

Both studies found very modest changes in the intervention groups despite intensive intervention. In the family heart study a 12% lower risk of coronary heart disease (on the Dundee risk score) occurred in the group subjected to intensive lifestyle intervention, and this was more apparent in those at highest risk. The authors of the OXCHECK study found that the prevalence of smoking, the rate of stopping smoking, and body mass index were not significantly different between the two groups studied; there was a significant difference between the groups in cholesterol concentration, but the difference was small, particularly in men. Both sets of authors point to the need for longer term follow up, but neither is optimistic about the likelihood of further improvement in its results. So the impact on public health is likely to be marginal.

This style of approach to the population through primary care alone is not going to produce large reductions in the risk of cardiovascular disease. Instead, the government will need to put more effective legislation in place to control use of tobacco and promote the consumption of healthy food. It will also need to reconsider the controversial new arrangements for paying general practitioners for health promotion activity, with their emphasis on data collection.⁶ In the meantime, these studies should not be interpreted as casting doubt on general practitioners' opportunistic use of routine consultations for health promotion.

General practice teams have good evidence for the effectiveness of clinical efforts in secondary prevention of vascular disease⁹ and growing evidence that a little professional support for people who are ready to change their lifestyles will improve outcomes.¹⁰ These are large tasks in themselves, and

there seems to be no justification for the ritualistic collection of risk factors when the public health benefits are marginal, less motivated patients are upset by the process,^{5,11} and the primary care professionals are demoralised by bureaucratic payments linked to targets and population coverage. The ethics of screening are clearly being ignored in the new contract imposed on general practitioners,¹² and the scientific evidence that existed before 1990 has been strengthened by the two papers in today's journal.

NIGEL STOTT

Professor of general practice

Department of General Practice,
University of Wales College of Medicine,
Cardiff CF3 7PN

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Mefloquine

In the prophylaxis and treatment of falciparum malaria

Mefloquine is a quinoline-methanol compound structurally related to quinine.¹ It is active against all the human malaria parasites, particularly multidrug resistant *Plasmodium falciparum*. Introduced a decade ago to treat falciparum malaria in Thailand, where multidrug resistance is a particular problem, it was formulated initially in a fixed combination with pyrimethamine-sulfadoxine to delay the onset of resistance. Unfortunately, that did not work, probably because of pharmacokinetic differences between the compounds and because *P falciparum* was already highly resistant to sulfadoxine and pyrimethamine when the combination was introduced.

By 1990, after five years of well controlled use, significant resistance to mefloquine was evident on the eastern and western borders of Thailand.² This has increased steadily in these regions, and, although cure rates have improved since the treatment dose of mefloquine was raised from 15 mg base/kg to 25 mg/kg,³ high grade resistance (that is, failure to clear parasitaemia) now occurs in about 15% of patients, and low grade resistance (recrudescence of the infection) in almost 50%. Fortunately, the situation is considerably better everywhere else in the tropics, although some strains of *P falciparum* from west and possibly east Africa are intrinsically resistant to mefloquine.

For treating uncomplicated multidrug resistant falciparum malaria mefloquine is an alternative to quinine or halofantrine and has the advantage that only one dose is necessary.

Compared with mefloquine, quinine is unpleasant to take because it has a very bitter taste and produces cinchonism (tinnitus, deafness, nausea, and dysphoria); patients are often reluctant to complete the necessary five to seven days' treatment. Where infections are known to be sensitive (that is, in most of the tropics) mefloquine 15 mg base/kg suffices, but for resistant infections 25 mg/kg is needed, and now on the borders of Thailand the addition of oral artesunate (10 mg/kg total dose) over three to five days is required for cure.⁴

The main adverse effect of antimalarial treatment with mefloquine is transient central nervous system toxicity; serious adverse effects (psychosis, encephalopathy, and convulsions) occur in about 1 in 1700 treatments with 15 mg/kg,⁵ and about 1 in 1200 with the higher dose of 25 mg/kg (F ter Kuile *et al*, unpublished observations). Less serious but still disabling effects, such as confusion, mental clouding, dysphoria, and sleep disturbances, are more common.⁶ Over half the patients given high dose mefloquine treatment complain of nausea, anorexia, dizziness, and fatigue, although both the drug and the disease contribute to these symptoms. As with other antimalarial drugs, children tolerate mefloquine better than adults and, interestingly, men better than women.³

Recommendations on antimalarial prophylaxis are always difficult and often controversial; the subjects are healthy and do not tolerate even minor adverse effects, they may forget to take the tablets, and, even if they do remember, the drugs

may not be effective because of resistance or vagaries in pharmacokinetics. The withdrawal of pyrimethamine-sulfadoxine (because of lethal cutaneous reactions and blood dyscrasias) and amodiaquine (because of agranulocytosis and hepatitis) for antimalarial prophylaxis in the mid 1980s gave rise to considerable divergence of opinion on what should replace them in areas where *P falciparum* was resistant to chloroquine.

There were no right answers, and national differences emerged. The Americans did not like proguanil, despite ample evidence of efficacy in vitro and in vivo, even when *P falciparum* was resistant to pyrimethamine. The French thought that chloroquine should be taken daily and not weekly (with some justification) but the north Europeans (including the British) continued to recommend chloroquine weekly together with proguanil. Meanwhile the Australians continued with pyrimethamine-dapsone (Maloprim), although nearly everyone else ignored it. Meanwhile doxycycline was shown to be an effective alternative in areas of multidrug resistance, although many doctors were reluctant to prescribe an antibacterial for prolonged periods. Mefloquine was known to be effective nearly everywhere, but it had a reputation for adverse effects on the central nervous system, and so was kept in reserve.

This has now changed, and opinions are reconverging. After a series of small studies and extensive prescription in Switzerland (where mefloquine is manufactured), two large series have reported recently that antimalarial prophylaxis with weekly mefloquine is both effective and well tolerated.^{7 8} Indeed, the risks of serious neurotoxicity after prophylactic mefloquine (about 1 in 10 000 in one study⁷), were similar to those with chloroquine, and were certainly much lower than the risks associated with treatment of malaria. Furthermore, if serious adverse effects were going to develop they occurred within the first month of prophylaxis in three quarters of cases.

Consequently, the United States and some European countries now recommend mefloquine as the drug of choice for short term protection (less than three months) in areas where malaria is resistant to chloroquine. Lack of experience with longer courses explains the three month limit. Lack of experience rather than evidence of toxicity also explains why mefloquine has not been recommended in children weighing

less than 15 kg. Detailed recommendations from Britain have been reported recently in the *BMJ*.⁹ These state that for everyone except pregnant women mefloquine is the drug of choice for short term antimalarial prophylaxis in resistant areas. The usual adult dose is 250 mg (base) or 3.5 mg/kg once weekly. Prophylaxis with mefloquine should not be given to people with a history or family history of convulsions or major psychiatric disorders.

It is often recommended that mefloquine should not be given with digoxin, calcium channel blockers, or β blockers, although there is no convincing evidence of an adverse interaction. Mefloquine augments the electrocardiographic changes induced by halofantrine (particularly QT prolongation), and these two drugs should not be used together. Mefloquine is not advised during breast feeding, but the amounts excreted in breast milk are unlikely to have any effects on the baby. Although mefloquine is currently contraindicated in pregnancy, there is no convincing evidence of teratogenicity or any other adverse effects of treatment or prophylaxis with mefloquine in pregnancy. This restriction might also be lifted carefully in the future.

N J WHITE
Director

Wellcome-Mahidol University-Oxford Tropical Medicine
Research Programme,
Faculty of Tropical Medicine,
Mahidol University,
Bangkok 10400,
Thailand

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Murder in the NHS

Mistakes have been made in responding to an extraordinary case

Individuals and organisations cannot plan for the truly extraordinary. When a once in a millennium event occurs there is a high chance that people will react badly and make mistakes. The deliberate killing and injuring of children in a British hospital by nurse Beverley Allitt was just such an event,¹ and many mistakes have been made in the aftermath.

But for the diligence of the two consultant paediatricians, Drs Nelson Porter and Charith Nanayakkara, at Grantham and Kesteven Hospital Beverley Allitt would probably not have been convicted of murder. Now, however, nine months after she was convicted of killing four children and injuring nine more in the children's ward of Grantham and Kesteven Hospital,¹ the two consultants are without their jobs. They also fear criticism from the Clothier inquiry, set up by the secretary of state for health into the circumstances of the

murders and due to report next week. The consultants have not had a chance to defend themselves in public. Because of the decision to hold the Clothier inquiry in private, health service employees and the public cannot be sure that all the lessons that might have been learnt will be learnt. And, worst of all, services for children in Grantham have been diminished.

In an environment such as a children's ward, where staff are dedicated to providing the best possible care, the threshold for recognising covert acts of excess and inappropriate administration of therapeutic substances is high. It is not therefore surprising that several deaths had occurred before that threshold was reached. Nevertheless, when each individual unexplained death occurred the consultants quite properly sought help from their regional tertiary paediatric centre in Nottingham. In one case Dr Nanayakkara sought