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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]

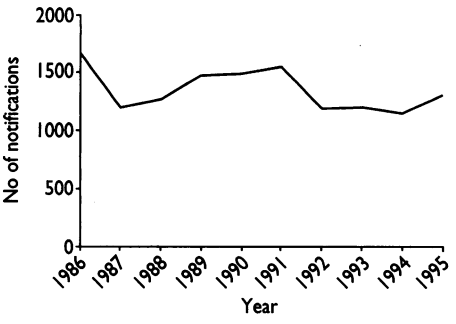

Fig 1—*Notifications of malaria in England and Wales, 1986-95*

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.)
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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

time, which contrasts with a finding of an earlier study by them of similar duration, which indicated that the slope of the fall in glomerular filtration flattens if antihypertensive treatment is continued for a long time.[5]

Because of possible hidden biases in observational studies it is premature to recommend special treatment for patients with diabetic nephropathy who are homozygous for the deletion polymorphism until prospective randomised studies have been carried out.

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Course on basic surgical skills is being run by all surgical colleges

EDITOR,—A recent press release produced by the Royal College of Surgeons of England about the launch of a new course on basic surgical skills for surgical trainees gives the impression that the course has been derived and promoted solely by the Royal College of Surgeons of England.[1] This is inaccurate. This mandatory course has been derived on an intercollegiate basis and not solely by the Royal College of Surgeons of England. Its content has been formulated with input from all four royal surgical colleges, and the teaching format is standardised, such that skills acquired from proscriptive exercises during one course held in a particular college or region are identical with those acquired during a course held in another college or region.

The item about the course in Medicopolitical Digest is correct in stating that this is the first mandatory course for any specialty and must be completed to a satisfactory standard before a doctor is eligible to take the new AFRCS examination or the MRCS examination at the Royal College of Surgeons of Edinburgh, England, Glasgow, and Ireland.[1] The item is inaccurate in saying that the groups will be limited to 18: the Edinburgh college, for example, intends to increase participants to at least 20 per course, to deal with the expected heavy demand for participation. Another inaccuracy is that, although various courses on anastomosis have been piloted by the Royal College of Surgeons of England for two years, they have also been piloted by its sister colleges. Furthermore, final intercollegiate agreement on the format of the course was agreed only last May. Subsequent changes to the content of the course and assessment of candidates will be reviewed in 12 months' time by all four colleges.

It is vitally important for surgical trainees to realise that they can attend courses on basic surgical skills not only at the Royal College of Surgeons of England and in its associated regions but also in Dublin at the Royal College of Surgeons in Ireland, in Glasgow at the Royal College of Physicians and Surgeons, and in Edinburgh at the Royal College of Surgeons. The emphasis throughout the formulation of the course has been the major step forward in intercollegiate agreement and cooperation. The press release from the English college seems to undermine this fundamental philosophy.

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1 Beecham L. College launches new course for surgical trainees. *BMJ* 1996;313:1086. (26 October.)

Conflict of interest

Conflict of interest statement should be abolished

EDITOR,—Since the *BMJ* introduced the requirement that authors should declare any conflict of interest at the foot of papers and other articles[1] such conflicts have rarely, if ever, been admitted. I wonder whether this reflects the truth.

The purpose of scientific publication is to present the results of observations or experiments in such a way that readers can assess their veracity and importance in terms of scientific knowledge. In the case of a medical journal, this includes their relevance to clinical practice in cost-benefit terms in their widest sense, and hence their relevance to the allocation of resources. Only when there are absolutely no outside influences or pressures that might modify the presentation of results in such a way as to compromise their interpretation can there be said to be no conflict of interest. Scientists must be objective to a saintly degree if they can truly state that their wish to justify a substantial proportion of their life's work or what they regard as their most brilliant innovation has never influenced the mode of their presentations. This might merely be to emphasise those results that prove their theory or to press harder for publication of those things that they feel most deeply about. Indeed, it could be said that it is the innovator's duty to do these.

If an author has accepted funding from any pressure group or from any charity that restricts itself to funding particular diseases or groups of the population, let alone any money from a government agency for its own agenda, then it is difficult to avoid conflict of interest. This might arise from an agency's funding policy or, where a "popular" charity has particular ease in raising money, from distortion of the perceived need, because the greater the funds available the more the publications about that particular subject.

A change in the wording to "no undeclared conflict of interest" would solve the second group of problems but not the first. Perhaps it would be better to end the charade altogether and return to the old fashioned virtue of trusting the integrity of authors. This might allow a few charlatans to get away with it, but one should not forget that mistrust, like other forms of pessimism, is a self fulfilling prophecy.

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1 Smith R. Conflict of interest and the BMJ. *BMJ* 1994;308:4-5.

Does the *BMJ* attempt independent ascertainment?

EDITOR,—A colleague and I recently wrote a letter about two papers on alcohol consumption and the risk of heart disease.[1] We were critical of the message that these articles gave, which, in simplistic terms, was that alcohol is good for you. I have since been informed that the research reported by Eric B Rimm and colleagues[2] was funded by some of Europe's leading producers of alcoholic beverages (through the International Life Sciences Institute).

The authors' paper ends with the statement "Conflict of interest: None." I assume that it is primarily for the author of an article to decide what constitutes a conflict of interest, but I wonder whether the *BMJ* has any guidelines on this. In addition, does the *BMJ* attempt any independent ascertainment of potential conflict of interest? Specifically, does a conflict of interest arise when research is funded by a company or companies whose profits may be appreciably affected by the outcome that is reported? Clearly, major drug companies often fund clinical trials of their products, but this is usually evident in the reporting of the work.

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1 Whitaker L, Ward H. Alcohol consumption and risk of coronary heart disease. *BMJ* (in press).
2 Rimm EB, Klatsky A, Grobbee D, Stampfer MJ. Review of moderated alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits? *BMJ* 1996;312:731-6. (23 March.)

**We are currently reviewing our policy on conflict of interest and will soon be suggesting some changes. We have learnt that authors often have conflicts of interest that they do not declare. One reason that authors don't declare conflicts may be the idea—epitomised by C K Connolly's letter—that there is something mendacious about a conflict of interest. This is not so. Conflicts of interest are common, and there is nothing wrong with having a conflict of interest. What is more of a problem is not to declare a conflict of interest.

A second reason why authors may not declare conflicts of interest is that they are confident that their judgment has not been influenced by the conflict. There is considerable evidence that conflicts of interest do influence judgment,[1] but this influence will usually be subconscious. We cannot know if a conflict of interest has influenced our judgment.

Our policy is not to try to eradicate conflict of interest. Rather, we want simply to disclose conflicts. Readers can then make up their own minds on whether authors' judgment has been influenced.

In answer to Luke Whitaker's questions, the *BMJ* does have guidelines on what constitutes a conflict of interest. These guidelines are sent to authors. Authors are asked to declare a conflict of interest or to sign to say that they do not have one. We do not—and could not—independently verify these statements. A conflict of interest clearly does arise when research is funded by an organisation whose business may be affected by