Table 1—*Result of Medline search for "case-control studies," "questionnaires," and "family practice" 1992-6*

MeSH heading	No of citations
1 Case-control studies	9172
2 Questionnaires	14 786
3 Family practice	6863
1+3	21
2+3	548

questionnaire studies to case-control studies was 1.6:1, whereas for family practice the ratio was 26:1.

The time has come to redress the balance and move on from placing too much emphasis on questionnaire surveys as a quantitative method of research in general practice.

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1 McAvoy BR, Kaner EFS. General practice postal surveys: a questionnaire too far? *BMJ* 1996;313:732-4. [With commentaries by S Lydeard and by M P Springer and H W J van Marwijk.] (21 September.)
2 Black N. Why we need observational studies to evaluate the effectiveness of health care. *BMJ* 1996;312:1215-8. (11 May.)
3 Hennekens CH, Buring JE. *Epidemiology in medicine*. Boston: Little, Brown, 1987.

Surveys demand too much time

EDITOR,—I suppose that I identify myself as one of the general practitioners who do not respond to postal surveys as defined by Brian R McAvoy and Eileen F S Kaner—older, more experienced, and possibly under stress.[1] But there is another reason for the failure to complete and return questionnaires.

Over the past few months I have been collecting (not returning) questionnaires and now have a total of 19. Eight of these are "national" surveys, nine are from my family health services authority or health authority, and the remaining two I am unable to classify. One offered to advise me of the results; five had "threatening" deadlines (this must be completed and returned by ...). The only incentive to completion was the chance to win a weekend in Amsterdam. Given that each questionnaire would take some 10-15 minutes to complete, filling them all in would take 3-4 hours of my time. I recollect that in my first 10 years in general practice I completed perhaps one survey a year.

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Scotland's new chief medical officer welcomes reforms of training

EDITOR,—A recent item in Medicopolitical Digest implied that I (now the chief medical officer in Scotland) was critical of the current reform of postgraduate training.[1] This is not the case. I welcome the reforms, and during my chairmanship of the Scottish Council for Postgraduate Medical and Dental Education I helped to alter the funding and delivery of postgraduate training. My purpose at the BMA's clinical meeting in Istanbul was to highlight several unresolved issues that could adversely affect implementation of the reforms and compromise moves towards a health service delivered by consultants.

I did indeed emphasise the problems posed by a reduction in the hours of training, and, while I subscribe totally to the view that specialist training can be condensed if training programmes are structured, we must be careful to ensure that the consultants who emerge are sufficiently experienced to fulfil the demands expected of them. Junior doctors in some acute specialties are aware that a reduction in working hours may adversely affect their training if carried too far, and there have been heartening moves to define and monitor the quality of training offered to them. I strongly oppose any return to the prolonged unstructured apprenticeships of the past, but I suspect that some doctors pursuing careers in highly specialised areas may elect to gain additional experience after completing conventional specialist training.

I am not enthusiastic about the suggestion that consultants produced by the new training programmes will be identified as junior consultants, and I suspect that most of them would find this offensive. We all, however, need to accrete experience throughout our professional life, and many newly appointed consultants will find the help of senior colleagues particularly welcome at the start of their consultant career. In surgery there is a growing acceptance that the nature of a consultant's working week may change as his or her career progresses, and this could be beneficial as far as support for new colleagues and an increased role in teaching are concerned.

It would be tragic if the potential benefits of the reforms of training were lost because of failure to make the necessary adjustments elsewhere in the system. The successful development of all aspects of our NHS will depend on the continued commitment of a motivated and sufficiently numerous consultant workforce. Postgraduate training is no exception.

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1 Beecham L. New Scottish CMO criticises training reforms. *BMJ* 1996;313:947. (12 October.)

Adverse events associated with mefloquine

Study in returned travellers confirms authors' findings

EDITOR,—The excess of disabling neuropsychiatric side effects of mefloquine reported by P J Barrett and colleagues has attracted attention.[1] Focus on disabling reactions has detracted from milder disturbances, which may be sufficiently common to reduce compliance and increase the risk of malaria.[2] We conducted a questionnaire based survey among recently returned travellers to assess the impact of adverse reactions on compliance.

Altogether 347 questionnaires were returned (response rate 60.5%), 255 of which were from respondents who had been born in malaria free areas, were based in Britain, and were attending our hospital for reasons not involving malaria. The median age of these 255 patients was 30.5 years and their median length of travel 3.2 months. One hundred and thirteen respondents had taken mefloquine, 81 had taken chloroquine plus proguanil, and 61 had used alternative regimens or no prophylaxis. The rates of reported side effects were high: 80 (71%) respondents who had taken mefloquine and 52 (64%) who had taken chloroquine plus proguanil reported one or more side effects. Depression and anxiety were more common in those who had taken mefloquine, with 23 (20%) of this group and 8 (10%) of those who had taken chloroquine plus proguanil reporting symptoms ($\chi^2 = 3.86$, $P<0.05$). Only 16 (14%) of those who had taken mefloquine and 11 (14%) of those who had taken chloroquine plus proguanil, however, reported having stopped their prophylaxis because of side effects.

Forty five (30%) travellers to Africa and eight (8%) travellers to other destinations had been treated for symptoms of malaria at least once. Among the travellers to Africa 24 (26%) of the 94 who had taken mefloquine and 17 (40%) of the 43 who had taken chloroquine plus proguanil had been treated for symptoms of malaria, and seven had stopped using prophylaxis as a result. The drugs used for treatment varied and in some instances were potentially ineffective or dangerous.

Although people attending hospital are not representative of travellers as a whole, our survey supports Barrett and colleagues' findings of an increased frequency of neuropsychiatric side effects in people taking mefloquine. Side effects severe enough to necessitate discontinuation of prophylaxis were, however, similar in people taking mefloquine and those taking chloroquine plus proguanil. A high proportion of the cohort had received treatment for symptoms of malaria while abroad. Travellers need advice on drugs' side effects before they travel and should ideally be provided with emergency treatment for use if malaria is diagnosed abroad. They should be warned of the risk of breakthrough infections and advised not to stop their prophylaxis without seeking medical advice.

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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 Cook GC. Malaria prophylaxis. *BMJ* 1995;311:190-1.

Women may be more susceptible to adverse events

EDITOR,—The methodology that P J Barrett and colleagues used in their study comparing adverse events associated with mefloquine with those associated with chloroquine plus proguanil for antimalarial prophylaxis[1] is similar to that used in a study that Kass and I carried out.[2] We, however, compared mefloquine with doxycycline, which is widely used by Australians and North Americans as the alternative to mefloquine for travellers to chloroquine resistant areas.[3] Our subjects were enrolled in the study prospectively, at the time that their drug was chosen, and received a postal questionnaire after returning from their trip. It is reassuring that, with respect to the tolerability of mefloquine, our results were so similar to those of Barrett and colleagues (table 1)

Barrett and colleagues detail the cases of 10 people who used mefloquine and suffered disabling neuropsychiatric adverse events. They do not, however, comment in their discussion on the fact that eight of these subjects were women. This would represent a rate of disabling neuropsychiatric events in women taking mefloquine of 8/698 (1.1%). In our study all disabling adverse events occurred in women taking mefloquine, with a rate of major neuropsychiatric events of 3/171 (1.8%). Two of the three women

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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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)[5] 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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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, Bemard 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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