and appreciable fatality rate from, diarrhoeal disease. Moreover, continuing an active promotional programme for oral rehydration therapy rather than antidiarrhoeal agents will have useful benefits: domestic and national costs will be reduced and lives saved.

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- Costello AM de L, Bhutta TI. Antidiarrhoeal drugs for acute diarrhoea in children. *BMJ* 1992;304:1-2. (4 January.)
- WHO. *The rational use of drugs in the management of acute diarrhoea in children*. Geneva: WHO, 1990.
- Market research and diarrhoeal disease control programmes. *Dialogue on Diarrhoea* 1988;32:4-5.
- Viswanathan H, Rohde JE. *Diarrhoea in rural India. A nationwide study of mothers and practitioners*. Vision Books, New Delhi: Unicef, 1990.

SIR,—Anthony M de L Costello and Tariq Iqbal Bhutta's arguments against using antidiarrhoeal drugs for children with acute diarrhoea in developing countries are correct.¹ What may not be generally appreciated, however, is the frequency of use of these drugs in so called developed countries and the potential hazards associated with them. The central nervous system manifestations of intoxication with antidiarrhoeal agents continue to be reported in the West.² My experience of patients suffering from verotoxigenic *Escherichia coli* infections in western Canada is that the frequency of use of pharmacological agents is not much different from that reported a decade ago in patients with gastroenteritis.³

In addition to direct toxicity on the central nervous system I have been concerned about the potential ability of some antidiarrhoeal agents to complicate the outcome of acute bacterial gastrointestinal infection.^{4,5} Although there is precedent for associating some antimotility agents with a poor outcome of gastrointestinal disease, colleagues and I have found a strong association between their use in verotoxigenic *E coli* infection and its progression to the haemolytic-uraemic syndrome.⁴

We have extended our studies to examine risk factors for the central nervous system manifestations of the haemolytic-uraemic syndrome and have found a strong association between prolonged use of an antidiarrhoeal agent and such manifestations (odds ratio 7.5; 95% confidence interval 1.5 to 37.8) (unpublished findings). Though this association leads us to hypothesise that an indirect cause and effect relation exists whereby the use of pharmacological agents enhances absorption of toxins after bowel immotility (that is, toxin mediated damage), we are also concerned that some of the neurological effects may be a direct result of the drugs themselves. The excretion of some of these agents is probably impaired in patients with the nephropathy of the haemolytic-uraemic syndrome.

These concerns should lead to a reassessment of our own practices in addition to those of developing countries.

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- De L Costello AM, Bhutta TI. Antidiarrhoeal drugs for acute diarrhoea in children. *BMJ* 1992;304:1-2. (4 January.)
- McCarron MM, Challoner KR, Thompson GA. Diphenoxylate-atropine (Lomotil) overdose in children: an update (report of eight cases and review of the literature). *Pediatrics* 1991;87:694-700.
- Morrison PS, Little TM. How is gastroenteritis treated? *BMJ* 1981;283:1300.
- Cimolai N, Carter JE, Morrison BJ, Anderson JD. Risk factors for the progression of *Escherichia coli* O157:H7 enteritis to hemolytic-uremic syndrome. *J Pediatr* 1990;116:589-92.
- Cimolai N, Carter JE. Gender and the progression of *Escherichia coli* O157:H7 enteritis to hemolytic-uremic syndrome. *Arch Dis Child* 1991;66:171-2.

SIR,—In their editorial Anthony M de L Costello and Tariq Iqbal Bhutta point out that an important reason for prescribing antidiarrhoeal drugs is that glucose and electrolyte based oral rehydration solution does not reduce the number of stools so parents do not consider that the diarrhoea is getting better.¹ This was true even of some developed countries until a few years ago, and it is only continuing education that has produced a remarkable change.

In 1985, 41 216 patients attended this accident and emergency department. A total of 246 general practitioners had been responsible for their care. Ninety one of these patients were children with acute diarrhoea, who had been prescribed antidiarrhoeal drugs by 67 general practitioners. Each of these attendances was followed up by a questionnaire, a telephone call, and a home visit to inquire about the reason for prescribing antidiarrhoeal drugs. Sufficient information was obtained on 89 children, who had been prescribed antidiarrhoeal drugs by 65 general practitioners.

When asked the reasons for prescribing the drugs, 11 general practitioners, who had prescribed them for 14 patients, did not know the dangers. Ten general practitioners, who had prescribed the drugs for 13 patients, said that they were aware of the dangers but still thought that there was a place for antidiarrhoeal drugs. Thirty general practitioners prescribed oral rehydration therapy but submitted to parental demands for antidiarrhoeal drugs. Fourteen general practitioners continued to prescribe antidiarrhoeal drugs for 21 patients because they had stopped explaining to patients the reason for oral rehydration on its own.

A programme of education through lectures and newsletters resulted in a dramatic reduction in the number of general practitioners prescribing antidiarrhoeal drugs and an understanding by the community of the dangers of such agents.² An audit of the 109 children who presented with acute diarrhoea in 1991 showed that only two of them had been prescribed antidiarrhoeal drugs.

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- Tachakra S, Black A, Potts D, Idowu A. General practitioners' use and expectations of an accident and emergency department. *J R Soc Med* 1990;83:600.

Homozygous haemoglobin O Arab disease and conjugated hyperbilirubinaemia

SIR,—S A Ibrahim and colleagues' findings of familial cases of homozygous haemoglobin O Arab (Hb O Arab) and a close association with conjugated hyperbilirubinaemia (Dubin-Johnson type) in Sudan is interesting.¹

Dubin-Johnson syndrome has been reported to be relatively common in Papua New Guinea.^{2,3} Furthermore, I showed that 15% of patients suffering from an infective disease at Port Moresby possess a defect in bromsulphthalein excretion (resulting from regurgitation of bromsulphthalein conjugates from liver to plasma) after an intravenous load (which is similar to that observed in Dubin-Johnson syndrome), although the characteristic pigment is not present in a liver biopsy specimen.⁴ I hypothesised that these people might possess a forme fruste of this disease which is overtly displayed during stress (resulting, for example, from an infection). Clusters of the Dubin-Johnson syndrome polymorphism have also been

recorded in Iranian Jews and Indian, Pakistani, Japanese, Chinese, and Hong Kong populations.^{3,4} The selective advantage of this gene is obscure, but one suggestion is that it confers a protective effect against falciparum malaria,² the milieu within the hepatocyte being unsatisfactory for schizogony to take place.¹

Hb O Arab has been documented in Israel, Kenya, Jamaica, the United States, and Bulgaria as well as Sudan³; a hypothesis has been proposed that this haemoglobinopathy was carried from Bulgaria (where the highest prevalence has so far been recorded) to the northern parts of east and west Africa during the days of the Ottoman empire. If Hb O Arab is protective against falciparum malaria, as Ibrahim and colleagues claim, it would seem worth while to look for it in people in Papua New Guinea, where it might also be associated with Dubin-Johnson syndrome. Its presence would be of considerable interest in the context of geographical (and ethnic) drift of the Dubin-Johnson syndrome and Hb O Arab genes and hence to biological anthropologists with an interest in the Pacific area.

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- Ibrahim SA, Mustafa D, Mohamed AO, Mohed MB. Homozygous haemoglobin O disease and conjugated hyperbilirubinaemia in a Sudanese family. *BMJ* 1992;304:26-7. (4 January.)
- Vaughan JP. Chronic familial jaundice in Papua New Guinea. *PNG Med J* 1969;12:128-9.
- Vaughan JP, Marubio AT, Maddocks I, Cooke RA. Chronic idiopathic jaundice in Papua and New Guinea: a report of nine patients with Dubin-Johnson's or Rotor's syndrome. *Trans R Soc Trop Med Hyg* 1970;64:287-92.
- Cook GC. Defect in plasma clearance of bromsulphthalein in Papua New Guineans with systemic infections. *Q J Med* 1980;49:491-500.
- Sarjeant GR. *Sickle cell disease*. Oxford: Oxford University Press, 1985:23.

SIR,—Cases of the homozygous state of haemoglobin O Arab (Hb O Arab) such as that reported by S A Ibrahim and colleagues are uncommon but have been reported previously, although not in association with Dubin-Johnson syndrome.

People with the homozygous state seem to fall into two distinct groups. One group suffers symptomatic recurrent anaemia and jaundice, such as described in Bulgaria,¹ Yugoslavia,² and Turkey³; the second group is made up of asymptomatic people in whom the finding is incidental, such as a Moroccan patient⁴ and a pregnant Tunisian woman reported on recently by this department.⁵ There seems to be no particular laboratory marker for the disparity between the two groups, which may be attributable to other factors such as intercurrent illness or environmental effects.

The distribution of the Hb O Arab gene among the populations of north Africa, Palestine, and eastern Europe is of anthropological interest and has led to speculation about its origin; correlation with other genetic markers such as blood groups suggests that it is of African origin,⁷ although some suggest that it originated in East Thrace (Bulgaria).² The gene's geographic distribution seems to be related to the extent of the Ottoman empire; spread was facilitated by the Turkish army recruiting the natives of occupied areas and deploying them elsewhere.

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