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MEMORANDUM

TO: Concerned Colleagues
FROM: Elton Kessel, M.D.
DATE: 5 November 1993

SUBJECT: AVSC Technical Statement: Quinaorine Pellets for
Nonsurgical Female Sterilization

This Statement is flawed on three counts: (a) misinterpretations of the Lancet article, (b) failure to make a reasonable risk/benefit assessment of the method, and (c) over emphasizing the importance of some misstatements in the Lancet article. *There are* also a few historical misimpressions. Some of the misinterpretations appeared in letters to the editor of Lancet and were answered in the 2. October 1993 issue,

I shall first indicate needed corrections and clarifications to the Statement by page and paragraph and then make some general comments *on* the Statement,

Page 1, last paragraph, Studies for FDA approval for use of intrauterine quinacrine for sterilization have not been submitted to the FDA. FHI obtained an IND in 1982 based on toxicology studies at Johns Hopkins University, and a first pre hysterectomy study involving ten women was performed in San Antonio, Texas, under this IND. This initial work, as well as earlier clinical trials of the method before 1979 in Chile and India, was supported by AID, Further admissions to international trials have been supported by the International Federation for Family Health with private funds and a grant from IDRC in Canada, and by the Center for Research on Population and Security with private funds. None of the international clinical trials were designed to obtain FDA approval. No pharmaceutical firm has taken an **interest** in obtaining FDA approval, because of the unfavorable patent situation from their point of view. Lack of FDA approval does not imply a poor record of safety and efficacy,

Page 2, paragraph 1. The Toxicology Panel of WHO was asked by the UNFPA to review a research proposal submitted to the UNFPA by the International Federation for Family Health. This included results of toxicology studies conducted at **Johns** Hopkins University, The WHO Toxicology Panel at first pointed out a few reservations concerning the Johns Hopkins studies and later recommended that all toxicology studies be repeated and possibly extended, The question of what additional toxicology studies are needed *is to be on* the agenda of a planned WHO consultation, The

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terminology "quinacrine instillation" should be reserved for the earlier studies of a liquid slurry of quinacrine. Quinacrine pellets are inserted in the uterus,

Page 2, paragraph 2. Large scale field trials are under way in India, Pakistan **and** Vietnam, Health professionals, primarily in medical schools of **over** ten developing countries, and representatives of the public in official agencies of China, India, Indonesia, the Philippines, and Vietnam have initiated **or** are about to start clinical **trials** of the method. They all require a consent form that details the method's permanent nature and all subjects are advised **of** alternate methods of contraception. The principal investigators of these trials are aware of the lack of approvals of FDA and WHO. They have evaluated known safety and efficacy information and decided a trial of the method is warranted in their local areas. The official trials are for the purpose of deciding whether or **not** to add this method to their service programs. It is unfortunate that **American** population organizations, except for FHI, have largely ignored this method. The opportunity to rigorously analyze and debate the safety and efficacy of this method has been available for some time.

Page 2, paragraphs 4 and 5. Of course, proper counseling is required for this and all family planning methods. Possible misuse of this method must be balanced against both the benefits of increased prevalence of contraception made possible by this simple and inexpensive method and its **lower** complication rate and case fatality compared to surgical sterilization.

Page 3, paragraph 1. The change from slurry to pellet form of quinacrine was made by Dr. Zipper to avoid accidental intravascular administration of the slurry which was subject to pressure on intrauterine instillation.

Page 3, paragraph 2. In the Dubin, et al., studies, no monkeys died at 7.5 times the human pellet dose when pellets were placed intraperitoneally in the monkeys. The AVSC! statement is needlessly alarmist here. Besides the toxicology studies for intrauterine and intraperitoneal administration, there is extensive experience with oral administration in humans for long periods of time and at much higher doses **per** month than used for sterilization. Present knowledge of **over 80,000 quinacrine sterilization cases, involving over 160,000** intrauterine insertions of quinacrine without a case fatality is reassuring.

Page 3, paragraph 4. FHI support of studies involving **new** intrauterine insertions of quinacrine was discontinued in the late years of the Carter administration -- not in 1989.

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Page 3, **paragraph 5.** The FHI study concludes, "no evidence was found of excess cancer risk associated with quinacrine pellet sterilization."

Page 4, **paragraph 3.** The authors do not extrapolate failure rates or side effects to all 31,781 cases. As stated in their answer to letters to the editor of Lancet (pp 869-871, October 2) the failure rates were shown to illustrate wide variation between studies. They state the side effects in the different studies were similar and detail these for 508 cases in Namha Province. Safety factors in terms of complications, ectopic pregnancies and malformations are completely reported. The authors conclude that the quinacrine pellet method is safer than surgical female sterilization. This conclusion is valid,

Page 4, paragraph 4-6. The initial inclusion criteria were as stated, "at least 30 years old and had to have at least two living children, the youngest being at least three years old." This inclusion criteria was adhered to throughout the study for women with two living children, but was gradually relaxed for women with more living children. This should have been mentioned in the methods section of the article.

Page 5, paragraph 1-4. The statements are not conflicting. All cases were followed up and used for reporting complications, total pregnancies, ectopic pregnancies and malformations. Calculation of life table rates was to illustrate wide variation between studies, a finding that would surely not disappear by including all cases (see also "letters to the editor, October 2). The December '5, 1992, date in Table 2 should read May 12, 1992. The day and month was transposed in editing, and the error overlooked in reading the proof,

Page 5, **paragraph 5.** The denominator for calculation of ectopic pregnancy incidence was all cases in the Namha studies as stated. The calculation is made by adding all months of use from last insertion to study cut-off date and dividing by 12,000.

As mentioned in the "letters to the editor," a separate analysis is planned by the authors covering variation in ectopic pregnancy rates.

Page 5, paragraph 6. The high failure rate in this province is further evidence of marked variation in pregnancy rates between provinces (see also "letters to the editor"). However, most cases in Hatinh Province had only a single insertion of quinacrine pellets.

Page 5, paragraph 7. Skill is defined on pg 216 as "consistent application of proper insertion technique."

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Page 6, paragraph 1. The authors do not extrapolate. The readers may if they wish. The authors say side effects were similar in the studies and give an example of data from one study.

Page 6, paragraph 2. Safety is always relative and must balance risks and benefits, as the authors have nicely done in the last paragraph of their article. Complications and case fatality of this method are clearly shown to be lower than for surgical sterilization. In an equal number of recent surgical sterilizations in Vietnam, there are two case fatalities. The authors cite the reassuring evidence from Chile concerning cancer risk. Only continued surveillance of many cases can document any risk of mutagenicity, and this, if it could be documented, would have to be compared to the large savings in lives of women of reproductive age in areas of high maternal mortality, not to mention complications and case fatality avoided compared to surgical sterilization,

Page 6, paragraph 4. A standard protocol for insertion (and possibly patient selection) is needed to evaluate efficacy. The authors are the first to document this and as mentioned in the "letters to the editor," they are presently conducting research using their large data set to determine what this standard protocol should be,

Page 6, paragraph 5. An important factor mitigating against the potential of coercion in use of this method in Vietnam is the emphasis given by the government on voluntary participation in their family planning program and the role of the Women's Union in monitoring this aspect of the program. It is also noteworthy that the central government has offered no financial incentives for quinacrine nonsurgical **sterilization** as it has for surgical sterilization.

It is, for course, always possible that some clinician, for whatever reason, would use this simple method without informing the woman. It is unlikely in Vietnam that this could be hidden and punishment of the clinician would likely be swift and severe, and *serve* as a deterrent to *any* repetition of such an event .

Perhaps an **ethicist** should be asked, "How many coercions equal one life of a woman of reproductive age -- or vice versa?" Risks of coercion with any simple family planning method must be balanced against its benefits. The same coercion arguments have been brought against Depoprovera and Norplant. The answer to these arguments is quality counseling and service monitoring,

General Comment:

It is unfortunate that AVSC did not submit its concerns regarding the Lancet article in the form of a letter to the editor to allow a response from the authors.

It is not the role of American organizations to decide whether the quinacrine pellet method of nonsurgical female sterilization is to be studied or used in service programs in other countries. This decision needs to be made by local and national political units based on their **own** risk/benefit assessments. Two provinces of Vietnam have decided to include the quinacrine pellet method in their family planning services. They need support for quality delivery of this new **service**. Several governments, especially in Asia, are in the clinical trial phase. They need support of a research organization like FHI.

The fear of coercion is not a legitimate reason to reject the quinacrine pellet method. Excellent counseling is needed for all family planning methods and especially for all permanent methods.

The authors of the Lancet paper summarize in the last two paragraphs the main advantages of this method for a developing country like Vietnam and conclude that, "This procedure represents our most cost-effective way of lowering maternal mortality." It would be cruel and immoral to deny this opportunity.

PROPOSED CONSENSUS STATEMENT
Quinacrine Pellet Nonsurgical Female Sterilization

1. A simple nonsurgical method of female sterilization that could be delivered by paramedics would raise contraceptive prevalence among high risk women in areas of high maternal mortality.
2. The quinacrine pellet method, with its standard protocol of **two** monthly transcervical insertions of **252 mg of** quinacrine to the uterine fundus has been shown to be safe and has acceptable efficacy, especially for areas with high maternal mortality.
3. The method is appropriate for service programs in areas of high maternal mortality, especially where health personnel in these areas are already trained in IUD insertion.
4. Service programs and large field trials of the method should include monitoring for birth defects among pregnancy failures carried to term.
5. Follow up of cases in the FHI study of cancer risk with quinacrine sterilization should continue.
6. In view of present human experience of the quinacrine pellet method, opportunities to monitor late sequelae in large field trials and service programs, and the extensive experience with this drug as an antimalarial, further toxicology studies beyond those conducted at Johns Hopkins University are not needed, unless an adjuvant is added to intrauterine quinacrine,
7. Where local governments have decided to add the quinacrine pellet method to their family planning service program, technical assistance should be offered to improve the quality of the new service.
8. Several governments are initiating clinical trials of the quinacrine pellet method. Technical assistance should be offered to improve the quality of these trials,
9. There are several leads to improving **efficacy** of the quinacrine pellet method. Among these are: a) defining the best insertion technique and patient selection for the method; b) the addition of **of** adjuvants such as antiprostaglandins, orally **or** intrauterine; and the advantages of post-insertion contraception. Research to prove or disprove these leads should proceed as a high priority in family planning research.
10. An international workshop should be held of persons presently active in trials of the quinacrine pellet method to accelerate exchange of ideas and documentation of present experience.