Psychological problems after mefloquine and chloroquine

EDITOR,—Most doctors will have taken chloroquine for short periods when travelling to exotic destinations. I had done so in Egypt, Jordan, and Syria: I had taken chloroquine for six weeks at any one time and felt confident about taking it for two years when I came to Papua New Guinea.

Initially I felt well, but after one month I became lethargic and would fall asleep in meetings. I had early morning waking and became very agitated. These symptoms I attributed to the humidity, then depression, and finally anxiety about being in a foreign country. I continued the treatment even though my hair began to fall out and my eyesight seemed to be getting worse. Medical colleagues advised me that the hair loss was due to stress or the heat. Finally I developed a rash, which was definitely petechial, every Monday after taking chloroquine, and my platelet count was on the lower limit of normal.

I was advised by a doctor to stop taking chloroquine. What was I to take instead, on the edge of the bush in a high malarial zone? Mefloquine was readily available from one of the volunteers with the American Peace Corps, so I took one tablet that night. Throughout the night I had tachycardia, my dreams were vivid, and I was convinced that I was going to die. The next day the flowers were larger and brighter and the stones on the way to work were hairy. I was on a trip that I hadn't planned. Fortunately, that morning four issues of the *BMJ* arrived; in one of them was an article on prophylaxis against malaria.¹ This gave me the information I needed. My luck was in again. Doxycycline is readily available in Palmyra, so I started a daily dose. I now feel well and energetic and am sleeping, and my appetite has returned—I feel normal.

Many travellers overseas will have experienced the lethargy, depression, and anxiety that I did and have put it down to the new country and the new job. Have they gone on to feel better, tolerating the drug, or have they put up with these psychotic feelings, never thinking that chloroquine could be the causal agent?

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1 Bradley DJ, Warhurst DC, on behalf of a meeting convened by the Malaria Reference Library. Malaria prophylaxis: guidelines for travellers from Britain. *BMJ* 1995;310:709-14. (18 March.)

Authors' reply

EDITOR,—The guidelines on malaria prophylaxis represent a consensus reached by 44 British specialists. The letters show how difficult it is to reach unequivocal conclusions in this field. The guidelines of 1993 gave equal place to two regimens for Africa¹ and left practitioners to decide between them, which they found unhelpful. The guidelines of 1995 gave a priority recommendation whenever possible. The committee thought that cumulative evidence on the use of mefloquine,² together with some deaths in British travellers taking proguanil plus chloroquine, had tipped the balance slightly in favour of mefloquine for highly endemic areas of sub-Saharan Africa. It is always difficult to balance the risks of rare catastrophic events such as death with those of the more frequent unpleasant side effects of prophylaxis. Clinicians see the latter; national statistics of a reference laboratory cover the former as well.

The guidelines already state that British experience points to a greater frequency of side effects from mefloquine than that in the widely quoted Swiss study, which showed greater prophylactic efficacy for mefloquine over chloroquine plus proguanil.³ Even Wetsteyn and de Geus, quoted by G C Cook, concur with the use of mefloquine in west Africa.

We believe that consensus improves compliance.

We sympathise with the position of Graham Morrison. The current guidelines are cautious about standby treatment because it was overprescribed after the 1993 guidelines were issued. Charles Godden's experience, which was due to persistence of hypnozoites of *Plasmodium vivax* that was insensitive to chloroquine, is uncommon but not unique. The guidelines primarily aim to make doctors aware of the risk of malaria in returned travellers, and discussion has centred on whether to emphasise the first three months (maximum risk of falciparum malaria) or the first year (98.5% of all cases of imported malaria).

We disagree with Ashley Croft's statement that the guidelines describe mefloquine as innocuous. The high incidence of side effects will not surprise users of antimalarial drugs, but Croft's study lacks a measure of severity. An operational definition, such as cessation of chemoprophylaxis or admission to hospital, would give a sense of proportion. Incidentally, paranoid feelings in this relatively small series were significantly more common in those taking mefloquine. The hypothesis that side effects depend on the ratio of dose to weight could be tested on Croft's data. Given the greater efficacy of mefloquine, Croft's data are consistent with the current guidelines. We agree that no one can be complacent about either malaria or antimalarial drugs.

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- 1 Bradley DJ. Prophylaxis against malaria for travellers from the United Kingdom. *BMJ* 1993;306:1247-52.
- 2 Lobel HO, Miani M, Eng T, Bernard KW, Hightower AW, Campbell CC. Long-term malaria prophylaxis with weekly mefloquine. *Lancet* 1993;341:848-51.
- 3 Steffen R, Fuchs E, Schildknecht J, Naef U, Funk M, Schlagenhauf P, et al. Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting east Africa. *Lancet* 1993;341:1299-303.

"Deadly Experiments"

UK's programme was open and ethical

EDITOR,—The Channel 4 television programme *True Stories*, entitled "Deadly Experiments," which was transmitted on 6 July, was highly alarming and in many instances seriously misleading.¹ The programme referred to indefensible and unethical experiments involving the administration of plutonium to hospital patients in the United States as an adjunct to the Manhattan project. The programme subsequently claimed that similar "radiation experiments" were carried out in secret in the United Kingdom, without the consent of the participants. The facts, however, are these.

Firstly, the studies in question were legitimate projects addressing important health problems, which used radionuclides in doses equivalent to or lower than those used for routine diagnostic purposes. Many long term follow up studies of patients exposed to radioactive isotopes in tracer doses have not shown any increased risk to health over many years.

Secondly, the only study that did not fall into the above category was a postmortem analysis of the concentration of radionuclides of barium and strontium in bone, carried out during the period in which nuclear devices were being tested in the atmosphere. It did not involve the direct administration of radioactive substances.

Thirdly, the claim that these studies were secret is absurd. All were published in reputable journals between 1953 and 1971 on the conclusion of the work.

Fourthly, it has been an explicit requirement of the Medical Research Council since 1953 that

informed consent should be obtained from all participants in research. We have been able to speak to the lead investigators in two of the studies concerned and both are emphatic that such consent was obtained. In the case of the Asian women discussed in the programme, I am told by the principal investigator that the local authority made an Asian health visitor available to him when he sought consent, and a member of the patient's family or a close friend who was fluent in English was also present on each occasion. It has not been possible to speak to others about studies that took place up to 45 years ago. The situation with respect to the postmortem studies discussed in the programme seems to have been that permission for postmortem examination was obtained in accordance with standard practice. It seems unlikely that the precise nature of the samples to be obtained would have been discussed, but one might speculate that this would have been out of concern for the sensitivities of the relatives and not for reasons of secrecy.

The alarmist nature of this programme must have caused needless anxiety to many people who have participated willingly in research and to those who have received tracer doses for routine diagnostic purposes, as well as causing unnecessary distress to many bereaved parents.

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1 Tobias JS. Good intentions are not enough. *BMJ* 1995;311:203. (15 July.)

No evidence of harm from tracer studies

EDITOR,—Many readers will have seen the Channel 4 television programme *True stories* on 6 July entitled "Deadly experiments . . . A series of government funded experiments conducted on human guinea pigs without their consent."¹ Work that I did² was mentioned, with a brief extract from a much longer filmed interview.

My research was fully reported in 1958.² By the 1950s iodine-131 tests had become routine for assessing thyroid function and superseded measurement of the basal metabolic rate, which required admission to hospital. The patient's radiation exposure was low, but we were reluctant to use iodine-131 in pregnancy, even though thyroid function and diagnosis of thyrotoxicosis in pregnancy remained uncertain. In 1956, however, the low dosage iodine-132, with a half life of 2.3 hours, became available. Sir Edward Pochin, in agreement with Professor W C W Nixon, suggested that iodine-132 might be used in pregnancy. Twenty five pregnant patients were selected for investigation, but only 16 completed the protocol. All had given informed consent. A test dose of 0.22 MBq of iodine-132 was used, giving 0.21 cGy to the maternal thyroid and 0.0011 cGy to the maternal and fetal gonads. We found that thyroid iodine uptake was indeed increased in pregnancy, and the test became available for clinical use. The patients were not formally followed up, but their records were later traced and there was no evidence of harm in mothers or children.

Use of radioiodine for diagnosis and for treatment of thyrotoxicosis has not caused either cancer or leukaemia, but fallout after atomic weapons tests and after the accident at Chernobyl has been followed by a small excess of thyroid carcinoma, especially in children.

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1 Tobias JS. Good intentions are not enough. *BMJ* 1995;311:203. (15 July.)
2 Halnan KE. The radio-iodine uptake of the human thyroid in pregnancy. *Clin Sci* 1958;17:281-90.