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Death of a study: WHO, what, and why

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Earlier this year *The Lancet* received a package of material, much of it highly critical, relating to a report that we had published in July, 1993. A few weeks later virtually the same package arrived from a different source. The accompanying messages were broadly similar, essentially saying that the work in question had come in for heavy criticism and that the project itself had been abruptly halted. All this had taken place without any consultation with the researchers or proper debate.

The study was by Hieu and colleagues in Vietnam and described the use of quinacrine pellet sterilisation in more than 30 000 women in that country.⁷ In this issue, Professor Hieu, Director of the Maternal and Child Health/Family Planning Department at the Ministry of Health in Hanoi, outlines his concerns, expressing dismay at the manner in which his work has come under attack. *The Lancet* is no stranger to controversy and its correspondence section is open to all (matters relating to efficacy and operator skill had in fact been aired in letters published in the Oct 2 issue, p 869), so why have Professor Hieu and his colleagues been treated in this underhand fashion?

To begin to understand the story, some background information may be helpful. Quinacrine hydrochloride (mepacrine, Atabrine) was developed in the 1920s and was initially used as an antimalarial agent. Chemically it is 6-chloro-9-(1-methyl-4-diethylamine) mutylamino-2-methoxyacridine, and it differs from chloroquine only in having an extra benzene ring rather than a quinolone. Subsequent infection-related uses were for tapeworm infestation, amoebiasis, and giardiasis. Quinacrine has also been used in connective tissue diseases such as systemic lupus erythematosus, where it is thought to act via suppression of antigen formation; in addition, its sclerosant properties have been exploited in the management of malignant

pleural effusions.² The sclerosant actions led to the development of quinacrine as a method of non-surgical female sterilisation, since instillation of quinacrine "slurry" into the uterus was shown to occlude the fallopian tubes. The tubal work was done by Zipper and colleagues in Chile and began in the 1970s. When the results of instillation were found to be haphazard, Zipper went on to devise a pelleted form of the drug that could be introduced transcervically via a modified copper T intrauterine device **inserter**.³

Quinacrine shows high-affinity binding to nuclear and chromosomal DNA by intercalation between adjacent base-pairs.* Toxicological evaluation of the drug remains inadequate. Quinacrine is a positive mutagenic agent in bacterial systems, but evidence in mammalian systems is inconclusive. Conversely, at least two rodent studies have shown anticarcinogenic activity of quinacrine with respect to bladder and mammary **cancer**.^{4,5} The data were judged sufficient for US Food and Drug Administration (FDA) approval for phase 1 clinical trials in Texas in the 1980s, when quinacrine pellets were inserted into volunteers 24 hours before **hysterectomy**.⁶ However, reports of an apparent cluster of cancer cases during long-term follow-up in Chilean quinacrine users prompted researchers from Family Health International, the charity that funded the work, to conduct a retrospective cohort study spanning the period 1977-1991. Their conclusion was that "no evidence was found of excessive cancer risk associated with quinacrine pellet transcervical sterilisation" (Sokal D, et al, unpublished). There was a single uterine leiomyosarcoma, and continued surveillance of the cohort was recommended. Moreover, the charity had earlier asked a panel of toxicologists to evaluate the carcinogenesis question, and their 1990 report as Hieu notes this week, uncovered no relevant human data.

In September, 1993, 2 months after publication of Hieu's report in *The Lancet*, the Association for Voluntary Surgical Contraception (AVSC) in New York prepared a technical statement on the subject which it distributed to interested parties. The conclusion was that there were unresolved questions about the safety and efficacy of the method, and that AVSC "continues to consider it an experimental technique that requires further trials". They were also concerned about free and informed choice and demanded that the matter should be addressed with a "loud voice".

On Dec 2, 1993, AVSC hosted a meeting in New York that was attended by representatives of WHO and of other organisations. As Hieu points out this week, the quinacrine pellet method was extensively discussed, and yet none of the authors of his report was invited to attend. The WHO position at the meeting was that there should be no clinical trials; the WHO representative was apparently alone in taking that stand. The matter of possible coercion of trial participants did come in for discussion since the method is so simple to deliver: Hieu, in response to letters mentioning such worries in *The Lancet* of Oct 2, had already said categorically "there is no coercion in our programme".

On Dec 6, Mme Linda Demers, Director of the United Nations Population Fund (UNFPA) in Hanoi, requested the official WHO position on the quinacrine pellet method of sterilisation. Accordingly, she sent a fax to Dr Frank Webb at the Special Programme of Research, Development and Research Training in Human Reproduction (HRP) and he replied the next day. These letters have been widely circulated and were among the items in the two packages received by *The Lancet*. Webb began by saying that "many people are very much disturbed by the recent paper in *Lancet* reporting research undertaken in Viet Nam. I attach a statement from AVSC [the statement mentioned above] issued in response to this paper and **which was formulated following contributions by, among others, this Programme** [our italics]. He went on: "a more detailed critique of the paper is available in HRP, but is not appropriate for public consumption". He also attached a statement issued by HRP's Toxicology Panel in response to a specific proposal submitted to UNFPA by Dr Elton Kessel at Family Health International 2 years earlier. Dr Webb continued "WHO experts and FDA officials have said that they would be very surprised if quinacrine did not turn out to be carcinogenic". Yet the April, 1991, toxicology panel report merely recommended that the method should not be pursued until systematic toxicology of the drug given into the uterus had been done.

The WHO critique of Hieu's paper that Webb attached for Mme Demers' attention is remarkable in several respects, including some choice vernacular language-eg, patients were mentioned as being possibly "pissed off". One observation was that the method "has been much 'pushed' by a few enthusiasts who have not generally sought (or even resisted) involvement of organisations such as our Programme". Such clear signs of pique make one doubt the objectivity of the analysis.

In February this year *The Lancet* inquired of WHO why their criticisms had not been brought out into the open. We invited WHO to prepare a letter for the correspondence columns to which we could get the authors of the Vietnamese study to reply. WHO's response was less than informative. No letter for publication was forthcoming, and the recommendation, from HRP director Dr Giuseppe Benagiano, was that we should approach AVSC to write the letter since that organisation had gathered together all the criticisms.

This is no way to evaluate research. That WHO should resort to anecdote and misinformation and then try to duck the question is reprehensible. Maybe now, with the publication of Hieu's letter, WHO-and AVSC-will have the courtesy, and the courage of their convictions, to air their criticisms properly for the first time. Meanwhile, as Prof Malcolm Potts⁶ commented on a follow-up visit to Vietnam as a member of a team from International Projects Assistance Fund, "international agencies now find themselves in the embarrassing position of pontificating according to Northern standards on a much needed South-South technology they failed to support in a timely manner earlier". At this juncture Hieu surely deserves the last word: "Unsubstantiated opinions of unidentified WHO experts and FDA officials should not be accepted by the scientific community in this attempt to undermine our decision to move forward with this method".

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- 1 Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31 78 1 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. *Lancet* 1993; 342: 213-17.
- 2 Wallace DJ. The use of quinacrine (Atabrine) in rheumatic diseases: a reexamination. *Semin Arthritis Rheum* 1989; 18: 282-97.
- 3 Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. *Int J Gynaecol Obstet* 1980; 18: 275-79.
- 4 Kanamaru H, Hashimura T, Yoshida O. Effects of retinoids and inhibitors of arachidonic acid metabolism on tumor-promoter-induced soft agar colony formation of mouse epidermal cells and rat urinary bladder cells. *Jpn J Cancer Res* 1988; 79: 1043-47.
- 5 McCormick DL. Anticarcinogenic activity of quinacrine in the rat mammary gland. *Curcinogenesis* 1988; 9: 175-78.
- 6 Potts M. Quinacrine method of family planning. *Lancet* 1994; 343: 662.
- 7 Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. Non-surgical female sterilisation. *Lancet* 1993; 342: 870-7 1.