Gut 1994; 35: 582–586

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

Persisting diarrhoea and malabsorption

Most diarrhoeal episodes acquired during tropical exposure subside spontaneously within a few days.[1] A few continue for a longer period[2,3]; what therefore constitutes chronicity (or persistence)?[4] An arbitrary span of ≥two weeks seems a valuable 'cut off' point.[5] Prolongation of an acute infection (for example, *Salmonella spp* or amoebic colitis), progression to a malabsorption state (see below), irritable bowel syndrome, and drug (usually antibiotic) associated disease (for example, *Clostridium difficile* infection) are all relevant.[5] A careful case history often provides a valuable clue(s) to the anatomical location of the important enteric lesion(s): watery or fatty stools usually reflect small intestinal disease, and bloody ones (sometimes accompanied by mucus or pus, or both) colorectal involvement. While postinfective malabsorption ('tropical sprue')[6] was formerly a classic (and common) entity, it has been superceded in prevalence by HIV enteropathy (Table 1). Here the length of history is likely to be ≥two to three months.

This review does not deal specifically with causes of chronic diarrhoeal disease in the indigenous populations of tropical and subtropical countries; these include ileocaecal tuberculosis (a mass is often palpable in the right iliac fossa), Mediterranean and Burkitt's lymphomas, Kala-azar, chronic calcific pancreatitis, chronic liver disease, severe protein malnutrition, and pellagra (common in maize eating communities).[2,3,7] These entities are very unusual in British travellers, although the first must be clearly borne in mind in those from the minor ethnic groups – especially those from southern Asia. HIV enteropathy (often coexistant with tuberculosis) is an important cause of chronic diarrhoea in African visitors to the United Kingdom.

The importance of gastric hypoacidity in the aetiology and pathogenesis of chronic diarrhoea has almost certainly been underestimated in the past; it is also important in HIV infected subjects.[8]

Small intestinal causes

The traveller usually presents to his/her physician with trivial symptoms: two to three semi-formed stools (without blood or mucus) per 24 hours; weight loss is minimal. This state may continue for weeks or months, often ending abruptly. Although the term tropical enteropathy[2,3,9] (villous blunting, infiltration within the lamina propria, associated with minimal enterocyte damage) is commonly applied (Table I), the scientific basis remains flimsy, and the mechanism of symptomatology unclear.[10]

TABLE I *Small intestinal causes of chronic diarrhoea in relation to tropical exposure**

Tropical enteropathy	
HIV enteropathy	
Postinfective (tropical) malabsorption	
Small intestinal parasitoses	
Giardia lamblia	Protozoa
Cryptosporidium	Protozoa
Isospora belli	Protozoa
Blastocystis hominis	Protozoa
(Sarcocystis spp)	Protozoa
(Cyclospora cayetanensis)	Protozoa
Strongyloides stercoralis	Nematode and trematode helminths
(Capillaria philippinensis)	Nematode and trematode helminths
(Fasciolopsis buski)	Nematode and trematode helminths
Gluten induced enteropathy	
Hypolactasia	

* Unusual presentations in the United Kingdom are given in parentheses.

Table I also summarises more dramatic causes of persisting diarrhoea. In a severe case, bulky stools – either fluid or fatty – are usual; weight loss has always occurred. HIV enteropathy features high on the list[11–13]; homosexual men are usually affected, but heterosexual transmission in travellers – especially those of African origin – is not uncommon. Clinically, chronic diarrhoea and weight loss are usually accompanied by 'fever'. Opportunistic infection (with viruses (for example, cytomegalovirus or herpes zoster), bacteria (*Salmonella spp*, *Campylobacter spp*, *Shigella spp*), protozoan (a coccidian – usually *Cryptosporidium spp*[14,15] or *Microsporidium spp*[16–19] – see below), or fungi (*Candida spp*), or all four, is usual. HIV involvement of the enterocyte is also important.[20,21] Postinfective malabsorption was formerly the most common cause of chronic small intestinal diarrhoea, malabsorption, and weight loss (in India, South East Asia, and Central America)[2,3,22–24]; however, with increasing use of antibiotics early in a gastrointestinal infection, overt disease is now unusual. It has now been recorded also in UK travellers to the Mediterranean littoral,[25] and in Africa.[3,6,24] Various hypotheses to explain the pathophysiology of the syndrome have been produced; it is characterised by small intestinal luminal bacterial overgrowth, and a genetic predisposing factor is probably important.[3,24] Methods for investigation are outlined below.

Small intestinal parasitoses are dominated by *Giardia lamblia*, a flagellated protozoan, which causes a spectrum of disease ranging from a travellers' diarrhoea like illness[1,2] to chronic malabsorption and weight loss – indistinguishable from postinfective malabsorption. Most chronic cases present with flatulent diarrhoea and weight loss; this may be extreme. Diagnosis and treatment are outlined below. The coccidia (Fig 1) are unusual causes of chronic diarrhoea/malabsorption in the absence of immunosuppression; heavy infections should be treated on merit (see below). A previously unrecognised protozoan (originally considered an alga) has now been causally implicated in chronic diarrhoea in travellers to Nepal and other Asian countries, and several other tropical areas (including the Caribbean and South America).[26–33] It is a cyanobacterium like body; the proposed name is *Cyclospora cayetanensis* (Fig 2). The most chronic small intestinal parasitosis is caused by *Strongyloides stercoralis* (especially common in the Caribbean); it can remain, due to its autoinfection cycle, a problem throughout the life of an infected subject. Infection may be accompanied by an intensely irritant rash affecting the lower abdomen and buttocks (*larva currens*). It is often associated with HTLV 1 infection; the nature of this relation remains obscure. In the 'hyperinfection syndrome', usually in an immunosuppressed subject, migrating larvae are usually accompanied by *Enterobacteriacaeae*; all organs can be affected. *Capillaria philippinensis*[34] produces chronic diarrhoea and malabsorption; infection was formerly confined to the northern Philippines and Thailand; cases have recently been recorded in Egypt and India.

Bacterial causes of chronic 'tropical diarrhoea' are

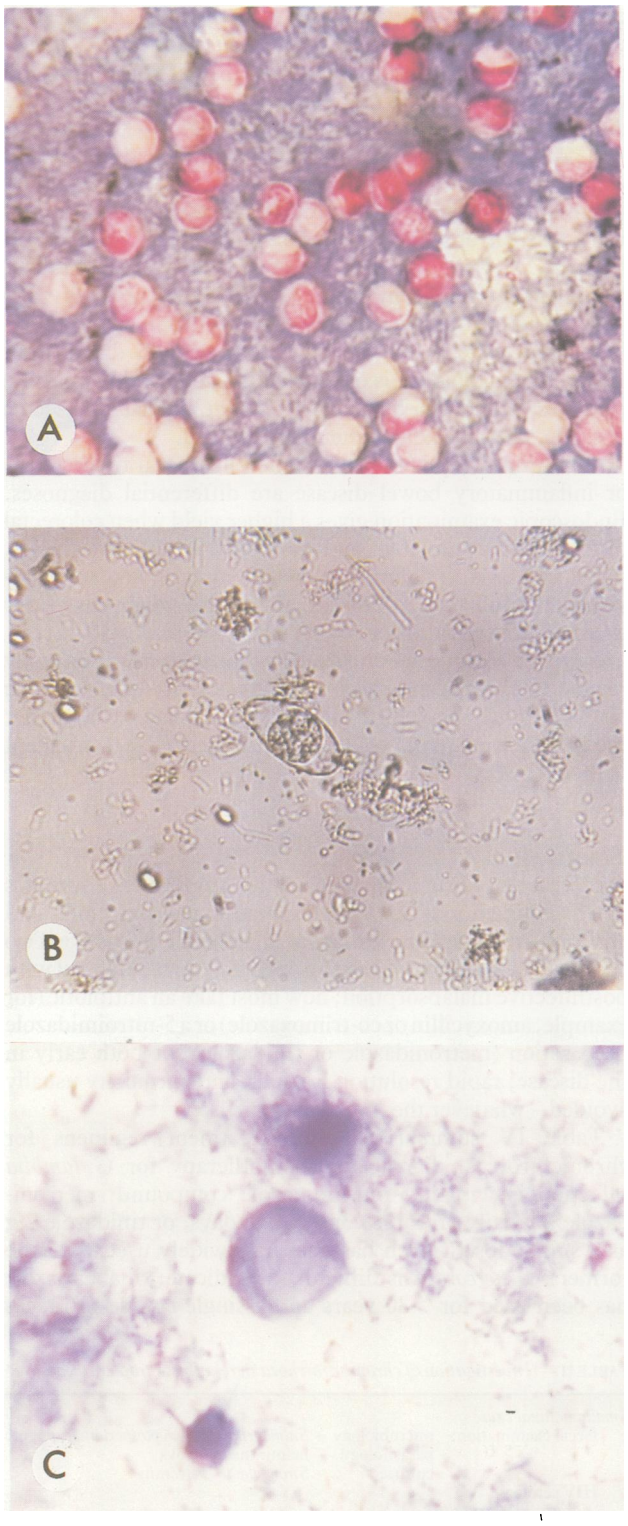

Figure 1: Coccidial protozoa that can be causatively associated with chronic 'tropical diarrhoea'. (A) Cryptosporidium spp *(×1000),* (B) Isospora belli *(×400), and* (C) Blastocystis hominis *(×1000).*

unusual; cases involving *Campylobacter jejuni*,[35] *Aeromonas spp*,[36] and *Plesiomonas shigelloides*[37] have been recorded. Dysgonic fermenter 3 has also been isolated.[38 39] The role of fungi remains unclear.[40]

Gluten induced enteropathy (coeliac disease) (in contrast with postinfective malabsorption, the small intestinal biopsy specimen is commonly 'flat') may present for the first time during, or shortly after tropical exposure[41]; the history often suggests postinfective malabsorption, and although there is no clinical response to tetracycline and folic acid, that to a gluten free diet is rapid. Presentation is presumably exacerbated by a change in the small intestinal luminal milieu.

Secondary hypolactasia is a common sequel to a small intestinal insult – especially an infection[42 43]; therefore, milk 'intolerance' is common in subjects exposed to a tropical or subtropical environment. The H_2 breath test is of value diagnostically.[44] Dietary lactose exclusion is often useful.

Colorectal causes

Visible blood, often associated with mucus/pus signifies colorectal pathology. *Shigella spp* and other colonic bacterial (for example, enterohaemorrhagic *E coli* or *Campylobacter spp*) infections can continue for several weeks, but this is unusual. Two common parasitic infections that cause chronic disease are: *Entamoeba histolytica* (a protozoan)[45 46] and less often *Trichuris trichiura* (a nematode helminth) – usually in infants and children (Table II). In a significant number of travellers, chronic symptoms are caused by inflammatory bowel disease – usually ulcerative colitis[47 48] – manifesting for the first time. The mechanism(s) responsible remains unclear; an acute infection – possibly caused by *E coli* – seems likely, and it is possible that an already damaged colonocytic luminal 'barrier' is further compromised by an enterotoxin(s). Elucidation of the precise mechanism is made difficult because the initiating agent(s) has been eliminated before the chronic lesion becomes overtly manifest. Post infective irritable bowel syndrome is usually associated with evacuation of small quantities of normal stool; this follows many 'insults', and is common among some ethnic groups in tropical countries.[49–55] It does not seem to be related to lactose ingestion,[56] and the pathophysiological basis is unclear.[57]

In *E histolytica* colitis, dystentery may not begin for 21 days or even longer after exposure; blood and mucus, often accompanied by fever, nausea, headache, and tenesmus, are usual. Colorectal shigellosis rarely becomes chronic, and is easily differentiated by laboratory investigations (see below). Amoebic colitis rarely progresses to a 'necrotising' course (sometimes accompanied by perforation)[45]; other complications are: appendicitis, amoeboma, haemorrhage, and stricture. Shigellosis may be complicated by: Reiter's syndrome (usually HLA-B27-associated) and (rarely) haemolytic uraemic syndrome.

Chronic diarrhoea caused by *T trichiura* infection is usually confined to infants and children; it is especially common in the Caribbean, where heavy infections are accompanied by hypochromic anaemia and rectal prolapse.[58]

Colorectal schistosomiasis (usually *Schistosoma mansoni* infection) can present with chronic bloody diarrhoea[2]; it is unusual in British travellers to an endemic area and more common in members of minor ethnic groups – especially Africans – after moderate/heavy infection, often during early life. Other relevant species are: *S japonicum*, *S mekongi*, *S intercalatum*, and *S matthei*.

Limited evidence shows that chronic colitis might result from direct HIV invasion of the colonocyte.[59]

By no means all colorectal lesions in travellers are related to tropical exposure; diverticulitis and colorectal carcinoma are important examples.

Iatrogenic and 'spurious' chronic diarrhoea

Drugs associated with chronic diarrhoea include: laxatives,[60 61] methyl dopa (used in hypertension), diuretics, magnesium[62] (peptic ulcer disease), and para-aminosalicylic acid (tuberculosis); excessive alcohol intake[63] and local (herbal) remedies are also relevant.

It is by no means always possible to identify a specific pathogen to account for chronic diarrhoea occurring after travel; in a retrospective study of 150 'idiopathic' cases all recovered without specific treatment after a mean (range) period of 15 (7–31) months.[64]

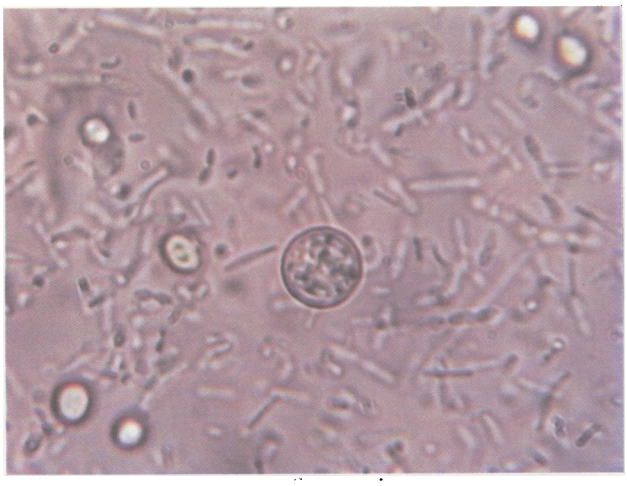

Figure 2: Cyanobacterium like body, which has recently been incriminated in chronic tropical diarrhoea – especially in Nepal (×1000); the proposed name is Cyclospora cayetanensis.

Investigations

The range of investigations should be tailored to the probable site of the pathological lesion.[65] Simple bench techniques often yield valuable results in the absence of sophisticated methods. Faecal leucocytes usually point to a bacteria associated colorectal lesion; they are more scanty in small intestinal disease and amoebic colitis. Bacteraemia is unusual in an intestinal infection. Invasive colorectal amoebiasis is best diagnosed from a rectal scrape snip; examination of a biopsy specimen takes a great deal longer.

Table III summarises some useful investigations in chronic small intestinal and colorectal diarrhoea. Faecal bacteria (and less often viruses) should be identified; special techniques are required when, for example, *Cl difficile* is sought. Eggs, cysts, and adult parasites must also be identified – preferably using a concentration technique. When a rectal scrape snip is not available, the best means of detecting *E histolytica* is in a fresh, warm faecal sample; mucus is most likely to contain motile trophozoites with ingested erythrocytes. When possible these should be cultured; isoenzyme studies will differentiate pathogenic from non-pathogenic zymodemes. Peripheral blood eosinophilia suggests an helminthic infection – either small intestinal or colorectal. When *S stercoralis* infection seems possible a faecal culture technique should be applied and larvae identified.

Serological tests are of value in the detection of invasive amoebiasis; an immunofluoresent antibody technique is usual, and the less sensitive and specific countercurrent electrophoresis and cellulose acetate precipitin tests are usually positive in the presence of colonocyte invasion. Invasive schistosomiasis is accompanied by a positive *Schistosoma spp* enzyme linked immunosorbant assay (ELISA) result. When HIV infection is considered possible, appropriate serology is required.

The 'Enterotest' (string test) – which consists of a gelatin capsule to which is attached a nylon thread – gives a high yield of positive results in *S stercoralis* (and also *S typhi*) infection; after an overnight fast the capsule is swallowed and withdrawn (bile stained) after four to five hours, when the distal end is smeared on a microscope slide.

Blood glucose response to an oral lactose load (50 g) is of value as a screening test for hypolactasia; a rise ≤1·1 mmol/l suggests the diagnosis. The following investigations are of value when an absorptive defect is considered: 72 hour faecal fat, oral D-xylose test, Schilling test, red blood cell folate, and serum B-12 concentration.

In differenting postinfective malabsorption from gluten induced enteropathy (a 'flat' mucosa is virtually diagnostic), small intestinal biopsy is of value. Protozoan and helminthic parasites should also be detected. When hypolactasia seems possible, disaccharidases should be assayed.

A barium study is indicated when ileocaecal tuberculosis or inflammatory bowel disease are differential diagnoses. Endoscopic examination gives a higher yield when colorectal disease seems possible and is of value in: amoebiasis, schistosomiasis, inflammatory bowel disease, and in exclusion (or confirmation) of an alternative diagnosis – for example, diverticulitis or colorectal carcinoma.

In a subset of patients, rapid intestinal transit is causally related to chronic diarrhoea[66]; the glucose-hydrogen breath test is of value. Idiopathic bile acid malabsorption (a further cause of chronic diarrhoea) can be assessed by measurement of ^{75}SeHCAT.[67]

Treatment

Prevalence of chronic diarrhoea after tropical exposure has fallen daramatically since widespread use of antibiotic and anti-protozoan agents for acute diarrhoeal disease.[68] Two decades ago many travellers to South East Asia returned with postinfective malabsorption; now most take an antibiotic (for example, amoxycillin or co-trimoxazole) or a 5-nitroimidazole preparation (metronidazole or tinidazole), or both early in the disease; rapid resolution is usual, and chronicity usually avoided – whatever the infective agent!

Table IV summarises some treatment regimens for chronic tropical diarrhoea. Chemotherapy for *G lamblia* infection is with a 5-nitroimidazole compound: metronidazole 2 g daily on three consecutive days, or tinidazole 2 g as a single dose (which has been less widely used than the former). *S stercoralis* is difficult to eradicate; thiabendazole has been used for >30 years and a single course produces

TABLE II *Colorectal causes of chronic diarrhoea in relation to tropical exposure**

Colorectal parasitoses	
	Entamoeba histolytica
	(Trichuris trichiura)
	Schistosoma mansoni
	(S japonicum)
Inflammatory bowel disease	
	ulcerative colitis
	(Crohn's disease)
Irritable bowel syndrome	

* Unusual presentations in the United Kingdom are given in parentheses.

TABLE III *Investigation of chronic diarrhoea in relation to tropical exposure**

Small intestinal cause		
faecal examination:	microbiology	– *Salmonella spp, Cryptosporidium spp*, etc
	parasitology	– helminths/cysts/ova
	culture	– *Strongyloides stercoralis*
HIV serology		
'Enterotest' (string test)		
small intestinal biopsy	morphology	– *Strongyloides stercoralis, Salmonella typhyi*
	parasitology	– helminths/protozoa
	culture	– *Salmonella spp*, etc
	disaccharidase assay	
peripheral blood glucose response to oral lactose		
hydrogen breath test		
absorption tests (see text)		
small intestinal radiology		
upper gastrointestinal endoscopy		
Colorectal cause		
faecal examination†	microbiology	– *Shigella spp, Clostridium difficile*
	parasitology	– helminths/cysts/ova
	E histolytica (isoenzymes)	
rectal scrape†/biopsy		
serology	*E histolytica, Schistosoma spp*	
barium enema		
colonoscopy		

* Peripheral blood eosinophilia suggests an helminthic cause, whatever the site of intestinal involvement. † When *E histolytica* is being sought, a fresh, warm faecal sample gives the highest yield of positive results.

TABLE IV *Treatment of chronic diarrhoea with an infective basis**

	Oral therapeutic agent	*Dose regimen (days)*	
Small intestinal causes			
postinfective malabsorption	tetracycline + folic acid	250 mg tds 5 mg bd	(30) (90)
Giardia lamblia:	metronidazole	2 g	(3)
	tinidazole	2 g	(1)
Cryptosporidium spp†	–	–	
Isospora belli†	co-trimoxazole	2 tab qds	(14)
Strongyloides stercoralis	albendazole	400 mg bd	(3)
	thiabendazole	25 mg/kg bd	(3)
(Capillaria philippinensis)	albendazole	400 mg bd	(3)
(Fasciolopsis buski)	praziquantel	15 mg/kg	(1)
Colorectal causes			
(Clostridium difficile)	metronidazole	400 mg tds	(7)
	vancomycin	125 mg qds	(7)
Entamoeba histolytica	metronidazole	800 mg tds	(5)
	tinidazole	1 g tds	(3)
(Trichuris trichiura)	mebendazole	100 mg tds	(3)
	albendazole	400 mg bd	(1)
Schistosoma mansoni	praziquantel	40–50 mg/kg	(1)
(Schistosoma japonicum)	praziquantel	40 mg/kg	(3)

* Unusual presentations in the United Kingdom are given in parentheses; † usually HIV associated. tds=thrice daily, bd=twice daily, qds=four times daily.

about a 70% cure rate; side effects can be troublesome. Albendazole (the newest benzimidazole) is more acceptable, but results of its efficacy are not so well reported. The nematode *Capillaria philippinensis*, and trematode (fluke) *Fasciolopsis buski* respond to albendazole and praziquantel, respectively. Spiramycin has achieved a place in chemotherapy of *Cryptosporidium spp*, but there is no satisfactory evidence for its efficacy; co-trimoxazole is effective in chronic *Isospora belli* infection.

Since the 1950s, tetracycline has formed the basis of chemotherapy for post infective malabsorption (Begg had concluded in 1912 that it had an infective basis)[22]; no other antimicrobial agent has been adequately assessed. Various chemotherapeutic regimens are currently in use, for example, tetracycline 250 mg thrice daily for 30 days plus folic acid 5 mg twice daily for 90 days.[2]

In an unusual case of persistent diarrhoea caused by *Shigella spp*, a quinolone – ciprofloxacin or norfloxacin – is indicated chemotherapeutically.[7]

A 5-nitroimidazole compound is the preferred agent for an *E histolytica* infection; despite reports of 'resistant' strains – mostly from India and China – no good evidence for this exists; there are no satisfactory in vitro data pointing to *E histolytica* resistance to 5-nitroimidazole in any geographical setting. The course must be followed by diloxanide furoate (a superior luminal amoebicide) 500 mg thrice daily for 10 days – which will kill cysts of a potentially invasive zymodeme (capable of initiating future disease); success rate after a single course is only about 70–80%.

Schistosoma spp responds to praziquantel; various regimens have been recommended and in general, *S japonicum* is more difficult to eliminate (several doses are usually used) than the other species.

The accurate incidence of antibiotic associated (pseudomembranous) colitis in travellers is unknown. Antibiotics are widely used by tourists (and others) and it seems possible that it is an underdiagnosed entity. Treatment is with either metronidazole or vancomycin.

In a 'difficult' case, in which the diagnosis is unclear despite extensive investigation, a chemotherapeutic trial of metronidazole or tinidazole (Table IV) seems justified.

Admission to hospital for observation of stool frequency and weight stability is of value when doubt arises that a case is genuine. In patients suffering from irritable bowel syndrome, diarrhoea usually stops during hospital admission; total faecal weight is normal although there may be several stools daily!

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