STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305

STANFORD UNIVERSITY SCHOOL OF MEDICINE
Department of Genetics
(415) 497-5052

November 17, 1975

COPY

Dr. Giuseppe Benagiano
Human Reproduction Unit
World Health Organization
1211 Geneva 27, Switzerland

Dear Dr. Benagiano,

As you know I have been preparing an assessment of the current status of toxicity control studies on the Alza erodible implant systems. I am happy to submit this interim report at the request of Dr. Edward E. Schmitt of Alza Research.

Dr. Schmitt has given me extensive proprietary information concerning the erodible norethisterone implant system and has discussed with me in detail the nature of the erosion products. I have not seen, nor did I consider it necessary at this stage to review, the original laboratory data on which the present picture of the chemical process of erosion is based. However, Dr. Schmitt did give me a most detailed account of the chemical nature of the products and their quantitative distribution under various conditions. They appear to have made a very wise choice indeed in their selection of constituents as being a priori most unlikely to present significant toxicity problems.

I have also reviewed a pathology study that they have conducted to date and their descriptions of the fate of implants in experimental animals. I believe that other experts can readily be found who would have more experience with conventional toxicity-pathological studies and might be able to uncover problems that were not evident to me. Although a slight inflammatory reaction and connective tissue incapsulation has been noted with some implants, these reactions are most unlikely to be avoidable with any implant at all and do not appear to pose any significant problem that would hinder the further development of this therapeutic approach on the basis of the present evidence. Needless to say, such studies will eventually have to be conducted over very much longer pariods of time and with human subjects in order to erase any conceivable doubt. There would appear to be no impediment on the basis of the studies so far to proceeding with clinical trials on human subjects.

I have offered Dr. Schmitt a list of suggested studies that I believe should be carefully studied for selection of the highest priority items for further investigation. They include:

1. The whole area of low-level chronic toxicity in mutagenesis and teratogenesis regimes. This must be proposed as a general precautionary measure in view of the scope of intended application of the systems, rather than because there is any manifest suspicion on the basis of current evidence. Protocols for these kinds of studies are already

sufficiently well crystallized to be generally accepted. They would include dominant lethal mutation assay in mice, in vitro bacterial mutagenesis and host-mediated bacterial mutagenesis, inactivation of DNA and of bacterial phage in vitro, and teratology studies on a few laboratory mammals. The test reagents for these studies should be chosen so as to give a very large scale amplification of potential toxicity and we discussed such measures as the use of finally divided polymer-hormone complexes; injections with the known oligomers; and with some of the other known degradation products of the polymer.

2. I did not as yet see specific documentation of purely chemical studies on the possible interaction of the steroids with the polymer as may occur during the fabrication of the implant. This should include consideration of all of the process steps that will be used in the final manufacture. There is a theoretical possibility of the occurrence of a small percentage of new chemical complexes between polymer constituents and steroid and it would be important to isolate and identify such complexes in order to permit a more aggressive analysis of their potential toxicity.

Similarly, more studies of the potential chemical reactions between the polymer constituents and amino acids and other body fluid constituents should be conducted at a purely chemical level, not withstanding the evident lack of toxicity of the systems as studied empirically so far.

The question of halogenicity of the implant materials and the possibility of occasional idiosyncratic sensitivity to them has not so far as I know been addresse If such reactions do appear - as may well be conceivable after repeated and perhaps interrupted implantations - this will not necessarily vitiate the use of the systems but may require the development of skin testing or other diagnostic procedures to identify such sensitivity. In a related vein I would urge that blood clotting and platelet function studies be included in further hematological analysi

More closely connected with the therapeutic efficacy than with the safety of the implants, I would recommend further studies on: (1) tne preconditioning of implants by emersion in water so that they are available for immediate initiation of release, and (2) more detailed studies on the terminal rate of release of hormone at the end of the life-time of the implant - a stage which is dealt with only by a rather shaky extrapolation at this time. To conduct these studies it will be necessary to use tracer-labelled agents and to make direct analyses for the blood levels and metabolic disposition of the agent and of the implant material.

Not withstanding, these critical considerations which will have to be pursued in unusual detail because of the enormous potential and equally enormous range of subjects at risk, the approach does indeed to be a most promising one and I would judge deserves continuing attention by WHO. I would be happy to continue in a consulting role on this project and believe that I can contribute to a continuing critical evaluation of the therapeutic systems. However, I believe it important that I place on the record that I have a long history of personal association with Dr. Alejandro Zaffaroni and that for this reason alone it would be inappropriate for me to be in a critical adjudicatory role with respect to WHO's continued investment in this particular direction.

Sincerely yours,

Joshua Lederberg
Professor of Genetics

cc: Dr. Edward E. Schmitt