HTLV-I ANTIBODY RESULTS IN ABORIGINAL PATIENTS

Reason for testing	Western blot positive	Male/female (WB pos)	Age (yr) (mean, range)
Norwegian scabies (n=5)	5 *(100%)*	4/1 (4/1)	39·8 (17–67)
Mild scabies (n=9)	3 *(33%)*	} 9/10 (4/2)	43·1 (13–79)
Other patients (n=10)	3* *(30%)*		
Total (n=24)	11* *(46%)*	13/11 (8/3)	42·4 (13–79)

*1 patient with chronic suppurative skin infection had equivocal western blot, but was positive on other tests and is included as positive here. Exclusion of this patient will increase statistical evidence for association between Norwegian scabies and HTLV-I.
WB pos=western blot positive.

HTLV-I infection were tested for antibody to HTLV-I. All had one or more of the following clinical conditions: Norwegian scabies, scabies, chronic infected skin lesions, recurrent chest infections, bronchiectasis, unexplained abnormal liver function tests, seronegative arthropathy, neurological disease, and unexplained renal abnormalities. No patient had ATLL or HAM/TSP. When appropriate, patients also had other tests, including plasma electrophoresis, immunoglobulin subclassification, B-cell and T-cell surface markers, HIV antibody, alpha-1 antitrypsin, and anti-nuclear antibody. Apart from polyclonal gammopathies in 5 patients, no other laboratory immunological abnormalities were detected. An additional 6 patients were tested for HTLV-I antibody, including 1 part-Aboriginal patient with end-stage Hodgkin's lymphoma and Norwegian scabies, and 5 white patients. All 6 were HTLV-I seronegative. HTLV-I antibody was tested in serum by a passive particle agglutination test (Serodia). Positive results were confirmed by western blot (HTLV1–2 version 2.3, Diagnostic Biotech) and enzyme immunoassay (HTLV-I, Cambridge Biotech).

5 of 5 Aboriginal patients with Norwegian scabies had unequivocal laboratory evidence of HTLV-I infection, but only 6 of 19 others were seropositive ($p=0·0187$, Fisher's exact test). Although not a case-control study, no significant differences in sex or age distribution were noted between patients with and without Norwegian scabies (table). However, in those with Norwegian scabies (all HTLV-I antibody positive), younger patients and males were more predominant, which contrasts with epidemiological evidence[6] and further implies that Norwegian scabies and HTLV-I are associated. Overall seroprevalence was 46% but patients were selected for testing because of other possible HTLV-I associated illnesses, which is the likely explanation for this high rate. Previous studies in local Aborigines show an HTLV-I seroprevalence of 14%.[7]

We believe uncharacterised immunological defects caused by HTLV-I explain the occurrence of Norwegian scabies in our patients. We conclude that Norwegian scabies is associated with HTLV-I infection, and suggest that in communities with a high seroprevalence of HTLV-I that Norwegian scabies may be a marker of infection.

We thank the staffs of the South Australian HIV Reference Laboratory and the National HIV Reference Centre, Fairfield, Victoria, for the relevant virological studies.

Department of Medicine,
Alice Springs Hospital,
Alice Springs, Northern Territory 0870, Australia

L. C. MOLLISON
S. T. H. LO
G. MARNING

1. Anonymous. Virus diseases: human T lymphotropic virus type I, HTLV-I. *Wkly Epidemiol Rec* 1989; **49**: 382–83.
2. LaLegranade L, Hanchard B, Fletcher V, et al. Infective dermatitis of Jamaican children, a marker for HTLV-I infection. *Lancet* 1990; **336**: 1345–47.
3. Nakada K, Kohakura M, Komoda H, et al. High incidence of HTLV-I antibody in carriers of *Stromgyloides stercoralis*. *Lancet* 1984; i: 633.
4. Burkhart CG. Scabies: an epidemiologic reassessment. *Ann Intern Med* 1983; **98**: 498–503.
5. Gracey M. Annie B. Cunningham lecture: nutrition and infections in Australian Aboriginal children. *Aust NZ J Med* 1991; **21**: 921–27.
6. Blattner WA. Epidemiology of HTLV-I and associated diseases. In: Blattner WA, ed. Human retrovirology: HTLV-I New York: Raven Press, 1990: 251–65.
7. Bastian I, Hinuma Y, Doherty RR. HTLV-I amongst Northern Territory Aborigines. *Med J Aust* (in press).

Antibody cross-reactions with lipopolysaccharide from *E coli* O157 after cholera vaccination

SIR,—Strains of *Escherichia coli* serotype O157:H7 are an important cause of haemolytic uraemic syndrome (HUS) in the UK[1] and North America.[2] Patients infected with *E coli* O157:H7 produce serum antibodies to the lipopolysaccharide of this organism, and serodiagnosis provides valuable evidence of infection, especially in the later stages of disease when *E coli* O157 cannot be isolated from patients' faeces.[3] Antibody-antigen cross-reactions have been demonstrated between the lipopolysaccharides of *E coli* O157 and bacteria such as *Yersinia enterocolitica*, *Brucella abortus*, and certain strains of *Citrobacter freundii*.[4–6] These cross-reactions must be taken into consideration when interpreting the results of serological tests.

Rabbit serum antibodies against the lipopolysaccharide from *Vibrio cholerae* O1-Inaba reacted with that of *E coli* O157. Rabbit serum antibodies against the lipopolysaccharide of *E coli* O157 reacted with the homologous lipopolysaccharide only.[7] Similarly, serum antibodies from patients with HUS caused by *E coli* O157 also reacted with the lipopolysaccharide of *E coli* O157 but not with that of *V cholerae* O1-Inaba. This observation suggested that patients with a history of cholera or individuals vaccinated with *V cholerae* might produce antibodies that would react with the lipopolysaccharide of *E coli* O157 in serological tests.

To investigate this possibility, sera from 9 healthy volunteers with no history of cholera or HUS but immunised with Cho/Vac cholera vaccine (Welicome) were tested for serum antibodies to the lipopolysaccharide from *E coli* O157 with a routine procedure established in our laboratory. Sera are diluted in phosphate-buffered saline and tested with an enzyme-linked immunosorbent assay (ELISA) based on *E coli* O157 lipopolysaccharide; values under 0·4 are considered antibody negative and sera with values over 0·7 are considered antibody positive. Sera giving ELISA values under 0·7 but over 0·4 are tested by the more definitive method of immunoblotting. 5 of the 9 volunteers' sera gave ELISA values between 0·4 and 0·7, and contained antibodies reacting with *E coli* O157 lipopolysaccharide by immunoblotting.

By established criteria, these results would have been considered indicative of infection with *E coli* O157. We concluded that interpretation of the results of serological tests needs to take into account the medical history of patients, especially those vaccinated against cholera. The serological response of patients with a history of cholera to the lipopolysaccharide of *E coli* O157 is unknown.

Laboratory of Enteric Pathogens,
Central Public Health Laboratory,
Colindale,
London NW9 5HT, UK

H. CHART
B. ROWE

1. Kleanthos H, Smith HR, Scotland SM, et al. Haemolytic uraemic syndrome in the British Isles, 1985–1988; association with verocytotoxin-producing *Escherichia coli*. Part 2: microbiological aspects. *Arch Dis Child* 1990; **65**: 722–27.
2. Karmali MA. Infection by verocytotoxin-producing *Escherichia coli*. *Clin Microbiol Rev* 1989; **2**: 15–38.
3. Chart H, Smith HR, Scotland SM, Rowe B, Milford DV, Taylor CM. Serological identification of *Escherichia coli* O157:H7 infection in haemolytic uraemic syndome. *Lancet* 1991; **337**: 138–40.
4. Chart H, Cheasty T, Cope D, Rowe B. The serological relationship between *Yersinia enterocolitica* O9 and *Escherichia coli* O157 using sera from patients with yersiniosis and haemolytic uraemic syndrome. *Epidemiol Infect* 1991; **107**: 349–56.
5. Chart H, Okubadejo OA, Rowe B. The serological relationship between *Escherichia coli* O157 and *Yersinia enterocolitica* O9 using sera from patients with brucellosis. *Epidemiol Infect* 1991; **108**: 77–85.
6. Chart H, Willshaw GA, Cheasty T, Rowe B. Structure and antigenic properties of *Citrobacter freundii* lipopolysaccharides. *J Appl Bacteriol* (in press).
7. Chart H, Cheasty T, Georgiou T, Rowe B. Antigenic cross-reactions between *Escherichia coli* O157, *Vibrio cholerae* (Inaba) and group N *Salmonella*. *Serodiag Immunother Infect Dis* (in press).

Halofantrine resistance in African countries

SIR,—Professor Brasseur and colleagues (April 3, p 901) account for the rapid emergence of *Plasmodium falciparum* resistance to halofantrine, contrasting with the absence of resistance to mefloquine in the Congo, by high drug-pressure from halofantrine. With the same micro-isotopic test with results expressed in IC_{50} (the

IN-VITRO RESISTANCE

—	Chloroquine	Quinine	Mefloquine	Halofantrine*
Brazzaville				
Resistant strains†	26/63 (41%)	9/74 (12%)	6/64 (9%)	3/67 (5%)
IC_{50} (mean, range)	93 (7–453)	181 (12–735)	8·9 (1·3–67)	0·9 (0·2–12)
Djoumouna				
Resistant strains†	10/20 (50%)	1/14 (7%)	0/12	6/11 (55%)
IC_{50} (mean, range)	63 (6–546)	161 (31–375)	3·4 (1·2–8)	12·2 (2·2–47·6)

*Resistance: Brazzaville *vs* Djoumouna, p=0·0001 (χ^2, Yates'), p=0·00025 (Fisher's). †(IC_{50} > threshold)/tested. Thresholds: 100, 350, 30, and 5 nmol/L, respectively.

concentration inhibiting ^{3}H-hypoxanthine uptake by 50%), we investigated[1] malaria drug resistance in Brazzaville city during March–April, 1990; that of Brasseur (study period not specified) was done in the village of Djoumouna, which lies 15 km to the west of the Congo capital.

It is unwise to state that halofantrine resistance occurred earlier than mefloquine resistance, since in 1990 we showed that 6 strains of *P falciparum* of 67 tested had a mefloquine IC_{50} over 30 nmol/L. The findings of the two studies (table) are contradictory for halofantrine, whereas those for chloroquine, quinine, and mefloquine are similar. Methodological difficulties with halofantrine could be responsible, but Brasseur and colleagues' in-vivo study seems to confirm high resistance. Their findings are striking since the drug was taken with milk, which should have ensured good absorption, and the blood tests (what enzyme-linked immunosorbent assay was used, with what results?) did not seem to reveal anything amiss.

How can we account for such selective resistance occurring so quickly in semi-immune subjects, especially since the results of tests in Paris in cases of imported malaria contracted in the Congo during 1990-92, mainly in non-immune subjects and in a context more likely to result in chemoresistance, were reassuring? None of the 8 Congolese strains tested showed in-vitro resistance to halofantrine (threshold 5 nmol/L); and this was also so for 15 strains from Cameroon.

Brasseur and colleagues' hypothesis of drug pressure is surprising because it implies: (i) no cross-resistance between mefloquine and halofantrine,[2] and if not, that the cross-resistance that has been demonstrated experimentally on the mefloquine to halofantrine sequence[3] would not be reciprocal; (ii) high pressure from a drug which, unlike mefloquine, is not used chemoprophylactically and which has a shorter half-life; and (iii) high consumption of halofantrine in Djourmouna, which is hardly compatible with the drug's cost and the average income of the villagers. The situation is different in the city for European expatriates[4] and the few indigenous inhabitants who can afford expensive drugs. However, both groups live some distance from Djoumouna where individuals locally have an especially high malaria transmission rate.[5] At the end of 1989, on the basis of a questionnaire administered by cluster sampling to 600 mothers, who were representative of the population of Brazzaville, the proportion of cases in which various antimalarials were used to treat suspected malaria in Congolese children was: chloroquine 47%, quinine 28%, amodiaquine 18%, sulphadoxine plus pyrimethamine 3·5%, and others 3·5%. Halofantrine, which became generally available in 1988, was mentioned in less than 0·5% of cases. Another survey in 1990, also by interview of mothers but including children attending inpatient and outpatient departments of the Brazzaville University teaching hospital (n=180), yielded similar data.

Drug use may change, but in view of the present serious financial situation in the Congo, a major swing towards expensive drugs would be surprising. Chloroquine, amodiaquine, and quinine are manufactured locally by the Congolese Pharmaceutical Laboratory. Considerable quantities of antimalarials are supplied directly or provided as aid (WHO, UNICEF, Coopération Française). These sources do not include aminoalcohols, and they are mainly responsible for supplying the local population.

If an explanation has to be found for reduced sensitivity towards aminoalcohols in Central Africa due to the effects of drug pressure, we would choose cross-resistance with quinine, which is taken in large quantities by the indigenous population since the emergence of chloroquine resistance. It is essential to draw attention to the continuing efficacy of 4-aminoquinolines in the Congo,[6] in the Central African Republic,[7] and in Gabon.[8]

Service de Parasitologie,
CHU Hôpital Sud,
80054 Amiens, France;
Département de Médicine Tropicale,
INSERM U313,
and Laboratoire de Pharmacologie Cynétique,
CHU Pitié-Salpétrière, Paris

B. CARME
F. GAY
M. P. HAYETTE
B. DIQUET
M. DANIS

1. Carme B, Gay F, Chandenier J, et al. Unexpected trend in chemosensitivity of *Plasmodium falciparum* in Brazzaville, Congo. *Lancet* 1991; **338:** 582–83.
2. Gay F, Bustos MDG, Diquet B, et al. Cross-resistance between mefloquine and halofantrine. *Lancet* 1990; **336:** 1262.
3. Rojas Rivero L, Gay F, Bustos MDG, et al. Mefloquine-halofantrine cross resistance in *Plasmodium falciparum* induced by intermittent mefloquine pressure. *Am J Trop Med Hyg* 1992; **47:** 372–77.
4. Carme B. Mesures antipalustres chez les expatriés au Congo. Tendances 1989–1992. *Ann Soc Belg Med Trop* (in press).
5. Carnevale P. Le paludisme dans un village des environs de Brazzaville. Science thesis, 1979, Université Paris XI, no 2175.
6. Carme B, Moudzeo H, Mbitsi A, Ndounga M, Samba G. Stabilization of drug resistance (chloroquine and amodiaquine) of *Plasmodium falciparum* in the semi-immune populations in the Congo. *J Infect Dis* 1991; **164:** 437–38.
7. Louis JP, Louis FJ, Trebucq A. et al. Chemoresistance of *Plasmodium falciparum* in central Africa. *Lancet* 1992; **340:** 610–11.
8. Gueret D, Migot F, Ringwald P, et al. Stabilité de la résistance de *Plasmodium falciparum* à la chloroquine entre 1987 et 1989 à Mounana, Gabon. *Bull WHO* 1992; **70:** 621–24.

SIR,—Professor Brasseur and colleagues' report seems to have several important flaws. Halofantrine drug-pressure in the Congo village where the study was conducted cannot be assessed by the volume of drug sale and prescription in the capital city, Brazzaville. Halofantrine is eliminated much faster than chloroquine, mefloquine, and pyrimethamine and is thus much less likely to exert drug-pressure. The clinical study included both non-immune young children and semi-immune adults, and the clinical status (symptom-free, uncomplicated or severe malaria) of the patients was not stated. Most importantly, Brasseur's definition of resistance was based solely on the positive smear on day 8. Despite halofantrine's notoriety for poor and variable absorption, data on the plasma concentrations were not presented or correlated with treatment failures. Even if the data were available, plasma concentrations of day 3 samples would not accurately reflect drug absorption since the elimination half-life of halofantrine is 1–2 days.

Although the range of IC_{50} values for chloroquine, quinine, and mefloquine fell within the range of values reported previously, the range of IC_{50} values for halofantrine (2·2–47·6 nmol/L) of 21 susceptible and resistant isolates from the Congo and Cameroon was about ten times higher than those reported by other investigators.[1,2] In our in-vitro study of more than 200 African isolates obtained from imported malaria cases in France since 1991, two of the highest IC_{50} values recorded in type RI halofantrine treatment failure (verified by high-pressure liquid chromatography [HPLC] measurement of plasma concentrations) were 7·4 and 14·0 nmol/L.[3] The reason for the raised IC_{50} values in Brasseur's study may be the poor solubility of halofantrine in water and the absence of control of their solution by HPLC.

Without plasma concentration data and in-vitro halofantrine susceptibility, positive smears on day 8 should be more cautiously interpreted as treatment failure, and are probably related to poor drug absorption, and not resistance, as Brasseur claims.

Department of Parasitology,
Hôpital Bichat-Claude Bernard,
75877 Paris, France

LEONARDO K. BASCO

1. Gay F, Bustos DG, Diquet B, et al. Cross-resistance between mefloquine and halofantrine. *Lancet* 1990; **336:** 1262.
2. Basco LK, Le Bras J. In vitro activity of halofantrine and its relationship to other standard antimalarial drugs against African isolates and clones of *Plasmodium falciparum*. *Am J Trop Med Hyg* 1992; **47:** 521–527.
3. Basco LK, Le Bras J, Gillotin C, et al. Type RI resistance to halofantrine in West Africa. *Trop Med Parasitol* 1991; **42:** 413–14.