

FOOD AND DRUG ADMINISTRATION  
ADVISORY COMMITTEE ON OBSTETRICS  
AND GYNECOLOGY

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MINUTES

SECOND MEETING  
January 20 and 21, 1966

Bureau of Medicine  
Arlington, Virginia

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COMMITTEE MEMBERS:

Dr. Louis Hellman, Chairman  
Professor of Obstetrics and Gynecology  
State University of New York

Dr. Karlis Adamsons  
Assistant Professor of Obstetrics and Gynecology  
Columbia University

Dr. Elsie R. Carrington  
Professor of Obstetrics and Gynecology  
Women's Medical College - Philadelphia

Dr. Eleanor M. Delfs  
Professor of Obstetrics and Gynecology  
Marquette University - Milwaukee, Wisconsin

Dr. Nicholson Eastman  
Professor Emeritus, Obstetrics and Gynecology  
Johns Hopkins University

Dr. Henry F. Fuller  
Clinical Associate Professor of Obstetrics and Gynecology  
University of North Carolina

Dr. Roy Hertz  
Scientific Director  
National Institute of Child Health and Human Development

Dr. Roger B. Scott  
 Professor of Obstetrics and Gynecology  
 Western Reserve University

Dr. Christopher Tietze  
 Director of Research  
 National Committee on Maternal Health

CONSULTANT TO THE COMMITTEE:

Dr. Philip Sartwell  
 Professor of Epidemiology  
 Johns Hopkins University

SPECIAL GUESTS:

Dr. Alfonse T. Masi  
 Johns Hopkins University

Dr. Philip Corfman  
 National Institute of Child Health  
 and Human Development

DR. JOSEPH D. WOLFSEY  
 Deputy Director  
 National Center for Health Statistics

Dr. Joseph D. McEville  
 University of Pittsburgh

Dr. Jean K. Weston  
 Director, Division of Drugs, AMA

Dr. Frank N. Allan  
 Boston, Massachusetts

INDUSTRY REPRESENTATIVES:

Eli Lilly and Company  
 Dr. John W. Durkin  
 Dr. F. Maas

Mead-Johnson and Company  
 Dr. Byron B. Clark  
 Dr. W. T. Spain

Ortho Pharmaceutical Corporation  
 Dr. G. Arnold Cronk  
 Dr. Nathan Millman

Parke, Davis and Company  
 Dr. P. F. R. de Caires  
 Dr. D. H. Kaump

G. D. Searle and Company  
 Dr. Irwin C. Winter  
 Dr. Talmage Hiebert

Syntex Laboratories, Inc.  
 Dr. Harry W. Rudel  
 Dr. K. J. Dumas

FOOD AND DRUG ADMINISTRATION STAFF:

Dr. Joseph F. Sadusk, Jr., Medical Director  
 Dr. Joseph M. Pisani, Deputy Medical Director  
 Dr. Paul A. Palmisano, Assistant for Medical Resources and Liaison  
 Dr. Clem O. Miller, Coordinator of FDA Committees  
 Dr. R. C. Bennett, DID  
 Dr. V. R. Berliner, DTE  
 Dr. W. Evans, DMR  
 Dr. R. M. Hodges, DND  
 Dr. S. Hsia, DTE  
 Dr. J. P. Jacobs, DMR  
 Mr. P. James, DMI  
 Dr. J. J. Jennings, DMR  
 Dr. F. O. Kelsey, DND  
 Dr. J. K. Lamar, DTE  
 Dr. D. G. Levitt, DMI  
 Dr. J. W. Long, DND  
 Dr. C. H. Maxwell, OMD  
 Dr. B. H. Minchew, OMD  
 Dr. D. C. McCollum, DMR  
 Dr. R. G. Smith, DND  
 Dr. H. I. Weinstein, DMR

EXECUTIVE SECRETARY:

Dr. E. M. Ortiz, DMR

January 20, 1966

Dr. Hellman opened the meeting. There being no preliminary remarks from the Chairman or Dr. Sadusk, Dr. Hellman called on Dr. Eastman to present the report of his Subcommittee.

Subcommittee on Thromboembolism

Dr. Eastman presented the report of the Subcommittee on Thromboembolic Phenomena of which he is Chairman. He stated that a pilot study to be started at Johns Hopkins will be later presented by Drs. Sartwell and Masi.

He went on to give a report of his analysis of death reports of thromboembolic phenomena obtained from the computer printout of the Food and Drug Administration. He stated that, in general, the death reports are inadequate, biased, and there is obvious underreporting. To prove this point, he stated that in 1962 and 1963, there were 10 deaths reported. In 1964, when there was approximately a threefold increase in the use of oral contraceptives, only 4 deaths were reported. He stated that the printout contained a total of 45 deaths, 7 of which occurred out of the U. S. Because of the inability to obtain adequate followup on those 7 cases, he is disregarding them. Of the 38 reports of deaths occurring in the U.S., 15 did not have the age of the patient. He pointed out that all but three of the reports stated that the deaths were due to thromboembolic phenomena. Dr. Eastman, as a result of this report, made two recommendations to the committee.

1. Any deaths reported with the use of oral contraceptives should be followed up immediately. An effort should be made to obtain as much information as possible as soon as the death is reported.

2. More complete information is needed on the incidence of thromboembolic phenomena in patients taking oral contraceptives. This information cannot be gained from just studying the number of deaths occurring in patients using oral contraceptives. He suggested that Dr. Sadusk send a letter to all the members of the American College of Obstetricians and Gynecologists (who total approximately 10,000) to encourage them to send directly to Dr. Sadusk a report of any deaths occurring on any of their patients who have been on oral contraceptives. This may improve the percentage of reporting, since many fatalities occur, but few are reported.

Dr. Delfs asked if some of that information could be obtained from the State Maternal Mortality Commissions.

Dr. Eastman then said that the State Maternal Mortality Commissions deal with pregnant women, which will practically exclude all oral contraceptive users.

Dr. Sadusk then made two statements in reply to Dr. Eastman's comments:

1. He is aware of the inadequate reporting, which is mainly due to the narrative way of reporting. Since the institution of the standard reporting form, the data submitted has been of higher quality and easier to put onto the computer.

2. He accepted Dr. Eastman's proposal to write a letter urging the physicians to report the deaths. He suggested that the letter be signed by the President of the American College of Obstetricians and Gynecologists, and that the members of the American Academy of General Practice be added to the mailing list.

Dr. Scott believes that the internist or the general practitioner will see more of these complications, and that a letter addressed to internists and general practitioners may produce better results.

Dr. Winter stated that:

1. He is aware that the complications and deaths are under-reported.

2. Industry makes an attempt to do an adequate followup on all reports of deaths and

3. He cannot personally oppose a proposal of the type suggested to report deaths. However, he would request the reporting physicians to submit to the Food and Drug Administration all the fatalities from thromboembolic phenomena and strokes. A report of fatalities only on patients taking oral contraceptives may result in a bias and would not give us much useful information.

Dr. Weston said that he is willing to publish any such letter in the JAMA and in the specialty journals.

Dr. Sadusk stated that he would like all strokes and other thromboembolic phenomena reported.

Dr. Eastman stated that he would like to know the incidence of thromboembolic phenomena which occur unexpectedly in normal healthy women.

Dr. Tietze suggested that we get published statistics on the mortality from thromboembolic phenomena.

Dr. Hellman then called on Dr. McEvilla to present his protocol.

Pittsburgh Study

Dr. McEvilla presented the proposed study to be conducted in Lawrence County, Pennsylvania. A Model Prescription Recording System Study has been established in this county. By means of this system, a record of prescriptions filled by pharmacists for the patient can be obtained for later retrieval. The information in the computer contains about 75-80% of all prescriptions. It is possible to retrieve the information on all prescriptions given to any one patient, on any one drug, or in any therapeutic class of drugs. All patients admitted to the hospitals with a primary diagnosis of thromboembolic phenomenon will be further identified as to the occurrence being surgical, non-surgical, post partum or post D&C. The complete drug profile will be retrieved on those patients. This data will then be sent to the physician for his evaluation of the possibility of the drugs causing the reaction. The information will then be supplied to the FDA. By means of this method, the incidence of reactions can then be tabulated by - (1) All drug products. (2) A particular drug. (3) The total population or (4) Any five-year age group, and (5) The amount of drug taken,

In answer to several questions Dr. McEvilla said that the information will be obtained solely from hospital records, that patients with previous history of thrombophlebitis could be excluded, and that he considered two years an adequate length of time to give significant results.

Dr. Winter made two points - (1) that the incidence of thromboembolic phenomena in the users of oral contraceptives be compared with non-users, and that (2) the definition of an oral contraceptive be made.

Dr. Hellman asked Dr. Winter what his definition is of a "user" and a "non-user".

Dr. Winter stated that he considers a person as a "non-user", if she has been off medication for three cycles.

Dr. McEvilla stated that in 1963, 1,702 patients had used oral contraceptives at one time or the other in Lawrence County. The total female population of Lawrence County, age 15-45, was approximately 23,000.

Dr. Tietze stated that this is a low figure for ever users of contraceptives. On a national basis, ever users amount to 15-20%; current users about 10%.

Dr. Rudel stated that this is a large Catholic community and this may affect the amount of oral contraceptives used.

Dr. Winter asked if there is a Planned Parenthood Foundation in Lawrence County.

Dr. McEvilla stated that the closest clinic is in Youngstown, Ohio.

Dr. Tietze suggested that we get the cooperation of the clinics in reporting reactions. He also stated that the study looks like a promising project. Dr. Cronk questioned whether the population is large enough for validity of results in a two year study.

Dr. Tietze stated that it would probably take five years unless the difference is very big.

Dr. Sadusk then suggested two ways to reduce the bias produced by the large Catholic population: (1) In the cases of thromboembolic phenomena, an investigator should talk to the patient confidentially to obtain accurate history of oral contraceptive intake and (2) an attempt should be made to trace the prescriptions for oral contraceptives filled out-of-town for patients who want to remain anonymous.

Dr. Upjohn then stated that the source of information should be kept constant for patients who had or did not have thromboembolic episodes. If the prescription is filled out of the county, it should be discarded.

#### Hopkins Study

Dr. Hellman then called on Dr. Sartwell to present his proposed study. In this study women, aged 20-39 discharged alive from Johns Hopkins Hospital with a diagnosis of unexplained thromboembolic conditions will be matched to a similar group of patients treated for other conditions. Interviewers will obtain a careful history to determine how many patients in both series received oral contraceptives.

Dr. Sartwell stated that minor modifications could be made according to needs, e.g., change in the age of the patients studied, definition of terms like "recent". He stated that patients are more likely to be hospitalized from thromboembolic episodes if they are on oral contraceptives and are more likely to be identified as oral contraceptive users if they develop thromboembolic episodes.

Dr. Masi then presented his own remarks regarding this study. He stated that a retrospective study can produce significant data. The study as proposed at Johns Hopkins will not accumulate enough patients to have statistically significant figures (135 females were discharged with a diagnosis of thromboembolic phenomena in a 3 year period. Of these, 12 to 25 cases were considered idiopathic). This study will serve as a pilot project to work out details for a larger project. A study 25 or 30 times larger than the Hopkins study may

yield significant data. A study this size can be carried out by the Commission on Professional Activities. The hospitals associated with this program are not teaching hospitals. They have good facilities for case retrieval, but may not have adequate facilities for selection of the controls.

Several questions were raised from the floor as to the accuracy of the matching by discharge diagnoses, relevant medical conditions (e.g. obesity), religion, racial origin, and social status. Dr. Masi stated that the matching will be a sophisticated procedure, but can be done, and that the Ann Arbor study (Commission on Professional Activities) will provide a large enough series. He stated that the occurrence of thrombophlebitis may be due to idiosyncrasies in certain patients. This aspect should be looked into.

Dr. Sartwell stated that data presently available do not suggest an increase in the incidence of thromboembolic phenomena after the introduction of the oral contraceptives.

#### Subcommittee on Efficacy and Safety

Dr. Adamsons presented the report of his Subcommittee on Efficacy and Safety. He stated that oral contraceptives have a high degree of efficacy. The sequential products seem to be slightly less efficacious than the combination. There seems to be an extremely high dropout rate in some of the clinical studies.

He said that when oral contraceptives are used for menstrual irregularities (amenorrhea or functional uterine bleeding) and dysmenorrhea, the patient has cyclic withdrawal bleeding, not a true period. Adequate followup after discontinuation of therapy is necessary in order to determine if the symptoms have been permanently relieved. He mentioned that functional uterine bleeding many times is self-limiting.

Dr. Adamsons did not see the rationale of the use of cyclic medication for the treatment of endometriosis.

Dr. Tietze and Rudel pointed out that the apparent high incidence of dropouts may be due to enlargement of the clinical study group.

Dr. Tietze pointed out that the actual dropout rate must be available.

The effect of tablets missed on the incidence of pregnancy was discussed by Drs. Adamsons, Tietze and Rudel. Dr. Rudel stated that the time in the cycle when the tablets are missed is a larger determining factor than the total number of tablets missed.

Dr. Scott stated that the oral contraceptives used cyclically may produce relief of symptoms in endometriosis. He asked for comments on "rebound fertility". Dr. Tietze stated that the occurrence of "rebound fertility" has not been definitely established.

The use of progestational agents in threatened abortion was then discussed. Dr. Delfs stated that in selected cases (approximately 20% of threatened abortions) progesterone could be expected to help. This product is of no value in cases of generic abnormalities of the fetus.

In answer to a question from Dr. Hellman, Dr. Adamsons stated that he has no data on the use of oral contraceptives in the menopause. Dr. Adamsons also told the members of industry that he prefers a larger series by a small number of investigators than vice versa. Dr. Crook replied that industry is obligated to report all the data obtained, whether large or small.

#### National Center for Health Statistics

Dr. Palmisano introduced Mr. Theodore D. Woolsey, Deputy Director, National Center for Health Statistics. Mr. Woolsey stated that his agency collects data obtained from the following sources:

1. National Vital Statistics (Death Certificates)
2. Life tables
3. Sample survey mechanisms (by interview, physical exam of selected subjects or hospital discharge data).

Mr. Woolsey answered several questions from the floor by stating that even though his agency has not done this in the past, it is possible to retrieve death certificates of all females aged 20-45 who died due to thromboembolic phenomena in order to obtain information as to medication received by these patients prior to death. The data obtainable are limited by the inadequate information supplied in the death certificates. These certificates have very little information on drugs, many times are not revised after an autopsy is performed, and the physicians who sign the certificates may not be completely acquainted with the cases.

Dr. Eastman and Scott stated that coroners' cases do not provide an accurate cross-section of the population for the study of deaths due to thromboembolic episodes.

Mr. Woolsey, in answer to Dr. Tietze, stated that the hospital data obtained by PHS comes from many hospitals regardless of the quality of care. The hospitals affiliated with the Michigan study have a good standard of care and work on improving it.

EXECUTIVE SESSION

Dr. Hellman suggested that the next committee meeting be held April 6th and 7th, that it be all devoted to Executive Session, that each subcommittee submit a complete report at that time, and that any meetings with industry be held from now on at subcommittee level.

Dr. Eastman brought up for discussion his two recommendations (1) that deaths reported must be followed up immediately, and that (2) a letter be sent to certain physicians requesting that they report deaths from thromboembolic episodes in young women.

There was considerable discussion as to who should sign the letter, to whom it should be sent, and the technique of reporting. Drs. Sartwell and Masi stated that this type of reporting is inaccurate, biased, and does not yield true incidence. Dr. Eastman pointed out that he is interested in getting information on all young women who die of pulmonary emboli.

Dr. Tietze suggested that the Committee endorse a study of death certificates. Dr. Eastman said that the Biomedical Committee could provide \$3,000 for this study.

Dr. Sartwell stated that the original budget of \$4,000 represents about 1/10 to 1/20 of the total cost of his proposed study, and that if industry is to finance it he will not permit any interference from industry. The Committee endorsed Dr. Sartwell's study and suggested that it be financed by FDA. The committee also approved Dr. McEvilla's study.

January 21, 1966 - Morning Session

Subcommittee on Carcinogenesis

Dr. Scott presented his report to the Committee. He stated that the sites to be considered where cancer may develop in oral contraceptives users are cervix, endometrium and breast. He does not believe that much significance should be given to the extrapolation of animal studies to humans.

By quoting data from several published and unpublished reports he gave the approximate incidence of malignancy in the three anatomic sites, and clinical data available to show if there is any difference in the incidence of cancer in contraceptive vs. non-contraceptive users.

Approximately 6.6 patients per thousand in the contraceptive user age group have carcinoma of the cervix on initial screening. Only 5% of the total cases of carcinoma of the endometrium occur in patients under 40. The exact incidence of breast cancer is unknown, but approximately 1 in 13 women will develop breast cancer during their lifetime.

An article by Drill indicates that the incidence of positive PAP smears is less in contraceptive users than will be expected in the general population. Dr. Scott mentioned that there are several reports in the literature relative to estrogens and breast cancer which he will review.

Dr. Scott summed up his presentation by pointing out several problems with which we have to deal in evaluating the relationship of oral contraceptives and carcinoma. Those problems are: (1) How much importance can be attached to the experiments using animals other than a human, (2) How accurate and significant are the clinical data relative to the association of sex-steroid hormones and cancer or so-called pre-cancerous conditions, (3) How reliable are base-line data when there are so many epidemiological variables to be considered. (4) Can the paucity of data presently available from patients receiving cyclic estrogen-progesterone pills allow the subcommittee to draw any conclusions. (5) Carcinogens in the human rarely have a latency period of less than 10 years, therefore, is it possible to arrive at any conclusions from the limited time interval of observations.

Dr. Hertz then presented his views on the relationship between oral contraceptives and carcinogenesis. He stated that the differences in the use of the material before us is due largely to the interpretation and emphasis of the data rather than differences recognized as facts available to us. Dr. Hertz first discussed the relevance of animal experimentation data. He stated that the estrogenic components of oral contraceptives represent the same biologic activity known to produce tumors in 6 species of animals in 8 anatomical sites. He stated that if a drug were identified that produced phocomelia in 6 species of animals, he wonders what the acceptance of that drug would be. Monkey studies for a 2-10 year period have been reported with no malignancies observed. From the result of these studies, it is assumed that the rodent data does not apply. The monkey study, however, is inadequate. The rodent study lasted for 30% of the life span of the animal, but no such experiment has been done in primates.

Dr. Hertz then discussed the clinical aspects of oral contraceptives and carcinogenesis. From his table of known human carcinogenic agents it is apparent that the minimum latent period is usually about 10 years.

from the exposure to the development of the carcinoma. The latent period is the time interval between the initial exposure and the recognition of the tumor. The length of the exposure is not that relevant. In the case of oral contraceptives as potential carcinogens, not enough time of observation has elapsed between the initial exposure and the time at which the tumor may occur. He stated that we have a backlog of animal data and we have inadequate primate data. He stated that we must accept the profundity of our ignorance of these actions on the body and accept that we need to provide the necessary data as time progresses. Estrogens have now been in use for over 20 years with no evidence of gross carcinogenesis reported, but we are now at the same stage as at the beginning of the association of smoking to lung cancer.

He then stated that only 5 epidemiologic studies comprising 700 patients were reported by Drill. The age group was menopausal, which is not relevant to young groups taking oral contraceptives. Dr. Hertz stated that we need a sounder study to correlate oral contraceptives and carcinoma. An adequate sample size is necessary. The figures currently available are not even adequate for a latent period of 1-2 years.

Dr. Hertz then listed a few misconceptions which give a false sense of security:

- (1) The idea that once the products are metabolized, the carcinogenic effect disappears.
- (2) Since no significant histopathologic abnormality is present in the tissues from exposure to onset of malignant change, we may get the impression that no damage has been done.
- (3) Since the endometrium sloughs off, there is no effect. This is not true, since only the superficial layer of the endometrium is shed. The lower layer, which received the hormonal effect, persists.

Even more important is the effect in the ovum. All ova are present at birth and are, therefore, exposed to all the drugs received by the mother. There is no continuing followup study of offspring of mothers with long-term exposure to oral contraceptives. In the case of thalidomide, teratogenic data was available about 3-4 months prior to the issuance of a statement that there is no relationship between thalidomide and phocomelia. He suggested that pediatric consultants to the committee give their opinion on followup in children born to mothers who had used oral contraceptives.

In summary, he stated that:

- (1) The drugs under discussion contain a substance which is in its biological action known to be carcinogenic in several organs in a wide variety of species.
- (2) It behooves the committee to apply to the study of carcinogenesis all the statistical data available.

Drs. Hertz, Eastman, Adamsons, Tietz & Delfs compared the hyper-estrogenic state of pregnancy with that induced by oral contraceptives. Dr. Hertz stated that during pregnancy (1) the highest elevation occurs in the estriol, which has low biologic activity; (2) there is a high amount of estrogenic substance concentrated in the amniotic fluid and (3) more hormones are secreted in the urine. He stated, however, that there is no evidence that estriol is less carcinogenic. Dr. Carrington suggested that in pregnancy the fetus conjugates a large amount of estrogen. Dr. Delfs stated that the oral contraceptives are metabolized by a different pathway than the estrogens and progesterone of a normal pregnancy.

Drs. Hertz, Tietze, Scott, Rudel, Delfs, Adamsons and Sadusk discussed the relative amount of hormones necessary to produce carcinoma in animals compared to the amount of hormones used for oral contraception. Dr. Hertz stated that the oral contraceptives may be used for up to 30% of the lifespan of the human. Dr. Scott asked if a dose of hormone sufficient to inhibit ovulation would produce effect on peripheral tissues. Dr. Rudel stated that synthetic progestins are more potent anti-estrogens than endogenous progestins. Dr. Hertz agreed, but stated that some animals developed carcinoma of the ovary after treatment with progestins. Dr. Adamsons pointed out that the turnover rate of cells is an important factor in the development of cancer. In answer to Dr. Hertz, Dr. Rudel compared the relative potency of the commonly used estrogenic substances by listing the amount necessary for cornification and control of menopausal symptoms: mestranol 20 micrograms, Ethinyl estradiol 2 mg., Premarin 2.75 mg. and stilbestrol 5 mg. The antiovolatory dose is roughly twice the above.

Dr. Sadusk, referring to the table of known carcinogens prepared by Dr. Hertz, stated that all known carcinogens to man act by local irritation.

Dr. Delfs mentioned the possibility of end organ carcinogenesis, and Dr. Adamsons mentioned the possibility that the metabolites may be the carcinogenic agents.

Dr. Hertz stated that cancer was produced with a low dose of estrogen on a susceptible strain of animals, but he pointed out that in humans some ethnic groups have higher incidence of carcinoma of the breast than others.

Subcommittee on Masculinization and Other Hormonal and Metabolic Complications

The report of the sub-committee on masculinization and other hormonal and metabolic complications consisted of separate presentations by Dr. Delfs and Dr. Carrington. Dr. Delfs listed the following as potential sites for detrimental effect by oral contraceptives: Pituitary, thyroid, ovary, adrenal, and liver functions. The action on the pituitary can be divided into anti-gonadotrophic and others. The oral contraceptives must interfere with pituitary gonadotrophins in order to inhibit ovulation. The question of increased fertility after cessation of treatment has been suggested but not settled. Other pituitary actions include: (1) Adrenal function (2) Thyroid function. The PBI and T3 are elevated because of increased protein binding of iodine. (3) Carbohydrate metabolism - there appears to be a potential increase in diabetics or a moving up of the age at which clinical diabetes is manifested. Dr. Delfs did not consider masculinization of the testis as a potential danger in oral contraceptive users.

Dr. Carrington suggested that the oral contraceptives may have effects similar to pregnancy in potential diabetics, i.e., increase in the glucose tolerance curve and mean insulin requirement. She stated that tests for diabetogenic effect of oral contraceptives be conducted in these predisposed patients.

In answer to the Dr. Adamsons, Dr. Hertz stated that oral contraceptives have anti-aldosterone effect. Dr. Hertz also discussed the action of estrogens on the liver. The decrease in dye excretion is due to competition of the estrogen with the dye for excretion. Dr. Delfs stated that we do not have any data on the possible detrimental effect on the liver by long term administration of estrogen.

Dr. Tietze mentioned that several thousand babies were born to women who became pregnant while on oral contraceptives, and none showed signs of masculinization. Dr. Delfs stated that this data is not significant since the mothers must receive the drug at about thirteen weeks gestation, and very careful examination is necessary to identify the effect in the infant.

Dr. Hertz stated that rats exposed to androgens for one day from the 4th to the 5th day of life have developed sterility similar to Stein-Leventhal syndrome.

Dr. Hellman, referring to Dr. Eastman's comments that deaths are poorly investigated and reported, proposed that a biostatistician visit the seven drug firms and prepare a separate review of their records of deaths. The source of financial support for this project was then discussed.

It was pointed out that all data on any individual case filed with FDA may be difficult to retrieve since the data are filed in chronological order of receipt rather than by case.

Dr. Adamsons emphasized that the oral contraceptives may have effect on the hypothalamic system, and psychologic evaluation should be done on oral contraceptive users. He announced his intentions to launch a pilot study at Columbia University to evaluate the feasibility of further investigating the effect of the oral contraceptives on the hypothalamic system and psychologic effects in general. Dr. Winter said he will forward to Dr. Adamsons some reports on these side effects which are available to him.

Executive Session - (Non FDA Observers and present)

Dr. Hellman proposed, and the Committee members accepted the dates of April 7 and 8 for the next session. He also mentioned that a June meeting may be necessary.

After a brief discussion Dr. Hellman stated that the Committee will submit a final report which will be rather brief, but more specific than a WHO report. This report will be backed by sub-committee reports added as appendices to the main report.

In answer to Dr. Tietze, Dr. Sadusk said that the press did not expect a press release after this January meeting.

Dr. Adamsons asked the committee members if, in their opinion, the sub-committee on efficacy has been too strict in its criteria for efficacy. He stated that the only proven indications for oral contraceptive drugs are contraception, endometriosis, and substitution of periods by withdrawal bleeding. In answer to Dr. Hertz, Dr. Hellman stated that the use in habitual abortion may be allowed if carefully worded. Dr. Scott mentioned that there is no rationale for the treatment of endometriosis with cyclic medication.

Dr. Hellman stated that all members of the committee expect to receive a copy of the latest approved labeling for each oral contraceptive on the market. These would be provided by the FDA staff.

Dr. Palmisano distributed the data from Dr. Slee's study on the incidence of thrombophlebitis in patients aged 20-39.

Dr. Hellman declared the meeting adjourned.

Submitted by:

Edwin M. Ortiz, M.D.  
Executive Secretary