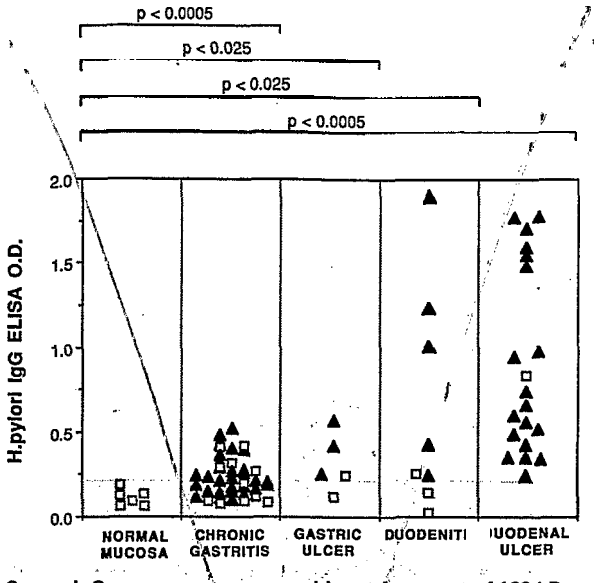

Serum IgG responses to a recombinant fragment of 128 kDa protein of *H pylori* in endoscoped dyspeptic patients.

Shaded area = mean absorbance + 2 SD of 20 negative controls with no *H pylori* antibodies by western blotting. ▲ = *H pylori* positive by Giemsa staining on antral mucosa; □ = *H pylori* negative by Giemsa staining on antral mucosa.

subjects with normal mucosa ($n = 6$, $p \leq 0.0005$, *t*-test) and chronic gastritis ($n = 43$, $p < 0.0005$). Only 55·8% of patients with chronic gastritis were seropositive (figure).

Since patients with peptic ulceration are more frequently infected with cytotoxin-producing *H pylori* strains than those with gastritis alone,[5] these combined immunological and bacteriological studies suggest strongly that strains expressing the 128 kDa protein are more ulcerogenic than non-cytotoxic strains.

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Potentially lethal thiamine deficiency complicating parenteral nutrition in children

SIR,—We report two cases of acute, severe encephalopathy and lactic acidosis due to thiamine deficiency in patients receiving parenteral nutrition (PN) that occurred within days of stopping parenteral vitamin supplements.

The first case, a 4-year-old boy on long-term home PN for short bowel syndrome, developed drowsiness, irritability, and vomiting over several hours. On admission he was encephalopathic with hypotonia and absent reflexes. A full infection screen was normal and an electroencephalogram confirmed encephalopathy. Plasma was pH 7·37, bicarbonate 16 mmol/L, base excess −10·5, and lactate 7·3 mmol/L (normal 0·6–2·0). Suspecting acute thiamine deficiency, we gave him intravenous thiamine 250 mg daily for 2 days. He recovered full consiousness within 12 h (plasma lactate 2·2 mmol/L. Red-cell transketolase activation by thiamine pyrophosphate before and 1 week after the start of supplementation was 80% and 25%, respectively. We later learned that vitamin supplements had been inadvertently omitted from his parental solution at home for 8 days before presentation.

The second case was a 6-year-old boy, also on long-term PN for short bowel syndrome. He suddenly became agitated, confused, and ataxic 10 days after stopping PN for a trial of enteral feeding supplemented with enteral multivitamins. A full infection screen was normal, and an electroencephalogram showed slow waves. Plasma pH was 7·40, bicarbonate 23·5 mmol/L, base excess −1, phosphate 1·54 mmol/L, anion gap 15, and lactate 3·0 mmol/L. He was given parenteral thiamine 250 mg 6 hourly for 2 days, and recovered within 8 h. Red-cell transketolase activation before and one week after treatment was 38% and 24%, respectively.

The percentage increase in transketolase activity when thiamine pyrophosphate is added to patients' red cells provides an indirect estimate of thiamine status. Estimates of the upper limit of the normal increase vary from 15·5% to 40%.[1] Thiamine deficiency has been described in adults on PN, and in alcoholics. It has also been documented in two children undergoing chemotherapy for solid tumours after receiving PN for 2 weeks with no vitamin supplements,[2] in a boy with severe lactic acidosis on PN for 21 days after bone marrow transplantation,[3] and in a boy with severe lactic acidosis after 20 days PN without vitamin supplements.[4] All these children responsed rapidly to parenteral thiamine. Our cases became ill after only 8 and 10 days without vitamin supplements, and severe encephalopathy rather than lactic acidosis was the most prominent feature. Each had previously been receiving the recommended daily dose of thiamine (1·2 mg).[5]

It is important to recognise how rapidly thiamine deficiency can occur, and that it is often lethal. The overall mortality is more than 50% in children.[4] The clinical presentation of deficiency may be more florid in children receiving parenteral glucose, when excess pyruvate is converted into lactate. The diagnosis should be considered in children on PN who present with an unexpected encephalopathic illness. Parenteral thiamine 250 mg 6 hourly for at least 2 days should be started, while waiting for the results of red-cell transketolase activation studies.

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Fast emergence of *Plasmodium falciparum* resistance to halofantrine

SIR,—*Plasmodium falciparum* resistant to mefloquine are often cross-resistant to halofantrine.[1] Resistance to halofantrine reached 72% of cases in an area where resistance to mefloquine was 66%.[2] To evaluate the possible outcome of large-scale use of halofantrine (ie, induction and/or selection of resistance under specific drug pressure), we have studied in-vivo and in-vitro responses to halofantrine, chloroquine, quinine, and mefloquine in two geographically related areas differing in halofantrine drug-pressure. Brazzaville in the Congo was selected because, by contrast with

FREQUENCY OF IN-VIVO AND IN-VITRO RESISTANCE TO FOUR ANTIMALARIAL DRUGS IN DJOUMOUNA (CONGO) AND KUMBA (CAMEROON)*

	Halofantrine	Chloroquine	Quinine	Mefloquine
Congo				
In vivo	22/121 (52/121)†	12/23	1/32	0/32
In vitro	6/11	10/20	1/14	0/12
EC_{50}‡	12·2 (2·2–47·6)	62·8 (5·5–546)	161 (31–375)	3·4 (1·2–8)
Cameroon				
In vivo	0/54	47/166	ND	1/50
In vitro	1/10	9/25	2/18	1/22
ED_{50}‡	4·3 (2·2–26)	41 (3·6–450)	72·6 (26–370)	4·5 (1·7–30)

*In-vitro assays were by micro-isotopic method.[4] Results are expressed in EC_{50}, the effective concentration providing 50% inhibition of 3H-hypoxanthine uptake by the plasmodium parasite.
†Including cases with delayed response to the drug.
‡Mean (range) ND = not done.

other African countries, halofantrine has been strongly marketed and widely used since 1989. Local drug suppliers (SEP and Laborex) tell us that halofantrine represents about 25% of all antimalarials sold in 1991-92. In an outpatient clinic in Brazzaville, we found that halofantrine accounted for 30% of the 580 treatments administered over 4 months in 1992. An area of south-west Cameroon (outlying regions of the city of Kumba) was used as a control, since halofantrine has not received government approval and is only occasionally imported by foreigners.

For in-vivo assays, halofantrine hydrochloride suspension was given as three intakes of 8 mg/kg 6 h apart, with a glass of milk to improve absorption.[3] Parasitaemia was followed up on thick blood smears from days 0 to 8. In the Congo village of Djoumouna, among 121 individuals studied (aged 1–50 years) 22 had parasites still detectable on day 8, which shows 18% of resistance to halofantrine at an RII/RIII level (table). Of those with a negative smear at the end of follow-up, many showed delayed course to becoming negative. 43% were still positive on day 4, and 26% were still positive on day 6. Thus, in addition to the 18% with true resistance, there was a subset of 25% with abnormal delayed responses to halofantrine. 4 resistant cases received a second halofantrine treatment on day 8, a regimen now frequently recommended to improve cure rates. Only 1 was cured while the other 3 remained positive up to day 15. To ascertain that halofantrine had been properly adsorbed, the blood concentrations of the drug and its main metabolite desbutylhalofantrine were measured in day 3 samples with an enzyme-linked immunosorbent assay. In Cameroon, by contrast, all 54 cases followed up (aged 2–15 years) were suceptible to halofantrine and all the smears were negative from day 4 onwards.

In-vivo assays with other drugs confirmed the existence of a high frequency of resistance to a standard 25 mg/kg chloroquine treatment in the two countries,[4,5] and showed that nearly all isolates were sensitive to quinine (8 mg/kg every 8 h over 7 days) and mefloquine (15 mg/kg in two doses over 1 day). Only 1 case in the Congo failed to respond to quinine and 1 to mefloquine in Cameroon.

Although in-vitro assays were done in fewer isolates, distinct from those studied in vivo, they confirmed the in-vivo assays. Among 11 isolates studied with halofantrine in the Congo, 6 responded only to high concentrations (EC_{50} 20–47 mmol/L), far above the cut-off of 4–8 nmol/L. By contrast, only 1 of the 10 Cameroon isolates had an elevated EC_{50} (26 nmol/L). Chloroquine resistance was found in 50% of the cases studied by in-vitro methods in the Congo and in 36% of those from Cameroon. Quinine and mefloquine resistence were rare in both areas (table).

Thus there is a high frequency and degree of resistance to halofantrine in the Congo. The contrasting low frequency of resistance to mefloquine and quinine suggests that halofantrine resistance was not a consequence of cross-resistance with the related antimalarial. Halofantrine drug-pressure over 3 years in the Congo seems the most likely explanation for the fast emergence of resistance in this country compared with other countries where similar pressure was absent. This interpretation is supported by experiments in rodents in which resistance could be easily induced.[6] Although mefloquine resistance may indeed lead to halofantrine resistance,[2,7] the reverse is not necessarily true, for instance when halofantrine resistance is first to occur as is the case in the Congo. This finding has therapeutic implications, since it suggests that mefloquine and/or quinine may still be valuable in some of the cases of halofantrine resistance.

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Antimalarial chemoprophylaxis for West Africa

SIR,—Dr Nathwani (Feb 27, p 565) raises an increasingly important and difficult question on the most suitable long-term antimalarial chemoprophylaxis for non-immune expatriates in West Africa. We agree that poor compliance is the major cause of ineffective protection against malaria.[1] We do not, however, agree that chloroquine/proguanil is becoming less effective in this region and that mefloquine should be considered for long-term chemoprophylaxis for this reason.

Nathwani wrongly interprets Lobel and colleagues' conclusions.[2] In this study, which was conducted during the dry season (October–April), the use of mefloquine 250 mg every 2 weeks (not weekly) showed low effectiveness and the long-term period was defined as 2–7 months. Mefloquine was apparently well tolerated with this regimen, but tolerance and side-effects of weekly drug intake were not evaluated. Lobel also concluded that non-compliance contributed to low effectiveness of mefloquine prophylaxis.

Breakthroughs have been reported with both mefloquine and chloroquine/proguanil prophylaxis.[3,4] Serious side-effects have not been reported with this combination, whereas neuropsychiatric adverse effects have been recorded with mefloquine.[5] Among the expatriates in African countries, women wanting pregnancy and young children have no other choice than chloroquine/proguanil. Another factor to take into consideration is the cost for long-term drug use. Mefloquine is twice as expensive as chloroquine/proguanil.

We are not aware of any prospective, controlled clinical studies comparing the effectiveness and tolerance of mefloquine and a combination of chloroquine and proguanil in Africa. Until more convincing clinical data are available, chloroquine/proguanil seems to be more suitable than mefloquine for long-term chemoprophylaxis in West Africa. We doubt if changing the dosing regimen from daily to weekly intake will enhance compliance.