

FOOD AND DRUG ADMINISTRATION
ADVISORY COMMITTEE ON OBSTETRICS
AND GYNECOLOGY

MINUTES

First Meeting
November 22 and 23, 1965

Bureau of Medicine
Arlington, Virginia

COMMITTEE MEMBERS:

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

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

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

CONSULTANT TO THE COMMITTEE:

Dr. Philip Sartwell
Professor of Epidemiology
Johns Hopkins University

SPECIAL GUESTS:

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

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

Dr. Gregory Pincus
Worcester Foundation for Experimental Biology
Shrewsbury, Massachusetts

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

INDUSTRY REPRESENTATIVES:

Eli Lilly and Company
Dr. Don Carlos Hines
Dr. H. H. Hines

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

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

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

G. D. Searle and Company
Dr. Victor A. Drill
Dr. Irwin C. Winter

Syntex
Dr. K. J. Dumas
Dr. Harry W. Rudel

The Upjohn Company
Dr. Harold L. Upjohn
Dr. Howard Angell

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
Mr. Julius Hauser, Executive Officer
Mr. Clem O. Miller, Special Assistant to the Commissioner
Dr. John F. Palmer, CMD
Dr. B. H. Minchew, OMD
Dr. Ralph G. Smith, Director, DND
Dr. John W. Winkler, DND
Dr. John Herendino, DMI
Dr. D. Levitt, DMI
Dr. A. Esch, ARB
Dr. M. L. Gibson, IDB
Dr. William Evans, DMR
Dr. R. M. Hodges, IDB
Dr. R. Bennett, NEB
Dr. John J. Jennings, DSB
Dr. E. Goldenthal, DTE
Dr. J. K. Lamar, DTE
Dr. D. C. McCollum, DSB
Dr. E. M. Ortiz, DSB

EXECUTIVE SECRETARY:

DR. ROBERT J. ROBINSON
Chief, Drug Surveillance Branch

INTRODUCTIONS - CHARGE TO THE COMMITTEE

Dr. Sadusk opened the meeting by introducing members of the Committee and key staff who were present.

For the official record, Dr. Sadusk asked the representatives from industry whether they wished to invoke the privileges of confidentiality for their records on oral contraceptive drugs. Industry was unanimous in declining to use this privilege, so that the Committee's work could be expedited.

Dr. Sadusk announced to the committee that Dr. Robinson would be the executive secretary.

Dr. Sadusk read the charge to the Committee as defined by the Secretary of Health, Education and Welfare - "The Advisory Committee on Obstetrics and Gynecology will advise the Medical Director and through him the Commissioner of Food and Drug concerning:

- (1) Trends in the advances in Obstetrics, Gynecology and related medical specialities.
- (2) The development of new protocols and changes in existing protocols which the Food and Drug Administration requires as a basis for evaluation of safety and efficacy of drugs used in the diagnosis, cure and medication, treatment or prevention of diseases of the female reproductive organs.
- (3) As assigned by the Medical Director, review pertinent data and furnish expert medical advice and recommendations relative to the safety and efficacy of specific uses and classes of drugs and devices employed in the practice of obstetrics and gynecology."

Dr. Hellman stated that the target date on a finalized report should be shortly after the March, 1966 meeting. He commended industry for waiving their special prerogatives regarding pending applications.

I: First Agenda Item: Total Requirements Necessary for Demonstrating the Safety and Efficacy of an Oral Contraceptive Drug.

A. Pre-Clinical Studies

Dr. Berliner of the Division of Toxicological Evaluation addressed himself to the preclinical aspects of this topic.

Dr. Berliner stressed what were considered to be cardinal

requirements for the preclinical evaluation of a drug. They were:

- (1) For the final evaluation for safety and efficacy the compound must have been tested by the route proposed for clinical use.
- (2) Components of a combination should be assayed first separately, but for the final evaluation, in the form of intended therapeutic formulation.
- (3) In cases of new compounds containing even slight changes in the chemical structure from an already existing and used compound, a reference to this close relationship cannot be accepted as evidence for safety in place of a complete experimental work up for the new compound.
- (4) Appropriate data to establish the absence of teratogenic potential should be furnished before phase 1 - 2 clinical studies are initiated, in addition to the toxicological background data required for phase 1 - 2 studies.

B. Clinical Studies

Dr. Hodges stressed the parameters for human laboratory studies. They included: (1) the endocrine function tests, (2) tests of the genitalia including smears, biopsies, etc., (3) hepatic and renal function tests, (4) hematological tests, and (5) fluid and mineral metabolic studies.

Dr. Hellman asked for comments from industry.

Dr. Cronk raised the question as to the numbers of patients in a study that would establish the validity of efficacy, and asked Dr. Tietze for a reply.

Dr. Tietze said that for the oral contraceptives a pregnancy rate of 0 - 2 per 100 woman years of use was established, but that an experiment must be designed to determine how large a sample will give an accepted tolerance with an accepted degree of probability.

Dr. Hallman commented on the brevity of studies, stating that it might be possible for a study to be so short as to be invalid, particularly where adverse experiences are involved.

Dr. Tietze stated that studies based on one month, six months, or many months are not reliable in giving the true ratio of fecundability in the population group. Dr. Tietze further stated that he did not know whether it was justifiable to request studies of such magnitude as far as numbers of patients were concerned, so as to assure that oral contraceptives were 100% effective. He stated that probably 2 pregnancies per 100 woman years or maybe one pregnancy per 100 woman years was a more realistic approach. Dr. Tietze thought that the studies submitted in support of efficacy for the oral contraceptives were long as compared to most studies performed to establish efficacy. Dr. Tietze said he saw no statistical evidence to support the theory that the pregnancies which occur in patients using these oral contraceptive drugs occur in the early months anymore than they do any other time during the period of use.

Dr. Drill of G. D. Searle, stated that the mechanism of action of the oral contraceptives seems to be rather clearly established through many different types of animal experiments. These animal experiments conclude that these contraceptive agents do block the elaboration of gonadotrophin from the anterior pituitary gland. He further stated that the human studies go hand in hand with the animal studies. He also stated that good human studies show that the injection of gonadotrophins in the female will stimulate ovarium function and that this function is not blocked by the administration of oral contraceptive drugs.

Dr. Pincus concurred in Dr. Drills' comments.

Dr. Adamsons asked Dr. Pincus if there was any evidence that these drugs interfered with the synthesis of pituitary gonadotrophins or interfered in their release after synthesis.

Dr. Pincus replied that from animal data it appears that there is an actual storage of gonadotrophins in the pituitary, therefore there appears to be a block in the releasing mechanism.

Dr. Hellman asked Dr. Hodges what would be the controls in the proposed clinical tests that he had alluded to earlier in the program.

Dr. Hodges replied that the patients would be their own controls by having base line studies performed before administration of the drug.

Dr. Hodges did state, however, that for the hematologic studies, there should be a controlled group equal to that of the studied group.

Dr. Hellman stated that although there appeared to be no good tests for hypercoagulability, if one is going to consider the problem then one should at least perform the existing tests.

Dr. Pincus stated that a Dr. Wessler had performed these tests in people who had suffered thromboembolic phenomena and had found no correlation between increase in certain of the coagulating factors and the occurrence of this clotting phenomena.

II: Second Agenda Item: The Problem of Transferral of a Patient from One Oral Contraceptive to Another When the Recommended Length of Usage of the First One Has Expired.

Dr. Robinson presented this agenda item. Dr. Hellman commented that there are two practices currently extant in the country, concerning the prescribing of oral contraceptives. The first, he states, is that the physician completely ignores the recommended time interval in the package insert. He further stated that a physician doing this with an unscrupulous patient who might suffer a severe adverse experience might find himself in a rather indefensible position. The second aspect to this problem, Dr. Hellman continued, is for the physician to refuse medication to the patient after the time interval had expired and have the patient leave and through another physician obtain the prescriptions without ever relating to the new physician that she formerly had been taking these oral contraceptive drugs.

The question raised by the committee as to any particular recommended time intervals for usage for these drugs was inserted in the labeling. They were told that this was based on the method by which drugs are approved in the Food and Drug Administration. This means that for an approval, there must be a certain number of patients taking a drug for a certain length of time and during this period of time the drug has proved to be both safe and efficacious. It was explained that this judgment had to be based solely on the material submitted in the new drug application by any given company, since a company with a new drug application is not permitted to reference their material to another company's application without the expressed permission from this other company.

It was pointed out that the oral contraceptives were probably unique in that they were one of a very few and possibly the only class of drugs where these time restrictions had been inserted in their labeling. It was further stated that one of the medical reasons for having done this was the undecided question as to whether long usage might not contribute to the genesis of cancer. The committee again raised a question of the logic in the restricted type of labeling by pointing out that drugs with lowest dosage forms had approval for less time than drugs that had the higher dosage form. They further stated that if one is going to correlate adverse drug experience with the quantity of a given drug administered at a given time, then certainly one should expect fewer adverse experiences with the lower dosage form, therefore, it would appear inconsistent

to have this lower dosage form approved for a shorter period of time than the higher one. Dr. Ralph Smith, Director, Division of New Drugs, was asked if he might shed some light on why these time restrictions were placed in the labeling of the oral contraceptives.

Dr. Smith stated that at the time they were coming through the Food and Drug Administration these drugs were the subject of much controversy; that the Food and Drug Administration had to rely on many outside consultants and advisors thus obtaining the best opinions available. He stated that he believed that the time limits were placed on these drugs mainly as a safe guard and as a precautionary step to more or less allay any severe criticism by large numbers of people who probably opposed the marketing of these drugs.

Dr. Hellman pointed out that there were no restrictions on length of time concerning the estrogenic substances.

Dr. Hellman invited some comment from industry and Dr. Winter responded. Dr. Winter stated that from the data available to him there were no instances of serious side reactions to these contraceptive drugs that were time related or that could be shown to be the result of lengthy usage of these drugs. Therefore industry saw no reason for time limits.

Dr. Fuller commented that the problem for the clinician was namely to provide a safe method of contraception for the patient and also to protect the physician from liability litigations.

Dr. Hollman asked Dr. Eastman if he cared to comment on the possibility of diabetes being a complication after long usage with these drugs.

Dr. Eastman replied that he could see no reason to expect different side effects after six, eight, or ten years usage of these drugs than occurred with four years of usage. He stated that he could not see a useful purpose in having these time restrictions imposed on this group of drugs. He did say, however, one serious consideration should be given in the usage of these drugs on long term basis. This consideration was the menopausal woman when there are major roentgenologic changes taking place, however, Dr. Eastman said this would represent a 20 year plus usage by a person taking this drug and it would be unreasonable to hold up approval of a drug for this length of time. Dr. Eastman further stated that there was no good evidence that diabetes mellitus would be a complication down the road in the usage of these drugs. Dr. Eastman, however, did state that there was some good evidence that multiparous females did appear to develop diabetes more frequently than those who had few births. Dr. Eastman further stated that if one accepts the premise that females using the oral contraceptives exist in a systemic state of pseudo pregnancy, then possibly this long and erroneously termed "pseudo-pregnancy" could be compared to that of grand multiparity and then diabetes might be a complication.

Dr. Hellman asked Dr. Corfman of the National Institute of Child Health and Human Development if he had some comments, either personal or those which would represent the policy of that institute. Dr. Corfman said he could not speak for the institute and had not given any lengthy deliberations to the question of time limits. However, he did state that it seemed rather illogical to impose a time limit on a group of drugs such as the oral contraceptives and have none on other groups of drugs.

Dr. Winter of G. D. Searle commented that since assuming these drugs do create a state of "pseudo-pregnancy" the fact that they are given in a cyclic manner, would tend less to produce the effect of a pregnancy and too, the very small quantities generally employed in most of these drugs today is such that it would appear to take many years of usage before the consummate effect of one nine months pregnancy would be observed on any organ in the human.

Dr. Hellman asked what was the committee's opinion concerning the switching from one drug to another after the first drug's time limit had expired.

Dr. Cronk said that his firm had had some experience with this type of experiment. He said that if the patient did not know that the dosage form was being changed, and that the tablets were identical in size and color there were no new exacerbations of the side effects when a dosage form was changed.

III: Third Agenda Item: The evaluation of data concerning the drug "Enovid" in considering the extension of time for its recommended use.

Dr. McCollum stated that Searle had submitted 181 cases of patients who had used Enovid 72 months or more, and another group of 64 patients in whom there had been some follow-ups, who also had supposedly been taking the drug for more than 72 months. He stated that the majority of the patients with endometrial biopsies showed atrophic endometria with a few showing hyperplasia. He drew attention to the fact that there were 12 class four Papanicolaou smears in that group.

Dr. Hellman raised the question about the 12 class four smears. He inquired whether these smears became class four smears while patients were taking the drug.

Dr. McCollum answered to the affirmative. Dr. McCollum explained that the endometrial biopsies were taken from these patients because they had demonstrated class four Papanicolaou smears.

Dr. Hellman asked Dr. Winter of Searle whether he cared to give more detailed information on the studies presented by Dr. McCollum. Dr. Winter said he had little or nothing to add to the statement at that particular time. Dr. Hellman then asked Dr. Pincus if he had any comments to make.

Dr. Pincus stated that there were 482 patients who have been taking Enovid for five years, 280 who have been on it for six years, 130 on it for seven years, and 74 on it for eight to ten years. He further stated that there were no new phenomena in patients who had been using the drug for more than four years, that by and large, the incidence settled down to a plateau after four years of usage. Dr. Pincus said that about 15% to 20% of the patients taking Enovid had elevated protein bound iodine determinations. This he said is a well known fact, and one sees it frequently in pregnancy. It is thought to be the effect of estrogen on thyroglobulin, that protein fraction which binds iodine. He said this is the basis for Dr. Hertz's thesis that these drugs cause a state of hyperestrogenism. Dr. Pincus believed this to be the specific effect of estrogen on the thyroid gland only. Dr. Pincus further stated that thyrotoxicosis has not been demonstrated to be a side effect associated with usage of the oral contraceptive drugs.

Dr. Adamsons asked Dr. Pincus if, in these patients who had been shown to have an elevated protein bound iodine, there were any clinical reasons to believe that this really might represent the hyperthyroid state.

Dr. Pincus replied that there had been two tests done to elucidate this problem, (1) serum cholesterol, which showed no changes consistent with the hyperthyroid state, (2) the radioactive iodine uptake by the gland which showed no increase in uptake.

Dr. Adamsons then asked Dr. Pincus as to performance in the psychological areas.

Dr. Winter said that he was familiar with some testing in this area, but as far as could be ascertained there were no changes in these people.

Dr. Tietze then addressed himself to the study of 300 women from whom Papanicolaou smears had taken. He raised the question as to why there should be only one class three smear, and twelve class four smears when ordinarily the reverse is usually found.

Dr. Winter assured Dr. Hellman that he would have clarification of this data in the greatest possible detail.

Dr. Pincus stated that in his studies the ratio of type 3 to type 4 smears was 30 to 1.

Dr. Hellman then asked Dr. Scott what would be the percentage of class three and class four and five vaginal smears in an unscreened population.

Dr. Scott began by answering that if you took class two, three, four and five smears and grouped them together, one would have a percentage of ten percent. If one takes the class three, four and five the figure is approximately 2.5%. If one then takes classes four and five one obtains a figure of approximately 0.9%.

Dr. Sadusk then mentioned to the group a compilation of tables obtained from the Bureau of Vital Statistics of the Public Health Service. These tables reflected deaths due to cerebral vascular accidents, according to races, in the female. He pointed out the tables reflect no increase in death rates from this cause from 1950 through 1964.

Dr. Sadusk mentioned that these tables would be discussed in some detail on the second day of the meeting.

Dr. Hellman then declared the open session of the Committee meeting closed, stating that the Committee would go into Executive Session and invited Dr. Corfman and Dr. Pincus to remain, along with certain designated members of the FDA staff.

Before the Executive Session began Dr. Sadusk requested from the industry representatives whether it would be possible to present at the second day's meeting the total number of patients using the oral contraceptives up to and including June of 1965.

EXECUTIVE SESSION

Again the question was raised as to whether there were any other drugs now marketed which bore time restrictions similar to the ones imposed on the oral contraceptive agents. The answer was again in the negative. It was pointed out that in 1960, it was probably reasonable to impose these restrictions

on the drugs in view of the fact that they were a new type of drug, also, there were no long term studies and the amount of break through bleeding which might occur was still undetermined. It was, however, thought that since the reporting of adverse clinical effects was much better now than it was previously, that the Food and Drug Administration actually was current with the drugs in this respect. However, Dr. Sadusk did point out to the committee that a possible danger existed in that if there were no pressures on industry to continue these long term studies, and up-date them, such data might not be obtained.

Dr. Hellman then asked what assurances would the Food and Drug Administration have that metabolic defects such as diabetes and the development of carcinoma would be picked up, or reported, if time limits were removed. He further asked what guarantee would the Food and Drug Administration then have that industry would continue its long term follow up. Dr. Sadusk stated that we have no guarantee in that area.

Dr. Hodges then pointed to the inconsistencies, not only in the labeling that alluded to certain time restrictions, but to other parts of the labeling of this class of drugs.

The question was raised as to whether there were current studies going on concerning metabolic disorders and/or cancer in the use of oral contraceptives.

Dr. Pincus responded that at the present time he is supervising a study sponsored by the American Cancer Society for a seven

year period involving 5000 users and 5000 nonusers of the oral contraceptives and expected it to be continued for a great number of years.

Dr. Pincus stated that he was sure that NIH was very interested in this problem and would probably sponsor some studies as well as probably the Public Health Service. He was of the opinion that this was too important a question for these agencies to overlook.

Dr. Sadusk pointed out that the only patients supervised by industry, who could be considered in a prospective study to determine whether metabolic and/or cancer were sequela of oral contraceptives therapy, are the patients who serve as a reservoir for these companies and are used for clinical purposes when a company wishes to extend the time limit on a currently marketed drug. He further stated that he thought the time had come for an agency such as the National Institutes of Health to sponsor a 20 to 25 year prospective study on a large population sample using these drugs.

Dr. Corfman stated that his institute has gone on record as being interested in this problem and has set up an oncology section.

Dr. Pincus said he was aware of a study by the National Heart Institute on the long term effects of the estrogens. He stated, unfortunately, this only included the estrogens.

Dr. Pincus gave some background on the original two year restriction on Enovid stating that the Worcester Foundation had supplied most of the clinical and experimental data for the marketing of this drug. He stated that at that time his group was able to assure Searle that Enovid was safe and certainly effective for two years. But from the scientific point of view they could go no further in giving assurances. Dr. Pincus also stated that at the time of the original application he was talking in terms of 260 women, but now with hundreds of thousands of women under investigation the picture is entirely changed.

Dr. Delfs raised the question of allowing a group (meaning industry), with the greatest vested interest, to be permitted to supervise long term prospective studies which regulatory agencies were going to use in order to monitor these drugs.

Dr. Scott pointed out that one of the reasons for concern already expressed about this class of drugs was that these drugs directly interceded with the normal biological functioning of females. These were not drugs, analogous to insulin, which were being substituted for normal hormones which were being secreted in a deficient manner.

NOVEMBER 23, 1956

Second Day Session

Dr. Sadusk noted the fact that Dr. Philip Sartwell of Johns Hopkins University, one of the consultants to the Committee was now present.

Dr. Winter then commented that the interoffice compilation on Enovid was amassed before the Searle Company was aware of the fact that Enovid was on the formal agenda and therefore was not complete, but only represented an example of data which the company had for the committee to peruse.

Dr. Winter then explained the 12 class four Papanicolaou smears which were alluded to in the previous days session. He stated that the grading system which this principle investigator used ran from 1 through 9 and that a class four was really a class two smear in the more conventional system and thus represented trichomonas vaginitis. Dr. Winter assured the committee that all of the class fours, which were alluded to previously, came from this one investigator and therefore these should be interpreted as class two or trichomonas vaginitis smears. He further explained that since Searle was aware that the committee would consider Enovid as such, a new compilation of long term usage for Enovid would be made, and as soon as it was available, it would be sent to the Food and Drug Administration for distribution to members of the committee. He anticipated that this compilation would be ready within the next ten days or two weeks.

IV: Fourth Agenda Item: Adverse Reactions of the Oral Contraceptives.

Dr. Donald Levitt made this presentation. Dr. Levitt stated that the Food and Drug Administration was not in possession of data as yet to establish a cause and effect relationship concerning many adverse reactions and these drugs. He further stated there were no data yet to establish a true incidence of an adverse effect. Dr. Levitt also stated that to the best of his knowledge these data were not available anywhere. He added that the initial problem is actually in the data collection. Dr. Levitt then explained that one of the most common lesions associated with these drugs was a phlebothrombosis, which under the international classification in hospitals was very frequently confused with a thrombophlebitis. He then referred to a chart from the Ann Arbor hospital group which demonstrated that the incidence of phlebitis and thrombophlebitis between the years of 1960 and 1964 was essentially unchanged.

The question was asked of Dr. Levitt as to what the sample in this hospital report represented, he replied that it represented approximately 13% of the hospital beds available today in the United States, or about 440 hospitals.

Dr. Tietze then inquired as to the expanding number of cases reported between 1960 and 1964. Dr. Levitt replied that in 1960 there were fewer hospitals in the program, and this was the reason for the expanding number of patients; this does not necessarily infer an increase in any type of incidence.

Dr. Tietze inquired as to whether the reports represent the admitting diagnosis or discharge diagnosis, or whether they represented all patients in whom this diagnosis was made in the hospital.

Dr. Levitt stated that this represented all the patients in whom the diagnosis of thrombophlebitis, etc., was made.

Dr. Tietze suggested that for practical purposes, in reviewing data of this type all findings be grouped together, i.e. thromboembolic phenomena, phlebitis and thrombophlebitis or phlebothrombosis.

Dr. Levitt then pointed out the information furnished by Dr. Sice and his group in Michigan. They showed that the peak age group from 1960 through 1964 for the occurrence of thrombophlebitis was 52 years of age. Dr. Levitt explained that this peak age group did not change during these years, and that if the incidence was becoming greater because of use of oral contraceptives then we should see the peak age incidence shifting toward the lower group.

Dr. Tietze suggested that we might get some assistance from NIH which was compiling a population study which would let us know in 1965 how many people were now using oral contraceptives and also how many people had ever used oral contraceptives.

Dr. Winter was asked what would be an estimate as to length of time it would take to get a pipe line filled, meaning drugs

to the druggist. He estimated, approximately two to three weeks was all that was required when a new drug was marketed before all the retail outlets had been stocked.

Dr. Tietze pointed out that in evaluating these data as far as adverse experiences were concerned it was necessary to differentiate between the current users of a drug and the ever users of the drug. The adverse experience should be pegged to the current users, since this is a much smaller group than the larger group which he called ever users, meaning people who had at sometime used the drug but who have discontinued it, maybe because of an adverse experience or for other reasons.

Dr. Tietze then said a third piece of data should be the number of women who have used a drug for a complete current calendar year.

Dr. Cronk was asked how he arrived at his estimated patient figures. He stated that pipe line factors, distribution data, and sales data were all considered plus prescription data and a correction was made for that which was in the pipe line and that a figure of 1,375,000 women during a given month was determined.

A question of strokes was brought up by Dr. Sadusk, who stated that he had an approximation of the total number of strokes reported, but on the print-out on the tables which were being

furnished by Dr. Levitt, there were no precise figures.

Dr. Levitt stated that all the post marketing data was going to be scrutinized for thrombophlebitis at all sites including pulmonary embolism and eye effects. Dr. Levitt again pointed out the difficulty in obtaining denominator data for these adverse experiences, thus precluding the determination of any reliable incidence rate.

Dr. Hellman then pointed out the gross under-reporting of adverse experience findings. He stated that in a city program where large numbers of persons were taking the oral contraceptives it was highly unlikely that any adverse experience would be reported.

Dr. Sadock then pointed out that it must be realized by all that the data which the Food and Drug Administration had could not be used to estimate an incidence. It is part of an early warning system only.

Dr. Tietze questioned whether this was an adequate early warning system. He pointed out that reports would be received in general from physicians only if one of two things were present:

1. An alert or a scare in the medical community existed, or
2. A very unique type of adverse experience occurred.

Dr. Upjohn commented that the first few months after a drug has been marketed the occurrence of adverse experience, at

least as reflected by the reports, is always higher than it is subsequently. He stated that this is probably due to the fact that as a doctor becomes more familiar with the types of adverse experiences associated with the use of a drug he neglects to report them. Thus, probably as a drug ages on the market under-reporting becomes the rule.

Dr. Adamsons asked Dr. Tietze what was the justification in trying to establish a cause and effect relationship in phenomena with extremely low incidence.

Dr. Sartwell commented that the two kinds of studies which would contribute to our knowledge in this area would be a case control study and a prospective study.

Dr. Sartwell continued that he thought that the consideration of the magnitude of the number of alleged deaths was deserving of more consideration than the other adverse experience data.

Dr. Hellman then referred to the dependability of figures. He inquired concerning the national incidence rate, in thromboembolic phenomenon, the increment necessary to be reflected.

Dr. Sadusk referred to a table which had been furnished by the Public Health Service and analyzed by one of their statisticians. The table referred to deaths from CVAs in women between 15 and 49 years of age running from 1960 to 1963 in

oral contraceptives. Dr. Drill stated that this premise is completely false. In that the incidence of thrombophlebitis during pregnancy is not higher than in the nonpregnant state; it is only in the postpartum state, that the occurrence is higher.

Dr. Tietze alluded to the postpartum incidence being ten times higher in Europe than it was in this country. He thought this was explained by the early ambulation of our patients in the U. S. as opposed to the postpartum patients in Europe. Therefore, maybe the coincidental development of thrombophlebitis in the American cases might have occurred after the patient was discharged from the hospital therefore not computed in the data.

Dr. Sartwell stated that the studies that we now have at hand were such that we would have the same problem ten years hence, that they do not go beyond the clinical impression phase. A good prospective study or, secondly, a selected case control study would be necessary for one to obtain more meaningful data.

Dr. Sadusk told the committee that studies on adverse experience in all drugs was being arranged for with the Kaiser Permanente Group. Dr. Sadusk further stated that the project would begin in the San Francisco hospital group, that this hospital group had a yearly census of about 200,000 patients. Dr. Sadusk said that if the first year's program was successful then the second

year program would include all of the out-patient clinics also. He emphasized that this is a long range plan, and that one could not anticipate any definite answers inside of three to five years from this type of study. He further stated that in keeping with the projected studies it would be possible to make a close study of a clinical condition. It was proposed that possibly a controlled group should consist of victims of automobile accidents and also victims of fractures; all of these people would be questioned, on hospital admission, if they were users or had been users of oral contraceptives.

Dr. Weston made comments to the fact that the Food and Drug Administration's program as well as the program sponsored by the American Medical Association was, at best, an early warning system.

Dr. Adamsons made a recommendation that psychiatric tests be included in the prospective study.

Dr. Sadusk stated that there would be three new projects starting after the first of the year (1966), at Massachusetts General Hospital, University of Pittsburgh, and Temple University. These proposed studies are basically designed to obtain numerators and denominators on adverse drug experience with many different types of drugs.

Dr. Tietze raised a question as to whether the Permanent study would cover every visit of a patient to the doctor or every

hospitalization whether the doctor thought the drug caused the visit of hospitalization or not.

Dr. Sadusk explained that there will be three separate programs going on at once and being fed on computer tape.

- (1) The medical librarian with her staff will put the diagnostic figure on the tape when the patient is discharged.
- (2) The pharmacy will furnish all drug usage data.
- (3) The development of reporting of adverse reactions which also goes onto the computer.

Dr. Winter addressed the committee and on behalf of industry and asked three questions:

- (1) A clear cut mandate from the committee as to what type of studies they desired.
- (2) The possible benefit to industry if it did pursue these studies, and
- (3) Precisely what type of control groups was indicated.

Dr. Hellman responded to Dr. Winter's query by stating that it was not the intent of the committee to propose an experimental model at this particular meeting; that he would hope that the assistance of Dr. Sartwell and Dr. Tietze would be obtained and a proposed model will be suggested to industry.

V: Agenda Item Four: The Therapeutic Indications, other than Contraception, for the Oral Contraceptive Drugs.

Dr. Edwin Ortiz made note of the fact that only one of the oral contraceptive products currently marketed has approved indications for use other than that for conception control. He then stated that there was in the Drug Surveillance Branch a supplement from another company, Ortho, for use in other areas than conception control.

The new claims for Ortho Novum are for amenorrhea, dysmenorrhea, functional uterine bleeding, and endometriosis. For amenorrhea, 87 patients were treated with the 10 mg. tablet, and 92 with the 2 mg. tablet. Those treated with the 10 mg. tablet appeared to respond better percentage wise than those with the 2 mg. For dysmenorrhea, 44 were treated with the 10 mg. tablet and 200 were treated with the 2 mg. one. The results demonstrated no significant difference between the 10 and 2 mg. size. Functional uterine bleeding was broken down into several different conditions. Menorrhagia, metrorrhagia, irregular menses, and polymenorrhea. The 10 mg. size tablets appeared to be more effective in the menorrhagia and metrorrhagia group than did the 2 mg. size.

In irregular menses 26 cases were treated with the 10 mg. and 105 with the 2 mg. size tablets. The percentage of effectiveness seemed to be about the same between the 10 and 2 mg. size. In polymenorrhea, the number of patients was very small but the 2 mg. tablets seemed to be more efficacious than the 10 mg. size. In endometriosis, 20 persons were using the 10 mg. size

and 49 the 2 mg. tablet. Dr. Ortiz pointed out that these dosages might not truly reflect the therapeutic ranges because, in many instances larger doses than 10 mg. would be used, and in some instances the treatment would be cyclical.

After the presentation, Dr. Hellman, challenged the validity of this type of submission for the approval of any supplemental new drug application which would include new claims.

Dr. Cronk of Ortho stated that the Ortho company had additional data which they would submit. He mentioned the fact that there were 10 textbooks which made comments to the fact that this type of drug was being used in amenorrhea, dysmenorrhea, polymenorrhea and endometriosis, even though the drug was not labeled for such indications.

Dr. Adamsons stated that these drugs were not treating amenorrhea, but that they were causing vaginal bleeding induced by the withdrawal of these drugs.

Dr. Delfs pointed out this might be construed as a substitution factor in pathologic states such as Turner's syndrome.

Dr. Hellman informed industry that there would be additional data needed on the carcinoma problem and other particular problems that the Committee was considering, but that the Committee would notify industry specifically of the kinds of data that were needed. He further stated that the Committee

would need data on metabolic problems, and masculinization. Dr. Hellman then announced that the next meeting of the Committee would be January 20 and 21, 1966. He then thanked the representatives from industry for their cooperation and willingness to assist in resolving these problems.

EXECUTIVE SESSION

The Committee began its executive session and the representatives of industry were excused.

Dr. Hellman then appointed the following subcommittees:

- (1) Subcommittee on Thromboembolism.
- (2) Subcommittee on Carcinoma.
- (3) Subcommittee on Other Complications, Hormonal and Metabolic.
- (4) Subcommittee on Requirements for Safety and Efficacy.

Dr. Nicholson Eastman was selected as chairman of subcommittee on thromboembolism with the members being Dr. Christopher Tietze and Dr. Philip Sartwell. The subcommittee on other complications would be chaired by Dr. Eleanor M. Delfs, with Dr. Elsie R. Carrington as the other member. The committee on carcinoma would be chaired by Dr. Roger B. Scott with Dr. Roy Hertz as a member with a proviso that Dr. Philip Corfman would fill in for Dr. Hertz until Dr. Hertz was available. The committee on total requirements for approval of a drug on the basis of

safety and efficacy would be headed by Dr. Karlis Adamsons with Dr. Henry F. Fuller as a member and with Dr. Philip Corfman as an additional member if Dr. Corfman were able to participate.

Dr. Hellman urged that the chairman of the respective sub-committees periodically submit progress reports to Dr. Sadusk.

The following motion was made by Dr. Eastman, second by Dr. Carrington and passed unanimously by the committee:

"The Advisory Committee on Obstetrics and Gynecology of the Food and Drug Administration has held its first meeting to evaluate the safety and efficacy of the oral contraceptive drugs. The Committee finds no need for immediate action on the recent reports of adverse experience with these agents. It believes that final recommendations on these matters can safely await the conclusion of its deliberations."

Dr. Scott moved and Dr. Fuller seconded a motion endorsing the interim across the board labeling for oral contraceptives.

The motion read:

"Although the Committee in a preliminary review finds no evidence of a cause-effect relationship between the use of oral contraceptive drugs and the reported neuro-ocular manifestations, the Committee endorses the action of the Bureau of Medicine in placing, as an interim

measure, a warning concerning these eye manifestations
in the labeling of all oral contraceptive agents
currently on the market."

This resolution was unanimously adopted.

The committee adjourned at 4:00 p.m.

Submitted by:

Robert J. Robinson, M.D.
Executive Secretary

1/14/66