Table 1—Comparison of results of study by Barrett and colleagues and study by Phillips and Kass.² Figures are numbers (percentages) of subjects except where stated otherwise

	Barrett and colleagues	Phillips and Kass
Total taking mefloquine	1214	285
Women taking mefloquine	698 (57)	171 (60)
Median duration of use (weeks)	7	6
Adverse effects (all grades) occurred	503 (41)	108 (38)
Events interfered with daily activities	143 (12)	32 (11)
Stopped taking drug owing to adverse effects	63 (5)	18 (6)

were admitted to hospital; the third had a seizure. Our study also found that basic travel, as opposed to group travel itself, was a major positive effect modifying variable for adverse events associated with mefloquine.

If this useful drug is not to be abandoned prematurely, prescribers must be given guidance about the pharmacology of mefloquine in women and possible interactions with recreational drugs. We fully inform potential mefloquine users about these issues and, when possible, give people two or three doses as a trial before they leave Australia. Initial poor tolerance of mefloquine can be greatly improved by altering the regimen to half a tablet twice weekly, although this has yet to be verified scientifically.

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- 1 Barrett PJ, Emmins PD, Clarke PD, Bradley DJ. Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. *BMJ* 1996;313:525-8. (31 August.)
- 2 Phillips MA, Kass RK. User acceptability patterns for mefloquine and doxycycline malaria chemoprophylaxis. *J Travel Med* 1996;3:40-5.
- 3 National Health and Medical Research Council Public Health Committee. *Malaria prophylaxis*. Canberra: Australian Government Publishing Service, 1993.

Manufacturer should also give incidence of "severe" adverse events

EDITOR,—Lariam Action believes that the incidence of adverse reactions to prophylaxis with mefloquine is far greater than the 22% claimed by the manufacturer, and so we were interested to see that P J Barrett and colleagues' paper supports that view.¹ The difference between the paper's finding that 41.4% of people who take the drug will experience an adverse event and the manufacturer's figure of 22% requires immediate explanation.

The manufacturer's stated incidence of "serious" adverse events of 1 in 10 000 is being questioned, as is the restrictive definition of "serious"; the manufacturer has not published a figure for "severe" side effects, which would be those defined in the paper as being grade 3. The fact that the manufacturer lumps together all adverse reactions other than those defined as serious into a category of "all others" belies the severity of those reactions. This omission also gives the manufacturer an arguing point on which to respond to any criticism—that is, it can issue statements arguing over the definition of "serious" rather than respond about the safety of the drug.

The paper states that disabling neuropsychiatric side effects, although experienced by 1 in 140 subjects, were temporary. Lariam Action disputes that view. Most people registered with

Lariam Action are ill (severely enough to be unable to work) up to three years after having taken mefloquine. Having been supported in our view of the incidence of adverse events by Barrett and colleagues' paper, how long do we have to wait for further research to be published that will support our view of long term illness being attributable to mefloquine?

The paper restricts itself to neuropsychiatric side effects, on which the publicity in the mass media has focused. I would draw attention to dysfunctions of the cardiac, hepatic, and nervous systems, which are also listed as side effects of mefloquine and which many of the people registered with Lariam Action have had or currently have. This paper only touches the tip of the iceberg.

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- 1 Barrett PJ, Emmins PD, Clarke PD, Bradley DJ. Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. *BMJ* 1996;313:525-8. (31 August.)

Risk-benefit ratio must be taken into account

EDITOR,—P J Barrett and colleagues report that mefloquine is associated with an excess of neuropsychiatric adverse events compared with chloroquine plus proguanil (27.4% v 16.0%).¹ While there are similarities in methodology between the authors' study and Steffen *et al*'s larger study,² there are crucial differences in assessment criteria. I propose that any differences in incidence reports are a function of the defining criteria and that this may account for the disparities in perceptions of the tolerability of mefloquine. Nevertheless, I wish to make several points.

The authors state that the study is too small to generate accurate data on rare events, and thus it cannot challenge previous reports of rates of serious neuropsychiatric events.²⁻⁴

Notwithstanding the limitations of the sample size, Barrett and colleagues report a higher incidence of "disabling" neuropsychiatric adverse events than previously described.²⁻⁴ They acknowledge that travellers experiencing adverse events are more likely to have responded to the questionnaire. If it is assumed that non-respondents did not experience side effects then sampling bias is inevitable. The figure of 41% for all adverse events associated with mefloquine, corrected for 792 non-respondents, decreases to 25% (Steffen *et al* quoted 24%), and the rate of disabling neuropsychiatric effects is similarly reduced from 0.7% (1 in 140) to 0.5% (1 in 200). This incidence of neuropsychiatric events falls within Steffen *et al*'s 24% total and is documented in the datasheet.

The lack of a significant difference in overall tolerability between the groups supports previous findings.²⁻³

Barrett and colleagues defined "disabling" as "preventing the traveller from undertaking the activity for which he or she made the journey." This is subjective, despite the subsequent rating. A more objective assessment of disability is given by the discontinuation rates, for which no difference was seen. Thus neither this study nor that of Steffen *et al* supports anecdotal reports of higher discontinuation rates with mefloquine.

We agree with the authors' conclusion that mefloquine is appropriate only when the risk of both malaria and resistance to chloroquine is high. Evaluating the overall risk-benefit of antimalarials demands an assessment of efficacy.

Mefloquine is 86% more effective than chloroquine plus proguanil in resistant areas,³ and this is the compelling factor for its use. Travellers must be informed of the increased risk of malaria (up by half in 1996 over 1995)³ and the possibility and nature of side effects and must be questioned about relevant predisposing conditions. This, with current advice on geographical patterns of resistance, will ensure that the most appropriate antimalarial is used.

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- 1 Barrett PJ, Emmins PD, Clarke PD, Bradley DJ. Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. *BMJ* 1996;313:525-8. (31 August.)
- 2 Steffen R, Fuchs E, Schildknecht J, Naef U, Funk M, Schlagenhauf P, *et al*. Mefloquine compared with other chemoprophylactic regimens in tourists visiting east Africa. *Lancet* 1993;341:1299-303.
- 3 Lobel HO, Miani M, Eng T, Bernard KW, Hightower AW, Campbell CC. Long term malaria prophylaxis with weekly mefloquine. *Lancet* 1993;341:848-51.
- 4 Croft AMJ, World MJ. Neuropsychiatric reactions with mefloquine prophylaxis. *Lancet* 1996;347:326.
- 5 Notification of infectious diseases. *Commun Dis Rep CDR Wkly* 1996;6:287.

Explaining about possible adverse events may reduce problems

EDITOR,—The adverse events reported by P J Barrett and colleagues in travellers taking mefloquine, who were recruited to the study when seeking telephone advice,¹ were subjectively much more severe and disabling than those described in a study from Swiss, Swedish, and American researchers published around the same time.²

Schlagenhauf *et al*'s study reports a similar incidence of adverse events that interfered with travellers' normal activities (11.9% compared with Barrett and colleagues' 9.2%) and a not dissimilar proportion of neuropsychiatric events.² Schlagenhauf *et al* followed up travellers recruited in a specialist travel clinic, where the neurobehavioural status, psychomotor function, performance deficit, and mood profile of people with adverse events and matched controls were examined. No significant differences were found between the groups, and none of the subjects with adverse events associated with mefloquine required medical attention or admission to hospital.

The discrepancy in the severity of events between these two studies is therefore striking, and one possible explanation could be the method of recruiting subjects. Travellers advised in a specialist clinic would be forewarned of side effects and therefore might respond to adverse events with less anxiety and fear than people who had not been made aware, or had not been adequately informed, of the risks and events associated with prophylaxis with mefloquine. Awareness may increase the anxiety threshold and thereby reduce the severity of neuropsychiatric adverse events. Good prescribing, which includes explanations of possible adverse events as recommended by the Committee on Safety of Medicines,³ may be the best way of reducing disabling side effects.

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- 1 Barrett PJ, Emmins PD, Clarke PD, Bradley DJ. Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. *BMJ* 1996;313:525-8. (31 August.)

- 2 Schlagenhauf P, Steffen R, Lobel HO, Johnson R, Letz R, Tschoop 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.)
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- 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 ago² but contrasts with a previous report from the same group.³

There are two possible reasons for the discrepancy between Parving and colleagues' initial³ and most recent¹ findings. Firstly, the controls in their first study were not matched to the cases for glycaemic control³ (unlike in our study²), 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 anti-hypertensive 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 and a codominant effect should have been considered at least. Also, the authors assumed a linear sustained decrease in the glomerular filtration rate over