2 Schlagenhauf P, Steffen R, Lobel HO, Johnson R, Letz R, Tschopp A, *et al.* Mefloquine tolerability during chemoprophylaxis: focus on adverse event assessments, stereochemistry and compliance. *Tropical Medicine and International Health* 1996;1:485-94.
3 Committee on Safety of Medicines. Mefloquine (Lariam) and neuropsychiatric reactions. *Current Problems in Pharmacovigilance* 1996;22:6.

Author's reply

EDITOR,—Lorraine Traer-Clark disputes our use of the word temporary when describing the neuropsychiatric side effects attributed to mefloquine. We cannot comment on the possibility that long term side effects may result from use of mefloquine, but the subjects who responded to our questionnaire reported that adverse events seldom lasted longer than a few weeks.

In response to Stuart Dollow I would point out that we were not attempting to compare our work with that of Steffen *et al*, whose definition of "serious" neuropsychiatric adverse events followed the rather restrictive definition of the Council for International Organisations of Medical Sciences. The point we intended to make was that there are intermediate levels of neuropsychiatric adverse events, experienced by 1 in 140 people taking mefloquine, which are sufficiently unpleasant to be classified by two independent physicians as disabling. This group would be excluded from analysis based on the council's criteria for serious adverse events.

Dollow suggests that non-respondents should have been included in the analysis. We considered this but decided that the experiences of non-respondents should not be predicted (indeed, reducing this proposal to the level of absurdity, one could argue that all the non-respondents had taken mefloquine and been so incapacitated that they were unable to respond to our questionnaire). Even if they were included, however, the frequency of temporarily disabling neuropsychiatric adverse events (0.5%) would be appreciable.

Dollow also criticises our definition of disabling as being subjective. We tried to reduce the subjective aspects of such a definition by processing the respondents' histories through two referees independently. Many neuropsychiatric adverse events are by their nature subjective and not readily quantified. This does not mean that they can be ignored. We doubt that a better assessment of disability is given by the discontinuation rates alone as we found that a number of people who had subjectively had very distressing adverse events had continued to take mefloquine, either because of medical advice to do so or because of their high level of concern about the possible risk of malaria.

Finally, Ron Behrens's speculation that travellers advised in a specialist clinic may be better prepared to cope with adverse events associated with mefloquine is interesting. The Swiss study to which Behrens refers was relatively small (420 participants). Arguably the results of that study may not be applicable to the population of travellers as a whole as the participants were highly selected. This may explain why the small number of disabling side effects that might have been expected from our study was not seen in the Swiss study.

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Advice to warn patients about rare side effects overturns accepted practice

EDITOR,—The Committee on Safety of Medicines recently advised doctors in Britain to warn patients who were being prescribed mefloquine about potential neuropsychiatric side effects, which occur with a frequency of around 1 in 10 000 to 1 in 20 000 patients.[1] This exhortation seems to overturn accepted practice that doctors should advise their patients about more common side effects but do not need to disclose rare ones.[2]

It is difficult to see the rationale for the committee's advice about mefloquine. I suspect that most clinicians would agree that patients should be given adequate information to judge whether to accept treatment. The committee's advice, however, suggests a paradigm shift to full disclosure of all the side effects associated with a drug. If the advice was extrapolated to all medical practice, patients would be confronted with a bewildering array of potential side effects with each new prescription and clinicians would be overburdened with the task. I suspect that few—with the exception of potential litigants—would benefit from this.

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1 Committee on Safety of Medicines. Mefloquine (Lariam) and neuropsychiatric reactions. *Current Problems in Pharmacovigilance* 1996;22:6.
2 Sidaway *v* Board of Governors of the Bethlem Royal and the Maudsley Hospital (1985) 2 WLR 480.

Patients may start to take cheaper over the counter regimens

EDITOR,—In their article on the future for self medication Colin Bradley and Alison Blenkinsopp highlighted several issues raised by the increasing deregulation of prescription only medicines, including concerns about safety and the monitoring of adverse reactions.[1] One recent development that they did not mention is last year's amendment to the NHS (General Medical Services) Regulations 1992, which has meant that since early 1995 prophylaxis against malaria has not been available on NHS prescription.[2]

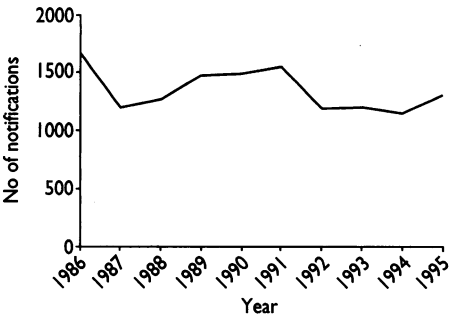

Fig 1—*Notifications of malaria in England and Wales, 1986-95*

One possible effect of this measure is an increase in the use of cheaper over the counter antimalarials in preference to antimalarials on private prescription. For instance, a six week course of chemoprophylaxis (for a stay abroad of one week) with mefloquine will cost £15.19, compared with £0.76 for a regimen of over the counter chloroquine or £7.69 for a regimen of over the counter chloroquine plus proguanil.[3] Mefloquine is now the preferred antimalarial for sub-Saharan Africa, and compliance is far better with mefloquine than with the complex alternative regimen of chloroquine plus proguanil.[4]

A recent case of falciparum malaria notified in a resident of this health authority who had taken chloroquine alone in preference to mefloquine for a visit to the Gambia highlights the potential dangers. There has also been an increase in notifications of malaria in England and Wales, from 1145 in 1994 to 1306 in 1995, a rise of 14%.[5] Although the number of cases of malaria is still lower than in the early 1990s and mid-1980s (fig 1), continuing vigilance is needed. It would be interesting to know whether during 1995 the amount of mefloquine dispensed fell or over the counter sales of alternative antimalarials increased.

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1 Bradley C, Blenkinsopp A. The future for self medication. *BMJ* 1996;312:835-7. (30 March.)
2 Department of Health. *Malaria prophylaxis: regulations permitting GPs to charge for prescribing or providing anti-malarial drugs.* Leeds: NHS Executive, 1995. (FHSL(95)7.)
3 Hollyoak V. Prophylaxis against malaria. *BMJ* 1995;310:1329.
4 Bradley DJ, Warhurst DC, on behalf of a meeting convened by the Malaria Reference Laboratory. Malaria prophylaxis: guidelines for travellers from Britain. *BMJ* 1995;310:709-14.
5 Communicable Disease Surveillance Centre. Notifications of infectious disease. *Commun Dis Rep CDR Wkly* 1996;6:6-7.

Effect of deletion polymorphism of angiotensin converting enzyme gene on progression of diabetic nephropathy

EDITOR,—Hans-Henrik Parving and colleagues report that patients with diabetic nephropathy who were homozygous for a deletion polymorphism of the angiotensin converting enzyme gene progressed more rapidly towards renal failure than did other diabetic patients with diabetic nephropathy once glycaemic control was controlled for in their analysis.[1] This is consistent with the results of a study that we published two years ago[2] but contrasts with a previous report from the same group.[3]

There are two possible reasons for the discrepancy between Parving and colleagues' initial[3] and most recent[1] findings. Firstly, the controls in their first study were not matched to the cases for glycaemic control[3] (unlike in our study[2]), yet diabetic nephropathy occurs only in patients with inadequate glycaemic control. Secondly, a deletion polymorphism of the angiotensin converting enzyme gene may act on the progression of, but not susceptibility to, diabetic nephropathy. In Parving and colleagues' latest study subjects homozygous for the deletion had more severe renal disease at baseline than the other patients, since they received more antihypertensive treatment.[1] This could have been due to sampling bias in the study, which was a retrospective study of a small number of patients in one centre; alternatively, the patients homozygous for the deletion could have been more susceptible to diabetic nephropathy than the other patients because of their homozygosity. Whether the deletion polymorphism acts on susceptibility to or severity of diabetic nephropathy, or both, is currently debated. There is growing evidence, however, that it can affect both the risk of and progression of diabetic nephropathy, as we found in a multicentre study of 494 insulin dependent diabetic patients with proliferative retinopathy.[4]

Parving and colleagues compared patients homozygous for the deletion with the other patients in their study, though there is no evidence supporting such a comparison: we found a dominant effect of the deletion allele for risk of diabetic nephropathy,[2 4] and a codominant effect should have been considered at least. Also, the authors assumed a linear sustained decrease in the glomerular filtration rate over