

FOOD AND DRUG ADMINISTRATION

OBSTETRICS & GYNECOLOGY

ADVISORY COMMITTEE

FIFTH MEETING

JANUARY 16, 1967

CRYSTAL PLAZA BUILDING # 5

ROOM 1114

2211 JEFFERSON DAVIS HIGHWAY

ARLINGTON, VIRGINIA

AGENDA

Opening Remarks: Dr. Louis M. Hellman, Chairman
Dr. Herbert L. Ley, Director, Bureau of Medicine

1. The Development of Food and Drug Laws and Regulations
William W. Goodrich
 - A. Drugs
 - B. Devices
2. Present Use and New Developments in the Field of Intra-uterine
Contraceptive Devices - Dr. Sheldon Segal
3. Quality Control of Intra-uterine Devices
Dr. John Mc Shefferty
Director of Pharmaceutical Development,
Ortho Pharmaceutical Corporation
4. Results of Clinical Experience with Intra-uterine Devices
Dr. Christopher Tietze
5. Follow-up On the Report On the Oral Contraceptives
Dr. E. M. Ortiz
6. CONCLUSIONS AND RECOMMENDATIONS - Dr. Louis M. Hellman

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Dr. Hellman opened the meeting with a brief introduction. Dr. Ley read the charge to the committee.

LEGISLATIVE BACKGROUND:

Mr. Goodrich, Assistant General Counsel, HEW, gave the definition of devices and explained the development of rules and regulations pertaining to devices. A device is defined as an instrument, apparatus or contrivance for the mitigation of disease. He stated that the new drug law, which offers good control over drugs, does not extend to devices. At the present time drugs are well regulated under the new drug and antibiotic regulations. They require preclearance and may be taken off the market, shifted from over-the-counter to prescription, etc. The Federal Government has authority over devices only if they do not fulfill the labeling claims for the products. In the case of intrauterine devices the only action the FDA can take is on the basis of misbranding after the product is marketed. Efforts were started about ten years ago to regulate devices.

Mr. Goodrich pointed out that the present law for devices is inadequate and that preclearance for safety and efficacy is needed. In answer to questions from the members of the committee Mr. Goodrich stated that even quack devices are very hard to prosecute and that the new laws should require advance clearing for devices in interstate commerce. Dr. Tietze emphasized that a new law for devices should not be limited to intrauterine devices. Mr. Goodrich concurred.

The handling of the problem of modification of design of an intrauterine device while being studied in humans was then discussed. Mr. Goodrich stated that in early stages of testing a certain amount of latitude is allowable. He pointed out that step by step preclearance is not used for drugs at the present time. Dr. Hellman asked if there is any adverse reaction reporting program planned. Mr. Goodrich stated that there is. Any alarming experience should be reported at once and routine experience reported at regular intervals. Under the present regulations the FDA looks for cases from the literature and then publishes a statement of policy. Dr. Ley pointed out there is resistance from industry to extending the drug regulations to devices. He stated that with devices the safety factor is the major item. Performance will vary according to the user. Four major areas for regulations are contemplated:

- 1) No interference with the private M.D. or investigator.
- 2) If the manufacturer distributes the devices for investigational use the government should have control over these investigations.
- 3) Certain materials should be pre-cleared.
- 4) Preclearance of sophisticated devices.

QUALITY CONTROL:

Dr. McShefferty from Ortho Pharmaceutical Corporation gave a presentation on manufacturing controls for the intrauterine devices distributed by Ortho. The polyethylene, either in a pellet or powder (depending on the particular device) is mixed with barium sulfate. The devices are checked for imperfection as well as resistance to stretching. These devices are not sold sterilized and it is recommended that the practitioner sterilize them by immersion in Zephiran Solution. No particulate matter in the Zephiran solution has been noted by Ortho after soaking these devices for one month. Dr. McShefferty also stated upon questioning that batch-by-batch testing for tissue reaction is not done.

Dr. McShefferty also stated that there is no apparent change in the physical characteristics of the polyethylene after two years at body temperature. The committee then discussed the approximate number of users of IUD's at the present time. Since few figures are available at present it was decided to try to obtain distribution figures from the major manufacturers and distributors.

BIOLOGICAL ASPECTS:

Dr. Segal gave a presentation of biological effects of intrauterine devices. Intrauterine devices depress fertility in all species but the mechanism is different in different species. In some animals they may depress ovulation by pituitary action, in others they may have a unilateral ovarian effect in the ovary on the same side as the horn which has the IUD, while in still others they may affect sperm transport or tubal motility.

Dr. Segal stated that in humans interference with tubal transport is strongly suspected but has not been proven. In humans there is an increase in FAN's in the basement membrane of the endometrium. There is also a 100% contamination of the endometrium with microorganisms for about 72 hours after insertion.

Three different investigators have looked into myometrial function after insertion. One noted an increase in uterine activity for the first few days after insertion, then quiescence. Another has noticed no change at insertion or thereafter, while a third has noticed no change at insertion but has described a labor type contraction pattern at menstruation time.

Dr. Segal stated that over 2 million insertions of devices have been done throughout the world. In Korea and Taiwan 500,000 to 750,000 have been inserted; in Turkey the total is about 100,000 while in South America about 50,000 have been inserted. The figures for India and Pakistan are not available. These last two countries have a fairly large number of users as compared to other countries. Dr. Segal stated that approximately 1 million IUD's have been available to the profession in the United States. Usually after two years seventy percent of the users keep the device in situ. In other countries this figure runs about 50%. He stated that the reordering rate may provide an indication of the use of devices in this country.

Dr. Tietze suggested that the Committee could get information concerning insertion by months from 50 major health departments. Dr. Kohl suggested that reorder estimates be obtained from the manufacturers.

Dr. Segal continued his presentation stating that there are various recommendations as to the time of insertion.

- 1) Relationship to the last parturition. There tends to be a higher expulsion rate if inserted immediately post delivery. After 72 hours post-partum there is better retention, while after 96 hours the expulsion rate is similar to that seen 6 weeks post-partum.
- 2) Relationship to the last menstruation. There seems to be no effect on uterine activity. The advantages of insertion immediately after the menses are:
 - a) Less dilation of the cervix is required.
 - b) There is less bleeding.
 - c) There is practically no chance of insertion in a gravid uterus.
- 3) Insertion after incomplete abortion. There seems to be no apparent increase in pelvic inflammatory disease if the device is inserted immediately post abortion.

Dr. Segal then discussed some side effects:

- 1) Bleeding is probably the most common side effect. When encountered immediately after insertion this is probably traumatic. There is no apparent explanation for the latent bleeding encountered.
- 2) Possibility of carcinogenic potential. The study currently under way in Barbados is up to 30,000 women years of use. This may yield some figures as to cervical dysplasia and possibly carcinoma. No study currently in progress will give figures regarding endometrial carcinoma.
- 3) Pelvic inflammatory disease. The Barbados study will provide this information.

CLINICAL ASPECTS:

Dr. Tietze mentioned the incidence of ectopic pregnancies with intrauterine devices. He stated that intrauterine devices prevent uterine and ectopic pregnancies but seem to be more efficacious in the prevention of uterine pregnancies than ectopic pregnancies. Dr. Tietze then presented a cumulative report of clinical data obtained under the auspices of the Population Council on users of intrauterine devices. The data presented is contained in the Seventh Progress Report of the Cooperative Statistical Program for the Evaluation of Intrauterine Devices dated September 30, 1966 and published elsewhere.

FOLLOW-UP ON ORAL CONTRACEPTIVE REPORT:

Dr. Iay then presented to the Committee a progress report on the ten recommendations contained in the report on oral contraceptives.

- I. The pilot study at Johns Hopkins is currently being expanded.

- II. The study at the University of Pittsburgh is to be terminated in March of 1967. Currently negotiations are in progress with Kaiser to expand the present contract to include study of oral contraceptives. Dr. Corfman stated that Dr. Segal and he will hold a meeting with members of the Kaiser Fermente group since the FDA apparently cannot fund a contract this fiscal year.
- III. Action taken same as #II.
- IV. Surveillance has been strengthened by (1) organizing a Task Force on Adverse Reactions under the direction of Dr. Ruskin (2) Soliciting requests from potential users of information so as to provide a better service (3) revision of the standard form 1639.
- V. FDA adverse reactions reporting program has been reviewed by a staff member from NIH.
- VI. At a meeting in October of 1966 this question was discussed with the manufacturers.
- VII. This function is more suited for NIH.
- VIII. Uniform labeling for oral contraceptives has been developed.
- IX. The time limitations have been discontinued under revised labeling.
- X. Applications for lower dosage compounds are being accepted and their processing expedited.

Dr. Hellman appointed several Task Forces. They are to meet separately and furnish a report at the next meeting of the Committee, which will be held in May of 1966. The task forces will be constituted as follows:

1. Utility, Effectiveness and Safety
 - Dr. Tietze (c)
 - Dr. Sartwell
 - Dr. Kohl
2. Pelvic Inflammatory Disease
 - Dr. Scott (C)
 - Dr. Delfs
 - Dr. Masi
3. Histopathologic Effects
 - Dr. Hertz (C)
 - Dr. Carrington
 - Dr. Adamsons
4. Biological Action
 - Dr. Segal (C)
 - Dr. Corfman
5. Legislative Recommendations
 - Dr. Fuller (C)
 - Dr. Hellman
 - Dr. Eastman

Respectfully Submitted,
E. M. Ortiz, M.D.
Executive Secretary

