Persisting diarrhoea and malabsorption

Most diarrhoeal episodes acquired during tropical exposure subside spontaneously within a few days. A few continue for a longer period; what therefore constitutes chronicity (or persistence)? An arbitrary span of ≥two weeks seems a valuable "cut off" point. Prolongation of an acute infection (for example, *Salmonella spp* or amebic 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. 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 While postinfective malabsorption ("tropical sprue") was formerly a classic (and common) entity, it has been superseded in prevalence by HIV enteropathy (Table 1).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 ileoceleal 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). 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 coexistent 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.

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 abruptly ending. Although the term tropical enteropathy (villous blunting, infiltration within the lamina propria, associated with minimal enterocyte damage) is commonly applied (Table 1), the scientific basis remains flimsy, and the mechanism of symptomatology unclear.

Table 1 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; 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*), protozoa (a coccidian – usually *Cryptosporidium spp* or *Microsporidium spp* – see below), or fungi (*Candida spp*), or all four, is usual. HIV involvement of the enterocte is also important. 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), 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, and in Africa. 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. Methods for investigation are outlined below.

Small intestinal parasites are dominated by *Giardia lamblia*, a flagellated protozoan, which causes a spectrum of disease ranging from a travellers' diarrhoea like illness 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). 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 "hyperfecction syndrome", usually in an immunosuppressed subject, migrating larvae are usually accompanied by *Enterobacteriaceae*; all organs can be affected. *Capillaria philippinensis* 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
Persisting diarrhoea and malabsorption

Secondary hypolactasia is a common sequel to a small intestinal insult – especially an infection\textsuperscript{41} –; therefore, milk ‘intolerance’ is common in subjects exposed to a tropical or subtropical environment. The H\textsubscript{2} breath test is of value diagnostically.\textsuperscript{42} Dietary lactose exclusion is often useful.

Colorectal causes

Visible blood, often associated with mucus/pus signifies colorectal pathology. 

Shigella spp. and other colonic bacterial \textit{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 \textit{a protozoan}\textsuperscript{64} and less often \textit{Trichuris trichiura} \textit{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\textsuperscript{65} – manifesting for the first time. The mechanism(s) responsible remains unclear; an acute infection – possibly caused by \textit{E coli} – seems likely, and it is possible that an already damaged colonic crypt 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.\textsuperscript{66} It does not seem to be related to lactose digestion,\textsuperscript{44} and the pathophysiological basis is unclear.\textsuperscript{77}

In \textit{E histolytica} colitis, dysentery 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);\textsuperscript{31} other complications: are: appendicitis, amoeboma, haemorrhage, and sticture. Shigellosis may be complicated by: Reiter’s syndrome (usually \textit{HLA-B27-associated}) and (rarely) haemolytic uremic syndrome.

Chronic diarrhoea caused by \textit{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.\textsuperscript{44}

Colorectal schistosomiasis (usually \textit{Schistosoma mansoni} infection) can present with chronic bloody diarrhoea;\textsuperscript{33} 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: \textit{S japonicum}, \textit{S mekongi}, \textit{S intercalatum}, and \textit{S matthei}.

Limited evidence shows that chronic colitis might result from direct HIV invasion of the colonocyte.\textsuperscript{43}

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,\textsuperscript{46} methyl dopa (used in hypertension), diuretics, magnesium\textsuperscript{68} (peptic ulcer disease), and para-aminosalicylic acid (tuberculosis); excessive alcohol intake\textsuperscript{44} 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.\textsuperscript{44}

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 \textit{Campylobacter jejuni},\textsuperscript{82} \textit{Aeromonas spp.},\textsuperscript{84} and \textit{Plesiomonas shigelloides}\textsuperscript{85} have been recorded. Dysgonic fermenter 3 has also been isolated.\textsuperscript{88} The role of fungi remains unclear.\textsuperscript{89}

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\textsuperscript{90}; 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.
Investigations

The range of investigations should be tailored to the probable site of the pathological lesion. 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. Bacteremia is unusual in an intestinal infection. Invasive colorectal amoebiasis is best diagnosed from a rectal scrape slide; 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, Clostridium difficile is sought. Eggs, cysts, and adult parasites must also be identified – preferably using a concentration technique. When a rectal scrape slide is not available, the best means of detecting Entamoeba 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 Schistosoma spp 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 immunofluorescent 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 'Entertest' (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 B12 concentration.

In differentiating postinfecive 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 ileo-caecal 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*; the glucose-hydrogen breath test is of value. Idiopathic bile acid malabsorption (a further cause of chronic diarrhoea) can be assessed by measurement of 7SeHCAT.**

Treatment

Prevalence of chronic diarrhoea after tropical exposure has fallen dramatically since widespread use of antibiotic and anti-protozoan agents for acute diarrhoeal disease.*** Two decades ago many travellers to South East Asia returned with postinfecive 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 Giardia 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>
<thead>
<tr>
<th>TABLE III</th>
<th>Investigation of chronic diarrhoea in relation to tropical exposure*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Small intestinal cause</strong></td>
<td><strong>faecal examination:</strong> microbiology – Salmonella spp, Cryptosporidium spp, etc</td>
</tr>
<tr>
<td><strong>HIV serology</strong></td>
<td><strong>Entertest</strong> (string test)</td>
</tr>
<tr>
<td><strong>small intestinal biopsy</strong></td>
<td>morphological – Salmonella spp, enteropathogenic E. coli, E. histolytica, <strong>parasitology</strong> – helminths/cysts/ova</td>
</tr>
<tr>
<td><strong>disaccharidase assay</strong></td>
<td>culture – S. stercoralis, <em>Salmonella</em> spp, etc</td>
</tr>
<tr>
<td><strong>peripheral blood glucose response to oral lactose hydrogen breath test</strong></td>
<td>assimilation test/see text</td>
</tr>
<tr>
<td><strong>small intestinal radiology</strong></td>
<td>upper gastrointestinal endoscopy</td>
</tr>
</tbody>
</table>

**Colorectal cause**

| faecal examination | **microbiology** – *Shigella* spp, Clostridium difficile |
| **parasitology** – helminths/cysts/ova |
| **entero-anaerobic** E. histolytica (isoenzymes) |
| **rectal scrape/biopsy serology** | culture – S. stercoralis, *Salmonella* spp |
| **barium enema colonoscopy** | **|}

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

** Peripheral blood eosinophilia suggests a 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

<table>
<thead>
<tr>
<th>Oral therapeutic agent</th>
<th>Dose regimen (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline + folic acid</td>
<td>250 mg tds (30)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>25 mg bd (90)</td>
</tr>
<tr>
<td>Tinidazole</td>
<td>2 g (1)</td>
</tr>
<tr>
<td>Praziquantel</td>
<td>2 g (1)</td>
</tr>
<tr>
<td>Albendazole</td>
<td>25 mg/kg (3)</td>
</tr>
<tr>
<td>Mebendazole</td>
<td>100 mg qds (3)</td>
</tr>
<tr>
<td>Mebendazole</td>
<td>400 mg bid (1)</td>
</tr>
<tr>
<td>Prasanthi manaxo</td>
<td>40-50 mg/kg (1)</td>
</tr>
<tr>
<td>Schistosoma japonicum</td>
<td>40 mg/kg (3)</td>
</tr>
</tbody>
</table>

*Unusual presentations in the United Kingdom are given in parentheses;† usually HIV associated.*

<table>
<thead>
<tr>
<th> </th>
<th><strong>Ovaria lactea</strong></th>
<th><strong>Cryptosporidium spp</strong></th>
<th><strong>Isospora belli</strong></th>
<th><strong>Strongyloides stercoralis</strong></th>
<th><strong>Fasciolopsis buski</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>tetracycline</td>
<td>—</td>
<td>co-trimoxazole</td>
<td>albendazole</td>
<td>400 mg bd (3)</td>
</tr>
<tr>
<td>Prasanthi manaxo</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Albendazole</td>
<td>400 mg bd (3)</td>
</tr>
<tr>
<td>Schistosoma japonicum</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Praziquantel</td>
<td>15 mg/kg (1)</td>
</tr>
</tbody>
</table>

**Colonial coccidia**

<table>
<thead>
<tr>
<th><strong>Cryptosporidium difficile</strong></th>
<th><strong>Enzootic histolytica</strong></th>
<th><strong>Trichuris trichiura</strong></th>
<th><strong>Schistosoma mansoni</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>vancomycin</td>
<td>tinidazole</td>
<td>Mebendazole</td>
</tr>
<tr>
<td>400 mg tds (7)</td>
<td>125 mg qds (7)</td>
<td>1 g tds (3)</td>
<td>100 mg tds (3)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>—</td>
<td>—</td>
<td>Albendazole</td>
</tr>
<tr>
<td>400 mg bid (1)</td>
<td>—</td>
<td>—</td>
<td>400 mg bid (1)</td>
</tr>
</tbody>
</table>

**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 (pseudo-) membranous 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! **G C COOK**

**Hospital for Tropical Diseases, St Pancras Way, London NW1 8PE**

Cook
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G C Cook

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