment. The most common reactions observed were nausea, vomiting, anorexia, and weakness[279]. Sodium antimony dimethylcysteine tartrate (NaP) is a new antimonial compound developed on the basis that dimethylcysteine reduces the toxicity of antimony without affecting its antiparasitic action[280]. A dose of 400 mg NaP daily for five days by intramuscular injection has been shown to be effective against *S. mansoni* in Venezuela[281] and *S. japonicum* in the Philippines[282] although cardiac toxicity was unacceptably high in the latter study.

A series of nitrofuran compounds have been synthesized in Shanghai. In general, they are highly effective in laboratory animals and human subjects infected with *S. japonicum*, but their toxic effects, notably muscle cramps, psychiatric effects, and gastrointestinal disturbances, are too severe to consider their widespread use at this time[157].

Further clinical trials have been carried out with niridazole. Twenty-nine of 30 patients with light *S. mansoni* infections were cured with niridazole

after three to six months follow up in London[283]. In *S. japonicum* infections about 50% of the patients treated with 20 mg/kg per day for five days remained negative for eggs one year after treatment[284].

In a therapeutic trial of niridazole in Leyte[285], patients with *S. japonicum* infection were given 20-25 mg/kg/day for 14 days and 59% were negative and egg count reduced by 98% six months after treatment. However, transient psychic side effects were observed in some of the patients, and the authors conclude that this drug should be given under close medical supervision. A new, rapid method for screening compounds for prophylactic activity against *S. mansoni* infection in mice has been developed. Niridazole was the most active prophylactic agent of those studied and stibocaptate was completely inactive[286].

Hycanthone is a new thioxanthone compound which was originally isolated in 1960 as an active metabolite of lucanthone. It is nine to 10 times more active than lucanthone against *S. mansoni* infections in hamsters when given orally and a single dose of hycanthone by injection has the same activity as five daily oral doses[287]. In human *S. mansoni* infections, cure rates of 80% or better were obtained with a single intramuscular injection of doses of 2 to 3·5 mg/kg[288]. In St Lucia six months after a similar dose only 28% of patients were no longer excreting eggs but the total egg excretion in the group of 94 patients had been reduced by 97%[289]. Hycanthone should not be used in the presence of impaired liver function. Fatalities due to acute liver failure have occurred[290] but are inadequately documented at the time of writing. The most common adverse reaction is vomiting, and the incidences range from 25 to 78% in various treatment series. The other side effects include headache, vertigo, weakness, myalgia, anorexia, diarrhoea, and weight loss. A study of the side effects of hycanthone in patients with *S. mansoni* infections showed that a single intramuscular dose was better tolerated than five daily oral doses[291].

In an area of Bahia State, Brazil, excellent results were reported using a single intramuscular injection of hycanthone at a dose of 2·5 mg/kg[292]. In another study from Brazil, doses of hycanthone of between 1·5 mg and 3·0 mg/kg/day cured 75% of patients given a single intramuscular dose and 100% of patients given five daily oral doses[293]. Hycanthone is less effective (49%) in patients with recent infections (two to eight months) of *S. mansoni* than in patients with infections that have existed for one year (84·7%)[294]. In a study of hycanthone in East Africa 70% of patients with *S. mansoni* infection were cured and in the remainder egg output was significantly reduced[295]. Hycanthone is ineffective for *S. japonicum* infections in mice and hamsters[296].

Resistance to high doses of hycanthone has been demonstrated in the first to fourth generation of adult schistosomes (*S. mansoni*) originally exposed to high doses of the drug in mice[297]. Hycanthone has also been shown to be a frameshift mutagen in cultures of *Salmonella* and T4 bacteriophage during growth in *Escherichia coli* K12[298]. These findings have caused concern since hycanthone has already been given to more than 300 000 patients and greater use is anticipated. Certainly the results from Brazil, Rhodesia, and St Lucia suggest this is a promising drug for the treatment of *S. mansoni*.

Filtration of *S. mansoni* adults from the portal circulation by extracorporeal blood circulation is possible as part of the surgical treatment of portal hypertension[299]. It can be attempted in unanaesthetized patients canalized by the umbilical vein[300]. Shunting for portal hypertension in hepatosplenic schisto-

somiasis[301] is less popular than it was in some highly endemic areas in the tropics; as mentioned in the previous review, such information as exists suggests people with this type of portal hypertension usually have good parenchymal liver function and seldom die even after repeated haematemeses. Also the repercussions of removal of the spleen may be dangerous, especially in malarious areas, and splenorenal shunts not infrequently thrombose.

Han-Jong Rim[302] has recently reviewed the chemotherapy of all trematode infections except schistosomiasis. In the past clonorchiasis and opisthorchiasis have been treated with antimony preparations, gentian violet, emetine hydrochloride, chloroquine diphosphate, bithionol, and dithiazanine iodide, etc. Although clinical improvement and negative or reduced egg counts will temporarily result from the use of these drugs permanent cures are doubtful. Hetol (1 4-bis-trichloromethylbenzol) continues to give good cure rates (67-87%) in clonorchiasis with flatulence and nausea as the only side effects at doses of 50 mg-70 mg/kg twice daily for five days[303]. A trial of the same drug under the name hexachloroparaxylene (Chloxyle) in a daily dose of 600 mg/kg for five days gave a complete cure in 49% and reduced egg output in another 43% of 420 patients with opisthorchiasis[304]. In these and other clinical trials this compound appears both safe and effective yet the manufacturer of Hetol has discontinued further trials because, as mentioned in the previous review, serious side effects have occurred in laboratory animals. Dogs given 60-180 mg/kg daily for 30 days develop hypochromic anaemia, leucopenia, psychic effects, and lesions in the liver and kidney. In fascioliasis both this drug[305] and bithionol[207] have been shown to be effective. Chloxyle is still available from China.

In a study of the chemotherapy of hydatid disease in Rumania the investigator claimed that good results were obtained in nine of 11 patients treated with prolonged courses of proguanil and one patient treated with a prolonged course of chloroquine[306]. A new method for the treatment of hydatid cyst in man involves the sealing of the operative area by freezing and then injecting a 0·5% solution of silver nitrate which destroys the scolices. This method is said to have yielded excellent results in 20 surgical cases of intrahepatic hydatid disease[307]. Aqueous iodine appears to kill scolices more effectively *in vivo* and *in vitro* than either alcohol or formalin[308].

A recent review of all aspects of *Taenia saginata* infection, including chemotherapy, concluded that niclosamide (Yomesan) is the drug of choice for this infection[217]. In further trials paromomycin sulphate (Humatin) has been shown to be successful in treating *T. saginata*, *T. solium*, *Diphyllobothrium latum*, and *Hymenolepis nana* though the number of patients studied was small and we need more information[309,310].

The older drugs for the treatment of intestinal nematodes such as santonin, oil of chenopodium, carbon tetrachloride, tetrachlorethylene, gentian violet, hexylresorcinol, have been replaced by newer, less toxic drugs. Some of the more recent drugs that have been developed are thiabendazole, pyrantel pamoate, Jonit, tetramizole, dichlorvos, stilbazium iodide, and mebendazole.

Thiabendazole has gained wide acceptance as a broad-spectrum anthelmintic for the treatment of gastrointestinal helminthiasis of man and domestic animals. Side effects are dizziness, nausea, vomiting, and abdominal pain. The mean cure rate for *Strongyloides stercoralis* is 96%, *Enterobius vermicularis* 94%, hookworms (*A. duodenale* and *N. americanus*) 77% and *Ascaris* 77%. The drug is of variable efficacy in the treatment of cutaneous larva migrans,

trichinosis, dracunculosis, and trichostrongylosis[311]. Prolonged courses of thiabendazole for up to four weeks are usually effective in intestinal capillariasis[312].

Pyrantel pamoate (Combantrin) is effective against *Ascaris*, hookworm, and *Enterobius*[313,314,315]. Because it can be given in one dose (10 mg/kg), has minimal side effects, and is tasteless, it is particularly useful for the treatment of *Enterobius* infections.

Jonit (phenylene-diisothiocyanate 1, 4) is effective against both *A. duodenale* and *N. americanus* although it is more effective against the latter. The usual dose is three 100 mg capsules given at 12-hourly intervals after meals. Side effects are anorexia, nausea and vomiting, and diarrhoea but these are usually transient and tolerable[316]. More severe side effects are abdominal pain and dizziness. The drug cured over 90% of patients with hookworm in Colombia[317]. In Thailand the mean reduction of the egg load of *N. americanus* was 89% and the percentage cure rate was inversely related to the pretreatment egg load[318]. Two studies concluded that the efficacy and safety of Jonit for hookworm infection is comparable to that of tetrachlorethylene and bephenium[319,320].

Tetramisole exerts a rapid and prolonged paralysing effect on nematodes. Cure rates are about 95% with *Ascaris* and 80% with hookworm but it is inactive against *Trichuris* and *Enterobius*[321]. In one study of 1000 cases of ascariasis a single dose (80 mg for children under 12 years and 150 mg for patients over 12 years) 93·6% of patients were cured[322]. The levo-isomer is the most active form of tetramisole and is well tolerated even at several times the recommended dosage (2·5 mg/kg in a single dose). In a trial comparing the efficacy of tetramisole and piperazine in African children infected with *Ascaris* 94% were cured with tetramisole (2·5-5 mg/kg) whereas 85% were cured with piperazine citrate (3 g for children under 20 kg and 4 g for children over 20 kg)[323]. Although piperazine salts are only recommended for the treatment of ascariasis, it has again been shown that piperazine causes an 82% reduction in the faecal egg count in patients infected with *N. americanus* and *A. duodenale* but complete cures were not achieved[324].

Stilbazium iodide cured 80% of Brazilian patients infected with both *Ascaris* and *Trichuris* when given in a dose of 20 mg/kg twice daily for three days[325]. Side effects of nausea, vomiting, and abdominal cramps were observed in 25% of the patients. A single oral dose of dichlorvos (6-12 mg/kg) has been reported to cure 85-90% of *Trichuris* infections and is said to produce infrequent and mild side effects[326,327]. Further investigations are necessary to confirm the efficacy and safety of dichlorvos. The pentavalent organic arsenical difetarsone has recently been reported to produce cure rates of 81-88% in institutionalized patients in Britain infected with *Trichuris*[253].

Mebendazole (methyl-5-benzoylbenzimidazole-2-carbamate) is the newest of the 'broad-spectrum' anthelmintics. In a preliminary trial, a single dose of 100 mg cured 90% of patients infected with *Enterobius*[328]. In clinical trials that are as yet unpublished, it is said also to be effective for *Ascaris*, hook worm, *Trichuris*, tapeworm,and *Strongyloides*. It is claimed that mebendazole produces virtually no side effects even at dose levels of 400 mg tid for one week, which is several times the therapeutic dose. Very little of the drug is absorbed. Further clinical trials are awaited.

Conclusion

Amoebiasis and schistosomiasis can each be described as a Trojan horse in the arena of tropical medicine. Apparently simple problems to the neophyte, on close inspection they contain such complex factors that no simple solutions are possible. For this reason a lot of space is devoted to them in this review. We remain optimistic that eventually as knowledge grows, solutions will become apparent to many of the problems concerned with these two pernicious human infectious diseases.

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The Tropical Disease Bulletin has been a valuable reference source for this review. Where possible, references have been consulted in the original. The names of commercial manufacturers and trade names are provided for identification only, and their inclusion does not imply endorsement by the United States Public Health Service, nor does the exclusion of commercial manufacturers' or trade names imply nonendorsement by the Service.

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