

Letters to the Editor

Quinacrine family-planning method

SIR—Your April 23 editorial accuses the World Health Organization (WHO) of having declined your request to comment publicly upon a paper by Hieu et al reporting a clinical trial of the quinacrine method of female sterilisation of more than 30 000 women in Vietnam. You also implicitly accuse WHO of discourtesy and lack of courage for not airing criticisms openly; for resorting to anecdote, misinformation, and anonymity; and for trying “to duck the question”. This letter is in response to these unfounded charges.

When we read Dr Hieu's paper, published in *The Lancet* of July 24, 1993, and then received several negative comments from scientists and from national and international organisations, we decided that the right way to deal with the issue was to have a detailed discussion of quinacrine, including the *Lancet* report, by a group of experts and then-and only then-issue an official statement. It was decided to include such a discussion in a meeting on female sterilisation already scheduled to be held in Geneva on July 25-27, 1994. Vietnamese participation has been invited and the Government has nominated a Vice Minister of Health. The Association for Voluntary Surgical Contraception (AVSC) has already convened an expert meeting (in which WHO participated) that has led to a statement about quinacrine and a critique of the article. In referring you to AVSC we were trying to be helpful rather than “less than informative”. No “WHO critique of Hieu's paper” exists. We do have on file the confidential review by a staff scientist made in a private capacity for the editor of another journal which we cannot make public. This was made clear by Dr Francis Webb in his letter to Ms Linda Demers, the UN Population Fund (UNFPA) country director for Vietnam. This confidential review was not sent to Ms Demers by Dr Webb or by anyone else, as you have wrongly stated in your editorial. We were as disturbed as you that Dr Webb's letter to Ms Demers should have been widely circulated.

Ms Demers, in response to a request from the Vietnamese Ministry of Health, asked WHO on Dec 6, 1993, for information on quinacrine sterilisation. She was sent a copy of the document prepared by AVSC and the report of the toxicology panel of the WHO Special Programme of Research, Development, and Research Training in Human Reproduction (HRP). The review by the toxicology panel had been done in 1991 in response to a request from UNFPA, one of HRP's co-sponsors, which had received a proposal from Dr Elton Kessel for funding of quinacrine trials. The panel concluded that additional toxicological studies were needed before clinical trials of the method should proceed. Considerable advances in toxicology had been made in the decade since the FDA decision to allow a phase I study and the preclinical requirements are now very different from those of the early 1980s. One concern was the observation that quinacrine was mutagenic in the Ames test, and the panel recommended formal toxicological studies on possible carcinogenicity of quinacrine administered into the uterus. The report was made available to UNFPA and to Dr Kessel, whom Dr Hieu acknowledges as one of the two

people who provided technical assistance to the study in Vietnam.

In the letter accompanying the documents sent to Ms Demers, Dr Webb mentioned that the mutagenicity observed had led toxicology experts to say that they “would be very surprised if quinacrine did not turn out to be carcinogenic”. This was an opinion expressed during informal discussions, not the formal conclusion of a meeting convened by WHO. “Carcinogenic” in this context refers to animal models.

HRP's toxicology panel follows internationally accepted norms on the research and development of drugs for human use. Successive stages of clinical testing have to be preceded by stringent toxicological evaluation. The panel does not apply two standards—one for “northern” (developed) countries and less stringent standards for “southern” (developing) countries—as your editorial appears to favour. For some twenty years WHO has been falsely accused of dual standards on the use of injectable contraceptives in developing countries that were not approved in their country of origin. The obvious example is depot medroxy-progesterone acetate, which has now been approved in the USA, largely as a result of data provided by WHO. Now WHO is criticised for continuing to recommend that the same stringent safeguards for the testing and use of contraceptives should apply to both developed and developing countries. The approval, in the early 1980s, by the US Food and Drug Administration of a phase 1 clinical study (equivalent to a short-term, limited, human toxicology test) of the instillation of quinacrine into the uterus of a small number of women who, 24 hours later, underwent hysterectomy, can provide no justification for a field study in the 1990s of quinacrine in almost 32 000 women.

I will not comment on the wisdom of utilising private correspondence, without our prior knowledge or permission, for quotation in a scientific debate, and will limit myself to reminding you that an official WHO position is only given out after approval of the document through the appropriate channels. Indeed, in Dr Webb's letter the only reference to a “WHO position” is contained in a sentence that reads “WHO's position is that further clinical research is not justified until various toxicological issues have been resolved”. This sentence reflects the current position of WHO and is based on the unanimous recommendation of the HRP toxicology panel.

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