

FOOD AND DRUG ADMINISTRATION  
BUREAU OF MEDICINE  
SIXTH MEETING  
OBSTETRICS AND GYNECOLOGY ADVISORY COMMITTEE

May 18 and 19, 1967

Crystal Plaza Office Center

Arlington, Virginia

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Members of the Committee Present:

Dr. Karlis Adamsons (first day only)  
Dr. Elsie Carrington  
Dr. Philip Corfman  
Dr. Eleanor Delfs (first day only)  
Dr. Nicholson Eastman  
Dr. Henry Fuller  
Dr. Roy Hertz  
Dr. Schuyler Kohl (second day only)  
Dr. Alfonse Masi  
Dr. Philip Sartwell  
Dr. Roger Scott  
Dr. Christopher Tietze

Consultants to the Committee Present: Dr. Sheldon Segal

Chairman: Louis M. Hellman, M.D.

Executive Secretary: Edwin M. Ortiz, M.D.

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PROCEEDINGS

Dr. Hellman opened the meeting.

Prospective Study:

Dr. Ley introduced Dr. Anderson for his report on the feasibility of a collaborative study on the adverse effects of contraceptive drugs. Dr. Anderson heads a pro tem task force which has investigated the problem from the standpoint of methodology. It would take several years for the evaluation of carcinoma associated with oral contraceptives, about 3 or 4 years for the study of thromboembolic phenomena, while the study of carbohydrate and other metabolic effects could be resolved in a much shorter time. The studies could be either prospective or retrospective. The drugs are either combination or sequential, and in each category there are several brand names with different chemical composition. Dr. Anderson stated that in order to conduct an adequate study using several study centers, the protocols must be standardized and the forms and procedures must likewise be very similar in all centers. A very high degree of monitoring is required. He stated that the only realistic hope for obtaining useful

information from a collaborative study is to closely monitor a long-range study of quite limited scope.

His recommendation was for FDA to locate responsibility for the pursuit of this matter in one unit created for the purpose and to staff realistically in accordance with the degree to which it was decided to press on. To continue as in the past would not produce, he stated.

Dr. Ley stated that a cooperative study is almost doomed, since we are almost obligated to use the available facilities. Dr. Hellman pointed out certain difficulties associated with the use of the facilities of Kaiser Permanente. Dr. Anderson noted that the purpose of the existing Kaiser contract with FDA is to extract from the hospital records information of value for adverse drug reactions. He stated that the new contract is aimed at collecting information from the inpatient records, outpatient records, pharmacies and house calls. This information will be in one information system in order to try to correlate the occurrence of certain diagnoses with the use of certain drugs. It will take approximately one and half years to get going on this study, which includes oral contraceptives but is not specifically aimed at this drug category any more than any other category.

He referred to the need for two types of studies with respect to contraceptive drugs.

1. Specific laboratory-oriented studies requiring limited numbers of subjects.
2. Epidemiologic studies of broader nature requiring large numbers of subjects.

Dr. Corfman agreed with this analysis and stated that some studies of both types are currently contracted for by NIH.

Dr. Anderson suggested the formation of HEW policy requiring the cooperation of NIH, the FDA and the Children's Bureau and any other part of HEW funding birth control programs in assuring the collection and submission of certain information as part of any such program receiving Federal support.

Dr. Hellman mentioned the necessity of a protocol to study congenital malformations in children born to women previously on oral contraceptives.

Dr. Segal noted that the Population Council supports studies, and some investigators might alter the design of their studies to suit the FDA needs if we let them know what we are interested in. At present the Population Council has three grants on carbohydrate and lipid metabolism and that there is also a study in progress of the possible lack of resistance to tuberculosis in women on oral contraceptives.

Dr. Tietze stated that in view of the difficulties associated with setting up prospective studies we should consider some retrospective studies similar to the reports currently available from the United Kingdom on vascular disease. He remarked that all three studies were done retrospectively and

one of those studies is almost identical to the current study sponsored by the FDA.

British Report:

Dr. Ley mentioned the possibility of a representative from Great Britain discussing the British findings with the Obstetrics and Gynecology Advisory Committee. He stated that Dr. Cahal is to come to Canada in June and asked the Committee if they would be interested in meeting with Dr. Cahal and possibly Dr. Witt.

Dr. Tietze stated that Dr. Cahal has some information not yet published in the BMJ. He expressed agreement with the editorial.

Dr. Tietze stated that even though the oral contraceptive users are young middle class women, in whom the mortality is very low, you come out ahead on oral contraceptives. There are certain risks from anything and contraception is no exception.

Dr. Tietze added that we need to get detailed information before it appears in the press. Dr. Hellman remarked that the British have concluded part of the study and their conclusions are not different from those of the Sartwell report.

Dr. Tietze suggested the use of the National Office of Vital Statistics to gather some information on mortality.

Dr. Ley remarked that there is a long lag in reporting, as long as two years.

Dr. Sartwell stated he agrees with Dr. Anderson about a cooperative prospective study. He stated that they look better than they turn out.

After a brief discussion the members of the committee decided to meet with a representative from the United Kingdom even if it doesn't coincide with the next scheduled meeting on devices.

Pincus-Rutstein Study:

Dr. Corfman introduced the study by saying that it is based on experience in Puerto Rico and Haiti and stated that Dr. D. Siegel of NICHD will give more information on the subject.

Dr. Siegel said that 12,000 patients were followed up in 3 clinics in Puerto Rico. Six thousand patients were on oral contraceptives and 6,000 patients served as controls. The main interest of the study was the effect of oral contraceptives on breast and cervical carcinoma. He mentioned that the study has been quite unsuccessful in adequate follow-up of the patients. Approximately one-third of the patients never came back after the initial examination. He stated that the organizers of the study would like to see a physician come in and follow the patients.

Dr. Tietze stated that the study is not suitable for the study of thrombo-embolic phenomena. He said that a thromboembolic phenomenon is a sudden occurrence. Unless the group is under constant medical supervision it is not feasible to conduct such a clinical trial. He stated that Planned Parenthood only gives contraceptive advice and is therefore not a good group to use.

Dr. Masi thought that some money could be allocated for a Puerto Rico type follow-up and that the study could be started with Dr. Pincus' sample and then enlarged.

Dr. Tietze stated that if a large sum of money was involved you would need a quasi-captive population. He stated that the population in Puerto Rico is difficult to deal with from that standpoint. An alternative solution would be to persuade the Department of Defense to allow the study of dependents and military personnel for that purpose.

Dr. Corfman stated that Dr. Rutstein would like to have a physician come in and examine the patients and conduct the clinical evaluation.

In answer to Dr. Hellman's question, Dr. Corfman replied that Dr. Rutstein lacks the time and money necessary for adequate follow-up.

Dr. Tietze then stated that the only advantage of the Puerto Rico study is the observation of the survivors of a long range treatment with oral contraceptives.

#### Depo-Provera for Contraception:

Dr. Armstead presented a preliminary medical officer's report of the use of Depo-Provera for contraception. After presenting the animal toxicity data and the human pharmacology studies he summarized the efficacy data obtained to date. Depo-Provera has been used as an injectable female contraceptive agent in dosage regimen of 150 mg. every 3 months in 1320 patients who completed 8,760 patient months of treatment. Of these 288 completed 11 months. The study was performed by 10 investigators in clinics and by 32 physicians in their private practices.

Four patients became pregnant while on the drug, three within 60 to 85 days after receiving the initial injection and a fourth about 45 days after receiving a second injection. This represents 0.55 pregnancies per 100 women years. Eight pregnancies were reported following discontinuation of treatment. They occurred from four and one half to 14 months after the last injection.

A total of 356 subjects have dropped from this study for all reasons, for a dropout rate of 27.8 percent. The major reason for drop out was bleeding, which accounted for 8.6 percent of the subjects. During the course of the study 96 to 99 percent of the women had bleeding and or spotting on one or more days during their time in the study. Laboratory studies were fairly well within normal limits.