

## COMMENTARY

**Quinacrine sterilisation revisited**

Benagiano's letter (Sept 3, p 689) about transcervical quinacrine, pellet research for non-surgical female sterilisation omits a historical perspective and does not discuss the differences of opinion concerning the appropriateness of proceeding with current and expanded clinical trials concurrently with \*additional toxicology testing.

During my term as founding president of the International Fertility Research Program, now called Family Health International (FHI), international clinical trials of the quinacrine pellet method of non-surgical female sterilisation were organised in cooperation with the inventor of the method, Dr Jaime Zipper of Santiago, Chile. By subcontract to Johns Hopkins University, toxicology studies were completed that enabled PHI to obtain in 1981 an Investigational Exemption for a New Drug from the United States Food and Drug Administration (FDA). After resigning from FHI in 1982, I provided technical assistance for official trials of this method in China, India, Indonesia, the Philippines, and Vietnam as Secretary General of the International Federation for Family Health. Informal trials were also initiated in several other countries with the support of the federation and of the Center for Research on Population and Security. The report of the Vietnamese field trials published last year<sup>1</sup> has been criticised by the World Health Organization Special Programme of Research, Development and Research Training in Human Reproduction (HRP)<sup>2,3</sup> and by the Association for Voluntary Surgical Contraception,<sup>4</sup> which emphasised in particular the concerns of feminist groups. In Geneva last month HRP brought together the main combatants for a consultation on the development of new technologies for female sterilisation. The debate revealed their different value judgments concerning standards for contraceptive research, which I now summarise.

At the outset of the debate HRP made clear its policy for a single global standard for contraceptive research, rejecting a risk-benefit criterion used by the Vietnamese participant to justify the field trial in that country. The HRP standard is of necessity a North standard and it has to follow guidelines of regulatory agencies in industrialised countries—eg, the FDA.<sup>5</sup> The FDA considers risks and benefits of contraceptive research as they pertain to Americans. However, the benefits of contraception in terms of morbidity and mortality prevented, as well as the socioeconomic concerns of rapid population growth, are greater for a developing country such as Vietnam. In applying a North standard for contraceptive research to a developing country, HRP has made a value judgment that is not based on science or logic.

The difference between WHO research programmes in this regard is noteworthy. Thus the WHO Special Programme for Research and Training in Tropical Disease (TDR) favours a risk-benefit guideline that takes account of the circumstances in which the research is conducted.\* Both programmes follow accepted procedures for phase I, phase II, and phase III clinical studies, but TDR is more likely to encourage these to proceed concurrently when the benefits seem to outweigh the risks of the trial.

One of the arguments given by HRP for not accepting the risk-benefit guideline of TDR is that tropical diseases involve risks and benefits to identifiable subjects, whereas the health benefits of preventive measures such as contraception in the form of averted morbidity and mortality can only be documented statistically. This preference for identifiable deaths rather than statistical deaths is another value judgment by HRP.

In Geneva, the concerns of feminists were discussed.

Some of them question the desirability of contraceptive research involving women volunteers, especially for the development of methods that are not completely under a woman's control, that lend themselves to coercion, or that affect the hormonal or immune system of women. To the extent that feminist groups can influence government or donor agency policy, they can materially influence contraceptive research.

Donor agencies such as the United States Agency for International Development (USAID) have self-imposed regulations. Clinical research that they support must follow FDA guidelines irrespective of the potential benefit of that research to the country in which it will be conducted. FHI had approved a phase II clinical trial of the quinacrine pellet method of non-surgical female sterilisation in Vietnam with private funding. This trial was delayed by the government of Vietnam after they received a letter from WHO warning that quinacrine is probably carcinogenic,<sup>2,3</sup> and is now likely to be further delayed because FHI has been given the responsibility and support by USAID to take this method through the FDA approval process.

Occasionally a new contraceptive method uses a drug that is accepted for another purpose. This is so for the quinacrine pellet method of non-surgical female sterilisation—quinacrine has been widely used as an antimalarial by the oral route, in much higher doses and over longer periods than those needed for sterilisation by intrauterine administration. The FDA gives physicians the option to use an approved drug for a non-approved indication.<sup>6</sup> Nevertheless, FDA or HRP approval for intrauterine use requires the full range of standard toxicology studies and phase I and phase II clinical studies; this process would probably take six years and over a million dollars before phase III studies, to document efficacy of the method, could begin. By comparison with surgical sterilisation early complications with the quinacrine method are fewer and less severe<sup>7</sup> whereas efficacy is lower but improving.<sup>8</sup> Toxicologists believe that the risk of cancer is low or non-existent.\* Risk-benefit assessments conducted by several South countries have led to decisions to pursue clinical trials of the method rather than to wait out a six-year period.

When it comes to contraception research, the North has the resources and the technical capability to conduct preclinical toxicology studies that the South can ill afford, while the South can more economically document efficacy, acceptability, and early safety in trials of a new contraceptive method. The main contraceptive methods in use today and approved by North regulatory agencies—eg, hormonal methods including oral preparations, injectables, and implants, and intrauterine devices—all had their efficacy, safety, and acceptability documented in clinical trials in developing countries before pharmaceutical companies or foundations went to the expense of completing toxicology studies or clinical trials required by North regulatory agencies. Any organisation that attempts to develop a new contraceptive method entirely within a North regulatory framework will have, to invest heavily and be prepared for long delays before the clinical safety and efficacy of the method are assured.

The only sensible global standard is a risk-benefit one that will vary according to the circumstances of the country involved in the research. A simple guide to

determining benefits is the estimate for rural areas of South countries that each sterilisation prevents two births. If maternal mortality is, say, 3.8 per 1000 live births as estimated for Vietnam, then each 1000 additional sterilisations done by a new method such as quinacrine pellets will prevent 7.6 maternal deaths. No one has suggested that the method could kill that number of women. In over 80000 procedures carried out so far, there has not been a case-fatality reported whereas there were three case-fatalities for a similar number of surgical sterilisations in Vietnam.

The HRP consultation in Geneva closed without a consensus among the participants as to the next steps for the quinacrine pellet method. WHO insisted that no clinical trial should be conducted until there had been more laboratory and animal toxicology studies. Other participants thought that clinical trials should continue concurrently with toxicology studies; they reasoned that the long-term risks will eventually be determined by epidemiologic studies involving many women who have used the method for a long time. And that was what happened for most contraceptives in use today.

Elton Kessel

Department of Public Health and Preventive Medicine,  
Oregon Health Sciences University, Portland, Oregon, USA

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