Sodium fluoride has been administered to strengthen the bones of patients with myeloma, on the grounds that the dense fluorosis that occurs might do this and prevent spontaneous fractures. In a trial of low and high dose fluoride administration compared with a placebo Harley *et al.*[12] were unable to show any differences between the three groups in survival, progression of skeletal change, loss of height, incidence of pain, loss of performance, or requirement for radiotherapy. They concluded that by itself fluoride made no difference. Carbone *et al.*[13] studied the bone formed after giving fluoride and found that it contains no more calcium as a result, the bone being inferior in quality and just as likely to fracture. Others have felt that the concurrent administration of vitamin D, calcium, androgen, and fluorides may be effective, but there are no controlled studies on this point. It seems that fluoride by itself is of little benefit.

Hypercalcaemia

A major metabolic complication involving bone is hypercalcaemia. A complaint of general weakness, tiredness, lassitude, anorexia, nausea, vomiting, thirst, constipation, drowsiness, or even abnormal mental behaviour should raise the possibility of this complication and the diagnosis is confirmed by showing a raised serum calcium level. Mild symptoms with a slight rise of the serum calcium level may be managed by a low calcium diet, increased fluid intake, and immediate and effective chemotherapy. If this fails then prednisolone in a daily dose of 60 mg with oral neutral phosphate in doses of 1 to 2 g in the first 24 hours is effective. Until chemotherapy controls the tumour disodium hydrogen phosphate, 10 g daily (a total daily phosphate administration of 2 g), will be needed to keep the serum calcium level within normal limits.[14] Theoretical objections that calcium may be deposited in vital areas such as the kidneys must be considered in relation to the situation of a patient with steroid-resistant hypercalcaemia, a life-threatening occurrence. The role of calcitonin, glucagon, and diphosphonates is under investigation.

Viscosity Syndrome

Plasmapheresis is the method of choice for treating the viscosity syndrome in macroglobulinaemia or myeloma. This syndrome —which may give rise to a variety of symptoms such as deterioration of vision with eventual blindness, a reduced level of consciousness ending in coma, heart failure, renal failure, and intractable bleeding—is caused by increased plasma viscosity due either to excess of the "M" component or to large polymers formed from it. In patients who bleed probably several factors (including coating of the platelets, inhibition of thrombin activity, or adsorption of clotting factors) are responsible for the damage to the mechanism of coagulation. The N.C.I.-I.B.M. Cell Separator which is designed for the collection of leucocytes from the peripheral blood may be used as an efficient and safe method of plasma exchange.[15] There is a dramatic arrest of bleeding or recovery of consciousness after its use.

Progress in the management of myeloma has been disappointingly slow. Nevertheless, the demonstration that cross resistance to alkylating agents may not be present, our continuation or maintenance treatment is inadequate, and the understanding of the kinetics of the myeloma cell, should stimulate new approaches to the management of this disease.

I am grateful to Professor Raymond Alexanian and Professor Daniel Bergsagel for kindly allowing me to quote from papers that they are shortly publishing.

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Imported Diseases in General Practice

Gastrointestinal Disorders

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Gastrointestinal upsets must be as common throughout the world as upper respiratory infections. In 70-80% of cases the cause is unknown, the illness is shortlived, and the patient does not seek medical advice. Precisely because the upset is usually trivial, ready access to doctors in Britain means that the traveller runs the twin risks of over-treatment and failure to diagnose serious conditions. As usual, a careful history with particular attention to the patient's social and geographical background, together with some knowledge of the distribution of disease for which Professor Brian Maegraith's small book is invaluable,[1] are more likely to influence the outcome than indiscriminate use of drugs such as antibiotics, whose value is doubtful.

No one is immune from gastrointestinal upsets, but the young —for example, schoolchildren returning from holidays abroad— and the elderly are particularly susceptible and often suffer more serious disease. Moreover, the immigrant population of Europe is more mobile than it used to be and it is important to ask a

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foreign resident if he has recently visited his home country. Patients with achlorhydria and those who have had gastric operations are said to be more susceptible to gastroenteritis, while patients with ulcerative colitis or the irritable gut syndrome may develop an exacerbation of symptoms due to the rigours of travel. It is not safe to assume, however, that an attack in such a subject is an exacerbation rather than a new infection.

Though there may be a good deal of overlap, it is possible to consider gastrointestinal disorders according to the type of clinical picture with which they present. Occasionally more than one cause may be responsible for symptoms.

Gastroenteritis

TRAVELLERS' DIARRHOEA

Though it is part of the folklore of Britain that travellers' diarrhoea particularly afflicts visitors to Southern Europe, the Middle East, and South America, it occurs in countries as well developed as the United States, and one wonders how many people coming to these islands are similarly affected. Nevertheless, it is commoner among inhabitants from the northern hemisphere who travel abroad,[2] and affects particularly those of higher socio-economic status. It is assumed to be infective, but an organism can be isolated only in 15-35% of patients. *Escherichia coli*, salmonella, giardia, and viruses have been implicated, and recently yersinia species have been isolated from travellers to Southern Europe who develop diarrhoea and abdominal pain—which may simulate acute appendicitis and may be followed by erythema nodosum. Changes in climate and food habits may be equally important, because the upset usually starts within a few days of visiting a new country. Overindulgence in unfamiliar foods such as chillis, peppers, and garlic may also be responsible. Rather surprisingly, Loewenstein *et al.*[2] found that precautions such as drinking bottled water, avoiding fresh fruit and salads, and prophylactic bowel antiseptics did not prevent "turista" in delegates to a Mexican congress.

The onset of symptoms is sudden, with diarrhoea, tenesmus, and abdominal cramps; vomiting is less common. The loose stools are accompanied by much frothy material but seldom blood. The attack lasts two to three days, and is accompanied by dehydration and prostration only in the very young and the elderly. The stools may remain loose for a week or ten days.

FOOD-POISONING

Food-poisoning usually begins within a few hours of the meal and commonly other people are affected, and vomiting is prominent. The condition is usually mild, though since the cause is an endotoxin, prostration may occur quite rapidly. The usual organisms are staphylococci from food handlers, clostridium from meat (with pronounced diarrhoea), and salmonella from poultry and cooked meats. Many types of salmonella including *Salmonella typhi* may cause an illness resembling food-poisoning. Vibrio species, including *Vibrio cholera*, may cause gastroenteritis, and they have been associated with diarrhoea from eating seafood products in the Far East. Recently *Bacillus cereus* from cooked rice in Chinese restaurants has been recognized as a cause.

GIARDIASIS

Giardia lamblia, an active protozoon which is found in the duodenum and small intestine, is of world-wide distribution. Infestation is said to be present in 10% of the world population, and it is currently the commonest parasite in Britain. There may be no symptoms, but it sometimes causes severe diarrhoea, with nausea, vomiting, abdominal cramps, and loose, foul-smelling stools.[3] The patient may become quite ill. Infection is acquired from water, food, or direct contact; the incubation period is 10-12 days; and humidity and poor sanitation are responsible for its spread. Repeated examination of fresh, warm stools for cysts is necessary to make the diagnosis, and this is important since treatment with mepacrine or metranidazole is curative.

WORMS

Very few cause diarrhoea but their distribution is so widespread that they may be suspected in people returning from the tropics, the Middle East, and Far East. The intestinal fluke, fasciolopsis, common in the Indian subcontinent and South-East Asia, may cause diarrhoea, especially in children. Strongyloides may produce symptoms resembling food-poisoning, sometimes with a systemic illness. Suspicion of worms should be aroused if there is an associated history of "dermatitis," "urticaria," or constitutional upset; blood should be examined for eosinophilia and stools for larvae, cysts, or eggs.

Dysenteries

BACILLARY DYSENTERY

Bacillary dysentery (shigellosis) varies from a mild to severe illness. While perhaps only 10% of cases of sonnei dysentery are associated with diarrhoea, *Shigella flexneri* infection is accompanied by the typical bloody stools and much tenesmus, and *Sh. dysenteriae* from the Far East causes the most serious illness. Incubation varies from one to three days and several people are likely to be affected. Classically, there is sudden onset of fever, malaise, abdominal cramps, and diarrhoea with large numbers of loose stools, containing pus, mucus, and blood—though the latter may be absent. Dehydration and prostration occur in the more severe cases. Sigmoidoscopy shows generalized hyperaemia and oedema of the bowel. A fresh stool, or better still a rectal swab particularly of mucus, should be cultured, but a negative result does not exclude the diagnosis.

Salmonella and *E. coli* may also cause a dysentery-like illness, and schistosomiasis, especially *Schistosoma mansoni* and *S. japonicum* infections, which occur mainly in South America and the Far East with only a few foci in the Middle East, produce dysenteric symptoms a week or two after penetration of the skin by the cerceriae.

MALIGNANT MALARIA

Malignant (falciparum) malaria is endemic in Africa, the Indian subcontinent, the Far East, and South America. The incubation period is about 12 days and clinical manifestations are protean. One such is a gastrointestinal syndrome resembling bacillary dysentery, with blood in the stools due to capillary involvement, abdominal cramps, and vomiting; fever and dehydration are usually present. Scanty parasites may be found in the peripheral blood. The index of suspicion should be high in any person who becomes ill after returning from an endemic area since early treatment will prevent a fatal outcome.

AMOEBIC DYSENTERY

Amoebic dysentery is a much more insidous illness and a third of patients do not have diarrhoea, but complain of fatigue, aching, and psychosomatic symptoms. Stools are foul-smelling and contain blood, but abdominal discomfort is unusual. Attacks tend to recur and many years may elapse between episodes. The characteristic motile amoebae containing cysts and red cells may be found on prompt examination of a fresh specimen of diarrhoeal stool in warm saline, but a better method may be to examine scrapings of ulcers obtained at sigmoidoscopy.

Cholera

Present outbreaks of cholera are due to the El-Tor vibrio, which produces a higher ratio of asymptomatic cases and sometimes carriers, with spread within families, especially where sanitation is inadequate. The Indian subcontinent and South-East Asia are endemic areas, but outbreaks have occurred in Southern Europe and North Africa. Vaccination results in about 60% protection but lasts only a few months. Mild diarrhoea may be due to cholera, but the usual attack is severe and indistinguishable from Asiatic cholera. After an incubation period of one to three days there is an explosive onset of profuse watery diarrhoea, accompanied by vomiting, cramps, and rapid dehydration and collapse, making admission to hospital urgent. The clinical picture is due to the effect of endotoxin on the small intestine, which results in profound losses of water and electrolytes. Vibrios are easily identifiable in the "rice-paper" stools.

Salmonella and other types of food poisoning may produce a cholera-like syndrome.

General Gastrointestinal Symptoms

ENTERIC FEVERS

Typhoid and paratyphoid usually present insidiously with general symptoms due to the bacteraemia, but occasionally there is early diarrhoea, especially in children, and gastrointestinal complaints may be prominent in paratyphoid infections. After an incubation period of about 10 days there is gradual onset of remittent fever, headache, dry cough, and anorexia. Constipation and abdominal distension are prominent, the abdomen is tender, the spleen enlarged, and rose spots may be present on the trunk. Diarrhoea with green or grey watery stools supervenes during the third week at the height of the fever, toxaemia, and delirium. Organisms may be cultured from the blood and bone marrow during the first week and from the stools from the second week on, when there is a rise in the Widal O titre.

VIRUS HEPATITIS

Both infectious and serum hepatitis are worldwide in distribution and should always be considered in people with gastrointestinal complaints, especially those who have come from areas where the diseases are common—for example, Southern Europe, the Middle East, and tropical countries. It is well to remember that incubation may take up to six weeks for infectious hepatitis and up to six months for serum hepatitis. The initial symptoms of abdominal discomfort, anorexia, nausea and vomiting, and alteration in bowel habit are often attributed to gastroenteritis, and may be present for ten days before jaundice appears. Early recognition may be helped by finding excess urobilinogen or bilirubin in the urine during the pre-icteric stage. A sample of blood should be obtained from patients who have been abroad to test for hepatitis-associated antigen, since the frequency of serum hepatitis is high and there may be no history of infection by parenteral means.

Persistent Diarrhoea

An attack of diarrhoea which does not subside soon after returning from abroad should be fully investigated. The following possibilities should be borne in mind:

(1) Inappropriate treatment of the original illness with antibiotics, with subsequent alteration in bowel flora or the development of monilial infection.

(2) The presence of giardia or amoebae which have not been excluded by repeated stool examination.

(3) The development of malabsorption, characterized by steatorrhoea and weight loss, due to giardiasis, parasites such as strongyloides, or tropical sprue. The latter is particularly likely in those who have lived temporarily in the East—for example, military personnel, voluntary workers, and young people who take the overland route to India.[4]

(4) Disaccharidase deficiency—for example, lactose intolerance—which may be congenital or may have been acquired as a result of the original gastrointestinal disturbance. Exclusion of milk may cure the diarrhoea.

(5) The irritable gut syndrome, gluten enteropathy, or ulcerative colitis initiated or aggravated by the original insult to the bowel.

(6) Tuberculosis especially if the patient is an Asian, or intestinal lymphoma if he comes from the Middle East.

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Any Questions?

We publish below a selection of questions and answers of general interest

Diagnosis of Primary Biliary Cirrhosis

Can primary biliary cirrhosis be diagnosed by the presence of mitochondrial antibodies and the increased concentration of IgM in blood? Are these mitochondrial antibodies specific for ductular epithelium (biliary)?

Though mitochondrial antibodies are found in high frequency in primary biliary cirrhosis (90-95%) they are also found in other varieties of possible autoimmune cirrhoses, such as active chronic hepatitis (30-40%) and cryptogenic cirrhosis (10-20%). An increased concentration of IgM in the blood is often present in primary biliary cirrhosis but again there is some overlap with other varieties of cirrhosis. Testing for mitochondrial antibodies can be of diagnostic help, particularly in the sometimes difficult distinction of primary biliary cirrhosis from surgical causes of obstructive jaundice, such as gall stones or carcinoma, in which mitochondrial antibodies are not found. These antibodies are not organ specific and the existence and pathogenetic importance of antibodies to biliary ductular epithelium is questioned. Though the presence of mitochondrial antibodies together with compatible clinical and biochemical changes will make primary biliary cirrhosis very likely, liver biopsy should also be carried out (unless there are specific contraindications), for the histological appearances can be quite distinctive during the early stages of the disease.