COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

HEARINGS

BEFORE THE

SUBCOMMITTEE ON MONOPOLY

OF THE

SELECT COMMITTEE ON SMALL BUSINESS

UNITED STATES SENATE

SECOND SESSION

ON

PRESENT STATUS OF COMPETITION IN THE PHARMACEUTICAL INDUSTRY

PART 17

ORAL CONTRACEPTIVES (VOLUME THREE)

APPENDIXES

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PREFACE

The Committee on Obstetrics and Gynecology expresses its appreciation to the Commissioner of the Food and Drug Administration and his staff for cooperation in the arrangements for its meetings, the preparation of reference material, and in particular, for their readily available consultation. The Committee also thanks the representatives of the pharmaceutical industry for their assistance and prompt submission of requested reports.

The preparation of this report has required consultation with numerous scientists whose help is gratefully acknowledged. Their continuing cooperation ensures that this report and others to follow will attain a crucial goal—a fully aware and accurately informed medical profession and public.

The Committee thanks Dr. Ralph M. Wynn, Professor and Head, Department of Obstetrics and Gynecology, University of Illinois at the Medical Center, Chicago, Illinois, Dr. John J. Schrogie, Bureau of Medicine, Food and Drug Administration, Ina Friedelson, Press Relations Staff, Food and Drug Administration and Florence Gubitz, State University of New York, Downstate Medical Center for assistance in preparation of this manuscript.

The Committee reports with deep regret the untimely death of Dr. Roger B. Scott, which deprived it of his sage counsel.

* Deceased.

CHAIRMAN'S SUMMARY

LOUIS M. HELLMAN, M.D.

Since the publication of the last Report on the Oral Contraceptives in 1966,* scientific as well as public interest in this method of family planning has remained high. The reservations of the first report appear to have been justified. Concern about the immediate and long-range side effects of the hormonal contraceptives has increased as scientific investigations have uncovered a host of diverse biologic effects, and as the drugs have become available to increasingly large segments of the world's population.

Adverse reactions are continually reported in the scientific literature and the lay press. Since the vast majority of the reported adverse experiences are conditions which occur spontaneously in women of reproductive age, identification of an etiologic relation has been difficult and slow.

An increased risk of thromboembolic disease attributable to the use of hormonal contraceptives has now been defined in both Great Britain and the United States. Other risks, such as those of hypertension, liver disease and reduced tolerance to carbohydrates, have not been quantitated with the same precision. Some of the risks have been recognized by isolated clinical observations, whereas others have been predicted on the basis of experiments with animals or merely on theoretical grounds.

Controversy has centered about two areas: the scientific data required to establish an etiologic relation and the balance between acceptable risk and potential benefit. The voluntary submission of reports by individual doctors to scientific journals, to the pharmaceutical industry, or directly to the Food and Drug Administration is fragmentary at best. Since the data on the natural incidence of the disorders in question are not available, it is impossible to ascertain whether the haphazard voluntary reporting of an adverse reaction in fact represents an increase in the suspected complication. The limitations as well as the value of a voluntary reporting system for providing an initial warning of serious complication have been noted frequently. There is no easy escape from this dilemma. The current aggregate pharmacological experience with the oral contraceptives is unique, however, in that large numbers of healthy young women are using potent drugs for a purpose other than the control of disease. An improvement in national reporting of some of the alleged complications is therefore merited. If the annual national rates of incidence of the various complications thought to be associated with hormonal contraceptives were known, trends presently unsuspected might be quickly uncovered.

This pharmacological experience is unique also in the attention it has received by the press throughout the world. Particularly in Great Britain and the United States the Press has attempted to keep the public informed of each discovery and each reported difficulty. Such reporting is the quickest way to satisfy the public's right to know.

The task of conveying complicated scientific information to the public is a responsibility requiring well-informed and accurate reporting, based on a judicious appraisal of data. Neither the public nor the press is well served if information is exaggerated, mitigated, or suppressed. In the final analysis, both the physician and the layman must evaluate the risks of the hormonal contraceptives in comparison with other methods of contraception or no contraception at all. They can do so wisely only when they have access to all available information, accurately and dispassionately presented.

It is difficult to separate fact from fiction at the forefront of scientific discovery. Evaluation in the area of hormonal contraception has proved formidable to the best informed scientists. The epidemiological problems are unique, requiring refinements in technique not yet fully realized. Case reporting, particularly isolated experiences, may be inconclusive. Thromboembolic disease is but one example. Eight years were required from the time of the first reported death to establish the relative risk and an etiologic relation to the hormonal contraceptives. By reviewing a welter of scientific studies of varied value, the press has acquired an increasing awareness of the problems through hard work and study. So too have physicians and the public. This difficult course could have been shortened and made more efficient by periodic, well structured, and responsibly led impartial conferences of scientific writers. The pattern was

* Report on the Oral Contraceptives, Advisory Committee on Obstetrics and Gynecology, Food and Drug Administration, August 1, 1966.

established 11 years ago by the American Cancer Society, when its science writers seminars were created.

The risk of thromboembolism associated with the oral contraceptives has been compared with that from pregnancy, cigarette smoking, and automobile accidents. Such comparisons are probably irrelevant, contributing little to evaluation of the relative risk. The task of balancing the risk against the benefit to the individual and to society must eventually be met. As contraceptive practices spread to all segments of our society, it becomes virtually essential that the requirements of effectiveness and safety, and the desirability of inexpensiveness and lack of association with coitus be satisfied. Oral contraceptives have proved to be highly acceptable to many couples who had found other methods inconvenient or impractical.

(a) Action on recommendations of the 1966 report on the oral contraceptives

The Committee is gratified by the prompt response of the Food and Drug Administration to the majority of its previous recommendations as follows:

Recommendation I.—A large case-control (retrospective) study of the possible relation of oral contraceptives to thromboembolism.

Result.—A study was developed at Johns Hopkins University School of Hygiene and Public Health with Food and Drug Administration support. Results document an increased risk in the drug users, roughly comparable to that observed in the epidemiological studies in Great Britain.

Recommendation II.—Continuation and support of studies such as the ones being carried out by the Kaiser Permanente group in California and the University of Pittsburgh group in Lawrence County, Pa.

Result.—The Kaiser study is operating under support from the National Institute of Child Health and Human Development. Food and Drug Administration support to the project in Lawrence County, Pa. was discontinued for administrative reasons, but a locally sponsored central audit of prescriptions is operating.

Recommendation III.—Support of additional controlled population prospective studies utilizing groups of subjects that are especially amenable to long-term followup, such as married female employees of certain large industries and graduate nurses.

Result.—A prospective study of the effects of oral contraceptives on cervical epithelium has been underway since 1967. Other prospective studies of effects of contraceptives on cervical cytology have been initiated recently. Corollary studies of possible effects on the breast will also be implemented.

Recommendation IV.—Continuation and strengthening of the present surveillance system of the Food and Drug Administration.

Result.—At the present time, all adverse reactions to the oral contraceptives reported to the Food and Drug Administration from the Hospital Reporting Program, manufacturers, consumers and physicians are collected and reviewed by the Division of Drug Experience, Bureau of Medicine, where they are coded and stored in a computerized facility. Reports are then transmitted to the Division of Metabolic and Endocrine Drug Surveillance, Office of Marketed Drugs where serious reactions are collected separately in a card file. This Division is responsible for preparation of a yearly tabulation of these serious adverse effects which is submitted to the Commissioner. A separate listing is also made by staff in the Office of Marketed Drugs.

Recommendation V.—Review of the mechanism of storage, retrieval, and analysis of surveillance data.

Result.—The data are stored by both computer and hand-tabulated forms. The data still cannot be retrieved easily or quickly. In addition, there is a serious difficulty with followup of individual cases because there is no uniform indexing or coding method between source and recipient. Thus, reduplication of reports or difficulties may result. Data are analyzed according to simple criteria of drug used, age of patient, severity, and nature of adverse reactions, etc. But further statistical analysis is not useful since the total population providing the date is not known.

Recommendation VI.—A conference be held between the Food and Drug Administration and the respective drug firms concerning uniformity and increased efficiency of reporting.

Result.—Not held.

Recommendation VII.—Priority be given to support laboratory investigations concerning all aspects of the hormonal contraceptive compounds.

Result.—The Food and Drug Administration and the National Institutes of Health are supporting several studies on carbohydrate metabolism, lipid metabolism, renal function, blood coagulation mechanisms, potential carcinogenic effects and other studies in animals and man.

Recommendation VIII.—Uniformity in labeling contraceptive drugs.

Result.—Accomplished.

Recommendation IX.—Discontinuance of time limitation of administration of contraceptive drugs.

Result.—Accomplished.

Recommendation X.—Simplification of Administrative procedures to allow reduction in dosage of already approved compounds.

Result.—Although no formal policy has been enunciated, the sponsors of new products that represent either reductions in dosage or changes in dosage schedule have been permitted to submit reduced quantities of preclinical and clinical information. It has been suggested, however, in view of these reduced requirements that the quality of the studies submitted in support of efficacy be improved; that is, the majority of studies should include patients beginning therapy rather than those being switched over from another hormonal contraceptive and should not generally include postpartum patients or those who are breast feeding.

(*b*) *Utilization*

American women are sufficiently interested in oral contraception to continue its use despite some alarming reports in the national press. By early 1969 twenty preparations of oral contraceptives, combined and sequential, were being distributed in the United States at the rate of approximately 8.5 million cycles per month. Combined progestin-estrogen products prescribed in 20- or 21-day cycles account for 80 per cent of this total. As a result of the gradual trend toward the use of lower dosages, over 90 per cent of the combination tablets now prescribed contain 2.5 mg. or less of the synthetic progestin. The estimates of use for 1969 are twice as high as those listed in the national fertility survey of 1965. This apparent doubling of the numbers suggests a much wider use among older women and those of limited education. Such a trend could be forecast from the increased availability of contraceptive services in many of the poorer areas of our big cities.

The use of oral contraceptives has spread in foreign countries as well. Among the countries without laws prohibiting the distribution of contraceptives, only Japan and the U.S.S.R. now prescribe the general distribution or sale of these drugs. The estimate of world-wide distribution of oral contraceptives is now approximately 18.5 million cycles per month.

All available evidence indicates that the continuation rates of oral contraceptives are higher than those of traditional methods of contraception, such as the diaphragm, and lower than those of intrauterine devices. In its previous report the Committee indicated an anticipated use of 6 million cycles monthly in the United States in 1970. If the present estimate of 8.5 million cycles is correct, the Committee's projections were conservative.

(*c*) *Efficacy*

The theoretical effectiveness of the combined hormonal contraceptives is reflected in a pregnancy rate of approximately 0.1 per hundred women per year. The theoretical effectiveness of the sequential oral contraceptives appears to be somewhat lower as indicated by a pregnancy rate of 0.5 per hundred women per year. The usually given pregnancy rates, reflecting "use-effectiveness," average 0.7 per hundred women per year for the combined regimen and 1.4 per hundred women per year for the sequential regimen.

Effectiveness, judged by the total number of pregnancies, is significantly higher with oral contraceptives, combined or sequential, than with intrauterine devices or any of the traditional methods. The pregnancy rates among users of diaphragms with contraceptive paste thus appear to be 10 to 30 times higher than those among users of oral contraceptives; those among users of intrauterine devices are 2 to 4 times higher.

(*d*) *Methods under evaluation*

Since the Committee's last report, pharmaceutical firms have continued to investigate synthetic progestins and estrogens in an effort to reduce side effects while maintaining maximal efficacy. For example, the most recently

approved combination product contains one-third the dose of estrogen and about one-tenth the dose of progestin as was present in the original contraceptive. Steroids that are stored in and slowly released from adipose tissue after oral ingestion are currently under study with the aim of creating a pill that may require administration only once a month. Unpredictable uterine bleeding remains a problem, however.

Intramuscularly injected steroids with a prolonged effect that may last for one or more months have been widely studied. Although these compounds may suppress ovulation, uterine bleeding is often an unpredictable complication. The delay before resumption of ovulatory cycles often lasts from 12 to 21 months. There is considerable variation among patients. To regulate the uterine bleeding some investigators have administered oral or parenteral estrogen. Doing so, however, detracts from the simplicity of this purely progestational regimen.

Low-dose continuous progestin therapy has been investigated in several countries. Drugs of this kind exert their contraceptive effect without the addition of estrogen and without the inhibition of ovulation. The pregnancy rate appears to be approximately 2 per hundred women per year. Approximately two-thirds of the women studied have some cycle irregularity.

The contraceptive action of low-dose progestins provides for the first time the possibility of long-term, reversible control of fertility by single administration of a hormone. Steroids may be released at a low and constant rate from capsules, made of various silicones, that are small enough to be inserted under the skin with a hypodermic syringe and that may last possibly as long as three years. Such implants could be removed if subsequent fertility were desired. If the clinical studies that have recently been initiated prove fruitful, this form of hormone administration may well become an important development in contraception.

(*e*) *Thromboembolic disorders*

An etiologic relation between oral contraceptives and an increase in some thromboembolic disorders has been disclosed by several groups of investigators using retrospective methods of inquiry and studies of mortality trends. In 1967 the Royal College of General Practitioners in Great Britain undertook interviews of young women with vascular disease. By comparing patients with superficial thrombophlebitis with a suitably matched series of controls, it could be shown that the risk of developing thrombophlebitis was tripled in women who used oral contraceptives. In a second study, Vessey and Doll investigated young women admitted to several hospitals in the northwest of London with a diagnosis of idiopathic thrombophlebitis. These patients also were matched with suitable controls. A third study involved all of the deaths that occurred in England, Wales and Northern Ireland during 1966 in women between the ages of 20 and 44 whose death certificates referred to thrombosis or embolism of the pulmonary, cerebral or coronary vessels. The results of the second and third studies are summarized in Table 1.

TABLE 1.—USE OF ORAL CONTRACEPTIVES IN WOMEN SUFFERING FROM "IDIOPATHIC" THROMBOEMBOLIC DISORDERS (EXPECTED NUMBERS IN PARENTHESES)

Disorder	Source of data	No. of affected women with a history of oral contraceptives		No. studied		Relative risk: users to nonusers
		Used	Not used	Affected women	Control women	
Deep-vein thrombosis or pulmonary embolism	Inpatients	26 (5·0)	32 (53·0)	58	116	8·6 to 1
	Deaths	16 (4·2)	10 (21·8)	26	998	8·3 to 1
Cerebral thrombosis	Inpatients	5 (1·0)	4 (8·0)	9	(1)	10·0 to 1
	Deaths	5 (1·5)	5 (8·5)	10	(1)	5·7 to 1
Coronary thrombosis	Inpatients	0 (0·7)	13 (12·3)	13	(1)	
	Deaths	18 (11·4)	66 (72·6)	84	(1)	1·7 to 1

[1] As in the corresponding control groups for women with deep vein thrombosis or pulmonary embolism.

(From Doll, R.: Brit. Med. J. 2:69–76, 1969.)

According to these British investigators, in the absence of other predisposing causes the risk of developing deep vein thrombosis, pulmonary embolism, or

cerebral thrombosis is increased about eight times by the use of oral contraceptives, while the risk of developing coronary thrombosis is apparently unchanged. The results of these three studies led the Food and Drug Administration to order the following change of labeling for the oral contraceptives:

"1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

"Studies conducted in Great Britain and reported in April, 1968[1] estimate there is a seven to tenfold increase in mortality and morbidity due to thromboembolic diseases in women taking oral contraceptives. . . .

"The conclusions reached in the studies are summarized in the table below:

COMPARISON OF MORTALITY AND HOSPITALIZATION RATES DUE TO THROMBOEMBOLIC DISEASE IN USER AND NON-USERS OF ORAL CONTRACEPTIVES IN BRITAIN

Category	Mortality rates		Hospitalization rates (morbidity)
	Age 20–34	Age 35–44	Age 20–44
Users of oral contraceptives	1. 5/100, 000	3. 9/100, 000	47/100, 000
Nonusers	0. 2/100, 000	0. 5/100, 000	5/100, 000

"No comparable studies are yet available in the United States. The British data, especially as they indicate the magnitude of the increased risk to the individual patient, cannot be directly applied to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may be different."

Since that time Vessey and Doll[2] have continued their retrospective study to include a larger group of patients matched with controls. The results of this study confirm the findings of the previous investigation.

Another retrospective study of cases of thromboembolism and an equal number of matched controls has been completed as detailed in Appendix 2A. This study necessitated a search for cases in five large cities in the United States. The subjects were women of reproductive age who were discharged alive over a recent three-year period from 43 teaching hospitals. Additional requirements for inclusion in the study were the absence of a history of any acute or chronic condition that might predispose to thromboembolism, absence of a history of a prior attack of the disease, reasonable certainty of diagnosis, and presumption of fertility. The controls were women admitted to the same hospitals in the same six-month period. These controls were matched by race, age, marital status, parity, residence, and hospital-pay status. The controls were in good health prior to hospitalization and free from evidence of sterility. The cases and the controls were interviewed in their homes after discharge from the hospital to ascertain whether they had used oral contraceptives before hospitalization. Other topics were included in the questionnaires.

Most of the acceptable cases had thrombophlebitis, pulmonary embolism, or both; a few had cerebral or retinovascular disease. The risk of thromboembolism to a woman using hormonal contraceptives was estimated by indirect methods to be 4.4 times that of the non-user. The excess risk did not persist after cessation of use, nor did prolonged continuation of use enhance the risk. No striking differences among contraceptive products were found except for an excess of the use of sequential compounds among the cases, as compared with the controls.

The excess relative risk was calculated for each diagnostic grouping and for each demographic class of subjects in which the numbers were large enough

[1] Inman, W. H. W. and Vessey, M. P., British Medical Journal, 2:193–199, 1968. Vessey, M. P. and Doll, R., British Medical Journal, 2:199–205, 1968.

[2] Vessey, M. P. and Doll, R., Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. British Medical Journal, 2:651, 1969.

to permit evaluation. The findings of this study are in general agreement with those previously reported from Great Britain.

These studies together establish an etiologic relation between thromboembolic disorders and the use of oral contraceptives. Quantitatively they suggest that the mortality from thromboembolic disorders attributable to the oral contraceptives is about three per 100,000 women per year adding slightly less than 3 per cent to the total age-specific mortality in users of these drugs.

(*f*) *Carcinogenesis*

Much indirect evidence suggests that steroid hormones, particularly estrogen may be carcinogenic in man. These data are derived from experiments on laboratory animals in which long-term administration of estrogen resulted in cancer in five species. Although all physical and chemical agents that are carcinogenic in man produce malignant tumors in experimental animals also, evidence of the carcinogenicity of estrogen in other species cannot be transposed directly to man. Suspicion lingers, however, that the results in laboratory animals may be pertinent to man. Many difficulties arise in the epidemiological elucidation of this suspected relation. The principal obstacle is the long latent period between the administration of a known carcinogen and the development of cancer in man. Thus far, no properly devised prospective or retrospective studies have provided an adequate solution to this problem.

The Committee has focused its attention on three target organs: cervix, endometrium, and breast. Estrogens may produce a variety of epithelial changes in the human cervix of uncertain prognostic significance. A study of women attending the Planned Parenthood Clinics in New York City has revealed a higher prevalence of epithelial abnormalities that the investigators considered to be carcinoma in situ among women using oral contraceptives than in those who use the diaphragm. The Committee believes that this study does not prove or disprove an etiologic relation between the oral contraceptives and these cervical changes. The epidemiological and diagnostic problems inherent in these studies are discussed in the Task Force Report.

Although estrogen causes epithelial changes in the human breast, its carcinogenic effect on that organ has never been proved. Even in women with frank mammary carcinoma, estrogen produces variable changes in the clinical course of the disease. For example, ovariectomy leads to regression of metastatic breast carcinoma in approximately half of premenopausal women. Exogenous estrogens cause either regression or stimulation of similar tumors in menstruating women but induce regression in about half of post-menopausal women. The reasons for these paradoxical effects of estrogen on breast cancer are not clear.

In accordance with suggestions in the last report, the Food and Drug Administration has required mandatory testing for all currently licensed and investigational hormonal contraceptives on monkeys throughout their lifetimes and on dogs for 7 years. Thus far the presently licensed compounds have not produced tumors in these two groups of laboratory animals. Two estrogen-progestin combinations have, however, induced mammary tumors in beagles. Because these two compounds offered no clear therapeutic advantage over previously available hormonal contraceptives, clinical investigation was discontinued. This decision still leaves unresolved the question of similarity in hormonal induction of mammary tumors in a highly suceptible canine strain and in man. Continued testing of the presently available drugs is indicated.

Currently available data on death rates from genital and mammary cancer in women in the United States do not clarify the problem of association between steroids and carcinoma. The long latent period of action of known carcinogens (10 years) and the length of time between diagnosis and death eliminate vital statistics as a source of information about this association until the mid-1970's or later.

The massive program of prophylaxis launched against cervical cancer in this country has accomplished a steady decline in deaths from the disease. The common practice of repeating cervical cancer in this country has accomplished a steady decline in deaths from the disease. The common practice of repeating cervical smears, annually or semi-annually, in women taking oral contraceptives has contributed to the decline, but it has clouded the question of the effect of oral contraceptives on cervical cancer.

Since there is no method of early detection of mammary carcinoma compara-

ble in efficacy to that of the cervical Papanicolaou smear, the problem of the possible carcinogenic effect of oral contraceptives on the breast remains unresolved. The Committee suggests that carefully designed retrospective studies using a case-control method similar to that employed in the investigation of thromboembolism may answer this perplexing question. A pilot study to ascertain feasibility is already in progress at the Johns Hopkins Hospital. If this method proves successful, several larger studies should be immediately initiated.

Lacking conclusive information about the applicability of existing animal data to women and sufficient observations of human disease the Committee concludes that potential carcinogenicity of the oral contraceptives can be neither affirmed nor excluded at this time. Clinical surveillance of all women taking oral contraceptives must be continued. A major effort to resolve the questions about steroid-induced neoplasia in human beings should be undertaken.

(g) Metabolic effects

Hormonal contraceptives produce numerous effects on many organs, for example, the liver, the thyroid, and the adrenal. They also affect some of the body's homeostatic mechanism; for example, they produce changes in salt and water metabolism and occasionally induce hypertension. Recently morphologic changes in blood vessels have been described. In many areas where alteration in function or structure has been noted, basic information is lacking. Little is known, for example, about the effects of the oral contraceptives on water metabolism or renal function.

Observations that large doses of estrogen hasten epiphyseal closure in girls has created fear that oral contraceptives may limit growth. Such concern is unjustified, however, because these drugs are usually prescribed only after the growth spurt and in doses far smaller than those required to stunt growth.

There is no evidence at this time that any of these drug-induced metabolic alterations pose serious hazards to health. The systemic effects of the drugs are so fundamental and widespread, however, that continued medical surveillance and investigation is required.

COMMITTEE RECOMMENDATIONS

1. Well designed studies be initiated and supported to elucidate or eliminate the relation of the hormonal contraceptives and carcinoma of the breast and uterus.

The relation of exogenous steroid hormones to the induction of cancer in man is the major unsolved question in the widespread use of the current hormonal contraceptives. Funds to investigate this relation are urgently needed. An international conference on epidemiologic design or projected studies should be beneficial.

2. Long term support be supplied to investigate the basis and prognosis of the metabolic alterations produced by the hormonal contraceptives.

The Task Force Report on Metabolic Effects of the hormonal contraceptives reveals a paucity of basic knowledge. Substantial research support is needed to close these information gaps.

3. Substantial support be supplied to develop new methods of contraception.

The current methods of contraception have inherent risks and disadvantages. These are enhanced when modern contraceptive methods are introduced into underdeveloped countries. Generous research support to discover new methods with decreased risks and fewer disadvantages is essential.

4. The National Institutes of Health support a National Fertility Survey in 1970.

Adequate data on contraceptive usage are not available after 1965. Support for a quinquennial survey should be established.

5. Financial support be made available to make possible local reporting of certain diseases.

Reporting of certain diseases such as cancer from selected localities would be of obvious benefit. The annual incidence of cancer reported from Connecticut is currently available only as late as 1962 while the report from New York, exclusive of New York City, is more up to date. These reports, if current, and if extended to include adequate samples of the general population,

could be used to indicate trends. With the rapid proliferation of very potent therapeutic agents, such reporting becomes more of a necessity.

6. The Food and Drug Administration assure adequate surveillance of approved contraceptive drugs.

The inadequacy of surveillance of contraceptive drug use in the United States and other countries is apparent. Voluntary reporting of adverse reactions tends to be capricious and may be misleading. The Committee recommends setting up test centers utilizing large contraceptive clincs, with identical record systems and good follow-up to record and report adverse reactions. In addition, the Committee recommends the implementation of an international conference to discuss ways and means of promoting rapid and accurate transmittal of information about adverse drug reactions to responsible authorities.

7. Strengthen the surveillance system of the Food and Drug Administration.

This recommendation from the previous report has not been satisfactorily implemented. A system should be devised so that when adverse reaction reports are received, they are made readily and immediately accessible.

8. An annual conference of scientific writers on contraceptive knowledge and accomplishment be held under auspices of the Food and Drug Administration or the Department of Health, Education and Welfare.

Years ago the American Cancer Society sought by means of annual conferences of science writers to make available data on research, treatment and etiology of malignant disease. These conferences made for a vastly better informed press. In view of the public interest in population and its control similar conferences in this area appear to have merit.

CONCLUSION

Although the Kefauver-Harris Amendments of 1962 indicate that the term "safe" has reference to health of man, nowhere do they define safety. Discussing this ubject before the Subcommittee of the Committee on Government Operations of the House of Representatives,[3] the Commissioner of FDA pointed out that no effective drug can be absolutely safe. Therefore, evaluation safety of a drug requires weighing benefit against risk.

The Advisory Committee on Obstetrics and Gynecology has continued to assess the risk of oral contraceptives in this light, weighing knowledge of potential hazards against benefit. It has periodically reviewed the labeling of these compounds, repeatedly advocated strict surveillance by physicians, and recommended the accumulation of additional information about biological action and clinical effects. This report states the benefits of these compounds compared with those of other contraceptives.

Specific risks as well as requisite practices for follow-up of patients have been detailed in the labeling of all hormonal contraceptives. When these potential hazards and the value of the drugs are balanced, the Committee finds the ratio of benefit to risk sufficiently high to justify the designation safe within the intent of the legislation.

[3] Hearing before Subcommittee of the Committee on Government Operations, Drug Safety, H.R., 88th Cong., 2d Sess. 149–154, 1964.

TASK FORCE REPORTS

August 1, 1969

As in the previous Report on the Oral Contraceptives, the Committee was divided into four task forces, each headed by a chairman, as follows:

TASK FORCES

1. Utilization, Effectiveness, and Current Investigations
   - S. J. Segal, Ph. D., Chairman
   - H. F. Fuller, M.D.
   - C. Tietze, M.D.
2. Thromboembolic Disorders
   - P. E. Sartwell, M.D., Chairman
   - A. T. Masi, M.D.
   - S. G. Kohl, M.D.
3. Carcinogenesis
   - R. Hertz, M.D., Chairman
   - B. M. Peckham, M.D.
   - C. Tietze, M.D.
4. Biologic Effects
   - P. A. Corfman, M.D., Chairman
   - K. Adamsons, M.D.
   - E. R. Carrington, M.D.
   - E. M. Delfs, M.D.

The report of each Task Force and the Chairman's Summary have been carefully reviewed and unanimously approved by the Committee as a whole. The summary of this report incorporates the conclusions drawn up by the individual task force reports which are appended in detail.

APPENDIX 1

REPORT OF THE TASK FORCE ON UTILIZATION, EFFECTIVENESS, AND CURRENT INVESTIGATIONS

S. J. Segal, Ph. D., Chairman

UTILIZATION

American women are interested in oral contraception. By 1965 they were consuming progestin and estrogen tablets at the rate of 2,660 tons yearly. One of every four married women under age 45 had used or was using an oral contraceptive. Actual users in 1965 numbered 3.8 million; 2.6 million women more had discontinued use. These estimates from the National Fertility Survey of 1965 (11) are based on interviews with a carefully drawn sample of American women. To the extend that the sample excluded unmarried women, married women separated from their husbands, and users of oral contraceptives over age 45, the figures are underestimates of the total experience with oral contraceptives up to 1965. The survey revealed that the use of oral contraceptives was much greater among younger than older women. Of women under 30, more than two-fifths had already used the pill; of women over 40, fewer than one-tenth had used it. The number of years of schooling proved to be a variable of major relevance. The percentage of users varied strongly and positively with the extent of education, from 37 per cent for college graduates to 12 per cent for women with less than high school education. Thus, by 1965 nearly one third of all American women who ever used any method of contraception reported having used the pill (18).

National survey data have not been assembled after 1965. Estimates of subsequent use of oral contraceptives are based on manufacturers' reports and market surveys. By early 1969, twenty preparations of combination or sequential oral contraceptives were being distributed in the United States at the rate of approximately 8.5 million cycles per month.[1] The apparent doubling of the number of current users since 1965 suggests much wider use than four years ago among older women and women of limited education. Combined progestin-estrogen products prescribed in 20- or 21-day cycles account for eighty per cent of this total. There has been a gradual trend toward the use of lower dosage forms, so that over 90 per cent of the combination tablets prescribed contain 2.5 mg. or less of the synthetic progestin.[1]

The use of oral contraceptives abroad has spread rapidly since this Committee's last report was issued. Among countries that regulate drug distribution, only Japan and the USSR proscribe the general distribution or sale of hormonal steroids for contraceptive purposes. In India hormonal contraceptives are approved for commercial sale but not for general use in the governmental family planning program. It is estimated that the world-wide distribution of oral contraceptives in early 1969 was 18.5 million cycles per month.[2]

CONTINUANCE OF USE

According to the National Fertility Survey of 1965 (11), almost three out of four American women starting oral contraception continued to use the method for at least one year, and more than three out of five continued for at least two years. These estimates are based on terminations as a result of side effects and other problems of use; terminations for reasons not related to the method are excluded.

Continuation rates after two years of use were eleven to twelve points higher for women under thirty years of age and for those with fewer than three births than for older women and those of higher parity. Continuation was related also to the women's level of education, ranging from 50 per cent after two years for women who had not completed high school to seventy-one per cent for those with one or more years of college. The survey also revealed the marked improvement in continuation rates for women who had started oral contraception in 1964 to 1965, compared with those who started earlier, possibly reflecting fewer side effects resulting from lower dosage as well as increased confidence in the method. The maximal rate of discontinuation was observed during the early months of use.

Continuation rates reported in clinical studies cannot be compared with the results of the National Fertility Survey without giving appropriate consideration to the special circumstances of each study, including the socioeconomic and cultural characteristics of the patients and the possible effects of any special efforts on the part of the investigator to encourage continued medication. However, all available evidence indicates that continuation rates with oral contraception are higher than with traditional contraception, such as the diaphragm and lower than with intrauterine devices in the same or comparable populations (16, 19).

FUTURE USE

In its previous report the Advisory Committee presented rough estimates of the anticipated future use of oral contraceptives in the United States. Assuming, series B. population projection,[3] 46 per cent of each cohort of married women starting oral contraception at the same rate as the women who were under 25 years of age in 1965, no further changes to oral contraceptives by older women, and about 60 per cent of those who ever used the drug remaining current users, the following were tabulated.

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[1] This estimate is based on data provided by the National Prescription Audit, R. A. Gosselin & Company, Inc., Dedham, Massachusetts, October, 1968, and information provided by the major manufacturers of oral contraceptives in the United States.

[2] This estimate was made by R. L. Belsky, Population Council, New York, and was based on information provided to him by major manufacturers, United States Agency for International Development, International Planned Parenthood Federation and Swedish Developmental Agency.

[3] Current Population Reports, Series P-25, No. 329, March 10, 1966.

PROJECTED NUMBER OF WOMEN IN MILLIONS USING ORAL CONTRACEPTIVES

Year	Ever users	Current users	Total women (15–44 years)
1970	10	6	43.3
1975	13	8	46.9
1980	16	10	51.9
1985	19	12	56.4

If the estimate of 8.5 million cycles distributed monthly reflects reasonably well the number of current users of oral contraceptives in early 1969, it would appear that the Committee's projections were conservative, at least to the present time.

EFFECTIVENESS

Taken according to the regimen prescribed, oral contraceptives of the combined type are almost 100 per cent effective in preventing unwanted pregnancy. Major clinical reports published between 1962 and 1967 cover an aggregate of some 200,000 cycles of medication. In these studies only 15 pregnancies occurred unassociated with the omission of one or more tablets, according to the statements of the users. The corresponding pregnancy rate, reflecting the "theoretical effectiveness" of the method, is approximately 0.1 per 100 women per year. The theoretical effectiveness of the sequential oral contraceptives appears to be somewhat lower, as indicated by a pregnancy rate of 0.5 per 100 women per year, based on 70,000 cycles and 25 pregnancies, apparently resulting from method failure (15).

Computation of pregnancy rates for oral contraceptives comparable to those available for other methods requires the inclusion of so-called patient failures, apparently resulting from the omission of one or more tablets during the cycle. Thus defined, the pregnancy rate reflects "use-effectiveness" and averages 0.7 per 100 women per year under the combined regimen and 1.4 per 100 women per year under the sequential regimen, according to published reports (15.). The absence of any pregnancies in a number of reports results from sampling variation, as do higher rates in other studies.

Theoretical effectiveness and use-effectiveness are significantly higher for combined contraceptives than for intrauterine devices (9), the condom, the diaphragm used with spermicidal jelly or cream, vaginal foam, and vaginal jelly or cream used with the diaphragm (6). The rate shown for "condom or diaphragm" under the heading of method failures is based on the experience of couples who used these methods for purposes of family limitation, after they had achieved the number of children they wanted (12). Strictly speaking, this rate reflects use-effectiveness in the hands of a highly motivated group of users; the pregnancy rate reflecting theoretical effectiveness should be a little lower. The number of couples available for study was too small to permit the computation of separate rates for the two methods.

The pregnancy rates shown in Table 2 do not include unplanned pregnancies after contraception has been stopped for reasons other than the wish to conceive. A statistical method for evaluating such pregnancies has recently been developed (17), and several studies are in progress to ascertain their frequency after discontinuation of oral contraception. This broader concept of "extended use-effectiveness" is of particular importance for the evaluation of oral contraceptives since the nature of the regimen permits a sharp distinction between cycles of use and cycles of non-use. If a woman fails to take oral medication and conceives, as is often the case, the method is usually exonerated. If she fails to use consistently a coitus-connected method, and conceives, the pregnancy is more likely to be charged to method failure.

HORMONAL CONTRACEPTIVES UNDER CURRENT INVESTIGATION

Suppression of ovulation—Oral preparations

Since 1966, when this Committee issued its last report on oral contraceptives, pharmaceutical firms continued to investigate different combinations or doses of synthetic progestins and synthetic estrogens in an effort to reduce side effects of antiovulant therapy while maintaining a high degree of effec-

tiveness. The dose of progestin has gradually been reduced from over 9 mg. in the original preparations to 0.5 mg. The dose of estrogen, ethinyl estradiol or its three-methyl-ether, has been reduced from 0.15 mg. in the first marketed product to 0.05 mg. It is not yet possible to draw conclusions concerning the various newer dosage combinations with respect to either efficacy or side effects. The combination product introduced most recently contains 0.5 mg. of a synthetic progestin, norgestrel, and 0.05 mg. of ethinyl estradiol (6).

TABLE 2.—PREGNANCY RATES PER 100 WOMEN PER YEAR

	Method failures	All pregnancies
Oral contraceptives:		
Combined regimen	0.1	0.7
Sequential regimen	0.5	1.4
Intrauterine devices:		
Large lippes loop	[1] 1.9	2.7
Saf-T-Coil	[1] 1.9	2.8
Condom or diaphragm	2.6	
United States clinics:		
Diaphragm used with spermicidal jelly or cream		17.9
Vaginal foam		28.3
Vaginal jelly or cream alone		36.8

[1] Pregnancies with IUD in situ. All rates for IUD's and traditional methods are for the first year of use.

Steroids that are stored in adipose tissue after absorption from the gastrointestinal tract are being investigated for possible one-pill-a-month contraceptive therapy (5). The investigation is aimed at calibrating the oral dose of the combination that will result in a month-long release of steroid from the adipose tissue at a level that will suppress ovulation while maintaining an acceptable pattern of endometrial bleeding. The problem of unpredictable endometrial bleeding has not yet been resolved (12).

Suppression of ovulation: Parenteral preparations

Intramuscular injections of steroids can give a depot effect, adjusted to last a single month or for several months. The most widely studied compound for injectable hormonal contraception is a 6-alpha-methyl-17-alpha-hydroxyprogesterone acetate; several thousands of women have been included in studies in many countries. The regimen investigated most completely is 150 mg. injected every 90 days, although studies are also in progress with semiannual injections of 400 mg. With this procedure, ovulation is generally suppressed through an interference with the midcycle peak of LH (8).

Ovarian follicular development appears, nevertheless, to proceed, so that endogenous estrogen production may not be completely obliterated. The endometrial pattern, however, reveals that the established estrogen-progestin balance is far from normal. As a result, uterine bleeding is unpredictable for women on this regimen. There is considerable variation among patients but by the end of a year the majority of women have atrophic endometria and are amenorrheic. A pregnancy rate below 1 per 100 women per year has been obtained with this procedure. There is, however, considerable delay in the restoration of ovulatory cycles after discontinuation. Delays in ovulation from 12 to 21 months are not uncommon and the time required for the establishment of a regular ovulatory pattern after treatment is still not certain. In order to regulate the pattern after treatment is still not certain. In order to regulate the pattern of endometrial bleeding, some clinicians have employed the periodic administration of estrogen either orally or by injection as an adjunct to injected progestin. Since this procedure requires monthly return visits, or self-administered monthly courses of oral estrogen, it detracts considerably from the method's simplicity.

Hormonal contraception without suppressing ovulation

(a) Oral Preparations-A new type of hormonal contraception is now being investigated in several countries. This innovation in hormonal contraception is continuous low-dosage progestin therapy, which imparts an antifertility effect

without added estrogen and without inhibiting ovulation. The basis of the antifertility action remains uncertain.

During the investigation of oral progestin-estrogen contraceptives, several investigators concluded that ovulation was occurring in a significant percentage of cycles, even though the antifertility effect was almost absolute. Yet it was not until 1965 that work was reported implying that ovulation suppression could be dispensed with entirely while still retaining a potent antifertility effect (10). In this early study, a synthetic progestin, 6-chloro-6-dehydro-17-alpha-acetoxy-progesterone was given alone at the low dose of 0.5 mg. daily to a group of nearly 1,000 women with normal cycles. The women were seen monthly during the period of investigation, which covered close to 10,000 cycles. Fourteen pregnancies occurred, thirteen of which were ascribed to failure of patients to take the medication regularly. Considering only the single so-called "method-failure," a pregnancy rate of 0.2 per 100 women per year can be calculated. When all unintended pregnancies are considered regardless of reason, the pregnancy rate is 2.1 per 100 women per year. Approximately two-thirds of the patients had some irregularity in the cycle during the twenty-month study period. The studies were subsequently expanded to include observations on 50,000 cycles, with more than 600 women observed for over two years. In this broader experience, 159 method failures were reported, giving a pregnancy rate of roughly 2 per 100 women years of use (7).

With this particular compound at the dosage employed, problems with control of the cycle appear to be a handicap, but the contraceptive effectiveness of the continuous progestin method seems clearly established. As a consequence, several other synthetic progestins have been placed under clinical investigation at doses intended to replicate the low-dose effect. Experience is sufficient with two of these compounds to indicate confirmatory results. With one of them, norgestrel, anti-fertility activity can be achieved with a daily oral dose of 0.075 mg. (4). More than 1,000 women have been observed for approximately 7.000 cycles, including over 400 women for at least one year. The ten reported pregnancies suggest a pregnancy rate of 1.6 per 100 women per year. Similar results have been achieved with respect to both control of cycle and fertility control with the use of 0.5 mg. daily of megestrol acetate (1). An innovation in the study of this compound is the use of an oil-filled gelatine capsule instead of a tablet, with the aim of achieving more uniform absorption and reduction of a cyclic irregularity. A cooperative statistical evaluation involving thousands of subjects in several countries is now in progress.

Although the mechanism by which the uninterrupted daily administration of these progestational agents creates a state of infertility without inhibiting the pituitary and suppressing ovulation remains uncertain, the possibilities can be narrowed down considerably. That the therapy does not interfere with ovulation suggests that the mode of action may be transport of sperm or ovum, the fertilization process, transport and development of the zygote, or the preparation of the endometrium for nidation. Histologic evidence from biopsy material suggests that endometrial changes are not responsible for the antifertility effect. Sperm transport could be affected as it passes through the cervical mucus or higher in the female tract. Although the preliminary reports tended to emphasize changes in cervical mucus that could create a barrier hostile to spermatozoa, such changes are not necessarily correlated with the antifertility effect. Future investigation will be required to establish the effect of continuous progestins at doses that do not inhibit ovulation on such key factors as tubal transport rates of gametes and the process of fertilization.

b) Parenteral Administration-The discovery of the antifertility action of low-dose progestins, based on uninterrupted administration, opens up for the first time the possibility of singly-administered, long-term, reversible control of fertility by hormonal means, in a manner that would allow for maintenance of ovarian function and menstrual cycles. A possible application of this principle is suggested by experiments demonstrating that steroid hormones may be released at low and constant rates from capsules made of various silicone polymers (3, 13). One such material poly-dimethylsiloxane, is already used widely in surgery. Capsules containing the synthetic steroid, megestrol acetate, have been inserted subdermally into female rats, rabbits, and monkeys, and biologic evidence of slow and constant release of the hormone has been

obtained (2). Animal experiments suggest that this route of administration increases the potency of megestrol acetate to approximately 10 times that of the oral route.

A capsule small enough to be inserted under the skin through a hypodermic needle can be filled with an adequate supply of this progestin to last for more than three years. Contraceptive implants of this type could be removed at will, and there is no reason to believe that subsequent fertility would be impaired. Depending on the outcome of clinical studies that have been recently started (14), this form of low-dose progestin contraception may very well be one of the next developments in contraceptive methodology.

References

1. Avendano, S., Tatum, H. J., Rudel, H. W., and Avendano, O. A clinical study with continuous low doses megestrol acetate for fertility control. Amer J. Obstet Gynec (in press) 1969.
2. Chang, C. C. and Kincl, F. A. Sustained release hormone preparations: 3. Biological effectiveness of 6-methyl-17-alpha-acetoxpyregna-4, 6-diene-3, 20-dione. Steroids 12:689, 1968.
3. Folkman, J. and Long, D. M. The use of silicone rubber as a carrier for prolonged drug therapy. J. Surg Res 4:139, 1964.
4. Foss, G. L. Oral contraception with continuous microdose of norgestrel. J Reprod Fertil Suppl. 5:145, 1968.
5. Guiloff, E., Berman, E., Osorio, R., Monteglio, A. and Lloyd, C. W. Once-a-month contraceptive pill. Presented at 25th Annual Meeting, American Fertility Society, Miami, Fla., 1969.
6. Laurie, R. E. and Lewis, E. F. A clinical review. J Reprod Fertil Suppl. 5:95, 1968.
7. Martinez-Manautou, J., Giner-Valasquez, J., Cortez-Gallegos, V., Aznar, R., Rojas, B., Guittierez-Najar, A., Rudel, H. W. Daily progestogen for contraception: Clinical study. Brit Med J 2:730, 1967.
8. Mishell, D. R., El Habashy, M. A., Good, R. G. and Moyer D. L. Contraception with an injectable progestin. Amer J Obstet Gynec 101:1046, 1968.
9. Population Council: Cooperative statistical program for the evaluation of intrauterine devices. Unpublished data.
10. Rudel, H. W., Martinez-Manautou, J., and Maqueo-Topete, M. Role of progestogens in hormonal control of fertility. Fertil Steril 16:158, 1965.
11. Ryder, N. B. and Westoff, C. F. Use of oral contraception in the United States, 1965. Science 153:1199, 1966.
12. Sagi, P. C., Potter, R. G. and Westoff, C. F. Contraceptive effectiveness as a function of desired family size. Population Studies 15:291, 1962.
13. Segal, S. J. Future aspects in contraception. Excerpta Medica Int. Congr. Series No. 133, Proceedings Vth World Congr. on Fertility and Sterility. Stockholm, June 16, 1966, p. 1028, 1967.
14. Tatum, H. J. History and current status of implant contraceptives. Progress in Conception Control, J. B. Lippincott Company, Philadelphia (in press) 1969.
15. Tietze, C. Oral and intrauterine contraception: effectiveness and safety. Int J Fertil 13:377, 1968.
16. Tietze, C. Comparison of three contraceptive methods: diaphragm with jelly or cream, vaginal foam, and jelly/cream alone. Journal of Sex Research 3:295, 1967.
17. Tietze, C. and Lewit, S. Statistical evaluation of contraceptive methods: Use-effectiveness and extended use-effectiveness. Demography 5:931, 1969.
18. Westoff, C. F. and Ryder, N. B. United States: Methods of fertility control, 1955, 1960 and 1965. Studies in Family Planning 17:1, 1967.
19. Westoff, C. F. and Ryder, N. B. Duration of use of oral contraception in the United States, 1960–1965. Public Health Rep 83:277, 1968.

APPENDIX 2

REPORT OF THE TASK FORCE ON THROMBOEMBOLIC DISORDERS

P. E. Sartwell, M. D., Chairman

A. THROMBOEMBOLISM AND ORAL CONTRACEPTIVES: AN EPIDEMIOLOGICAL CASE-CONTROL STUDY [1, 2, 3]

PHILIP E. SARTWELL, ALFONSE T. MASI,[4] FEDRICO G. ARTHES, GERALD R. GREENE [5] AND HELEN E. SMITH

The suspicion that oral contraceptives might predispose women toward vascular occlusive phenomena arose about 1961, largely from the publication of case reports. An *ad hoc* committee (1) in 1963 advised that "comprehensive and critical" studies to look into the possibility be conducted. Nevertheless, little was done in this direction, despite the great increase in the use of these potent drugs. By the time the Advisory Committee on Obstetrics and Gynecology of the Food and Drug Administration began to prepare its first report on the oral contraceptives in 1965, it was evident that an epidemiologic study was even more urgently needed than in 1963. The present study was begun in November, 1965, in direct response to this need.

The primary aim of this study has been to evaluate the reported association between taking oral contraceptives and development of thromboembolism. The retrospective (case-control) approach was used. This was appropriate in view of the low incidence for idiopathic thromboembolism at the reproductive ages, which made a prospective approach extremely difficult, costly and slow to yield results. A series of previously hospitalized cases of idiopathic thromboembolism in women of reproductive age was identified, matched controls were secured from among other hospitalized women, and both groups were interviewed to ascertain whether they had used oral contraceptives before the hospitalization.

The term "idiopathic thromboembolism" is used in this report to refer to cases in women who at the time they developed thromboembolism did not have any medical, surgical or traumatic condition that is associated with this disease.

MATERIALS AND METHODS

A pilot study was first conducted at the Johns Hopkins Hospital. Ten suitable cases were found, and 20 matched controls were selected. One finding of the pilot trial was that a high proportion of women, even at these relatively young ages, who were hospitalized with thromboembolism had medical, surgical or traumatic features in their histories that made them ineligible for study. Another important result was that they knew, or at least stated, quite confidently their histories of use of oral contraceptives. This finding was consistent with the opinions of workers who had done surveys of contraceptive practices, and justified proceeding with the study. To be sure, the statements of respondents, although given with assurance in most cases, could have been wrong, but it was not feasible to attempt to verify them from independent sources. The finding of six cases who had used oral contraceptives out of a

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[2] This study was supported by the Food and Drug Administration Contract Number FDA 67–10; the Family Planning and Evaluation Section of the Epidemic Intelligence Service, National Communicable Disease Center, Atlanta, Georgia; and the Population Council, through Grant Number M68.06.

[3] Accepted for publication in American Journal of Epidemiology.

[4] Present address: University of Tennessee School of Medicine, Memphis. Dr. Masi was a Senior Investigator under the Arthritis Foundation.

[5] Dr. Greene was, during this study, an Epidemic Intelligence Officer, National Communicable Disease Center.

The authors are grateful to all the persons in the collaborating hospitals who helped in data gathering. There are several hundred such persons and it would be impossible to list them all here, but the liaison physicians are named in Appendix 1. Advice and assistance came willingly from many others who were asked to help. Dr. James W. Long and, later, Dr. John J. Schrogie of the F.D.A. deserve special mention. Dr. Carl W. Tyler and Dr. Sheldon J. Segal provided much-needed support.

In the Pittsburgh phase of the study Dr. John C. Cutler, head of the Population Division of the University of Pittsburgh Graduate School of Public Health, kindly assumed a share of the administrative responsibility. Record numbers of potential cases and controls were provided from the Hospital Utilization Project (H.U.P.) through the cooperation of Dr. Paul Lewis and Mr. Donald Doyle.

total of 10 cases, while none of 20 controls had used them, made it mandatory to continue the study.

The plan was to have the interviews deal with other topics including medications of various types taken before the hospitalization in question (e.g. analgesics, tranquillizers and sedatives, drugs for weight control), the respondent's previous health and the medical and reproductive history of her husband and herself. The interview was designed to avoid concentrating the respondents' attention on a possible drug-thromboembolism relationship and thereby possibly obtaining biased answers. Also, this led to the exclusion of a few respondents who had disqualifying conditions not revealed in the hospital history. Information concerning education, economic status and employment was obtained.

Interviews in the main study were done by interviewers employed and supervised by National Analysts, Incorporated. Respondents were assured that their identity would not be divulged.

For the main study, it was decided initially to conduct the search for cases and controls among patients discharged within the past three years from large hospitals affiliated with medical schools and located in large cities closest to the base of operations. Ultimately, hospitals in five cities—Baltimore; Washington, D.C.,; Philadelphia; New York City; and Pittsburgh—were invited to participate. For inclusion, women had to be married, age 15 to 44 inclusive, and discharged alive from the hospitals within three years. The marital requirement was based on the expectation that contraceptive histories would be more reliable and obtained with greater ease from married women. The other requirements were based on considerations of the ages at which women use oral preparations of ovarian hormones and synthetic steroids as contraceptives and the limits of time over which they would be likely to remember what medications they had been taking before hospitalization. The choice of cities and hospitals was dictated by practical considerations related to ease and economy of case selection and interviewing. Every hospital that was asked to participate in this study, with a single exception, agreed to do so; difficulties in financial arrangements were responsible for the one hospital's inability to take part.

As to the medical conditions included, all forms of intravascular (venous or arterial) thrombosis, with or without pulmonary embolism, including cerebral and coronary thrombosis, were investigated, as well as pulmonary emboli without a known source. The term thromboembolic disease will be used to indicate this entire group of conditions.

Cases were excluded from this study on the following grounds as determined from the hospital history: having a chronic condition which was thought to predispose to thromboembolism; having had recent precipitating events such as surgery or trauma; pregnancy; sterility; having conditions which might be considered as contraindications to oral contraceptives; and having conditions which might be considered as reasons for avoidance of pregnancy. Review of the literature and consultation with many authorities was accomplished to determine conditions or factors associated with or predisposing to thromboembolism. The object was to include as cases only those patients who had no known predisposing or precipitating factors. The following are the principal conditions of this type which served to exclude patients: any past history of vascular disorders including varicose veins, or prior thromboembolic event; diabetes; hypertension, with recorded systolic blood pressure of 180 or diastolic of 100; rheumatoid, gouty arthritis or any of the rate connective tissue disorders; hypo- or hyperthyroidism, untreated; any history of other chronic systemic conditions known to predispose to thromboembolism, e. g. cancer, heart or blood diseases; obesity (over 15% overweight; hemoglobin values below 8 or above 16 gms percent; childbirth, major trauma or surgery within six weeks prior to onset of thromboembolic event; various systemic infections within four weeks of onset; localized infection (abscess, carbuncle) or pneumonitis within 14 days prior to onset; minor trauma or inflammation (bursitis, tendinitis) of tissues site of subsequent thrombosis within two weeks: and unusually strenuous activity for the individual, or prolonged inactivity or immobility within two weeks.

Reasonable medical evidence to support the diagnosis of thromboembolism was required. It is well known that pulmonary embolism, cerebral thrombosis and cerebral embolism are difficult to diagnose accurately in the absence of pathological evidence, unless supported by procedures such as lung scans and

angiography. Only cases in which the hospital diagnosis was unequivocal were accepted, and the records were reviewed independently by two physicians, one a board-qualified internist, who rejected those cases which they considered doubtful.

Controls were female patients discharged alive from the same hospitals in the same 6-month time interval. In addition to these matching factors, they were individually matched to the thromboembolism cases on age (within the same five-year span), marital status, residence, race, parity (three classes—0, 1–2, 3 or more prior pregnancies), and hospital pay status (ward, semi-private or private). The small inaccuracies in matching are explained by differences between statements on the hospital records and interviews, the latter being accepted, and also by occasional inability to obtain a perfect match. The same exclusions, on the basis of infertility or chronic disease, applied to the controls as to the cases. Controls for the most part were admitted for acute medical or surgical conditions, trauma including fractures and dislocations, and elective surgery such as nose and throat operations.

Two controls were picked for each case in nearly all instances, in order that the case need not be dropped from the study if the first control proved unavailable for interview.

In the course of the study, several changes were made, although the original plan was followed exactly throughout for the main study group of married women with idiopathic thromboembolism. In Philadelphia, New York City and Pittsburgh, unmarried cases and controls were included, as it had become evident that idiopathic thromboembolism was relatively frequent among younger, unmarried women and it seemed unwise to disregard this source of case material.

In Philadelphia, the interviewing of the unmarried cases and controls was undertaken by students at the Woman's Medical College of Pennsylvania, under the direction of Dr. Judith Mausner, instead of by interviewers employed by the market research firm. This was done after the regular interviewing session had ended and when it was decided to query unmarried patients.

RESULTS

The final study group consisted of 175 cases. These cases were selected from 2,648 women who had final diagnoses of thromboembolic illnesses at the 47 participating hospitals and whose illnesses were considered sufficiently likely to meet the study criteria as to warrant the preparation of a medical abstract. Obviously, there was a high degree of selection and the series cannot be considered as representative of all hospitalized thromboembolism, even in these hospitals. Table 1 gives the derivation of the study group.

Some exclusions were for uncertainty of diagnosis, some because of a prior attack of thrombophlebitis, but the great majority were for evidence, either in the history or physical or laboratory findings, of conditions that were regarded as possibly predisposing to thromboembolism. Three of the most common of these were obesity, varicose veins, and hypertension. Doubtless some patients with these conditions were included, and likewise some patients were probably erroneously excluded, since it was necessary in many instances to interpret conflicting or incomplete statements in the hospital record. For example, many patients were not weighed while in the hospital and the examination record was often uncertain as to the presence of obesity.

The diagnoses of the study group are presented in Table 2. Thrombophlebitis was the most frequent; diagnoses of phlebothrombosis were, for purposes of this study, included under thrombophlebitis. Pulmonary embolism was encountered with equal frequency as the only diagnosis, and in association with peripheral thrombophlebitis. Cerebral and retinal vascular lesions were infrequent. Coronary artery disease was not represented, since all cases investigated had evidence of a predisposing condition such as hypertension or diabetes, or else of infertility resulting from surgical procedures.

Table 3 indicates that most controls were found among women admitted for elective surgical procedures, with acute surgical conditions, acute infections, trauma, and acute medical conditions appearing less frequently. As in the selection of cases, potential controls with chronic medical conditions were usually rejected. After the records of patients matching a case on those demographic factors which were available in the record room index had been drawn

for inspection, it was sometimes necessary to reject more than 100 before finding a patient who met the additional matching criteria for a control.

Three-fifths of the cases were married at the time of the episode, 85% were white, and nearly one-half were treated in New York City hospitals (Table 4). Although records were searched for cases over a three-year span, owing to the duration of the study, illnesses were spread over a five-year period, most of them occurring in the period from 1965 to 1967 inclusive. The highest case-frequency was in the age class 20–24, the next highest at 40–44. Various sources indicate that thromboembolism incidence increases sharply with age, but so also do the chronic illnesses which disqualified patients for this study. The age distribution of the series is a function of these two determinants, and doubtless others as well, such as patterns of use of oral contraceptives. It should not be taken as reflecting differential risk of thromboembolism.

Table 5 shows the distribution of some characteristics on which preliminary matching was not attempted. Differences between cases and controls with regard to the family income, the patient's religion and the patient's maximum weight fell short of conventional levels of significance. There were differences, significant at the 5% probability level, in the patient's education (although not in the husband's education, for married patients), the proportion who were working just before their hospitalization, and the proportion who were working at a medically-related job (or whose husbands had a medically-related job). There were indications that hospital employees, and particularly student nurses, had a greater chance of being hospitalized if they developed thromboembolism. Therefore the data were reanalyzed excluding those pairs in which the case was a student nurse. The difference in educational level and the difference in proportions working outside the home were found to be no longer statistically significant, but the difference in the proportion employed in a medically-related position remained.

The respondents were shown a list of 13 contraceptive method's and asked to identify those they had used within the two years prior to hospitalization, by reading back the corresponding letters (e.g., Method B. Method F). Many had used more than one method. Differences between cases and controls were generally quite small, and statistically not meaningful, except for the oral contraceptives, which had been more often used by cases. Thus the birth control practices of the two groups were similar, as indicated additionally by the fact that 114 cases and 101 controls had used one or more methods (Table 6).

The time at which the cases and controls who had used oral contraceptives within two years prior to admission terminated their use is presented in Table 7, which shows a marked disparity in use up to the time of admission, but virtually none in use that terminated more than one month prior to admission. This is taken as evidence that there is no continuation of excess risk after use of the hormones is stopped, and analysis of case-control differences will therefore be confined principally to use within one month prior to admission. It is assumed that the few cases who had terminated use during the month before admission were, at the time they stopped, already suffering from the conditions for which they were hospitalized.

The duration of use of oral contraceptives is shown in Table 8, both for the product used last before hospitalization and for all products used in the two-year period, together with the corresponding percentages based on all users. The probability of a series of differences as large or larger than that observed is greater than 0.5. Thus, there is no evidence from this material that the risk is enhanced with duration of use.

No aboslute significance may be attached to the distribution of duration of use in the case series, since it is similar to the controls. It presumably results from the interaction of the increasing pipularity of oral contraceptives over the interval studied, and the tendency of some patients to discontinue their use because of minor side-effects. It cannot be inferred that the period from 1 to 5 months' administration is more likely to be hazardous than any other.

Majority opinion holds that the proper analytic method for the study and testing of differences between case and control groups where pairing has been practiced is to preserve the paired relationship, although the results usually are not greatly different from those using the conventional group comparison. The derivation of the relative risk of persons possessing an attribute getting a

disease, compared to persons not having the attribute, can be expressed very simply in the context of a 2 x 2 table constructed as follows:

Cases	Controls	
	Attribute present	Attribute absent
Attribute present	a	b
Attribute absent	c	d

The sum of the numbers in the four cells is the number of case-control pairs.

The relative risk of acquiring the disease (thromboembolism) for persons having the attribute (use of oral contraceptives) is the number in cell b divided by the number in cell c. A test of significance of the difference between the numbers in cells b and c, where $b>c$, with correction for continuity, is a χ^2 test in which $\chi^2 = (b-c-1)^2/(b+c)$, with one degree of freedom.

Table 9 shows the relative risks for various subdivisions of the material, computed in this way, together with an indication of the statistical significance of each difference. For the entire series of 175 case-control pairs the relative risk is 4.4 with confidence limits of 3.1 and 6.8. Since pairing was on so many factors, no statistical adjustments are needed. No material differences in the relative risk are seen according to age, race, or marital status, but the number of pairs of nonwhite subjects and for some other subdivisions is too small to be sure that a difference does not exist.

For each diagnostic group in which numbers were sufficiently large to allow any statement to be made, there was a higher risk for users than non-users of oral contraceptives.

The brand names of the products used within two years before admission were analyzed. There were 16 cases and 6 controls who had used more than one product during the interval. The respondents were shown samples of the various tablets, as well as a list of the names of 14 different products—in some cases, as many as four produced by a single manufacturer. For many of these products the combined number of case-users and control-users was too few to yield any evidence as to whether they differed in their capacity to produce thromboembolism.

A special situation exists with respect to the sequential formulations. Sequential is the term for oral contraceptive formulations in which tablets containing only an estrogenic compound are taken for 20 or 21 days of the cycle, followed by the administration for 5 days of estrogen plus a progestogen. Three of these products were used by one or more subjects. Altogether, 15 cases and no controls had used them within one month of hospitalization. Contrasting the ratios of cases to controls—15:0 for sequential users, 52:23 for users of all other products—the difference is statistically significant. Of the 15 sequential users, 7 had pulmonary embolism, without a known thrombophlebitis, while only 11 of the other 160 cases had pulmonary embolism. Appendix 2 gives the frequency of use of the different formulations by cases and controls.

DISCUSSION

When case reports began to appear linking the use of oral contraceptives with intravascular occlusive states, two features of the problem made it difficult to decide whether the association was genuine: the fact that millions of women were adopting the use of the method, and the fact that the illnesses often occurred long after beginning use of the product.

An ad hoc committee (1) in 1963, the advisory committee on obstetrics and gynecology of the F.D.A. (2) in 1966, and a WHO scientific group (3) in the latter year all found no definite evidence on which to incriminate these hormones in the production of thromboembolism, defined as venous thrombosis (exclusive of the veins of head and neck), or embolism of the pulmonary artery, or both. Beginning in 1967, however, there have appeared several reports, all from Britain, which strongly indicate a relationship. The first of

these (4) was carried out by selected members of the College of General Practitioners who reported on 147 women from their practices with thromboembolic disease (mostly superficial venous thrombosis) and 294 controls. The risk of venous thrombosis was estimated to be increased nearly three-fold among users of oral contraceptives.

A study of women who had fatal attacks of pulmonary, coronary and cerebral thrombosis and embolism in the year 1966 was made by Inman and Vessey (5). Among 26 idiopathic cases of pulmonary embolism, there was a clear excess of users of oral contraceptives over the number expected from the experience of control women; in 49 cases where predisposing conditions existed, there was a small, statistically insignificant excess. Findings for coronary thrombosis were conflicting. For cerebral thrombosis, there was again an association with the drugs, limited to patients without predisposing conditions.

The most significant study has been that of Vessey and Doll, a second report on which has recently been published (6). Although their study and the one reported in this paper are quite similar in design, they were planned and conducted entirely independently. The main differences are that Vessey and Doll excluded patients with only superficial thrombophlebitis but included those who had had previous attacks of thrombophlebitis. They interrogated 87 married cases of idiopathic deep vein thrombosis or pulmonary embolism, 19 of cerebral thrombosis, and 17 of coronary thrombosis. For 84 of the thromboembolism cases they interviewed two matched controls per case, or altogether 168 controls with other diseases. The subjects had been treated between 1964 and 1967 in 19 hospitals in the northwest region of metropolitan London. Large differences between cases and controls in the proportions having used oral contraceptives within one month before onset (or in the case of controls, entry to hospital) were found for the thromboembolism and cerebral thrombosis series, but none for the coronary thrombosis series. Little difference was seen between thromboembolism cases and controls according to type of contraceptive combination; none of the cases or controls had used the sequential preparations, but this is not remarkable, as only 3% of the oral contraceptives supplied in Britain during this period were sequentials. Duration of use was similar for thromboembolism cases and those controls who had used the hormones. The association was stronger for patients who had never had a previous attack of thromboembolism than for those who had, but interpretation of this observation is considered by the authors as impossible without further knowledge of the interaction between us of oral contraceptives and the predisposing factors associated with a history of previous disease. The thromboembolism cases tended to weigh more than controls, and to be above standard weight, a relationship that held irrespective of use of oral contraceptives. The authors consider that a suggestion in the preliminary report of their findings of an interaction between heavy smoking and use of oral contraceptives in the pathogenesis of thromboembolism is not supported by the complete figures. However, our examination of their data still seems to show an association of at least borderline significance between heavy smoking and thromboembolism.

They conclude that the relative risk of hospital admission for deep vein thrombosis or pulmonary embolism among married women who are oral contraceptive users appears to be 6.3, with confidence limits of 3.4 and 11.6. They also state that their estimate of the annual risk of hospital admission for these conditions plus cerebral thrombosis is about 0.5 per 1,000 for married women who are using oral contraceptives, and 0.06 for those who are not.

Drill and Calhoun (7) have reviewed the evidence linking oral contraceptives to thromboembolic disease, and have concluded that the incidence of thrombophlebitis is not increased when these drugs are employed. Their paper, published when only the preliminary report by Vessey and Doll had appeared, deals with a considerable number of complex issues. It has led to a vigorous correspondence in the columns of the Journal of the American Medical Association; the reader's attention is invited especially to the response by Doll, Inman and Vessey (8) and the reply by Drill and Calhoun, as well as the comments of Seltzer, and of Frederiksen and Ravenholt, in the same issue.

In view of the importance of the paper by Drill and Calhoun, its major points will be re-examined. Firstly, it placed emphasis on the disparity between the incidence rates of thrombophlebitis in nonpregnant women of child-bearing age as estimated by Vessey and Doll (.05 admissions per thou-

sand per annum, on the basis of 32 selected cases without evidence of predisposing cause) and other estimates. They quoted seven such estimates based upon hospital admissions, of which six, not restricted to idiopathic cases, ranged from 0.71 to 1.08. The seventh, for idiopathic cases only (and hence, more nearly comparable to the Vessey and Doll figure) was 0.65. This figure was derived from an unpublished study. In our experience, the proportion of idiopathic cases among patients hospitalized with thromboembolism is only about 15%. It would therefore seem desirable to review the definitions employed before accepting these data as placing the Vessey and Doll findings in question. Furthermore, as Vessey and Doll point out, superficial thrombophlebitis was probably included to an unknown extent in the statistics quoted by Drill and Calhoun, but was excluded from their own study.

The fact remains that in the prospective trials of oral contraceptives quoted by Drill and Calhoun, no excess risk of thromboembolism has been shown. They cited 51 such trials, reported in a previous review by Drill, which uniformly failed to show any increased morbidity. In these studies, detection of thrombophlebitis was not the principal aim and some of them were done before this possible risk had become widely recognized. Careful observation would be needed in order to ascertain, in the case of women who became dropouts from a clinic, whether a medical complication of the medication received, such as thrombophlebitis, might not have been one of the reasons for failure to return to the clinic.

The largest of these studies—in fact the only one with numbers adequate to test the hypothesis—is not in the medical literature; the only reference to it that could be found was a release issued by a voluntary agency. It is described as an extended trial of an oral contraceptive by women who, in order to be eligible for entry to the study, must already have used it for at least two years. Women who dropped out because of thromboembolism or for other reasons before that time were not included, and hence the woman-years of observation during the first two years of use are not relevant to the risk of getting thromboembolism; and yet these person-years have been included in estimating the expected number of cases. In other words, it appears probable that some at least of the women undergoing the first two years of use of oral contraception developed thromboembolism and discontinued use of the method for that reason, so that to base the rate upon those who did complete the first two years produces a spuriously low figure. Another doubtful feature of this study is that of the 58 occurrences of thrombophlebitis self-reported in this study, all but 17 were later rejected as having inadequate evidence for the diagnosis; yet we do not know if similarly strict criteria were followed in other experiences from which the general compartive incidence of thrombophlebitis has been estimated. Finally it should be noted that the authors of this study themselves state:

"This study was not designed to provide a comparative incidence of thrombophlebitis. Such an investigation would require more detailed follow-up examinations than were feasible in order to establish (1) a positive diagnosis of the condition, (2) the existence of recognized contributing causes, and (3) whether the patient was hospitalized. Satisfying these criteria is necessary to provide any meaningful comparison with the only reliable base-line incidence data for this disorder which is limited to idiopathic, hospitalized cases."

It is our opinion that the evidence presented by Drill and Calhoun, which constitutes the main negative evidence published to date, is inadequate to show that the incidence of thromboembolism is either unaffected or reduced by oral contraceptives.

The retrospective study method used by Vessey and Doll, and by ourselves, suffers from two possible biases as applied to thromboembolism. First, women who developed the disease while taking an oral contraceptive might be told by their physicians that the oral contraceptive was responsible, as indeed often happened. Thus, cases might have been more likely than the controls to give an affirmative history of oral contraceptive use. Clearly, the securing of information on contraceptive use from hospital histories would have led to severely biased classifications, but the interview method has, it is felt, largely eliminated this bias. It seems most unlikely that a woman would assert having used several types of contraceptives but deny that she had ever used the orals,

as many of the respondents did, if that were not the case. The error, if any, would lie in the controls failing to give affirmative answers to the question on oral contraception, which was asked in several ways in the course of the interview. The proportion of affirmative responses by married controls as to current use was similar to what would be expected from the Ryder-Westoff survey (9), specific for age and parity (18 observed, 15.7 expected).

The second possible bias is that those women who were oral contraceptive users may have been more likely to be hospitalized than other women with thromboembolism of equal severity. This latter possible bias can be tested for by comparing the findings in women with the more severe illnesses such as those in which pulmonary embolism was a factor, who would be treated in hospitals whatever their history of oral contraceptive use, with women who had only a superficial thrombophlebitis. Table 9 indicates that this bias was not present, since the relative risk for superficial thrombophlebitis is not greater than that for all cases.

The most important single difference between cases and controls found in this study which might tend to bias the results was the excessive number of student nurses and other persons who had hospital jobs or medically-related jobs—or whose husbands had such jobs—among the cases. This probably indicates a greater likelihood of employees receiving medical attention and being admitted to a teaching hospital if they develop this type of illness while working.

Analysis of the 26 unmarried student nurses who were the case-members of case-control pairs showed that all had thrombophlebitis of the lower extremity —of superficial veins in 5, deep in 21. Only 2 of these 26 cases had been using oral contraceptives, in contrast to 16 of 44 for the other unmarried cases. Hence, the relative risk if these student nurses were all excluded would increase from 4.4 to 4.6 (Table 9) and the bias produced by their inclusion tends to reduce the association of oral contraceptives with thromboembolism. The diagnosis was superficial thrombophlebitis of the lower extremity in about one-fourth of the medically-related cases, but only one-tenth of the remaining cases, indicating a tendency for milder cases to be admitted when they are either working in a hospital or in contact with medical people. This group included a physician, physicians' wives, physicians' secretaries, graduate nurses, licensed practical nurses, ward maids and others. It is also possible that some hospital jobs, which involve staying on one's feet for considerable periods, are conducive to thrombophlebitis of the lower extremities.

Although it was not desired to match cases and controls on religion, analysis showed that there was a tendency for the case and control members to be of the same faith more often than would occur by chance. This presumably resulted from both geographic factors and a trend toward selection of hospitals operated by church groups of the patient's faith. The effect of this inadvertent partial matching is speculative, but it is thought that if the contraceptive methods selected are related to the religion of the patient, as has been shown in analyses not included in this paper, and if oral contraceptives are associated with thromboembolism, then the relative risk will be underestimated, unless the analysis is kept specific for religious groups.

The absence of a significant difference in maximum weight between cases and controls does not indicate a lack of association between obesity and thromboembolism. Patients who were noted on the hospital record to be obese were disqualified for study. Furthermore, the cases and controls when interviewed were asked, not what they had weighed at admission, but what their maximum weight had been apart from pregnancy, and in what year; the maximum weight in many instances was reached several years before hospitalization.

Criticism has been voiced of some studies similar to this one, on the grounds that the final study group represented too small a proportion of the population of cases to be representative. In answer to such criticisms it is pointed out that while a large majority of hospitalized cases had one or another predisposing condition which led to their rejection, most of the women in the population who use oral contraceptives have none of them, and the aim of this study was to determine whether normal women are at risk. In the second place, finding a suitable control for a woman with a particular predisposing factor would present a great problem.

The question arises as to which component of the oral contraceptives is responsible for the intravascualr changes. Vessey and Doll were unable to detect any differences suggesting that one formulation carried more risk than another. This study indicated that the sequential products were more hazardous. Daniel and others in Cardiff, Wales (10) found that the suppression of lactation in puerperal woman by administration of the synthetic estrogen diethylstilbestrol was associated with an increased incidence of thromboembolism, at least among women over 25 years of age, as compared to puerperal women who were lactating. This was confirmed by Tindall (11) who reported that suppression by another estrogen, ethinyl estradiol, increased the incidence threefold. These findings, together with the known effects of estrogen on clotting mechanisms as summarized by Dugdale and Masi (12), suggest rather strongly that the estrogen is the more important agent involved in these adverse effects.

Even when the relative risk for oral contraceptive users has been established, it is necessary to estimate what proportion of initial attacks of idiopathic thromboembolism are attributable to oral contraceptives. This depends on the number of women who use the hormones and the level of incidence in non-users. The following approach was taken to make the estimate: the difference between the number of discrepant pairs in which the case only was a user, minus the number in which the control only was a user, was 57 minus 13, or 44. This may be considered an estimate of the actual number of individuals among the cases whose illnesses were attributable to the hormone. They constitute 44/175 or 25.1% of the total cases. This figure is of course subject to sampling error as well as the errors involved in the fact that the case series are not a probability sample of all the cases of thromboembolism in the community and the controls are not a probability sample of women in the same population. Nevertheless the estimate does give emphasis to the fact that the majority of cases of spontaneous, idiopathic thromboembolism, including many cases among hormone users, are not attributable to the hormones.

SUMMARY

A retrospective study of thromboembolism in females of reproductive age was conducted in five American cities. Cases were 175 women aged 15–44 discharged alive from 43 hospitals, after initial attacks of idiopathic thrombophlebitis, pulmonary embolism, or cerebral thrombosis or embolism. Idiopathic cases constituted only a small fraction of total thromboembolism patients. The 175 hospital controls were matched pair-wise with the cases on hospital, residence, time of hospitalization, race, age, marital status, parity and pay status. Both groups were free of chronic conditions either associated with thromboembolism or constituting contraindications to pregnancy, and were presumably fertile. They were interviewed to provide information on their use of oral contraceptives prior to hospitalization. Sixty-seven cases and 23 controls had used these products until within one month before they were hospitalized; 11 cases and controls had discontinued use earlier. Duration of use did not affect the risk. There were 57 case-control pairs in which only the case had used an oral contraceptive within one month compared to 13 in which only the control had done so. The relative risk of thromboembolism for the users is estimated to be 4.4 times that of nonusers. The risk was higher for users of sequential products. It is estimated that 25 per cent of the cases in this series were attributable to oral contraceptives.

ADDENDUM

The interesting observation has recently been made of a deficiency of patients in blood group 0 among cases of thromboembolism in women, and especially in women who were taking oral contraceptives, as compared to controls.[6] This difference in blood group distributions, although interesting, requires further substantiation and is not, in our opinion, large enough to warrant any modification in recommendations for administration of oral contraceptives at present.

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[6] Jick, H., Slone, D., Westerholm, B., Inman, W. H. W., Vessey, M. P., Shapiro, S., Lewis, G. P., and Worcester, J. Venous thromboembolic disease and ABO blood type. Lancet 1:539, 1969.

TABLE 1.—*Derivation of study group of interviewed cases of idiopathic thromboembolism*

Records abstracted at all hospitals	2,648
Rejected because of possibly predisposing condition	2,288
Rejected for other reasons [1]	99
Accepted as suitable cases; two controls chosen per case	261
Interview not obtained; case unavailable	56
Interview not obtained; case refused	16
Interview not obtained; neither control available	14
Case-control pairs interviewed	175

[1] Sterility (35), psychiatric diagnosis (11), unmarried (in first two cities studied) (25), living outside area where interviews held (7), deceased (9), other (12).

TABLE 2.—*Diagnostic classification of interviewed cases*

Thrombophlebitis of lower extremity:	
Superficial veins	27
Deep veins	81
Unspecified	7
Thrombophlebitis, other sites	4
Thrombophlebitis with pulmonary embolism	19
Pulmonary embolism	18
Intracranial (or carotid) vascular lesion	13
Retinal vascular lesion	6
Total	175

TABLE 3.—*Diagnostic classification of interviewed control patients*

Acute surgical condition	33
Elective surgical condition	92
Acute infection	20
Traumatic condition	11
Evaluation and diagnosis	14
Other	5
Total	175

TABLE 4.—DISTRIBUTION OF CASES AND CONTROLS WITH REGARD TO CHARACTERISTICS ON WHICH MATCHING OF CASE AND CONTROL PAIRS WAS DONE

	Cases	Controls
Marital status at hospitalization (matched):		
Married	105	105
Unmarried	70	70
Race (matched, from hospital record):		
White	[1] 149	150
Nonwhite	26	25
Location of hospital (matched by hospital):		
Baltimore	9	9
Washington	17	17
Philadelphia	41	41
New York City	83	83
Pittsburgh	25	25
Year of discharge from hospital (matched within 6 months in either direction):		
1964	16	16
1965	45	43
1966	54	59
1967	45	45
1968	15	12
Hospital pay status (matched):		
Private	31	32
Semi-private	108	110
Ward	34	32
Other	2	1
Age at time of hospitalization (matched to within 5 years):		
15–19	27	26
20–24	49	50
25–29	26	26
30–34	23	21
35–39	18	19
40–44	32	33
Reproductive events (including women unmarried at hospitalization) (matched by parity classes as follows: 0, 1–2, 3+):		
Mean number of pregnancies	1.81	1.81
Mean number of live births	1.51	1.53
Mean number of children living in household at hospitalization	1.34	1.35

[1] One control on interview was white contradictory to hospital records—matched on all other variables.

TABLE 5.—DISTRIBUTION OF CASES AND CONTROLS WITH REGARD TO SOME RELEVANT CHARACTERISTICS ON WHICH MATCHING WAS NOT ATTEMPTED

[Numbers in parentheses are exclusive of all pairs in which the thromboembolism case was a student nurse]

	Cases		Controls	
Total	175	(149)	175	(149)
Family Income:				
Under $4,000	19	(18)	17	(16)
$4,000 to $8,000	50	(48)	52	(47)
$8,000 to $15,000	61	(48)	67	(55)
$15,000 and over	42	(33)	32	(26)
Religion of patient:				
Protestant	66	(63)	59	(56)
Catholic	56	(47)	63	(53)
Jewish	47	(33)	44	(33)
Other, none or unstated	6	(6)	9	(7)
Education of patient:				
Less than 12 grades	28	(28)	32	(30)
High school completion	45	(43)	65	(59)
Some college	66	(43)	39	(26)
College completion, or post-graduate studies	36	(35)	39	(34)
Use of cigarettes prior to hospitalization:				
Nonsmoker	74	(63)	72	(61)
Less than ½ pack	17	(15)	20	(16)
About ½ pack	15	(13)	21	(16)
About 1 pack	55	(45)	42	(38)
About 2 packs, or more	14	(13)	20	(18)
Patient's maximum past weight:				
Under 120 pounds	22	(18)	27	(18)
120–159 pounds	110	(93)	115	(101)
160 and over	43	(38)	33	(30)
Employment status at hospitalization:				
Patient was working outside home	114	(88)	94	(74)
Patient not working	61	(61)	81	(75)
Patient (or husband) employed in a medical or hospital setting:				
Yes	77	(51)	36	(25)
No	98	(98)	139	(124)

TABLE 6.—METHODS OF CONTRACEPTION USED WITHIN 2 YEARS PRIOR TO ADMISSION [1]

	Cases	Controls
Oral contraceptives [2]	67	30
Condom	41	42
Diaphgram	40	34
Rhythm	21	14
Jelly, creams	19	9
Douche	11	11
Withdrawal	8	8
Other	18	15
Total women using one or more methods	114	101

[1] Many women had used multiple methods; hence, numbers in table not additive.
[2] Totals are smaller than in following tables because some women used the tablets for other than contraceptive purposes.

TABLE 7.—TIME OF LAST USE OF ORAL CONTRACEPTIVES PRIOR TO HOSPITALIZATION, FOR CASES AND CONTROLS WHO HAD USED THEM WITHIN 2 YEARS

	Cases	Control
Used up to admission	64	22
Discontinued within 1 month before admission	3	1
Discontinued 1 to 5 months before admission	4	5
Discontinued 6 to 11 months before admission	3	2
Discontinued 1 to 2 years before admission	3	4
Uncertain	1	0
Total	78	34

TABLE 8.—DURATION OF USE OF ORAL CONTRACEPTIVES WITHIN THE TWO YEARS PRIOR TO HOSPITALIZATION

	Last used product				All products			
	Cases		Controls		Cases		Controls	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Less than 1 week	3	3.8	0	----	2	2.6	0	----
1 week to 1 month	9	11.5	2	5.9	9	11.5	2	5.9
1 to 5 months	29	37.2	13	38.2	25	32.0	12	35.3
6 to 11 months	15	19.2	6	17.6	14	17.9	5	14.7
1 to 2 years	13	16.7	7	20.6	15	19.2	7	20.6
2 years	9	11.5	6	17.6	13	16.7	8	23.5
Total	78	99.9	34	99.9	78	99.9	34	100.0

TABLE 9.—PAIRWISE ANALYSIS OF USE OF ORAL CONTRACEPTIVES WITHIN ONE MONTH PRIOR TO ADMISSION ACCORDING TO VARIOUS ATTRIBUTES

Attribute	Total pairs	Used by both members	Used by case only	Used by control only	Used by neither	Relative risk [1]
		(a)	(b)	(c)	(d)	
Age:						
15–29	102	5	33	7	57	4.7***[2]
30–44	73	5	24	6	38	4.0**
Marital status:						
Married	105	8	41	10	46	4.1***
Unmarried	70	2	16	3	49	5.3**
Race:						
White	149	7	46	10	86	4.6***
Nonwhite	26	3	11	3	9	3.7
Location of hospital:						
Baltimore, Md., and Washington, D.C	26	2	9	4	11	2.2
Philadelphia, Pa	41	2	17	1	21	17.0***
New York City, N.Y	83	5	25	6	47	4.2**
Pittsburgh, Pa	25	1	6	2	16	3.0
Diagnosis:						
Thrombophlebitis, lower extremity, superficial	27	0	6	2	19	3.0
Thrombophlebitis, lower extremity, deep	81	4	22	5	50	4.4**
Thrombophlebitis, other	11	0	6	1	4	6.0
Thrombophlebitis and pulmonary embolism	19	3	4	3	9	1.3
Pulmonary embolism alone	18	2	12	1	3	12.0**
Retinal vascular lesion	6	0	0	1	5	----
Intracranial vascular lesion	13	1	7	0	5	7.0*
Total	175	[3] 10(10)	57(55)	13(12)	95(72)	4.4(4.6)***

[1] Computed as: $\frac{\text{number in which used by case only}}{\text{number in which used by control only}}$

[2] Probability, by chance alone, of a difference as great as or greater than that observed: *, less than .05; **, less than .01; ***, less than .001.

[3] Figures in parentheses are exclusive of pairs in which the case was a student nurse.

APPENDIX 1

LIST OF PARTICIPATING HOSPITALS WITH NAMES OF LIAISON PHYSICIANS, NUMBER OF RECORDS ABSTRACTED AND NUMBER OF ACCEPTABLE CASES OF THROMBOEMBOLISM FOUND [2]

Hospital	Liaison physician	Records abstracted	Cases found
Baltimore:			
1. Johns Hopkins Hospital [3]	Dr. Russell Nelson		
2. Union Memorial Hospital	James B. Brooks, M.D	25	5
3. Sinai Hospital of Baltimore	Albert I. Mendeloff, M.D	36	6
4. University Hospital	Robert Schultz, M.D	30	1
5. Baltimore City Hospital	Julius Krevan, M.D	31	0
Washington, D.C.:			
6. George Washington University Hospital	James Sites, M.D	36	7
7. Georgetown University Hospital	John F. Stapleton, M.D	45	2
8. Washington Hospital Center	Frederick W. Wolfe, M.D	75	10
9. Washington Sanitarium and Hospital	Mr. H. Stuart Nelson	34	31
Philadelphia:			
10. Philadelphia General Hospital	John P. Emich, Jr., M.D	73	2
11. Pennsylvania Hospital	Lennard L. Weber, M.D	76	8
12. Temple University Hospital	Russell R. de Alvarez, M.D	107	5
13 Jefferson Medical	Abram S. Benenson, M.D	106	17
14. Hahnemann Medical Center	Marshall Kalvan, M.D	43	2
15. Woman's Medical College	Elsie R. Carrington, M.D	10	0
16. Hospital of the University of Pennsylvania	Celso-Ramon Garcia, M.D	97	12
17. Lankenau Hospital	Angelo P. Angelides, M.D	29	2
18. Albert Einstein Medical Center	Mr. Bertram Zimmerman	103	10
New York City:			
19. New York Hospital (Cornell)	Ellen McDevitt, M.D	121	7
20. Columbia-Presbyterian Hospital	Karlis Adamsons, M.D	157	6
21. St. Luke's Hospital	Harold M. Tovell, M.D	72	10
22. Roosevelt Hospital	Ralph Gause, M.D	54	4
23. New York University Hospital	Stanley Zinberg, M.D	81	7
24. Long Island Jewish Hospital	Alexander H. Rosenthal, M.D	61	4
25. Jewish Hospital of Brooklyn	Morton A. Schiffer, M.D	36	13
26. Maimondes Medical Center	William Pomerance, M.D	64	
27. Methodist Hospital of Brooklyn	Allan C. Clemetson, M.D	31	1
28. Coney Island Hospital	Alosi Vasicka, M.D	21	4
29. City Hospital at Elmhurst	Joseph J. Rovinsky, M.D	22	2
30. Queens Medical Center	William A. D'Angelo, M.D	31	3
31. Kings County Medical Center	Schuyler G. Kohl, M.D	134	10
32. Mt. Sinai Hospital	Joseph J. Rovinsky, M.D	20	5
33. Bronx Lebanon Hospital (Concourse)	Edward E. Fischel, M.D	7	0
34. Albert Einstein College of Medicine	Seymour L. Romney, M.D	19	4
35. Montefiore Hospital	Tiffany Lawyer, M.D	24	3
36. St. Vincent's Hospital	Bernard Pisani, M.D	73	9
37. Brooklyn Hospital	Vincent Tricomi, M.D	12	0
38. Beth Israel Hospital	George Blinick, M.D	84	24
39. Bronx Municipal—Jacobi	Seymour L. Romney, M.D	18	1
40. Lenox Hill Hospital	H. R. Barber, M.D	37	5
41. Bronx Lebanon Hospital—Fulton	Edward E. Fischel, M.D	16	2
Pittsburgh:			
42. Mercy Hospital	(1)	88	7
43. Shadyside Hospital	(1)	70	5
44. Montefiore Hospital	(1)	61	7
45. Magee Woman's Hospital	(1)	69	3
46. Presbyterian-University Hospital	(1)	84	10
47. St. Francis General Hospital	(1)	60	2
48. Western Pennsylvania Hospital	(1)	65	4

[1] Dr. John C. Cutler, Chairman, Population Division, Graduate School of Public Health, University of Pittsburgh, assumed this responsibility in this city.

[2] In Baltimore and Washington, only married women were accepted. This list exceeds the number of case-control pairs reported in this paper because some cases, or their controls, could not be interviewed.

[3] Johns Hopkins Hospital was utilized for the pilot trial, and the cases secured are not included in the tabulations reported n this paper.

APPENDIX 2

ORAL CONTRACEPTION FORMULATIONS USED WITHIN ONE MONTH PRIOR TO ADMISSION, BY NUMBER OF CASE AND CONTROL USERS WHO COULD IDENTIFY SPECIFIC PRODUCT USED

Content of				No. of use	
Estrogen	mg.	Progestogen	mg.	Case	Controls
Sequential products: [1]					
Mestranol	.08	Chlormadinone	2	8	0
Ethinyl estradiol	.1	Dimethisterone	25	5	0
Mestranol	.08	Norethindrone	2	2	0
Combinations: [2]					
Mestranol	.1	do	2	14	9
Do	.1	Norethynodrel	2.5	14	1
Do	.075	do	5	5	2
Do	.1	Ethynodiol acetate	1	4	3
Ethinyl estradiol	.05	Norethindron acetate	2.5	3	4
Mestranol	.05	Norethindrone	1	3	2
Do	.06	do	10	2	1
Do	.15	Norethynodrel	9.85	2	1
Ethinyl estradiol	.05	Medroxyprogesterone acetate	10	1	0

[1] Estrogen administered for 20 or 21 days, estrogen plus progestogen for 5 days.
[2] Administered for 20 or 21 days.

References

1. Ad Hoc Committee for the Evaluation of a Possible Etiologic Relation of Enovid with Thromboembolic Conditions: Final Report on Enovid, Sept. 12, 1962
2. Advisory Committee on Obstetrics and Gynecology, Food and Drug Administration: Report on the Oral Contraceptives, Aug. 1, 1966. U.S. Govt Printing Office, Washington, D.C.
3. Clinical Aspects of Oral Gestogens. Report of a WHO Scientific Group. WHO Tech. Report Series No. 326, Geneva, 1966.
4. Royal College of General Practitioners: Oral Contraception and Thromboembolic Disease. J. Coll Gen Pract, *13:* 267–279, 1967
5. Inman, W. H. W. and Vessey, M. P. Investigation of Deaths from Pulmonary Coronary and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age, Brit Med J, *2:* 193–199, 1968
6. Vessey, M. P. and Doll, R. Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. Brit Med J, *2:* 651–657, 1969
7. Drill, V. A. and Calhoun, D. W. Oral Contraceptives and Thromboembolic Disease. JAMA, *206:* 77–84, 1968
8. Doll, R., Inman, W. H. W. and Vessey, M. P. "Concerning the British Data" (letter to the editor). JAMA, *297:* 1150–1151, 1969
9. Ryder, N. B. and Westoff, C. F., Use of oral contraception in the United States, 1965, SCIENCE, *153:* 1199, 1966
10. Daniel, D. G., Campbell, H. and Turnbull, A. C. Puerperal Thromboembolism and Suppression of Lactation. Lancet, Aug. 5, 1967, p. 287–289
11. Tindall, V. R. Factors Influencing Puerperal Thrombo-embolism J Obstet Gynaec Brit Comm, *75:* 1324–1327, 1968
12. Dugdale, M. and Masi, A. T. Blood clotting effects of the oral contraceptives *IN* Report on the Oral Contraceptives, Advisory Committee on Obstetrics and Gynecology, Food and Drug Administration, 1969 (in press)

B. TRENDS IN MORTALITY FROM THROMBOEMBOLIC DISORDERS

Philip E. Sartwell, M.D. and Charles Anello, Sc. D.

Mortality rates for thromboembolism have been examined for the main purpose of ascertaining whether these rates have changed in a way consistent with an effect of oral contraceptive use. A second purpose of this report is to

call attention to the dramatic increase in the rates for both males and females. Mr. Dean E. Krueger of the National Office of Vital Statistics has kindly made available the death rates discussed in this report.

All deaths of females aged 15 to 49 in the U.S. in the single year 1961 attributed to these causes were studied in order to establish with what other diseases they were linked. A list of decedents whose deaths had been coded to I.C.D.[1] numbers 463 (thrombophlebitis of the lower extremity), 464 (thrombophlebitis of other sites), and 465 (pulmonary embolism) was provided by Mr. Krueger. Other conditions listed on the death certificates were shown on the listing.

Deaths certified as having thrombophlebitis of the lower extremity (I.C.D. 463) as the underlying cause almost always bore mention on the certificate of pulmonary embolism as the immediate cause. A great variety of other conditions were listed on about half the certificates, and many of them are recognized as predisposing to thromboembolism. There were no cases that appeared from the evidence on the certificates to be misclassified in the sense of being properly attributable to surgical procedures, trauma, or childbirth; but in the numerous certificates that classified thrombophlebitis as the underlying cause and mentioned such conditions as subacute bacterial endocarditis, rheumatic heart disease, or carcinoma with metastases, the appropriateness of listing thrombophlebitis as the underlying cause may be questioned.

Deaths with thrombophlebitis of other sites (I.C.D. 464) as the underlying cause likewise had pulmonary embolism or infarction generally listed as the immediate cause. The site of thrombophlebitis was frequently the pelvic veins. Other conditions were listed on the certificate much more often than in the case of thrombosis of the lower extremity, and certificates that did not bear one or more other diseases were the small minority. Some certificates were clearly in error, the proper diagnosis being carcinoma, heart disease, blood dyscrasias, trauma, surgery or some other underlying condition. This group was less satisfactory as a series of primary vascular disease than I.C.D. 463.

Under I.C.D. 465, pulmonary embolism and infarction, thrombophlebitis was almost never mentioned on the certificate. About two-thirds of these cases had some other condition listed and in many instances, again, they would be considered as predisposing to thromboembolism. This class is considered to include patients presumed to have a thrombosed vein but without evidence of its site.

Among the more commonly mentioned conditions in association with all three diagnoses were pneumonia, obesity, diabetes, carcinoma, sepsis, prior surgery, rheumatic heart disease, and arteriosclerotic heart disease.

It is concluded that I.C.D. rubric number 463 is the most satisfactory of the three for study of trends of thromboembolism, but even this rubric probably includes some cases that are erroneously charged to thromboembolism by the certifying physician and it certainly includes many with well-recognized predisposing conditions.

For the initial analysis of mortality, the annual rates for each of these diseases (I.C.D. 463–465) as well as I.C.D. 466 (other venous thrombosis and embolism) in the United States were utilized for the period 1960–1966 inclusive, and for five 10-year age classes covering the span from 15 to 65, separately for white males and females. The rates increase approximately logarithmically with age over this age span, and somewhat more steeply in males, in such fashion that the male rates are lower in the youngest age groups and higher in the oldest age groups.

There is also an increase in rates with time, for all age-sex classes. This increase was approximately linear when plotted on semilogarithmic paper; that is, the increase was roughly logarithmic. Therefore, it was decided to take the natural logarithms of the rates and calculate the regression coefficients, fitting the regressions by the method of least squares. These regression coefficients ("b") and their standard errors are shown in Table 1 for the four combined thromboembolic conditions. All the 10 values are positive, indicating an upward trend with time, and all are significantly different from zero at a probability level of 0.05 or less, indicating that the increases are real in a statistical sense.

Comparisons were next made between the slopes for males and females in each age class. For two classes (15–24 and 55–64) the increase in rates for

[1] International Statistical Classification of Diseases, Injuries, and Causes of Death.

males was greater than for females; in the other three age classes the female slopes were steeper than the male, and the differences were somewhat larger. However, statistical significance at the conventional level ($p<.05$) was not reached for any age class (Table 2).

The use of oral contraceptives has rapidly increased since 1960 having become extensive around 1962. Therefore the data were examined to ascertain whether there had been a change in the slope at that time. Two periods were chosen: one of six years, 1956–1961; and one of five years, 1962–1966 (designated 1 and 2 respectively). Regression coefficients were calculated separately for each period in the same fashion as for Table 1 (Table 3).

For males, the slope increased in the second period in two of the five age classes, and for females, in four of the age classes (all except the oldest). The magnitude of the increases among females in the second time period is greater than that for males (and greater than that for the first time period), for the three age classes between 25 and 54. Although all the coefficients are positive, they are not significantly different from zero except in the oldest age classes (because of the short periods over which the regressions were computed), and most of the differences by sex are nonsignificant.

Mortality data for pulmonary embolism (I.C.D. 465) were examined separately by the same method for the period 1960–1966. As Tables 4 and 5 will show, these rates also increased significantly over the seven-year span, for both sexes. The rate of increase was greater for females than for males in all age classes studied except the youngest, but most of the differences were not statistically significant. Since the number of deaths from this one cause in the younger age classes is quite small, the failure to show a significant difference could be a consequence of the large sampling error.

In our opinion, these findings are consistent with the hypothesis that oral contraceptives have produced a small increase in the mortality from thromboembolism, but they do not add any great support to it.

Grounds for deciding whether the increases are wholly the result of changes in certification practice by physicians are lacking at the present time. If the increases are in part real, we should be looking for changed environmental factors that may be producing them.

In an endeavor to see whether they are related to oral contraceptives, two analyses of mortality trends have been published. The first, by Vessey and Weatherall (2), examined British statistics for deaths from peripheral, venous thrombophlebitis and pulmonary embolism. There has been an upward trend in both sexes, with a distinct suggestion of an acceleration in females at reproductive ages since these agents came into wide use. They concluded that this evidence was consistent with the hypothesis.

Markush and Seigel (1) have published a detailed analysis of mortality trends within the United States. Their conclusions also substantiate a possible association between oral contraceptive usage and increased mortality from thromboembolism. Both the British and American groups of researchers employed techniques of study similar to those described in this report.

In summary, recorded mortality rates for thromboembolic diseases in the United States at ages 15–64 have been increasing among both white males and white females. The rate of increase is greater for females than males. The increase was accelerated in the period 1962–1966 as contrasted with 1956–1961. These facts are consistent with the hypothesis that an increasing use of oral contraceptives is responsible for some of the thromboembolic mortality. However, because of the difficulty in diagnosis of these diseases and the possibility of changes in the practice of certifying underlying causes of death, we do not regard these findings as strong evidence for the hypothesis.

TABLE 1.—TREND OF MORTALITY FROM VENOUS THROMBOEMBOLISM (I.C.D. NUMBERS 463–466) FOR WHITE PERSONS AGED 15–64, UNITED STATES, 1960–66.

Age class	Sex	Regression coefficient [b]	Standard error of [b]	Pr (b=o)
15 to 24	M	+.1111	.0367	<.05
	F	+.1100	.0266	<.01
25 to 34	M	+.0577	.0211	<.05
	F	+.1092	.0254	<.01
35 to 44	M	+.0635	.0199	<.025
	F	+.1264	.0223	<.005
45 to 54	M	+.0483	.0122	<.025
	F	+.0724	.0168	<.01
55 to 64	M	+.0630	.0071	<.001
	F	+.0452	.0095	<.01

NOTE.—Regression coefficient b: numbers in this column represent values of b in the equation $y_t = a\, e^{bt}$, where:
t+year (from 1960 as tr)
y_t=death rate in year t
a=death rate when t=o
e=natural base of logarithms

The regression coefficient expresses the slope of the increase or decrease in rates, values with a positive sign indicating increase; b x 100 is approximately the percent increase per year. All the values of b in this series are positive. Pr (b=o) expresses the probability that a change as great as, or greater than, that observed would occur by chance alone. A two-tailed test was employed, using the F statistic with 1 and 5 degrees of freedom. 1F Pr (b=o) is less than .05, as it is in all this series, the slopes are significantly greater than zero.

TABLE 2.—DIFFERENCES IN SLOPES (B) BETWEEN FEMALES AND MALES, AND THEIR STANDARD ERRORS (FOR I.C.D. 463–466)

Age class	Difference in slope (f–m)	Standard error of difference
15 to 24	−.0011	.0453
25 to 34	+.0515	.0330
35 to 44	+.0629	.0299
45 to 54	+.0241	.0208
55 to 64	−.0178	.0119

TABLE 3.—TRENDS OF MORTALITY FROM THROMBOEMBOLIC CONDITIONS FOR 2 PERIODS, BY SEX AND AGE CLASS: WHITE PERSONS, UNITED STATES

Age class	Sex	Time period	Regression coefficient b	Standard deviation	Intercept ln a
15 to 24	M	1	.02	.09	.33
		2	.16	.06	.29
	F	1	.05	.02	.65
		2	.13	.05	.99
25 to 34	M	1	.03	.01	1.22
		2	.02	.03	1.62
	F	1	.06	.02	1.5e
		2	.11	.05	2.00
35 to 44	M	1	.03	.03	2.34
		2	.03	.02	2.67
	F	1	.04	.03	2.19
		2	.14	.02	2.52
45 to 54	M	1	.06	.02	3.34
		2	.04	.02	3.71
	F	1	.06	.01	3.03
		2	.12	.01	3.25
55–64	M	1	.06	.02	4.31
		2	.08	.07	4.56
	F	1	.08	.02	3.90
		2	.04	.01	4.30

Time Periods: 1: 1956–1962 2: 1962 1966. Logarithmic regression.

TABLE 4.—TREND OF MORTALITY FROM PULMONARY EMBOLISM AND INFARCT (I.C.D. NUMBER 465) FOR WHITE PERSONS AGED 15–64 BY SEX, UNITED STATES, 1960–1966.

Age class	Sex	Regression coefficient b	Standard error of b	Pr (b=o
15 to 24	M	+.1393	.0428	<.025
	F	+.1132	.0386	<.05
25 to 34	M	+.0340	.0183	N.S.
	F	+.1340	.0374	<.025
35 to 44	M	+.0855	.0157	<.005
	F	+.3119	.0225	<.005
45 to 54	M	+.0756	.0206	<.025
	F	+.0951	.0244	<.025
55 to 64	M	+.0690	.0148	<.02
	F	+.0753	.0116	<.005

See footnote to table 1 for interpretation of b and Pr (b=o).

TABLE 5.—DIFFERENCES IN SLOPES (B) BETWEEN FEMALES AND MALES, AND THEIR STANDARD ERRORS, FOR I.C.D. 465 (PULMONARY EMBOLISM AND INFARCT)

Age class	Difference in slope (f—m)	Standard error of difference
15 to 24	−.0011	.0453
25 to 34	+.0515	.0330
35 to 44	+.0629	.0299
45 to 54	+.0241	.0208
55 to 64	−.0178	.0119

References

1. Markush, R. E. and Seigel, D. G. Oral Contraceptives and mortality trends from thromboembolism in the United States. Amer J Pub Health 59:418, 1969.
2. Vessey, M. P. and Weatherall, J. A. C. Venous thromboembolic disease and the use of oral contraceptives. Lancet 2:94, 1968.

C. Trends in Mortality from Cerebrovascular Diseases

Gerald R. Greene, M.D.

The temporal analysis of cerebrovascular mortality consisted of a comparison of trends and ratios of white male and female death rates from these causes singly and combined (rubrics 330–334) from 1956 through 1966. Five ten-year age groups (15–64) were studied over this period. Numbers of deaths attributed to specific causes were taken from the annual publications of mortality data for the United States.

Oral contraceptives came into general use in 1961 and their use increased rapidly thereafter. If they are causing some of the deaths from cerebrovascular disease, female death rates from this cause might have risen more sharply than male death rates in the child-bearing age range, depending upon the independent factors affecting male mortality from these causes. However, no specific classification exists for death from these conditions occurring during pregnancy or the puerperium. Thus, if such deaths are included in the rubrics studied, a rise in the female death rates directly attributable to the oral contraceptives may be concealed by a falling birth rate and a decrease of central nervous system complications attributable to pregnancy and the puerperium.

Mortality from these combined causes (rubrics 330–334) declined over the ten-year period, as did intracerebral hemorrhage (rubric 331), which forms the majority of all deaths from this group. Rates in the age group 25–34 became higher for females than for males in 1965 and 1966 for the first time. This crossover is possibly significant if one assumes that deaths from cerebral embolism or thrombosis are often misclassified as other cerebrovascular deaths and may have been included in the rubric 331.

Death rates resulting from subarachnoid hemorrhage (rubric 330) rose

steeply and steadily for both males and females in the three age groups 35–44, 45–54, and 55–64 over the ten-year period. The rise in mortality from this cause was greater in females than males for all but the 15–24 year age group, in which there was little or no rise. No explanation for this finding is readily available.

In the lower two age groups, death rates from cerebral embolism and thrombosis (rubric 332) fluctuated widely with no definite trends. The actual number of deaths at these ages was very small, such that an excess of five to ten deaths from one year to the next caused a large relative increase in the death rate. In the older three age groups, death rates from cerebral embolism and thrombosis were stable from 1956–66 with the male rate uniformly higher than the female rate. The lack of a rise in female deaths at reproductive ages from cerebral embolism and thrombosis fails to support an association between the use of oral contraceptives and these conditions, barring the possible concealment of an effect by a lowering of pregnancy rates, as suggested above.

It is possible that such deaths are often coded to other cerebrovascular causes or that the frequency of fatal cerebrovascular complications of oral contraceptive use is so low in relation to other cerebrovascular diseases as not to be evident in mortality statistics. In any case, the analysis of these data does not warrant any conclusions regarding the influence of oral contraceptives on cerebrovascular mortality.

D. Effects of the Oral Contraceptives on Blood Clotting

Marion Dugdale, M.D. and Alfonse T. Masi, M.D., Dr. P. H.

Hemostasis can be thought of as occurring in stages: initial control of bleeding, which is effected by platelets; secondary control of bleeding, which is a function of clotting; and clot removal by fibrinolysis as the tissue heals. The concept of hypercoagulability arose as a natural outgrowth of clinical situations characterized by the inappropriate formation of intravascular clots. Its definition on laboratory grounds has proved more difficult.

Using the above outlined concept of normal hemostasis, it is logical to think that intravascular clot formation could arise because of excessive platelet adhesiveness of aggregability, an increased tendency of blood to clot, or insufficient removal of fibrin because of inadequate fibrinolysis. This approach has been used by numerous investigators in the study of clinical hypercoagulability. The processes of intravascular clot formation in arteries and veins are different. Platelet adhesion to damaged endothelium (or foreign surfaces) appears to initiate the formation of an arterial thrombus; in veins, clotting plays the major role. Both arterial and venous thromboses have been attributed to the use of oral contraceptives.

A large number of reports is available, describing the results of investigations of the coagulation and fibrinolytic system. A smaller number of reports deals with aspects of platelet function. The present report attempts to summarize these studies, which cover observations made by 41 investigators on about 1000 patients receiving oral contraceptives. Approximately 412 patients were studied during the first three cycles (short term group); 530 women were studied after more than 3 months of cyclic oral contraception (long term group). These results are compared with studies of hemostasis in approximately 650 pregnant women and on smaller groups receiving either estrogens (165 subjects) or progestins alone (104 subjects).

Since these reports come from widely scattered laboratories, methods have varied greatly, particularly in studies of the fibrinolytic system. The reviewers have attempted to group together comparable tests even though the methods used may have differed. Readers are referred to the original articles for methodologic details.

In all articles selected for this review there was an adequate number of appropriate control subjects. In all the tables the results will be given in terms of change from normal based on the normal values given by each investigator.

PLATELETS

In Table 1 we have summarized the rather scanty data on platelet number and function. Adhesion and aggregation, which are pertinent to the problems of arterial thrombus formation, deserve most attention.

The *in vitro* tests have been grouped under three headings: tests in which

adhesion to a foreign surface precedes aggregation, tests in which aggregation is produced directly by chemical means, and electrophoretic responses of platelets exposed to aggregating agents. The bleeding time is an *in vivo* measurement of platelet adhesiveness and aggregability.

These data may be summarized as follows:

Short-term use of oral contraceptives appears to have little effect on platelate except for altering their electrophoretic mobility. The physiological significance of this observation is unknown. Long-term use, in addition to changing the electrophoretic mobility, produces a rise in the platelet count in two-thirds of the users, and may increase the ability of the platelets to adhere to foreign surfaces.

Pregnancy seems to have little effect on platelets except, however, some studies demonstrate increased aggregability.

Administration of estrogens, particularly the synthetic forms, increases the responsiveness of platelets to aggregating agents. Capillary resistance, on the other hand, is increased by natural (Premarin) but not by the synthetic estrogens.

Progestins have no effect on platelet count or function.

The number of observations on platelet function is too small to permit any definite conclusions. The estrogenic component of oral contraceptives, however, may have an effect on platelets that favors the development of platelet aggregates *in vitro*, and presumably *in vivo* also.

CLOTTING

There is a considerable quantity of data pertaining to clotting in patients receiving oral contraceptives, as presented in Tables 2 and 3. For comparison, data are presented on clotting in pregnancy and in persons receiving estrogens or progestins alone.

The clotting tests fall into three groups: those that measure the unaided coagulation of the blood (clotting time, prothrombin consumption test, and thromboplastin generation test); those that measure coagulation in the presence of an excess of a procoagulant (the prothrombin and partial thromboplastin times); and those that measure activity of specific factors (the P & P test and the factor assays). The first two groups measure the speed at which blood clots and they might, therefore, shed some light on the question whether thrombosis is a result of rapid clotting. The factor assays, on the other hand, measure amount of potential coagulant activity. It has not yet been shown that an increase above usual levels in concentration of a procoagulant factor makes blood clot with greater ease or that it causes thrombosis.

Examination of the data on oral contraceptives shows that some changes from normal are evident soon after initiation of treatment with these agents. Other changes appear or become prominent only after several months of treatment. Early changes indicate an increased rate of clotting: the clotting time (and its variants) and the Prothrombin Consumption tests show rapid coagulation in about 20 to 25 per cent of the patients. With prolonged treatment the proportion of patients showing rapid clotting increases to about 35 per cent in these tests. A similar acceleration of clotting is seen in the Prothrombin and Partial Thromboplastin Times. The TGT, a more sensitive test, detects rapid clotting in about 66 per cent of the patients early in treatment. This number does not change with prolonged use of oral contraceptives.

The changes in pregnancy must be more subtle, since they are detected only in the TGT and PTT but also indicate increased rate of clotting. Data on the estrogens and progestins are scanty, but they suggest that progestins and natural estrogens do not accelerate clotting, whereas synthetic estrogens do.

Data pertaining to concentration of clotting factors during use of oral contraceptives show that some factors begin to increase promptly. A rise in concentration of fibrinogen occurs in about one half of the women. About one fourth show an increase in factor VIII, about three fourths in factors II and IX, and all in factor XII. Long-term use does not change in the proportion of patients showing these increases. With factors VII and X the rise in activity is slower. Both factors are increased in only one half of women early in therapy but after more than 3 cycles, virtually all women have high levels of activity. The levels reached do not appear to exceed those seen in pregnancy (28, 47). Factors XI and XIII and probably V are not affected by use of oral contraceptives. Once these changes have occurred there is no cyclic fluctuation.

The changes in pregnancy are not exactly comparable. Factors I and VII invariably rise from the outset. Factors VIII and X rise during the second and third trimesters in almost all women. Factor IX increases in about half the patients and factor II shows a slight rise in somewhat less than half. Factors V and XII show no change, and factor XIII decreases.

The data on effect of progestins alone are very scanty, but it is noteworthy that they have not been shown to alter the levels of factors I, VII, and X, all of which are increased by oral contraceptives. There are essentially no data of this type on the effect of estrogens.

FIBRINOLYSIS

Data pertaining to fibrinolysis are summarized in Table 4. The effect of oral contraceptives appears somewhat uncertain and a clear pattern does not emerge. Activator levels rise in all women after several months of use of these drugs, and the euglobulin clot lysis time falls in about half, suggesting increased fibrinolysis. The associated fall in plasminogen expected in such a state does not occur, however. Instead, an increase in plasminogen is seen in about two-thirds of the patients.

The pattern in pregnancy is much clearer, demonstrating hypoactivity of the fibrinolytic system with long euglobulin clot lysis time, decreased activator, increased antiplasmins, and increased plasminogen levels.

The data on estrogens are so scanty and inconsistent that no conclusions are warranted.

Progestins clearly enhance fibrinolysis although additional data on the components of the fibrinolytic system would be helpful.

SUMMARY AND CONCLUSIONS

The data as a whole are presented in condensed form in Table 5. If these data are examined in the light of our initial assumptions about the roles of platelets, coagulation and fibrinolysis in thrombus formation, we may form some tentative conclusions. Pregnant women appear to be in danger of inappropriate intravascular clotting, in that coagulation rate and potential are increased while fibrinolysis is depressed. On the other hand, the women using oral contraceptives is in a more balanced state in that coagulability is increased, but so is fibrinolysis.

Clinical experience, however, suggests that the opposite is the case, that is, pregnant women have little problem with thromboembolic disorders, whereas users of oral contraceptives have excessive disease of this type. Perhaps the explanation lies in the platelets. Platelets are little affected by pregnancy, whereas the steroid contraceptives increase their number and possibly their tendency to adhere and clump. The increased arterial thrombosis with oral contraceptives could be explained on this basis, although the increased incidence of venous thrombosis might not be so explained. The answer may well lie elsewhere, for example, in changes in the endothelium and vessel wall and in slowing of blood flow.[2]

With regard to the relation of composition of the oral contraceptives to their effect, the estrogen appears to predispose to enhanced platelet function and the acceleration of clotting, while the progestin leads to increased fibrinolytic activity. The amount of each component does not clearly affect the outlook. A few studies comparing the effects of high-dose and low-dose oral contraceptives did not show any great differences in platelet function, coagulation, or fibrinolysis between the two groups (37, 46, 53). There do not appear to be any differences in the thromboembolic effects of sequential and oral contraceptives other than those reported by Sartwell (Appendix 2A).

The changes brought about by the oral steroids are not immediately reversible upon discontinuing the drugs (2, 8, 22). One to several weeks are required for return to the normal pattern.

Among the 1000 patients surveyed, two developed thrombotic episodes: one fatal pulmonary embolus (1) and one cerebral artery oclusion (8). It may be significant that the first patient was paraplegic, and that platelets in the second showed a greater alteration in reactivity than in all other patients studied.

[2] See Reference 68, Appendix 4.

TABLE 1.—EFFECT OF ORAL CONTRACEPTIVES, PREGNANCY, ESTROGEN, AND PROGESTERONE ON PLATELET NUMBER AND FUNCTION [1]

	O.C.—short term	O.C.—long term	Pregnancy—all trimesters	Estrogens—<17 days. Natural (premarin) or synthetic	Estrogens—>1 month; synthetic only	Progestogens
Number of platelets	No change 75 (12, 16, 19, 22, 23) increased 3 (2).	No change 34 (28, 38, 58) increased 69 (2, 35, 69).	No change 64 (14, 28, 37, 51, 65).	No change 8+? (9, 45) decreased ? (24).	No change 50 (15)	No change ? (24) increased ? (24).
Bleeding time	No change 19 (36) prolonged 3 (2).	No change 10 (28) prolonged 3 (2).	No change 18 (28, 51).	No change 8 (9)	Decreased 13 (18)	
Adhesion (glass or latex)	No change 35 (38, 53)	No change 23 (28, 38) increased 12 (16).	No change 18+? (28, 37, 68).	No change 17 (9, 25) increased 25 (7).		No change 3 (8).
Aggregation: Response to ADP, noradrenalin, etc.		No change 10 (28)	Increased 3 (8) no change 13 (8, 28).	ADP: Increased 9 (25) Noradr: increased 9 (25).		No change 79 (8, 24).
Electrophoretic: Response to ADP, noradrenalin, etc.	Abnormal 3 (8)	Abnormal 9 (8)		ADP: No change p premarin; abnormal p synthetic 9 (25) Noradr: Min. change p premarin; abnormal p synthetic 9 (25).		
Capillary fragility				Decreased 30+? (17, 45, 59).	See footnote [2]	

[1] The number of patients is given for each result, followed by the references (in parenthesis) from which these values were obtained. ? indicates that no. of patients studied is not given by the authors.
[2] In scorbutic guinea pigs administration of natural, but not of synethetic estrogens, reduced the occurrence of spontaneous hemorrhage and decreased capillary fragility. 113 animals (27, 56).

TABLE 2.—EFFECT OF ORAL CONTRACEPTIVES, PREGNANCY, ESTROGEN AND PROGESTERONE ON COAGULATION TESTS

	O.C.—short term	O.C.—long term	Pregnancy—all trimesters	Estrogens—<17 days. Natural (premarin) or synthetic	Estrogens—>1 month; synthetic only	Progestogens
Clotting time and recalcification time.	No change 114 (1, 6, 14, 38, 64) decreased 39 (2, 13, 36).	No change 133 (1, 38, 64, 69) decreased 65 (2, 13, 35).	No change 39 (14, 37, 51) prolonged 11 (2).	Premarin—No change 8 (9) synthetic—decreased 10 (57).	Decreased 13 (18)	Decreased 10 (57) no change 76 (48).
Prothrombin consumption	No change 91 (36, 44) Increased 23 (2, 53).	No change 105 (28, 44, 49, 69) increased 63 (4, 59).	No change 25 (28, 37)		Increased 13 (18)	
T.G.T	No change 25 (14, 53) accelerated and increased 49 (2, 11, 13).	No change 40 accelerated and increased 75 (2, 13, 28, 35) decreased 11 (58).	No change 16 (14) Accelerated and increased 49 (2, 28, 67) (occurs in 2d and 3d trimesters).			
Prothrombin time	No change 243 (1, 6, 14, 23, 36, 46, 47, 56) decreased 49 (2, 11, 13).	No change [1] 383 (1, 29, 46, 47, 49, 56, 66, 69) decreased 103 (13, 35, 61, 62).	No change 142 (14, 46, 47, 56) decreased 15 (65).	Premarin—No change 8 (9) synthetic—decreased 10 (57).	No change 50 (3)	No change 83 (11, 66) decreased 10 (57).
Partial Thromboplastin time.	No change 224 (1, 36, 46, 47, 56, 64) decreased 53 (11, 23, 53).	No change 331 (1, 29, 46, 47, 49, 56, 64, 66, 69) decreased 91 (46).	No change 7 (56) decreased 134 (10, 46, 47).	Premarin—No change 8 (9).		No change 83 (11, 66).

[1] Decrease became apparent only after plasma had been stored. 42(61,62).

TABLE 3.—EFFECT OF ORAL CONTRACEPTIVES, PREGNANCY, ESTROGEN AND PROGESTERONE ON COAGULATION FACTOR ASSAYS

	O.C.—short term	O.C.—long term	Pregnancy	Estrogens 17 days natural or synthetic	Estrogens 1 month	Progestogens
I. Fibrinogen	No change 27 [1] (2, 6, 23, 64), increased 71 (22, 36, 38).	No change 120 (2, 35, 49, 64), increased 61 (3, 12, 22, 28, 38).	Increased 276 (10, 21, 22, 26, 29, 31, 33, 37, 41, 51, 65, 67) (rise starts in 1st trimester).	Increased 8+? (14, 58), variable 8+? (33, 42), decreased 25 (7).	----------	No change 8+? (33, 42).
II. Prothrombin	No change 34 (6, 23, 36), increased 103 (13, 22, 28, 38, 42, 56).	No change 82 (35, 49, 69), increased 166 (3, 13, 22, 28, 29, 38, 56).	No change 94 (22, 39, 65, 67), slight increase 42, (2, 29, 31, 51, 56).	No change 8 [2] (9)		
V	No change 154 (2, 6, 11, 13, 22, 23, 24, 36, 53), questionable increase 49 (38, 56).	No change 93 (2, 13, 22, 29, 49, 58, 69), questionable increase 152 (35, 38, 56, 69), decreased 10 (28).	No change 150 (28, 29, 31, 37, 39, 51, 56, 65, 67), slight increase 11 (2).	No change 8 [2] (9)		
VII	No change 123 [1] (6, 34, 46, 47, 53), increased 140 (11, 13, 22, 23, 38, 56).	Increased 433 (13, 22, 28, 29, 35, 38, 46, 47, 56, 58, 66).	Increased 240 (2, 22, 29, 31, 39, 47, 51, 56, 65, 67) (rise starts in 1st trimester).	----------	----------	No change 76 (48).
VIII	No change 170 (1, 6, 22, 34, 47, 53), increased 65 (23, 36, 38, 56), variable 4 (2).	No change 255 (1, 22, 28, 29, 47, 66, 69, 4), increased 81 (56, 69), variable 4 (2).	No change 18 (28, 51), increased 157 (2, 7, 22, 29, 31, 39, 47, 65, 67) (rise occurs in the 2nd and 3rd trimesters).	----------		
IX	No change 24 (14, 34, 36), increased 42 (23, 56).	No change 30 (28, 38, 69), increased 89 (56, 58).	No change 24 (14, 34, 36), increased 36 (28, 50, 67), rise starts in the 1st trimester).	----------		
X	No change 123 (6, 34, 46, 47), increased 118 (11, 22, 38, 56).	No change 11 (58), increased 311 (22, 29, 38, 46, 47, 56).	No change 16 (14), increased 221 (22, 29, 31, 39, 46, 47, 56, 67) (Rise occurs in the 2d and 3rd trimesters).	----------	----------	No change 76 (48).
XI	No change 42 (23, 56)	No change 78 (56)	----------	----------	----------	----------
XII	Increased 37 (56)	Increased 78 (56)	No change 8 (9)	----------	----------	----------
XIII	----------	No change ? (19)	Decrease 39 (68) (fall starts in the 2d trimester).	----------	----------	----------
P & P (11+VII+X)	No change 25 (4), increased 126 (2, 11, 14, 36, 38, 56).	No change 25 (4), increased 132 (29, 38, 56).	Increased 99 (14, 28, 37, 39, 56) (rise starts in 1st trimester).	----------	----------	----------

[1] Increases if a large dose is used (6).
[2] In dogs a single dose of premarin IV produces an immediate rise in II and V which persists for 4 hours.

TABLE 4.—EFFECT OF ORAL CONTRACEPTIVES, PREGNANCY, ESTROGEN AND PROGESTERONE ON FIBRINOLYSIS

	O.C.—short term	O.C.—long term	Pregnancy	Estrogens <17 days natural (premarin) or synthetic.	Estrogens >1 month	Progestogens.
Overall fibrinolytic activity	No change 6 (34) decreased 19 (136).	No change 16 (49)	Decreased 23 (22, 37, 51)	Decreased 7 (59)		Increased 76 (48).
Euglobulin clotlysis time	No change 107 (1, 6, 36), short 24 (22, 28), Variable 4 (2).	No change 79 (1, 70), short 24 (22, 28), Variable 4 (2).	No change 11 (2), prolonged 105 (5, 26, 28, 63) (rise starts in 1st trimestor).	Synthetic—short 8 (42)		Short 84 (42,48).
Plasmin	No change 18 (6, 64), increased 29 (11).	No change 57 (12, 64), decreased 9 (44).	No change 65 (10), decreased 25 (5).			
Plasminogen	No change 10 (6), increased 54 (2, 3, 6, 13, 38, 42), decreased 29 (11).	No change 27 (2, 12, 69), increased 50 (13, 28, 38, 44, 69, 70.)	No change 86 (21, 65), increased 131 (2, 5, 22, 35 37, 41) rise starts in 1st trimester).	Synthetic—no change 25 (7, 33), increased 8 (42), premarin—increased 8 (42).		Increased 8+? (33, 42).
Activator	No change 29 (6, 36), increased 41 (11, 38).	Increased 39 (12, 28, 38)	Decreased 115 (5, 10, 29, 37) (fall starts in 1st trimester), increased 30 (33).	Synthetic—no change 25 (7), decreased 8 (33).		Increased ? (33), no change 7 (11).
Anti-plasmins (including anti-UK).	No change 44 (2, 6, 13, 34, 64) decreased 41 (11, 38), increased 8 (42).	No change 79 (2, 13, 28, 49, 64, 70), decreased 29 (12, 38), increased 16 (69, 70).	No change 25 (5), increased 170 +(10, 22, 29, 33, 37, 41) (rise starts in 1st trimester).	Synthetic—increased 8 (42), decreased 25+? (7, 33), premarin—increased 8 (42).		Increased 8+ ? (33, 42).

TABLE 5.—SUMMARY

	O.C.'s	Pregnancy	Estrogens	Progestogens
Platelets	Increased number and possibly enhanced function.	Little effect	Enhanced function	No effect.
Coagulation	Definitely accelerated	Slightly accelerated	Accelerated by synthetic forms.	Do.
Level of activity of factors.	Increased	Increased		Do.
Fibrinolysis	do	Decreased	(?)	Increased.

References

1. Abrams, A. A. Sequential estrogen and progestogen therapy. Amer J Obstet Gynec 96:1005, 1966.
2. Amris, C. J. and Starup, J. The coagulation mechanism in oral contraception. Acta Obstet Gynec Scand 46:78, 1967.
3. Amundson, B. A. and Pilgeram, L. O. Observations on a relationship between steroid metabolism and the concentration of plasma fibrinogen. Thromb Diath Haemorrh 10:400, 1963.
4. Banks, A. L., Rutherford, R. N., Coburn, W. A., and Welsh, R. L. The relationship of clotting factors to dosage levels of estrogen and progestogen-like combinations. Int J Fertil 11:277, 1966.
5. Beller, F. K., Douglas, G. W., Morris, R. H., and Johnson, H. J. The fibrinolytic enzyme system in pregnancy. Amer J Obstet Gynec 101:587, 1968.
6. Beller, F. K. and Porges, R. F. Blood coagulation and fibrinolytic enzyme studies during cyclic and continuous application of progestational agents. Amer J Obstet Gynec 97:448, 1967.
7. Bennett, N. B., Bennett, P. N., Fullerton, H. W., Ogston, C. M., and Ogston, D. Effect of oestriol on platelet adhesiveness and fibrinolysis in men. Lancet 2:881, 1966.
8. Bolton, C. H., Hampton, J. R., and Mitchell, J. R. Effect of oral contraceptive agents on platelets and plasma phospholipids. Lancet 1:1336, 1968.
9. Borchgrevink, C. F.,, Andersen, R., Hall, J., Hatteland, K., and Ursin-Holm, A. "Premarin" as a haemostatic agent: failure to demonstrate any laboratory or clinical effect. Brit Med J 2:1645, 1960.
10. Brakman, P. The fibrinolytic system in human blood during pregnancy. Amer J Obstet Gynec 94:14, 1966.
11. Brakman, P., Albrechtsen, O. K., and Astrup, T. Blood coagulation, fibrinolysis and contraceptive hormones. JAMA 199:69, 1967.
12. Brakman, P. and Astrup, T. Effects of female hormones, used as oral contraceptives, on the fibrinolytic system in blood. Lancet 2:10, 1964.
13. Brehm, H. Circulation, blood coagulation and clinical observations during hormonal suppression of ovulation. Int J Fertil 9:45, 1964.
14. Brodsky, I., Lewis, G., and Ross, E. Effect of pregnancy or a progestational drug on blood coagulation as measured by the Thrombotest. Obstet Gynec 24:213, 1964.
15. Bronstein, S. B., Stough, A., and Long, I. R. Double blind placebo controlled efficacy and safety study with Quinestrol. Int J Fertil 12:274, 1967.
16. Caspary, E. A. and Peberdy, M. Oral contraception and blood platelet adhesiveness. Lancet 1:1142, 1965.
17. Clemetson, C. A. B., Blair, L., and Brown, A. B. Capillary strength and the menstrual cycle. Ann NY Acad Sci 93:279, 1962.
18. Cohen, A. Double blind intensive safety and tolerance studies during Quinestrol therapy in elderly women. Int J Fertil 12:266, 1967.
19. Coopland, A., Alkjaersig, N., and Fletcher, A. P. Reduction in plasma factor XIII (FSF) concentration during pregnancy. J Lab Clin Med 73:144, 1969.
20. Daniel, D. G., Bloom, A. L., Giddings, J. C., Campbell, H., and Turnbull, A. C. Increased factor IX levels in puerperium during administration of diethylstilboestrol. Brit. Med J 1:801, 1968.
21. Dieckman, W. J. and Wegner, C. R. Studies of the blood in normal pregnancy. Arch Intern Med 53:353, 1934.

22. Donayre, J. and Pincus, G. Effects of Enovid on blood clotting factors. Metabolism 14 Suppl: 418, 1965.
23. Egeberg, O. and Owren, P. A. Oral contraception and blood coagulability. Brit Med J 1:220, 1963.
24. Elert, R. Der Einfluss der weiblichen Keimdrusenhormone auf die Thrombozyten. Schweiz Med Wschr 76:1090, 1946.
25. Elkeles, R. S., Hampton, J. R., and Mitchell, J. R. Effect of oestrogens on human platelet behaviour. Lancet 2:315, 1968.
26. Gillman, T., Naidoo, S. S., and Hathorn, M. Plasma fibrinogen activity in pregnancy. Lancet 2:70, 1959.
27. Hajdu, A., Chappel, C. I., and Rona, G. The influence of estrogens on scorbutic bone lesions in guinea pigs. Experientia 21:466, 1965.
28. Hilden, M., Amris, C. J., and Starup, J. The haemostatic mechanism in oral contraception. Acta Obstet Gynec Scand 46:562, 1967.
29. Hougie, C., Rutherford, R. N., Banks, A. L., and Coburn, W. A. Effect of a progestin-estrogen oral contraceptive on blood clotting factors. Metabolism 14 Suppl:411, 1965.
30. Johnson, J. F. Changes in plasma prothrombin, Ac-globulin and antithrombin concentration following intravenous administration of estrogens. Proc Soc Exp Biol Med 94:92, 1957.
31. Kasper, C. K., Hoag, M. S., Aggeler, P. M., and Stone, S. Blood clotting factors in pregnancy; factor VIII concentrations in normal and AHF-deficient women. Obstet Gynec 24:242, 1964.
32. Lenahan, J. G., Stough, A., and Bronstein, S. B. Effect of Quinestrol on the coagulation mechanism. Int J Fertil 12:271, 1967.
33. Maki, M., Nagasawa, K., Nagayama, M., and Sasaki, K. Parameters of plasmin system during normal pregnancy, labor and puerperium and relation of sex hormones to plasmin system. Tohoku J Exp Med 85:1, 1965.
34. Mammen, E. F., Aoki, N., Oliveira, A. C., Barnhart, M. I., and Seegers, W. H. Provest and blood coagulation tests. Int J Fertil 8:653, 1963.
35. Margulis, P. R., Ambrus, J. L., Mink, I. B., and Stryker, J. C. Progestational agents and blood coagulation. Amer J Obstet Gynec 93:161, 1965.
36. Miller, S. P., Lee, S. L., and Ritz, N. Progestin-estrogen (SC 11,800) therapy and the hemostatic mechanism—a controlled study. Metabolism 14:398, 1965.
37. Nilsson, I. M. and Kullander, S. Coagulation and fibrinolytic studies during pregnancy. Acta Obstet Gynec Scand 46:273, 1967.
38. Nilsson, I. M. and Kullander, S. Coagulation and fibrinolytic studies during use of gestogens. Acta Obstet Gynec Scand 46:286, 1967.
39. Pechet, L. and Alexander, B. Increased clotting factors in pregnancy. New Eng J Med 265:1093, 1961.
40. Pepper, H. and Lindsay, S. Levels of platelets and eosinophilic leukocytes during the normal menstrual cycle and the administration of norethynodrel (Enovid). Int J Fertil 8:467, 1963.
41. Phillips, L. L. and Skrodelis, V. The fibrinolytic enzyme system in normal, hemorrhagic and disease states. J Clin Invest 37:965, 1958.
42. Phillips, L. L., Turksoy, R. N., and Southam, A. L. Influence of ovarian function on the fibrinolytic enzyme system. II. Influence of exogenous steroids. Amer J Obstet Gynec 82:1216, 1961.
43. Pilgeram, L. O. Blood coagulability and oral contraception. Brit Med J 1:883, 1964.
44. Pilgeram, L. O., Amundson, B. H., and Lofgren, P. E. Evidence for steroid control of the metabolism of profibrinolysis. Thromb Diath Haemorrh 11:94, 1964.
45. Polivoda, H. Treatment of thrombocytopenic hemorrhage with oestriol succinate. Nature 191:400, 1961.
46. Poller, L., Tabiowo, A., and Thomson, J. M. Effects of low-dose oral contraceptives on blood coagulation. Brit Med J 2:218, 1968.
47. Poller, L. and Thomson, J. M. Clotting factors during oral contraception: further report. Brit Med J 2:23, 1966.
48. Poller, L., Thomson, J. M., Tabiowo, A., and Priest, C. M. Progesterone oral contraception and blood coagulation. Brit Med J 1:554, 1969.

49. Powell, L. C., Guest, M. M., and Bond, T. P. Coagulation and fibrinolytic studies in women receiving an anovulatory drug. Amer J Obstet Gynec 93:167, 1965.
50. Rapaport, S. I. Proceedings of a conference: thromboembolic phenomena in women. p. 154, Chicago, G. D. Searle & Co., 1962.
51. Ratnoff, O. D. and Holland, T. R. Coagulation components in normal and abnormal pregnancies. Ann NY Acad Sci 75:626, 1959.
52. Reed, D. L. and Coon, W. W. Thromboembolism in patients receiving progestational drugs. New Eng J Med 269:622, 1963.
53. Robinson, R. W. Effects of estrogen-progestin combinations on clotting factors. Amer J Obstet Gynec 99:163, 1967.
54. Rona, G. The role of vascular mucopolysaccharides in the hemostatis action of estrogens. Amer J Obstet Gynec 87:434, 1963.
55. Rona, G. Experimental studies on vascular purpura and capillary hemostasis. Rev. Canad Biol 22:465, 1963.
56. Rutherford, R. N., Hougie, C., Banks, A. L., and Coburn, W. A. The effects of sex steroids and pregnancy on blood coagulation factors. Obstet Gynec 24:886, 1964.
57. Salvadori, B., Cagnazzo, G., Ciasca, G., and Giorgino, R. Progesteroidi di sintesi ed emocoagulazione. Ann Obstet Ginec 82:705, 1960.
58. Samuels, A. J., Lepowsky, F., and Tyler, E. Assay of selected hematologic and coagulation factors in patients on Provera. Int J Fertil 8:665, 1963.
59. Schersten, B. Remarks on hemostatics with special reference to their clinical use. Suom Laak lehti 13:855, 1958.
60. Schiff, M. and Burns, H. F. The effect of estrogens on mast cells and enzymes in connective tissue metabolism in humans. Laryngoscope 71:766, 1961.
61. Schrogie, J. J. and Solomon, H. M. Estrogenic hormones and blood coagulation. J Chronic Dis 20:675, 1967.
62. Schrogie, J. J., Solomon, H. M., and Zieve, P. D. Effect of oral contraceptives on vitamin K-dependent clotting activity. Clin Pharmacol Ther 8:670, 1967.
63. Shaper, A. G., McIntosh, D. M., and Evans, C. M. Fibrinolysis and plasminogen levels in pregnancy and the puerperium. Lancet 2:706, 1965.
64. Sobrero, A. J., Fenichel, R. L., and Singher, H. O. Effects of a progestin-estrogen preparation on blood coagulation mechanisms. JAMA 185:136, 1963.
65. Talbert, L. M., and Langdell, R. D. Normal values of certain factors in the blood clotting mechanism in pregnancy. Amer J Obstet Gynec 90:44, 1964.
66. Thomson, J. M. and Poller, L. Oral contraceptive hormones and blood coagulability. Brit Med J 2:270, 1965.
67. Todd, M. E., Thompson, J. H., Jr., and Bowie, E. J. Changes in blood coagulation during pregnancy. Mayo Clin Proc 40:370, 1965.
68. Wright, H. P. Changes in the adhesiveness of blood platelets following parturition and surgical operations. J Path Bact 54:461, 1942.
69. Ygge, J., Brody, S., Korsan-Bengtsen, K., and Nilsson, L. Changes in blood coagulation and fibrinolysis in women receiving oral contraceptives. Amer J Obstet Gynec 104:87, 1969.
70. Young, C. C., Mammen, E. F., and Spain, W. T. The effect of sequential hormone therapy on the reproductive cycle. Pacif Med Surg 73:35, 1965.

E. Cerebrovascular Diseases Associated with the Use of Oral Contraceptives: A Review of the Literature

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Numerous clinical reports indicate that neurologic complications may result from the use of oral contraceptives. These include vascular occlusive syndromes of the central nervous system and retina, migraine and other assorted cerebrovascular disorders. Retrospective epidemiologic studies by British investigators have demonstrated an etiologic relation between the use of oral contraceptives and idiopathic cerebrovascular disease. There is no evidence however, that the overall incidence of death or morbidity from cerebrovascular

disease has increased with time since the introduction of these compounds.[1] The most frequent serious complication associated with the oral contraceptives is peripheral venous thrombosis with or without the complication of pulmonary infarction.

This report focuses on occlusive disorders of the cerebral vasculature because they are the most common arterial complications reported from the use of these compounds and because they also allow consideration of intrinsic vascular alterations as an etiologic mechanism.

CLINICAL REPORTS OF CEREBROVASCULAR ACCIDENTS IN WOMEN USING ORAL CONTRACEPTIVES

From the time of the first report of an unexplained cerebrovascular accident in a young woman using an oral contraceptive by Lorentz (22) until the report by Walsh and colleagues (31), a total of 10 cases were described. Two of them were included as cases No. 10 and No. 20 in the Proceedings of a Conference on Thromboembolic Phenomena in Women Using the Oral Contraceptives (29) and the other eight, including three deaths, appeared in isolated reports in the British literature. Walsh (31) reviewed the latter eight cases and collected 61 additional ones from numerous colleagues following publication of an Editorial by Cogan (6) requesting that such cases be sent to Dr. Walsh. The available data on the 69 cases were analyzed according to age of onset, duration of oral contraceptive usage, and type of central nervous system involvement.

In 63 patients, the mean age at onset of illness of 28.9 years was older than the mean age of American married women using hormonal contraceptives (26). The average duration of usage was 9.7 months, but 60 per cent were using the drugs six months or less at the time of the incident. Some of the reported cases had a predisposing condition. The temporal relations between the onset and course of the disorder and the starting and discontinuation of the oral contraceptive suggested an etiologic role.

Pseudotumor cerebri was reported in four cases who were the youngest and had the longest duration of use. Stroke was reported in 17 cases, two of whom succumbed. Ocular involvement occurred in 20 cases; eight had optic neuritis and the remainder had retinal vascular involvement. Migraine was reported in only 10 cases. Finally ten other cases with neurologic syndromes had incomplete information. The authors concluded that the evidence warranted further study.

Illis and coworkers (17) from the National Hospital, Queen Square, London, compared the frequency of cerebral arterial occlusion among women aged 18–45 years before and after 1961. Only arteriographically proven cases were considered. Although the overall yearly admission rate from January, 1955 to July, 1965 seemed stable, four (22%) of 18 patients admitted since 1961 were known to be using hormonal contraceptives. This proportion of users is probably a conservative one. Nevertheless, of the 18 cases admitted from 1961 to July 1965, the number who might have been expected to be using oral contraceptives according to the estimates of the Family Planning Association would be less than one (0.375) as compared with the four observed. Although this difference is significant statistically, no definite conclusion is possible because of uncertainty as to the use of the drugs in the population from whom the series was drawn.

Shafey and Sheinberg (28) described a variety of neurological syndromes including occlusive cerebral artery disease (five cases), thrombosis of cortical veins (one case) and vascular headaches (28 cases). This series contained no patients with a previous history of migraine attacks before starting oral contraceptives. Three of their six "stroke" patients, including a fatality, were included among the 17 stroke patients reported by Walsh (31). Each of the four patients who had angiographic studies showed "beading" of the vessels supplying the infarcted area of brain. Similar angiographic changes were evident in the case shown to have thrombosis of cortical veins. The authors did not place great weight on this finding because of a paucity of degenerative or inflammatory changes in the vascular system of the brain or of the rest of the body.

[1] See Appendix 2C, Greene.

Three of the six cases with brain infarction had hypertension or a family history of vascular disease. Walsh (31) suggested that some women have a naturally increased susceptibility to such vascular complications which may be augmented by the oral contraceptives. Shafey and Sheinberg stated that their experience did not prove a specific relation between the oral contraceptives and neurologic disease. Nevertheless they noted that in the past 18 months they had seen four women under 30 years of age with cerebrovascular occlusive disease, whereas they had seen only two cases in this age group in the previous five years. All their patients with vascular headaches were relieved of their symptoms when the synthetic steroids were discontinued.

Bickerstaff and Holmes (5) reviewed the cases of cerebral arterial insufficiency from a large neurological referral practice in the Birmingham (England) area. Of 25 such patients under the age of 45 diagnosed in the three year period from 1964 through 1966, 18 (72%) had been using oral contraceptives, as compared with an estimated 9 per cent use (17). A personal communication from E. R. Bickerstaff dated January 14, 1969 revealed that of 12 additional cases of cerebral arterial insufficiency in 1967 and 1968, 10 (83%) had been taking hormonal contraceptives. The number of patients under the age of 45 seen with this condition in their practice who were not using oral contraceptives has not changed significantly since 1954 and has continued to average about two per year. Although the vertebral and basilar arteries are rarely involved in young patients, these vessels were affected in 6 of the 18 cases.

Gardner and coworkers (14) described focal neurological impairment of varying severity in 9 women between the ages of 23 and 45 years who were taking oral contraceptives. These patients had no predisposing disease except for hypertension in one and transient blood pressure changes in two. The authors stated that precipitation or change in the pattern of vascular headache in women taking oral contraceptives is a common clinical experience. All their nine patients experienced this type of change; it was accompanied by transient cerebral signs or symptoms lasting from 3 hours to two months in 5 cases and left a permanent disabling neurologic deficit in 4. During the period of observation they reported seeing no patients with the increasingly severe vascular headaches who were not using the oral contraceptives. Carotid arteriography performed in 2 patients several weeks after the onset of symptoms disclosed widespread segmental narrowing or occlusion of smaller cerebral arteries as well as the intimal irregularity, or "beading," of the carotid siphon previously reported by Shafey and Sheinberg (28).

Jennett and Cross (19) reviewed their experience in 104 females aged 15–45 who were fully investigated between 1956 and 1965, for carotid stroke at the Institute of Neurological Sciences, Glasgow, and concluded that there was no evidence that the oral contraceptives were responsible for cerebral arterial occlusion in young women. They also concluded that full investigation of cases of non-hemorrhagic hemiplegia in pregnancy showed that two-thirds are due to major arterial occlusion, and that cerebral venous thrombosis is not the usual cause as is commonly stated. It should be noted that during the last three years reported (1963–1965) the number of non-pregnant patients increased beyond the number that could have been anticipated from the experience of the preceding seven years. A yearly average of 3 non-pregnant patients with stroke were admitted from 1956 through 1962, but an average of seven occurred yearly thereafter.

Jennett and Cross (19) make the interesting statement with regard to cerebrovascular disease that, "mortality and morbidity statistics do not discriminate between pregnant and non-pregnant women, and if our experience were universal it might be expected that the figures for women in this age group in the ICD Rubrics 332 and 334 would include a number of pregnant women: since the contribution made by pregnant women to the deaths is disproportionate, the mortality statistics would be particularly liable to bias from this cause." If this reporting circumstance is true as it seems to be also in the United States and if mortality from cerebrovascular disease in women of child-bearing age shows no increase in the face of an increasing use of the oral contraceptives, then it is possible that the mortality statistics are reflecting a substitution of the risk due to oral contraceptives for the risk due to pregnancy.

Salmon and colleagues (27) reviewed the studies of neuro-ophthalmic sequelae in users of oral contraceptives as well as other important reports including that of Cole (8). There were 129 cases of migraine and 100 with other neurologic and ophthalmalogic diseases. They accumulated 70 cases of stroke in users of oral contraceptives. They classified them according to the presumed location of the lesion. Eighteen (26%) were believed to stem from either the vertebral, basilar or posterior cerebral arteries. The authors stated that prior to the availability of hormonal contraceptives, only 47 cases of spontaneously occurring stroke in healthy young females were reported when pregnancy or other predisposing factors were eliminated. None involved areas supplied by the vertebral or basilar arteries. Salmon (27) noted also that the reduction of the per cent of pregnant women in the population has not been accompanied by a reduction of morbidity due to these cerebral disorders, associated in part with pregnancy.

Ask-Upmark (2) mentioned similar cases associated with the use of oral contraceptives. One death occurred in a 40 year old woman.

The single autopsied case of a neurological catastrophe associated with the use of these drugs is reported by Altshuler (1). The patient was a 26 year old female in good health except for a long history of mild migraine. After eight months use of oral contraceptives she suddenly developed neurologic signs and symptoms suggestive of subarachnoid hemorrhage. She did not respond to therapy and died 7 days after admittance. At autopsy, thromboses of both internal carotid arteries and of the right middle cerebral artery were found with multifocal fibrinoid degeneration of small arteries and multiple areas of hemorrhagic infarction. Arteriolar degeneration and endarteritis in the papillary muscles of the heart with infarction was also seen. Microscopic study of the brain revealed several significant features. Small intracerebral vessels were involved. There was dilatation, stasis, erythrodiapedesis, intramural hematomas, and laminar splitting and with focal necrosis of the vessel walls. Fibrinoid swelling of minute vessel walls was also seen. The presence of the latter lesions indicated that the damage done by the causative agent was not limited to hypercoagulability in larger vessels but involved the cerebral microvasculature as well. The authors reviewed data from seven previously reported autopsied cases with thrombosis of the central nervous system but none described the microvasculature in such great detail.

Bergeron and Wood (3) reported their radiologic experience regarding cerebrovascular complications of the oral contraceptives observed during two twelve month periods at the Neurological Institute of New York. Of the 64 young women studied by cerebral angiography because of ischemic syndromes in 1966, arterial occlusions were documented in 9, of whom 8 had been taking the drugs. The year 1960 was selected for comparison; during this year 60 angiograms were performed but only two cases with arterial occlusion were found. One non-hormone related occlusion was seen in both years studied but the hormone-related occlusive disease increased from one (post-partum) in 1960 to eight women in 1966. Among the eight cases, the median age was 30 years and the average duration of use was 16 months. In all but one, branches of the middle cerebral artery were involved.

The authors believe that the number of reported cases of cerebrovascular accidents associated with the oral contraceptive is only a small fraction of the true number. Inman and Vessey (18) indicate that only 15 percent of the thromboembolic deaths of women who were taking the oral contraceptives in Great Britain were reported to the Committee on Safety of Drugs. Their experience like that of Shafey and Sheinberg (28) and Garner and coworkers (14) suggests that these patients almost always have some prodromal warning, usually significant headache, prior to the onset of the paretic event.

Levine and Swanson (21) reviewed nonatherosclerotic causes of stroke and contributed a report of a fatal case of a 31 year old woman who had been in good health except for migraine since age 16 and who had been taking oral contraceptives for 4 years. Four days before death she collapsed with a left hemiparesis and developed a right hemicranial headache. Postmortem examination showed no atherosclerosis, but the right middle cerebral artery was distended by an easily expressed clot, which was shown microscopically to be an unorganized thrombus. It evidently developed during the one day antemortem since the artery had been demonstrated previously to be patent. A large infarct was demonstrated in the right hemisphere. This case suggests that

interference with the cerebral small vessel had occurred at least four days antemortem and before a large clot developed in a major cerebral artery.

Levine and Swanson (21) also presented a differential diagnosis of ischemic strokes in young adults. They basically fall into two classes; the first resulting from atherosclerotic degenerative vascular disease due to diabetes, hypertension and hyperlipidemia, and the second resulting from various rarer diseases. It is likely in the latter class that clues will be found regarding the mechanisms of ischemic stroke in women using hormonal contraceptives. The rarer known causes of ischemic stroke in young adults include: 1) inflammatory-degenerative vascular disorders associated with connective tissue disease,, e.g., systemic lupus erythematosus, as reviewed recently by Johnson and Richardson (20), Takayasu's arteriopathy localized to the aortic arch or major branches, and granulomatous angiitis of the central nervous system; 2) embolic disorders due to fat, micro-organisms, tumor, air or thrombi; 3) hematologic-rheologic syndromes, e.g., sickle cell disease or trait, polycythemia and the dysproteinemias; and 4) migraine. The experience of these authors is confirmed by that of Berlin and colleagues (4), Humphrey and Newton (16) and by Louis and McDowell (23) who reviewed also the subject of cerebrovascular occlusions in young adults. Cross and Jennett (10) emphasized also the importance of pregnancy and the puerperium as a cause of ischemic stroke in young women.

EPIDEMIOLOGIC STUDIES RELATED TO STROKE AND THE USE OF ORAL CONTRACEPTIVES

The most definitive statistics currently reported on the association of morbidity and mortality from cerebral thrombosis and the oral contraceptives have derived from the retrospective studies initiated in Great Britain by the Committee on Safety of Drugs and by the Medical Research Council. In December 1964, the Committee on Safety of Drugs began an investigation into reports of deaths from thrombosis or embolism in women who were using the oral contraceptives. In July 1966, the Committee extended its investigation to cover all deaths of women aged 15 to 44 years that occurred in 1966, and in which cerebral thrombosis, coronary thrombosis or pulmonary embolism or infarction was mentioned on the death certificate.

The final results of the Committee on Safety of Drugs' investigation of deaths from pulmonary, coronary and cerebral thrombosis and embolism in women of child-bearing age was reported by Inman and Vessey (18). After exclusions, justified by the design of this type of retrospective study, 309 deaths among non-pregnant married women in England, Wales and Northern Ireland during 1966 were analyzed according to the presence or absence of predisposing conditions and the frequency of use of the oral contraceptives. One hundred and twenty women with adequate history of contraceptive practice were ascertained to have no predisposing condition; 26 dying of pulmonary embolism, 84 of coronary thrombosis and 10 of cerebral thrombosis. The remaining deaths were divided among 175 with predisposing conditions and 14 without sufficient evidence of contraceptive practice. Of the women dying without a predisposing condition, 16 of 26 attributed to pulmonary embolism, 18 of 84 to coronary thrombosis and 5 of 10 to cerebral thrombosis were using the oral contraceptive whereas the expected numbers from the control experience were 4.2, 11.4 and 1.5 respectively. The differences for pulmonary embolism and cerebral thrombosis are statistically significant, ($P<0.001$) and ($P<0.01$) respectively. With regard to cerebral thrombosis, five of the six women under 40 years had been using hormonal contraceptives while none of the four over 40 years had taken them. Thus, an association was demonstrated between the use of these compounds and death from idiopathic cerebral thrombosis in healthy British women.

The final report by Vessey and Doll (30) compared the use of oral contraceptives during the month preceding the onset of illness among the cases of idiopathic deep vein thrombosis, pulmonary embolism, cerebral and coronary thrombosis with that among controls admitted (1964–67) to 19 selected general hospitals of more than 300 beds in the area of the Northwest Metropolitan Hospital Board. Married females between the ages of 16 and 40 years inclusive who had relevant thromboembolic disorders without a predisposing condition or having been pregnant within three months were considered cases

for further study. Two carefully matched hospitalized control patients of the same age, marital status, parity and without evidence of predisposing conditions were selected for each case and the complete "triads" of interviewed idiopathic cases and matched controls were analyzed.

All records were reviewed which were coded under Rubrics 331–334, in order to detect cases of cerebral thrombosis not coded under Rubric 332. Abstracts of the records were reviewed by a neurologist without knowledge of the patients' contraceptive practices. Nineteen cases were accepted, of whom four had angiographic evidence of arterial occlusion. Eleven (58%) had been using hormonal contraception during the month before they became ill whereas 3.5 (18%) would have been expected on the basis of a control experience ($P<0.001$). The authors estimated that the risk of developing a cerebral thrombosis or other intracranial ischemic stroke syndrome, in the absence of any known predisposing cause, is about six times higher when oral contraceptives are used than when they are not.[2] Oral contraceptives were used by 3 of the 4 patients in whom the diagnosis was proven arteriographically. They also concluded that clinical, angiographic and postmortem evidence from their own and other series indicate that the thrombosis or occlusion affects the cerebral arteries rather than the cerebral veins.

A recent analysis of oral contraceptive use and mortality trends from thromboembolism in the United States was reported by Markush and Seigel (25). They compared the mortality rates during 1962–1966 among women aged 20–44 years with the rates for men and women in comparable age groups in previous years. They analyzed overall trends of mortality attributed to cerebral thrombosis and embolism (ICD 332) and could not find evidence of a general increase in women in the recent period or of an increase in females relative to males. Possibly improvements in the treatment of primary diseases such as hypertension and renal disease have compensated for an increase that would otherwise be seen. Also, as mentioned above, stroke in pregnancy is included under Rubric 332 and one might expect a downward trend in mortality from this type of stroke with decreasing birth rates. Nevertheless, an increased trend in mortality attributed to ICD 332 was detected for white females aged 25–29 and negro females aged 25–34.

Greene (15) analyzed also U.S. cerebrovascular mortality with regard to temporal trends before and after the introduction of the oral contraceptives. The results including ratios of white male to female mortality in the childbearing ages are consistent with the above-mentioned findings.

DISCUSSION

The purpose of this review of both clinical reports and statistical evaluations of the association of oral contraceptives with cerebrovascular disease is to ascertain whether or not an etiologic relation exists and also to gain clues as to possible biological mechanisms which might be operating. The available clinical data are consistent with an etiologic relation. The clinical reports suggest also that an unusual type of stroke, namely that involving the vertebrobasilar area of the brain, is occurring in about a quarter of the young women now experiencing stroke while using hormonal contraceptives. A close temporal association between the use of oral contraceptives and the onset of migraine-like headache has also been reported. These headaches often occur prior to cerebral ischemic infarction. The clinical evidence suggests that various neurological syndromes, seemingly related to vascular alterations with or without thrombosis, are related to use of the oral contraceptives.

The results of retrospective epidemiologic studies of mortality and morbidity from idiopathic cerebral thrombosis in Great Britain indicate a statistically significant association with the use of oral contraceptives. It is not possible with the existing data to estimate with assurance the magnitude of the increased morbidity and mortality risk of stroke among women using these compounds but it may be in the neighborhood of sixfold judging by findings of Inman and Vessey (18) and Vessey and Doll (30).

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[2] This relative risk is estimated from a ratio of cross-products, i.e., proportion of oral contraceptive users among cases (58%) x proportion of non-users among controls (82%) divided by the proportion of non-users among cases (42%) x proportion of users among controls (18%).

Non-atherogenic causes of stroke were reviewed since atheromata almost never could be documented as the direct cause of stroke in the autopsied women succumbing while on oral contraceptives. Furthermore, only rarely have strokes due to atheromatosis been reported in persons under thirty years of age. Non-atherogenic stroke develops in women during pregnancy or the puerperium, in women having migraine and in women with various systemic connective tissue diseases and especially system lupus erythematosus. Each of these conditions seems to be related closely to physiological or histological alterations of the vasculature of the brain. Few women who died while using hormonal contraception have had careful studies of the brain, and especially of its vasculature. The single reported autopsy revealed significant and impressive alterations of the small and medium-sized vessels.

Animal experimental studies of vascular effects of oral contraceptives are limited but those of Danforth and coworkers (12) in rabbits revealed an increase in the amount of muscle, a decrease in the amount of collagen, marked fragmentation of the reticulum, apparent loss of elastic tissue and a marked loss of acid mucopolysaccharides in large vessels. Qualitatively similar changes were found in pregnancy. Manalo-Estrella and colleagues (24) showed that these changes disappeared at variable rates after withdrawal of antiovulatory agents or the termination of pregnancy. The mucopolysaccharides return to normal within a day while other alterations revert at a slower rate. Cutts (11) demonstrated, in rats, that long-term administration of estrogen predisposes to vascular lesions resembling polyarteritis nodosa. It is tempting to speculate that oral contraceptives induce changes analogous to those in pregnancy and thus may alter the composition or architecture of cerebral blood vessels as suggested by Crocker (9) in considering fibromuscular dysplasia of the renal arteries found predominantly in multiparous women.

The review by Dugdale and Masi (13) of coagulation studies in women using hormonal contraception suggests that estrogen contributes to increased platelet function and accelerated clotting whereas progestin contributes to increased fibrinolytic activity. A few studies comparing the effects of high dose with low dose oral contraceptives did not show any great differences in platelet function, coagulation or fibrinolysis.

In order to understand the effects of the oral contraceptives on the vascular system and the blood clotting system it is necessary to consider the complex alterations in the endocrine system induced by these compounds as reviewed by Corfman (7). It is invalid to conclude that any changes occurring in women taking the oral contraceptives are entirely due to the estrogen or progestin without considering how these hormones alter the general endocrine and physiologic balance of the body.

SUMMARY AND CONCLUSIONS

1. A review of the major clinical reports of cerebrovascular occlusion in women using the oral contraceptives reveals a notable increase in the number of instances of cerebrovascular disease in healthy women of child-bearing age that have appeared since the introduction of the oral contraceptives.

2. Young women suffering from stroke while using the oral contraceptives almost always have some warning, usually significant headache, prior to the onset of the paretic event. In about one-fourth there is ischemia or infarction in the vertebral and basilar arterial system, a location which was previously considered rare in young healty women.

3. Cerebral arteries rather than veins are primarily involved. Limited angiographic and autopsy studies suggest intrinsic vascular alterations in addition to possible derangement of the hemostatic mechanisms.

4. Controlled retrospective studies of young women with cerebral thrombosis without a predisposing cause indicate a statistically significant etiologic relation with the oral contraceptives. There is a sixfold estimated increase in the risk of both morbidity and mortality.

5. Available statistical evidence concerning the overall mortality from cerebrovascular disorders in the general population of women of child-bearing age since the time of introduction of the oral contraceptives until 1966 indicates no significant change. There is neither a decrease which one might anticipate due to the decreased number of pregnancies and deliveries in the general population, nor an increase which might have been evident if the risk from the oral

contraceptives *per se* were greater than opposing forces of such mortality operating over this interval.

References

1. Altshuler, J. H., McLaughlin, R. A. and Neubuerger, K. T. Neurological catastrophe related to oral contraceptives, Arch Neurol 19:264, 1968.
2. Ask-Upmark, E. The relationship between thrombophlebitis, thrombosis, embolism and the use of the oral contraceptive agents, pp. 211–17 In Drug Induced Diseases, Eds. Meyler, L. and Peck, H. M., New York, Excerpta Medica Foundation, 1968, Vol. 3.
3. Bergeron, R. T. and Wood, E. H. Oral contraceptives and cerebrovascular complications, Radiology 92:231, 1969.
4. Berlin, L., Tumarkin, B. and Martin, H. L. Cerebral thrombosis in young adults, New Eng J Med 252:162, 1955.
5. Bickerstaff, E. R. and Holmes, J. M. Cerebral arterial insufficiency and oral contraceptives, Brit Med J 1:726, 1967.
6. Cogan, D. G. Do oral contraceptives have neuro-ophthalmic complications? Arch Ophthal 73:461, 1965.
7. Corfman, P., Adamsons, K., Carrington, E. and Delfs, E. Biologic effects of oral contraceptives In Report on the Oral Contraceptives, Advisory Committee on Obstetrics and Gynecology, Food and Drug Administration, 1969.
8. Cole, M. Strokes in young women using oral contraceptives, Arch Intern Med 120:551, 1967.
9. Crocker, D. W. Fibromuscular dysplasias of renal artery, Arch Path 85:602, 1968.
10. Cross, J. N., Castro, P. O. and Jennett, W. B. Cerebral strokes associated with pregnancy and the puerperium, Brit Med J 3:214, 1968.
11. Cutts, J. H. Vascular lesions resembling periarteritis nodosa in rats undergoing prolonged stimulation with oestrogen, Brit J Exp Path 47:401, 1966.
12. Danforth, D. N., Manalo-Estrella, P. and Buckingham, J. C. The effect of pregnancy and of Enovid on the rabbit vasculature, Amer J Obstet Gynec 88:952, 1964.
13. Dugdale, M. and Masi, A. T. Blood clotting effects of the oral contraceptives *IN* Report on the Oral Contraceptives, Advisory Committee on Obstetrics and Gynecology, Food and Drug Administration, 1969.
14. Gardner, J. H., Van Den Noort, S. and Horenstein, S. Cerebrovascular disease in young women taking oral contraceptives, Neurology 17:297, 1967.
15. Greene, G. R. Trends in mortality from cerebrovascular diseases *IN* Report on the Oral Contraceptives, Advisory Committee on Obstetrics and Gynecology, Food and Drug Administration, 1969.
16. Humphrey, J. G. and Newton, T. H. Internal carotid artery occlusion in young adults, Brain 83:565, 1960.
17. Illis, L., Kocen, R. S., McDonald, W. I. and Mondcar, V. P. Oral contraceptives and cerebral arterial occlusion, Brit Med J 2:1164, 1965.
18. Inman, W. H. W. and Vessey, M. P. Investigation of deaths from pulmonary, coronary and cerebral thrombosis and embolism in women of child-bearing age, Brit Med J 2:193, 1968.
19. Jennett, W. B. and Cross, J. N. Influence of pregnancy and oral contraception on the incidence of strokes in women of child-bearing age, Lancet 1:1019, 1967.
20. Johnson, R. T. and Richardson, E. P. The neurological manifestations of systemic lupus erythematosus, Medicine 47:337, 1968.
21. Levine, J. and Swanson, P. D. Nonatherosclerotic causes of stroke, Ann Intern Med 70:807, 1969.
22. Lorentz, I. T. Parietal lesion and "Enovid," Brit Med J 2:1191, 1962.
23. Louis, S. and McDowell, F. Stroke in young adults, Ann Intern Med 66:932, 1967.
24. Manalo-Estrella, P., Danforth, D. N. and Buckingham, J. C. Regression rate of vascular effects induced by pregnancy by norethynodrel-mestranol, Fertil Steril 16:81, 1965.
25. Markush, R. E. and Seigel, D. G. Oral contraceptives and mortality trends from thromboembolism in the United States, Amer J Public Health 59:418, 1969.

26. Ryder, N. B. and Westoff, C. F. Use of oral contraception in the United States—1965, Science 153:1199, 1966.
27. Salmon, M. L., Winkelman, J. Z. and Gay, A. J. Neuro-ophthalmic sequelae in users of oral contraceptives, JAMA 206:85, 1968.
28. Shafey, S. and Scheinberg, P. Neurological syndromes occurring in patients receiving synthetic steroids (oral contraceptives), Neurology 16:205, 1966.
29. Thromboembolic phenomena in women, Proceedings of a Conference, Chicago, Sept. 10, 1962, Copyright 1962, G. D. Searle & Co., Chicago.
30. Vessey, M. P. and Doll, R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A Further Report. Brit Med J 2:651, 1969.
31. Walsh, F. B., Clark, D. B., Thompson, R. S. and Nicholson, D. H. Oral contraceptives and neuro-ophthalmologic interest, Arch Ophthal 74:628, 1965.

APPENDIX 3

Report of the Task Force on Carcinogenesis

R. Hertz, M.D., Chairman

INTRODUCTION

It has been repeatedly demonstrated that the steroid substances used in oral contraceptives produce a wide variety of tumors in 5 species of experimental animals (10, 13, 17, 22, 31, 32). It is also known that all physical and chemical agents that are carcinogenic in man are also carcinogenic in animals (24). Moreover, these carcinogenic agents frequently produce tumors in the same organs in animals as they do in man. Hence there is a distinct interrelation between animal and human carcinogenic responses.

Steroid carcinogenesis in animals usually requires prolonged administration of hormone at relatively high dosage (13). Such administration of estrogen has elicited a carcinogenic response in rodents and in dogs but not in monkeys (6, 11, 36). It is therefore essential to ascertain whether such experimental findings in rodents and in dogs have any pertinence to the question of a potential carcinogenic effect of steroid contraceptives in women. To date, no properly devised prospective or retrospective study providing conclusive data bearing on this question has been completed.

In consideration of available animal studies and in the light of certain physiopathological considerations it is deemed advisable to focus our interest on the potential effects of steroid contraception on the epidemiology, pathogenesis, and clinical course of cancers of the cervix, endometrium, and breast in women.

CERVICAL CANCER

An extended body of data provides an adequate background for the consideration of the major epidemiological aspects of cancer of the cervix (3, 5, 9, 25, 43, 44). However, despite a broad area of common agreement regarding morphological criteria for cytological and histological diagnosis of cervical cancer, it is clear that in practice wide differences of interpretation of pathological and normal material are frequently encountered (16, 29, 30, 33, 35, 38). Nevertheless, evidence of a variety of cervical epithelial aberrations of indecisive prognostic significance has emerged (4, 41). The complexity of interpreting the true impact of steroid hormonal effects on the occurrence and behavior of these epithelial changes is manifest. This difficulty is augmented by attempts at comparison of such hormonally responsive changes with those seen in the newborn or during pregnancy (34, 39). In addition, certain diagnostic procedures such as punch biopsy will in some cases remove all evidence of disease, thereby frustrating any reliable prognostic interpretation.

Nevertheless, Barron and Richard (1) have provided a mathematical model for the quantitative assessment of the proportion of cases to be expected to progress from "dysplasia" to "carcinoma in situ" in a given test population. The Task Force considers this model to be eminently applicable to the problem at hand and recommends its use in the evaluation of the validity of further data presented for consideration in this area. Seigel and Corfman (40) and

Hertz and Bailar (23) have estimated the size of the sample required to answer this question as well as to provide other pertinent epidemiological data.

A survey of women attending the clinics of Planned Parenthood of New York City revealed a higher prevalence of epithelial abnormalities, diagnosed as carcinoma in situ, among women using oral contraceptives compared with those using the diaphragm (32a). These women had never been subject to systematic cytologic screening prior to this study, but some of them may have had Papanicolaou smears done in other cancer detection programs. The diagnosis was made in each case on the basis of a biopsy, examined by two pathologists without knowledge of the contraceptive used.

Women who had used oral contraceptives for one year or more were individually matched against diaphragm users with respect to five variables: age (5 classes), parity (2 classes), age at first pregnancy (3 classes including nulligravida), ethnic group (4 classes), and family income (2 classes). Because more women had used oral contraceptives (6,331) than the diaphragm (3,874) and because the distributions of the two groups of women in terms of the five variables were quite different, three matchings were performed: (1) one woman who had used the diaphragm against one who had used oral; (2) one diaphragm user against two pill users; and (3) one diaphragm user against three pill users. The three matchings produced, respectively, 2,351 pairs, 1,831 triplets, and 1,471 groups of four matched cases. In each matching the prevalence of epithelial abnormalities, diagnosed as carcinoma in situ, was about twice as high among those who used oral contraceptives as among those who used the diaphragm, and in each instance the difference was significant at the 5 per cent level of confidence.

Whereas these findings emphasize the urgent necessity of further research in this area, they do not, in the opinion of either the Task Force or the investigators, establish that oral contraceptives have a carcinogenic effect. Several important questions remain unanswered.

1. The prevalence of epithelial abnormalities diagnosed as carcinoma in situ, was higher among the 6,331 women who had used oral contraceptives for one year or more (9.8 per 1,000) than among the 21,177 women who were using other methods at the time of their first clinic attendance (5.6 per 1,000). There appears to be no further increment with duration of use of the pill. This finding is at variance with what would be expected in the case of a causal relation.

2. How do diaphragm users differ from pill users with respect to age at first coitus, frequency of coitus, number of sexual partners, and previous screening, all of which may contribute to the observed level of prevalence? It appears likely that all or most of these factors are correlated with one or more of the variables used in matching, but important residual differences may remain.

3. Finally, if there is a significant difference in the prevalence and, presumably, incidence of carcinoma in situ, is the reason for this difference a carcinogenic effect of hormonal contraception or a protective effect of the diaphragm, which may shield the cervix from coital trauma and possibly from infection?

Accordingly, the Task Force urgently recommends prospective studies of the effect of sustained oral contraception on the immediate and ultimate response of the cervical epithelium in a carefully observed and representative population of women.

ENDOMETRIAL CANCER

The demonstrated regression of endometrial cancer in response to large doses of progestin clearly indicates that this is a hormone-sensitive lesion (26, 28). Moreover, retrospective histological studies indicate a prolonged pathogenetic phase in the development of endometrial carcinoma (18, 19, 21, 42) Because this tumor is more occult, less is known about its incipient phases than about those of cervical cancer. For the same reason interpretation of epidemiological findings in relation to the pathogenesis of cancer of the corpus is difficult and conclusions are of limited value.

Accordingly, the Task Force does not regard studies relating specifically to endometrial cancer as a practical basis for evaluation of the carcinogenic potential of oral contraceptives.

BREAST CANCER

Concern about potential applicability of findings in laboratory animals to cancer of the breast in women is based on the following observations: ovariectomy leads to regression of pre-existing metastatic breast cancer in 30 to 50 per cent of premenopausal women (2, 7) ; a similar proportion of premenopausal women with breast cancer will exhibit biochemical evidence of exacerbation of disease following administration of exogenous estrogen (20, 37) ; about 50 per cent of postmenopausal women and a few premenopausal women will experience regression of disease following administration of exogenous estrogen (8, 27). It is therefore clear that women with breast cancer may exhibit a positive or negative response to exogenous estrogen.

It is, however, completely unknown whether exogenous estrogens or progestins significantly alter the preclinical phase of breast cancer detectable by mammography (14). However, qualitative alterations in epithelial elements of the breast have been observed in surgical material taken from patients taking oral contraceptives (15). Yet no valid data are available to confirm a causal relation between oral contraception and the occurrence of such lesions. In addition, an unknown proportion of women taking oral contraceptives complain of increased tenderness and turgidity of the breasts, but measurable enlargement of the breasts is rarely demonstrable.

The Task Force recommends appropriately devised retrospective case-controlled studies as well as prospective studies to resolve the problem of an effect of oral contraceptives on the incidence and course of mammary lesions.

CONCLUSION

Lacking definitive information regarding the potential applicability of existing animal data to women, the Task Force believes that neither the exclusion of a potential carcinogenic role of oral contraceptives nor affirmation of such an effect is justified. However, the inconclusive observations cited for carcinoma of the cervix necessitate a major effort to solve this problem definitively under optimally controlled conditions of study. Meanwhile, the precautions cutlined in our previous report (12) as desirable for all women of reproductive age are recommended with equal force for those using the oral contraceptives.

References

1. Barron, B. A., and Richart, R. M. A statistical model of the natural history of cervical carcinoma based on a prospective study of 557 cases. J Nat Cancer Inst 41:1343, 1968.
2. Beatson, G. T. On the treatment of inoperable cases of carcinoma of the mammae. Lancet 2:104, 1896.
3. Boyd, J. T., and Doll, R. A study of the aetiology of carcinoma of the cervix uteri. Brit J Cancer 18:18, 1964.
4. Candy, M., and Abel, M. R. Progestogen-induced adenomatous hyperplasia of the uterine cervix. JAMA 203:323, 1968.
5. Christopherson, W. M., Parker, J. E., and Drye, J. C. Control of cervical cancer: Preliminary report on community program. JAMA 182:179, 1962.
6. Crossen, R. J., and Suntzeff, V. Endometrial polyps and hyperplasia produced in an aged monkey with estrogen plus progesterone. Arch Path 50:721, 1950.
7. Currie, A. R. Endocrine aspects of breast cancer. The Williams & Wilkins Co., Baltimore, 1958.
8. De Nosaquo, N. Androgens and estrogens in the treatment of disseminated mammary carcinoma. JAMA 172:1271, 1960.
9. Dunn, J. E. The relationship between carcinoma in situ and invasive cervical carcinoma. Cancer 6:873, 1953.
10. Dunn, T. B. Cancer of the uterine cervix induced in BALB/C mice by an antifertility drug. Proc Amer Ass Cancer Res 10:21, 1969.
11. Engle, E. T., Krakower, C., and Haagensen, C. D. Estrogen administration to aged female monkeys with no resultant tumor. Cancer Res 3:858, 1943.
12. Food and Drug Administration Report on the Oral Contraceptives, Advisory Committee on Obstetrics and Gynecology. Aug. 1, 1966, U.S. Gov't Printing Office, Washington, D.C., pg. 8.

13. Gardner, W. V., Pfeiffer, C. A., and Trentin, J. J. Hormonal factors in experimental carcinogenesis. In Physiopathology of Cancer edited by F. Homburger, and W. H. Fishman, ed. 2, p. 152. Harper & Row Publishers, Inc., New York, 1959.
14. Gerson-Cohen, J., and Borden, A. G. Detection of unsuspected breast cancer by mammography. Ann NY Acad Sci 114:783, 1964.
15. Goldenberg, V. E., Wigenstein, L., and Mottet, N. K. Florid breast fibroadenomas in patients taking hormonal oral contraceptives. Amer J Clin Path 49:52, 1968.
16. Gore, H., and Hertig, A. T. Definitions in dysplasia, carcinoma in situ and microinvasive carcinoma of the cervix uteri (Gray, L., ed.) Springfield, Charles C. Thomas, 1964, pp. 83–109.
17. Griffiths, C. T., Tomic, M., Craig, J. M., and Kistner, R. W. Effects of progestins and castration on induced endometrial cancer in the rabbit. Surg Forum 14:399, 1963.
18. Gusberg, S. B. Precursors of corpus carcinoma, estrogens, and adenomatous hyperplasia. Amer J Obstet Gynec 54:905, 1947.
19. Gusberg, S. B. and Kaplan, A. L. Precursors of corpus cancer. Amer J Obstet Gynec 86:662, 1963.
20. Hall, T. C., Dadelick, M. M., Nevinny, H. B., and Kelley, R. M. Cellular prognostic factors in breast cancer hormone therapy. In Biological Activities of Steroids in Relation to Cancer, edited by G. Pincus and E. P. Vollmer, p. 483. Academic Press, Inc., New York, 1960.
21. Hertig, A. T., and Sommers, S. C. Genesis of endometrial carcinoma: I. Study of prior biopsies. Cancer 2:946, 1949.
22. Hertz, R. Experimental and clinical aspects of the carcinogenic potential of steroid contraceptives. Int J Fertil 13:273, 1968.
23. Hertz, R., and Bailar, J. C. III. Estrogen-progestogen combinations for contraception. JAMA 198:1000, 1966.
24. Hueper, W. C. Environmental cancer. In Physiopathology of Cancer, edited by F. Homburger and W. H. Fishman, ed. 2, p. 919. Harper & Row Publishers, Inc., New York 1959.
25. Jones, E. G., MacDonald, I., and Breslow, L. A study of epidemiologic factors in carcinoma of the uterine cervix. Amer J Obstet Gynec 76:1, 1958.
26. Kelley, R. M., and Baker, W. H. Clinical observations of the effect of progesterone in the treatment of metastatic endometrial carcinoma. In Biological Activities of Steroids in Relation to Cancer, edited by G. Pincus and E. P. Vollmer, pp. 427–439. Academic Prss, Inc., New York, 1960.
27. Kennedy, B. J. Massive estrogen administration in premenopausal women with metastatic breast cancer. Cancer 15:641, 1962.
28. Kistner, R. W. Treatment of carcinoma in situ of the endometrium. Clin Obstet Gynec 5:1166, 1962.
29. Koss, L. G. Diagnostic cytology and its histopathologic bases. 2nd ed. Philadelphia, Toronto: J. B. Lippincott Co., 1968.
30. Koss, L. G., Stewart, F. W., Foote, F. W., Jordan, M. J., Bader, G. M., and Day, E. Some histologic aspects of behavior of epidermoid carcinoma in situ and related lesions of the uterine cervix. A long-term prospective study. Cancer 16:1160, 1963.
31. Lipschutz, A., Iglesias, R., Panosevich, V., and Salinas, S. Ovarian tumors and other ovarian changes induced in mice by two 19-nor-contraceptives. Brit J Cancer 21:153, 1967.
32. Lipschutz, A., Iglesias, R., and Salinas, S. Ovarian tumors by a sterilizing steroid. Nature 196:946, 1962.
32a. Melamed, M. R., Koss, L. G., Flehinger, B. J., Kelisky, R. P., and Dubrow, H. Prevalence rates of uterine cervical carcinoma in situ for women using the diaphragm or contraceptive oral steroids. Brit Med J 3:195, 1969.
33. McKay, D. G., Terjanian, B., Poschyachinda, D., Younge, P. A., and Hertig, A. T. Clinical and pathologic significance of anaplasia (atypical hyperplasia) of the cervix uteri. Obstet Gynec 13:2, 1959.
34. Nesbitt, R. E. L., and Hellman, L. M. The histopathology and cytology of the cervix in pregnancy. Surg Gynec Obstet 54:10, 1952.
35. Okagaki, T., Lerch. V., Younge, P. A., McKay, D. G., and Kevorkian, A. Y Diagnosis of anaplasia and carcinoma in situ by differential cell counts. Acta Cytol (Phil) 6:343, 1962.

36. Overholser, M. D., and Allen, E. Atypical growth induced in cervical epithelium of monkey by prolonged injections of ovarian hormone combined with chronic trauma. Surg Gynec Obstet 60:129, 1935.
37. Pearson, O. H., West, C. D., Hollander, V. P., and Treves, N. E. Evaluation of endocrine therapy for advanced breast cancer. JAMA 154:234, 1954.
38. Richart, R. M. Colpomicroscopic studies of cervical intraepithelial neoplasia. Cancer 19:395, 1966.
39. Rosenthal, A. H., and Hellman, L. M. The epithalial changes in the fetal cervix, including the role of the "reserve cell." Amer J Obstet Gynec 64:260, 1952.
40. Seigel, S. J., and Corfman, P. Epidemiological problems associated with studies of the safety of oral contraceptives. JAMA 203:950, 1968.
41. Taylor, H. B., Irey, N. S., and Norris, H. J. Atypical endocervical hyperplasia in women taking oral contraceptives. JAMA 202:637, 1967.
42. TeLinde, R. W., Jones, H. W., Jr., and Galvin, G. A. What are earliest endometrial changes to justify diagnosis of endometrial cancer. Amer J Obstet Gynec 66:953, 1953.
43. Terris, M., and Oalmann, M. C. Carcinoma of the cervix. An epidemiologic study. JAMA 174:1847, 1960.
44. Wydner, E. L., Cornfield, J., Schroff, P. D., and Doraiswami, K. R. A study of environmental factors in carcinoma of the cervix. Amer J Obstet Gynec 68:1016, 1954.

APPENDIX 4

Report of the Task Force on Biologic Effects

P. A. Corfman, M.D., Chairman

INTRODUCTION

Many important studies of the biological effects of oral contraceptives have been published since the 1966 FDA Report on Oral Contraceptives (55) and the results have been summarized in part by Diczfalusy (45), Jeffrey and Klopper (83), and others (74, 103, 184). A detailed review of the nonendocrine effects was undertaken at a four-day conference in December, 1968, organized by the Harvard Center for Population Studies and supported by the National Institute of Child Health and Human Development. The proceedings of the conference are published under the title "The Metabolic Effects of Gonadal Steroids and Contraceptive Agents" (147).

This comparatively brief Task Force report does not attempt to include all of the extensive literature on the biological effects of oral contraceptives but identifies certain topics that the Task Force believes to be of particular importance. The effects of these agents on blood coagulation and thromboembolism are covered in another portion of the report. It is clear, however, that oral contraceptives have many varied effects on many organ systems. Indeed, there appears to be no organ system tested that is not affected in some way.

The ubiquitous effects of oral contraceptives probably relate to their high degree of contraceptive effectiveness, brought about through interference with several phases of the reproductive process. An influence on the hypothalamus or higher brain centers is probably responsible for the suppression of pituitary production of gonadotropins, leading secondarily to the inhibition of ovulation.

The second major effect is on the endometrium. The progestin acts as an antiestrogen, causing alterations in endometrial glands, and as a progestin, causing a pseudodecidual reaction. Both of these effects alter the ability of the endometrium to participate in the process of implantation.

The third effect is on the cervical mucus through prevention of the alterations that normally occur at the time of ovulation and appear to permit the ascent of sperm into the uterine cavity. Oral contraceptives cause the cervial mucus to remain thick and apparently hostile to the transmission of sperm. Oral contraceptives may affect tubal motility also and may alter the local ovarian reponse to gonadotropic hormones.

A consideration of the biological effects of oral contraceptives is complicated by the facts that there are many different compounds and several modes of

administration and that data derived from the study of one drug may not be relevant to the effects of another. Indeed, specific effects of an oral contraceptive depend on at least six variables:

1. the specific agent(s) employed
2. the absolute amount of each agent
3. the proportion between the two agents if more than one is used
4. the route of administration (usually oral or parenteral)
5. the length of time the agent is used
6. the age of the user

A wide variety of side effects or oral contraceptives has been described including delayed menses, amenorrhea, spotting, headache, nausea, vomiting, gastric distress, pelvic cramps, feeling of abdominal fullness, nervousness, anxiety, depression, dizziness, leg cramps, breast tenderness, breast enlargement, unusual fatigue, backache, hirsutism, acne, urticaria, chloasma, weight gain, weight loss, and changes in libido. These side effects are dependent on the six variables described.

There is some suggestion that selection of specific agents for specific patients may avoid many of the side effects. Certain authors (13, 44) suggest that the selection should be based on a proper balance among the postulated hormonal effects: estrogenic, antiestrogenic, progestational, antiprogestational, and androgenic. This point of view is valid with respect to the amount of induced cyclic bleeding. Bleeding with sequentials more often simulates natural flow than does bleeding with combined products, which often is diminished. Whether other side effects can be controlled by adjusting medication can be answered only by carefully designed clinical studies, using double blind techniques.

DRUG METABOLISM

A review of the current literature reveals a paucity of information on the absorption, distribution, excretion, and metabolism of contraceptive steroids (18, 106, 144). This death of information is remarkable in view of the widespread use of these effective agents. Of particular interest would be data on the absorption of these materials and the modification of their activity by the gastrointestinal tract. *Studies in these areas are recommended.*

The aromatization of 19-norsteroids in an acid environment has been reported by several investigators. These studies have demonstrated that a metabolite of norethynodrel (17 alpha-ethnyl-19-nor andros-4-ene-3 beta, 10 beta, 17 beta-triol) possesses a higher estrogenic activity when given orally than when given by injection. Because synergism and antagonism are known to exist between weak and potent estrogens, it is possible that a metabolite is responsible for the biologic and contraceptive effects of these agents.

It appears that 10 beta-hydroxy derivatives represent a large portion of the metabolites of some of the contraceptive steroids at least in the case with norethynodrel. Preliminary information from studies of norgestrel indicates that the compound is partially metabolized by a reduction of ring A. The use of ^{14}C-label in the ethynyl group in the same study indicated that about 6 per cent of the material appearing in the urine was in the "free" form; 33 per cent was a glucuronide and 25 per cent was a sulfate. The fact that a side chain rather than a ring structure was used in labeling the compound limits the usefulness of this information.

Since synthetic progestational steroids are usually mixtures of d- and l-forms, and since only the l- form has biologic activity identified by the usual means, it is important to know the relative proportions of these fractions in the products now in use. There appears to be no information about the contraceptive properties of the d- form and it cannot be inferred *a priori* that the lack of potency in the standard bioassay for estrogenic compounds indicates ineffectiveness as a contraceptive. It is theoretically possible that this form may interrupt the reproductive process at a stage that has not yet been ascertained.

REPRODUCTIVE ENDOCRINOLOGY

Understanding of the mechanisms and effects of oral contraceptives and similar steroids on pituitary function is incomplete as indicated by recent reviews (45, 103, 161, 163). Advance has been hampered in part by the lack of uniform and satisfactory assays to differentiate among total gonadotropins, FSH, and

LH, but the development of radio-immune techniques for measuring these biologic products undoubtedly will lead to progress in this field.

Most oral contraceptives produce a contraceptive effect by preventing ovulation through the suppression of the hypothalamic-pituitary system. Not all the agents seem to produce this effect in the same way but, in general, the immediate effect of dominantly estrogenic compounds is to reduce FSH, whereas the effect of progestins is to suppress the midcycle peak of LH without significantly altering the basal LH level. Prolonged administration of estrogens or estrogen-progestin combinations causes marked reduction in both FSH and LH (27, 53, 76, 107, 146). Many animal experiments employing various species (51, 76, 94) support the concept that oral contraceptives exert their effect by blocking estrogen receptor sites in the hypothalamus and pituitary with reduction of gonadotropin release and suppression of ovulation.

Resumption of ovulation after cessation of oral contraceptives is usually prompt, within 4 to 8 weeks in most cases. In a few women, however, amenorrhea persists for 6 months or longer (14, 21, 47, 49, 78, 114, 152, 153). Some believe that this phenomenon simulates the occasional period of extended anovulation that may follow pregnancy or lactation. Recovery after long-term suppression has been described (53). The pituitary recovers first (FSH first, then LH), followed by the ovary, and then the endometrium, which may require as long as three months to regain its normal histologic appearance and enzymatic activity. Although the small group examined showed resumption of ovulation rather promptly, clinical studies continue to report anovulation and amenorrhea from weeks to months after discontinuation of oral contraceptives. Several authors have outlined means of evaluating and treating women with this condition.

Pregnancy may be considered to be the prime indicator of adequate pituitary and ovarian function. While clinical observers agree that most women conceive "promptly" after the discontinuation of oral contraception, valid statistical information is scanty. To be sure, a number of investigators have reported the percentage of women who conveived among those who discontinued, or the distribution of pregnancies by number of months required for conception, or even conception rates per 100 woman-years of exposure. None of these measures is satisfactory. The first completely neglects the duration of follow-up. The second ignores the women who did not conceive. The third fails to take into account that the conception rate declines with time.

The closest approximation to the life table is the percentage of women who conceive during the first cycle after discontinuation. Some such figures have been reported, but they are so far out of line with earlier experience as to raise serious questions as to the completeness or accuracy of the information furnished to the investigators by their informants (67, 130, 169).

Pregnancy outcome was deemed satisfactory in these studies with no significant increase in abortion, prematurity, or developmental anomalies (9, 140). Continued study of this problem should be undertaken, however, since as noted below, there is evidence from laboratory animals that the suspension of ovulation is associated with fetal anomalies once fertility is restored.

Suppression of ovarian function secondary to pituitary suppression by oral contraceptives is evidenced by low estrogen excretion during treatment (107, 115). Flowers and associates (53) found estrogen levels during prolonged use of oral contraceptives to be much lower than those in normal cycles. The endometrium was found to be atrophic with reduced enzymatic activity.

Whether oral contraceptives have direct ovarian suppressive effects is controversial. One group (84) gave contraceptive steroids to amenorrheic women; their subsequent response to human gonadotropins showed no inhibition of the ovarian reaction. This observation supports the contention that the major suppression is at the hypothalamic level. Direct effects of oral contraceptives on ovarian weight and on histological and ultrastructural changes are suggested by some studies (172).

Oral contraceptives in higher doses (5 and 10 mg. of progestins) tend to decrease or stop lactation in many women in the first or second cycle of use (141, 149). Smaller doses are reported to have no significant suppressive effect on lactation (86), but radioactive tagged norethynodrel is excreted in breast milk (101).

REPRODUCTIVE TRACT

Virtually all structures of the reproductive tract are sensitive to the action of ovarian steroid hormones. It is not surprising, therefore that alterations are seen in the various components under the influence of steroid contraceptive agents. Differences depend upon the type and quantity of the compound used, the mode of administration, and the duration of use.

Vaginal cytologic effects are not remarkable but there is a shift toward basophilia with a predominance of intermediate cells during treatment with progestational agents (181). A distinct change is noted in the bacterial flora, with marked reduction in Doderlein bacilli, a remarkable increase in fungi, and a greater number of coccoid bacteria and trichomonads. Such alterations may be related to the increased sexual activity thought by some to occur in certain women who elect to use oral contraceptives.

Progestational compounds indice characteristic physicochemical changes in the cervical mucus (21, 118), including decreased viscosity, poor Spinnbarkeit, absence of arborization, a continuous alkaline pH with no tendency toward an increase in pH at midcycle, and the secretion of a viscous and cellular mucus that is hostile to sperm, as shown by inhibition of penetration and migration of spermatozoa in most treated subjects. With medication there is no cyclic variation in the content of proteins and no trend toward a specific ratio of the major proteins. In the normal cycle, however, a marked decrease in the albumin level and an increase in the mucoid level is noted immediately before and concomitant with ovulation, with reversal of this ratio shortly after ovulation. Inhibition of motility and of penetration of cervical mucus by sperm is demonstrable at all dosage levels of these oral contraceptives but these effects are less pronounced when small doses of progestins alone are used (112).

Biochemical changes in cervical mucus have not been extensively explored. The alpha-amylase content is increased more markedly after combined than after sequential therapy (71), and the glycogen content of the ectocervix is unaffected by steroid contraceptibes in women.

Remarkable morphologic changes induced by progestational hormones have been described (59, 109, 168). Hypersecretion and hyperplasia of the cervical glands, stromal edema, and increased vascularity are the most consistent responses. In Gall's (59) study of 103 randomly selected women receiving oral contraceptives for periods of 1 to 60 months, gross lesions that failed to stain with Schiller's solution were noted in 84 per cent of patients examined. Endocervical erosion or eversion, edema, and softening were the main features. Histological examination showed an inflammatory infiltrate consisting predominantly of plasma cells. Fibrin thrombi were observed in the capillaries and arterioles in about 50 per cent of the biopsy specimens. Atypical polypoid endocervical hyperplasia was found in three cases.

This latter lesion was first described by Taylor and associates (168) in 13 women (median age of 25 years) receiving low-dosage progestational agents. There had been no previous reports of such lesions in women on high-dosage birth control pills. All lesions were associated with an inflammation and they disappeared after discontinuation of the drug. Reversibility of the lesion in cases studied emphasizes the importance of recognition in order to avoid an erroneous diagnosis of adenocarcinoma.

The histologic appearance of the endometrium varies considerably with the type of steroid regimen employed, although prolonged administration tends to diminish these differences (45, 139, 142). Combined therapy is associated with a shortened period of proliferation followed by an early but brief and limited secretory activity in the epithelium of the endometrial glands. Thinning or regression of the endometrium takes place after a few cycles and may be so severe that withdrawal bleeding cannot occur. Prolonged periods of amenorrhea following cessation of treatment may result in part from this action of progestational agents. It is not yet clear whether this oversuppression affects primarily the endometrium, the ovary, the pituitary, or the hypothalamic cycle of gonadotropin-releasing-factors (53, 58, 153).

Endometrial effects during sequential treatment are less pronounced. The progestin induces a partial or early secretory pattern comparable to that of the 18th or 19th day of the cycle, but development of the spiral arterioles is suppressed (123).

Histochemical studies of endometrial tissues have provided some information

about changes in enzymatic activity during treatment. Acid and alkaline phosphatases and DPN diaphorase, which are clearly hormone-dependent, are greatly reduced (53). Alterations are demonstrable in activity of carbonic anhydrase, uterine peroxidase (170), beta glucuronidase, succinic dehydrogenase, lactic dehydrogenase, and several other enzymes (35). However, accurate appraisal of the changes described must be deferred because of deficiencies in standard values.

Myometrial hypertrophy, dilatation of sinusoids, and edema are recognized effects. Congestion and increased vascularity of tissues are noted during pelvic surgery when oral contraceptives are not discontinued for a sufficient period of time prior to operation (145). Uterine myometrial activity is not significantly changed during treatment, but if medications containing both estrogen and a progestin are used, an increase in contractility is noted on the 8th day after the medication is stopped (15).

Little is known regarding the effects of oral contraceptives on the rate of tubal transport of ova in women. Chang (32, 33) demonstrated that ovum transport was accelerated in animals given progestational agents and that early arrival of ova in the nuterus led to failure of fertilization, and to degeneration and expulsion of eggs from the uterus. He noted also that transport and capacitation of sperm were disturbed, but these effects were less pronounced than rapidity of ovum transport in the animals studied. Zanartu (189) found a few motile sperm in the uterus of treated subjects undergoing operations but none in fluid recovered from washings of the fallopian tubes. He therefore suggested that continuous dosage of chlormadinone prevents ascent of spermatozoa.

Suppression of ovulation is one of the most consistent although not invariable effects of steroid contraceptive agents. The ovaries appear grossly small and inactive (145). A few early follicles may be seen beneath the tunica but as a rule no corpora lutea are observed. Ostergaard and Starup (126) reported fresh corpora lutea in six women treated during the cycle in which laparotomy was performed; in most cases these corpora lutea were smaller than normal and they were not associated with elevated pregnandiol levels. Total absence of corpora lutea during treatment is reported in other studies in which culdoscopy was performed (8) and during abdominal operation (145). In Ryan's study (145) focal areas of cortical stromal fibrosis were observed in about half the patients on medication for one year or more. It is of particular concern that in this study thrombi were seen in the ovarian and uterine veins in three of the 27 study cases, but the significance of these observations cannot be assessed until data on control subjects are available.

LIVER

Moderate changes in liver function tests are seen in many symptom-free women on oral contraceptives. BSP (sulfobromophthalein) excretion is diminished with almost all oral contraceptive drugs in up to 40 per cent of women on medication. This effect appears to be dose-dependent (4, 92) and may be related to a fall in serum albumin concentration seen with the use of oral contraceptives (38). Plasma amino acid levels also fall with the use of these agents (37).

BSP is retained in plasma primarily conjugated to albumin, and its retention with oral contraceptives is related to the concomitant alteration in bile transport seen with the use of these agents. Such an effect is produced by all agents that have an alkyl group at the 17-alpha position of the steroid molecule. It is thought to result from inhibition of the glucuronyl transferase system, which participates in the metabolism of bilirubin.

Another commonly observed alteration in liver function is elevation in transaminase values in 20 per cent of patients (50, 100). An increase in SGOT also occurs (99), and in a small proportion of subjects a slight elevation in alkaline phosphatase levels is found. After cessation of treatment, all of these values return to normal over a period of time. These effects are more severe in postmenopausal women. For instance, in two studies BSP retention appeared to occur in most such women on oral contraceptives, and an increase in SGOT was almost universal. In these women, the tests also return to normal after the cessation of treatment.

Jaundice occurs in about one woman in 10,000 on oral contraceptives (124). Many patients have a typical history of nausea, malaise, and itching with

onset several weeks after medication is begun. Shortly thereafter they become jaundiced and they produce dark urine. Liver function tests show increased levels of bilirubin and moderately elevated levels of transaminases. Liver biopsies show canalicular and hepaticocellular bile stasis. Liver tests in most patients with this condition revert to normal within several weeks after the cessation of therapy. In a few, however, abnormal liver function tests persist for longer periods.

Schaffner (151) has divided patients who become jaundiced with oral contraceptives into three groups. The first group includes women who have recurrent cholestasis of pregnancy; the jaundice in these patients may result from an idiosyncrasy of the liver to the agents. The second group of patients includes those who have cholestasis without evidence of cellular damage or hypersensitivity; a similar effect is produced in the jaundice associated with anabolic steroids, probably a direct action of the oral contraceptives on the bile secretory apparatus. The third group shows cellular injury or sensitivity to the drug.

Several studies (147) have shown that in some experimental animals, as well as the human being, the inhibition of bile transport seen with oral contraceptives is largely an effect of estrogen. Clinical studies have confirmed this concept, and recent investigations of low doses of progestins alone as contraceptives have shown little or no effect on bile transport or BSP excretion.

The oral contraceptives affect numerous enzyme systems other than those already mentioned (135). Among other effects are increases in activity of beta-glucuronidase and isocitrate dehydrogenase activities and decreases in activity of lactic dehydrogenase, alkaline phosphatase, and transaminase activities. Alteration in the serum naphthylamidase isozymes is thought to be one of the most sensitive indicators of disturbances in liver function caused by oral contraceptives (6). Stoll and coworkers (165) found a correlation between increases in the level of glutamic oxalacetic transaminase and the histological demonstration of damage to liver cells. They believe that this effect is caused by the progestin rather than the estrogen in the oral contraceptive. Recent reports (29, 154) that oral contraceptives increase ceruloplasmin-oxidase levels reflect the well-established observation that estrogen alone has this effect (57).

The recently observed apparent enhancement of hypertension by oral contraceptives in certain women may come about in part through the increase in serum-renin substrate levels. The estrogens in oral contrceptives may exert this effect by stimulation of the hepatic biosynthesis of this enzyme. Oral contraceptives also increase aldosterone levels. Such alterations have been postulated to compromise the ability of the renin-angiotensin-aldosterone mechanism to respond to normal physiological stimuli (97).

Another effect of the estrogen in oral contraceptives on enzyme systems concerns that metabolism of cortisone. It decreases the ability of the liver to extract cortisol from the blood (148) and is possibly related to the decrease in urinary excretion of cortisol and its metabolites (129) that results from administration of estrogen Sandberg has postulated that the progestins may also participate in displacing cortisol from transcortin. Although the true significance of these effects is unknown, their relation to pituitary function in particular should be investigated.

Several studies have demonstrated the effect of oral contraceptives on aminolevulinic acid (ALA) synthetase, an enzyme that participates in the production of heme. The enzyme is normally produced at a low rate by liver cells. Oral contraceptives have been shown to increase ALA synthetase levels as well as urinary coproporphyrin in a significant proportion of healthy women (26). The relation between this finding and the observation that oral contraceptives protect women with acute intermittent porphyria from attacks, is of considerable interest (127).

The effects of oral contraceptives on ALA synthetase may also be related to interference by oral contraceptives with the metabolism or detoxification of certain drugs. Their effect on ALA synthetase and on P-450-cytochrome, a hemoprotein located in the endoplasmic reticulum of the liver cell, may be related to alteration by oral contraceptives of the capacity of the liver to transform drugs into biologically inactive substances. Oral contraceptives appear to increase the detoxification of meperidine but to decrease the detoxification of normeperidine, a metabolic degradation product.

These effects on detoxification are not the result solely of the enxyme-inducing potency of these drugs, since steroids are known to serve as substrates for the microsomal drug-metabolizing enzyme system in the liver. The drugs, therefore, compete with various exogenous substances for oxidative transformation by the enzyme system. The dual role played by sex steroids as both inducers and competing substrates makes it difficult to analyze the effect of oral contraceptives on the ability of the liver to detoxify specific agents (85, 89).

A recent review (143) of the hepatic toxicity of oral contraceptives concludes that these agents produce their effects through modifying permeability of the liver cell rather than causing parenchymal cell damage and that their use is probably not detrimental to the hepatic function of otherwise healthy women.

CARBOHYDRATE METABOLISM

Ovarian steroid hormones have been known for some time to modify carbohydrate metabolism. Early workers reported a decrease of glucose tolerance in diabetic animals treated with estrogen, but others (79, 80) demonstrated amelioration of diabetes in estrogen-treated rats; they attributed this effect to the induction of islet cell hyperplasia. Similarly, in human subjects, contradictory effects of gonadal steroids on carbohydrate metabolism are reported. Several (54, 167)) have shown that estrogens may lower the fasting blood sugar levels by as much as 20 per cent and that individuals with onset of diabetes in maturity may show lower insulin needs when estrogens are given. More recent work (82) has shown that estrogens such as mestranol, administered alone as well as in combination with norethynodrel, can cause a decrease in glucose tolerance. Androgens generally produce deterioration of carbohydrate metabolism in mammals (54, 96).

Explanation for these inconsistencies appears to depend on the chemical structure of the compound, the amount administered, and the individual sensitivity to the metabolic actions of these agents (12).

The preponderance of evidence indicates that glucose tolerance is diminished in women taking oral contraceptive drugs (61, 129, 132, 133, 157, 159, 186). Evidence of the abnormality is more pronounced with the oral than with the intravenous test. Similar findings with respect to greater frequency of abnormality in the oral, compared with the intravenous, test are seen in gravid women (16).

The impairment of glucose tolerance is more pronounced in women predisposed to diabetes and in those with latent or overt diabetes. These effects are well recognized in association with pregnancy. In studies in which a comparison can be made between the diabetogenic influences of pregnancy and oral contraceptives, the so-called diabetogenic effects of the drugs were shown to be of a lesser degree (12).

In nondiabetic subjects increased insulinogenesis is observed following both short-term and long-term use of oral contraceptives (159, 160). Effects are more pronounced with combined than with sequential regimens. In long-term use, the tendency is for glucose tolerance to return to normal while insulin levels remain elevated, suggesting that hyperinsulinism may serve as a compensatory mechanism for maintaining homeostasis of glucose.

Wynn and Doar (185) tested 67 subjects before and during oral contraceptive therapy (Group A) and 24 subjects during and after treatment (Group B). Glucose tolerance decreased significantly in approximately three-fourths of the subjects in Group A and improved in virtually 100 per cent of Group B after treatment was stopped. In contrast, there was a significant elevation of plasma insulin levels during therapy in Group A subjects in response to a glucose load, whereas insulin response was not significantly different in Group B subjects on or off treatment. These findings support the concept that increased insulinogenesis is essential for prevention of hyperglycemia in subjects receiving steroid contraceptives and raise the question of the capacity of pancreatic islet cells to sustain hyperactivity during long-term use of these agents.

In latent diabetic subjects or in women with overt diabetes, insulin response to steroidal contraceptive agents appears to depend upon the functional state of pancreatic beta cell activity. Gershberg (62) found a transient rise in immunoreactive insulin secretion in potentially diabetic patients during the first two months of treatment with oral contraceptives, but after three months glucose tolerance was impaired and insulin secretion returned to initial levels

despite hyperglycemia. In women with overt diabetes, glucose tolerance deteriorate promptly and immunoreactive insulin levels decreased at the half-hour and one-hour periods of the test.

Gold and his associates (64) showed that oral contraceptive-induced hyperglycemia demonstrable both during fasting and after glucose loads was accompanied not only by increased secretion of insulin but also by a significant increase in resistance to exogenous insulin. These findings accentuate the hyperglycemic potency of steroid contraceptives more strikingly than do studies performed in nondiabetic subjects. Whether prolonged administration of steroid contraceptives can result in exhaustion of the insulinogenic reserve and thus induce diabetes in women who are not genetically predisposed has not yet been ascertained.

Growth hormone secretion is known to be influenced by sex steroids. Frantz and Rabkin (56) demonstrated an elevation in HGH levels in response to estrogen, and Spellacy (156) showed significant increases also during a hypoglycemic stimulation test after administration of oral contraceptives. Gershberg (62) found elevation in potentially diabetic subjects of HGH levels that increased progressively during three months of treatment with medroxyprogesterone acetate. The importance of persistent elevation of HGH produced by oral contraceptives is unknown. A causal relation might be postulated between the increases in HGH and induced hyperglycemia and between increased insulin resistance and compensatory increases in circulating insulin.

Blood pyruvate levels are strikingly increased during oral contraceptive treatment. Elevated levels are demonstrable in the fasting state and after either oral or intravenous glucose tolerance tests in both obese and nonobese subjects (46). These effects can be produced with estrogen alone. The question of whether this is a direct effect of the estrogens or an effect secondary to increases in other circulating hormones such as cortisol, growth hormone, and thyroxin has not been ascertained.

These investigators (46) also studied the venous lactate-pyruvate ratio during infusion of sodium 1 (+)—lactate solution. Since conversion of lactate to pyruvate is obligatory for lactate metabolism, infusion of the stable solution was used to provide information about whether elevated levels of blood pyruvate and lactate in patients on oral contraceptives resulted from an increased rate of production or impaired removal of these metabolites. Close correlation of fasting blood lactate levels and the calculated endogenous production rate of lactate was observed in women on oral contraceptives and in controls, suggesting an increased rate of production. The authors further suggest that these metabolic alterations are caused by increased cortisol activity, probably at the hepatic level.

Substantial increases in plasma triglyceride levels are demonstrable during treatment and they remain elevated for months after discontinuation in long-term administration (60). This effect may have some bearing on the increases in plasma insulin levels previously described. In preliminary reports, Wynn and Doar (187) suggested that there was a slight increase in the nonesterified fatty acid levels in patients receiving progestational agents; in a subsequent study (186), however, with better matched controls, the same investigators found no significant differences in NEFA levels that could be related to treatment.

THYROID FUNCTION

In women receiving combined steroid contraceptives the PBI level is elevated approximately 25 to 40 per cent above pretreatment levels. Thyroxine-iodine (T4 by column chromatography) values are similarly increased and T3 resin uptake values are diminished. All demonstrated changes appear to result from estrogen-induced increases in thyroxine-binding globulin (TBG). A significant rise in the PBI can be induced with ethinyl estradiol in amounts as small as 0.01 mg. (3). Progestational agents alone do not alter the PBI or the triiodothyronine red blood cell uptake (77).

All of these effects can be explained on the basis of increased protein-binding induced by estrogen. The basal metabolic rate, cholesterol levels, and I-131 uptakes remain within normal limits. Concentrations of "free" thyroxine remain within normal range, suggesting that the functional status of the thyroid is unchanged (69). In addition, a normal response of the thyroid gland to small doses of TSH is maintained in patients on prolonged cyclic combination therapy (110).

Within two to four months after cessation of treatment, thyroid function tests are normal. Development of thyroid adenomas, hyperthyroidism, and hypothyroidism have not been reported.

ADRENAL FUNCTION

Alterations in adrenocortical function tests observed in patients on combined steroid contraceptives seem to result chiefly from the estrogenic properties of the drugs; there is no evidence of interference with normal pituitary-adrenal relations. Increased protein-binding of aldosterone and cortisol by transcortin (cortisol-binding globulin) is found. Levels of plasma cortisol are increased and the clearance rate of its urinary metabolites is decreased (48, 148). The conclusion that the marked reduction in urinary 17-ketosteroid and 17-ketogenic steroid excretion rates results from impairment of pituitary-adrenal function is based on the reduced response to the metyrapone test during administration of oral contraceptive agents (105, 116). This finding suggests a lack of compensatory increase in pituitary ACTH secretion. The response to the ACTH stimulation test, however, is essentially normal. Furthermore, in the Piromen test, in which the increase in plasma and urinary levels of cortisol and its metabolites presumably results from ACTH secretion, a normal response in the release of ACTH is reported.

Although there are discrepancies among these various studies of the effects of oral contraceptives on adrenal function, there is no evidence to date of adrenocortical insufficiency during surgical procedures or other stress in patients on contraceptive drugs. A possible exception is one clinical report of severe adrenocortical insufficiency associated with the use of oral contraceptives (42).

BLOOD VESSELS

Information regarding the effect of contraceptive steroids on the venous system is limited to clinical observation of increases in the diameter of venous vessels and in venous volume. It remains to be elucidated whether this increase in caliber of the vessels may lead to endothelial injury and exposure of blood to collagen and to the basement membrane. Goodrich and Wood (68) found a significant increase in the distensibility of veins in the calf following administration of contraceptive steroids. This increase was present over the range of venous pressure studied, namely between 5 to 30 mm. mercury and was accompanied by a 25 per cent reduction in mean linear velocity of venous blood flow.

The concentration of angiotensinogen in plasma appears to change consistently following administration of contraceptive steroids. Values up to eight times those of normal have been reported. The rise is observed within 4 days, usually reaching a maximum within 2 weeks. After discontinuation of medication the level may remain elevated for more than a month.

Changes in the concentration of renin are less consistent. It appears that the normal response to an elevation of angiotensinogen is a decrease in renin concentration, suggesting a mechanism of auto-regulation. Because the quantity of angiotensin that can be generated is limited, a large increase in the concentration of angiotensinogen is accompanied by only a twofold increase in angiotensin.

The clinical implications of these changes in the concentrations of angiotensinogen, renin, angiotensin, and aldosterone remain to be elucidated, since the changes are observed in most patients without a concomitant rise in blood pressure. No information is available at present regarding factors predisposing to the adverse effect of contraceptive steroids. They may include renal disease and an increased sensitivity to retention of sodium and water. According to present information, increases in blood pressure of susceptible women caused by contraceptive steroids are reversible even after prolonged use of the drug. It should be noted that elevation occurs in both systolic and diastolic pressures.

It has been suggested that venous hypertension may distend the endothelium of the valve pockets to the point at which injury occurs. Thus, it would be desirable to obtain measurements of venous pressure in peripheral veins in patients on contraceptive steroids and to ascertain whether usual physical activities lead to exceptional increases in venous pressure in excess of those observed in control subjects.

BLOOD PRESSURE

Estrogen and other contraceptive steroids are known to alter the concentration of substances thought to be important in the regulation of blood pressure. There are now several reports of hypertension associated with the use of oral contraceptives (97, 171, 183). Increase in plasma angiotensinogen following administration of estrogen was reported several years ago (75). More recently, elevated levels of plasma renin were found in normal pregnancy (24), and estrogen and progestin were found to increase the secretion of aldosterone (104). In addition, oral contraceptives are now known to enhance the reactivity to endogenous renin (97, 98).

It appears, therefore, that susceptible women may experience an increase in blood pressure following administration of contraceptive steroids. Because of the high prevalence of hypertension in the population it is difficult to identify with certainty the women in whom administration of contraceptive steroids has led to an increase in preexisting hypertension or has produced hypertension in previously normal women. Several cases, however, have been reported in which the etiologic relation has been established beyond reasonable doubt (97).

BLOOD CONSTITUENTS

Many studies (6, 7, 22, 29, 95, 102, 120, 135, 137, 158, 160, 173) have been reported describing the effect of contraceptive steroids and allied agents on plasma proteins and their metabolism. Their administration leads to decreases in haptoglobin, albumin, and total serum proteins, and dose-dependent increases have been reported for thyroxine-binding globulin and iodine-binding protein. Increases have also been reported for plasminogen, ceruloplasmin, estrogen-binding proteins, C-reactive protein, renin, factors VII and IX, fibrinogen, beta-glucuronidase and isocitrate dehydrogenase (6, 7, 102, 120, 158, 173). Only a few constituents are decreased by administration of estrogens: lipoprotein lipase, cholinesterase, lactic acid dehydrogenase, and alkaline phosphatase (23).

LIPIDS

Contraceptive steroids are known to increase the concentration of triglycerides and phospholipids, particularly lecithin, in the plasma of women (188). The principal effect is on the lipoproteins of very low and high densities. Hypertriglyceridemia has been consistently found to accompany the use of these agents; the responsible component of the contraceptive preparation appears to be the estrogen rather than the progestin.

According to presently held views, the site of action of estrogens upon triglycerides or lipoprotein synthesis is the liver. Since lipid synthesis requires insulin, it is possible that changes in lipid output are mediated via the effect of estrogens upon plasma concentration of insulin (136). Estrogens have also been implicated in modifying the removal of these lipids from the circulation. It has been demonstrated that the rise in lipolytic activity of plasma brought about by administration of heparin was decreased following administration of estrogens (73a).

Although changes in plasma lipids and lipoproteisn are appreciable following the administration of contraceptive steroids, there is no knowledge of the functional significance of these changes. No specific clinical disturbance has yet been attributed to the alterations in lipid and lipoprotein composition.

SALT AND WATER METABOLISM

The effects of oral contraceptives on water and electrolyte metabolism have not been studied in detail, but it is pertinent to describe the changes produced by individual steroids. For instance, progestin in approximately physiological doses causes a diuresis of sodium followed by retention even while the hormone is administered. The diuretic effect appears to predominate at higher dose levels, but it is not certain whether long-term progestin administration causes diuresis or retention of sodium.

The short-term natriuretic effect of progestin is opposite to that of estradiol-17 beta, which at high doses causes sodium retention. The effect of oral contraceptives on sodium excretion is sensitive to the proportions of its constituents. The overall effect, however, appears to be a decrease of sodium excretion (134).

The effects of these hormones on water metabolism are complex. Water can be retained or lost in association with sodium, potassium, phosphate, and nitrogen as part of anabolic or catabolic actions. Water can also be retained or lost in association with sodium and chloride in the expansion or contraction of extracellular fluid volume; these effects also are separate. Furthermore, the effects may be biphasic or even triphasic during hormone administration.

MINERALS

Several investigators (19, 65, 66) have shown no effect of oral contraceptives on levels or intestinal absorption of calcium, but a decrease in magnesium excretion has been demonstrated with a parallel decrease in serum magnesium levels. The data suggest that suppression of ovulation is associated with a poorly understood alteration in magnesium metabolism. Concern has been expressed over the observation that there is an association between soft water supplies and increased levels of cardiovascular disease in certain geographic regions. These interesting observations warrant confirmation.

Oral contraceptives have also been noted to increase serum copper and zinc levels (29, 125), as well as serum iron and total iron-binding capacity (25). The significance of these observations is not known, but estrogens have been known for some time to increase serum copper and ceruloplasmin levels (57).

KIDNEY

In proportion to the widespread use of oral contraceptives, remarkably little is known about their effects on renal function. These agents have been shown in recent years to be the cause of hypertension in certain women and this effect appears to be mediated in part through alterations in the angiotensin-aldosterone-renin system. It may also be mediated in part through the development of asymptomatic pyelonephritis developing secondary to ureteral dilatation, which is known to occur with these agents.

Ureteral dilatation is the only well-documented effect of oral contraceptives on the excretory system (111). Such dilatation disappears after medication ceases and it has been postulated to be due to progestins rather than estrogens. Comparable studies in the rabbit (115) demonstrated no ureteral dilatation but did show that these agents result in the disappearance of elastic fibers from the ureters.

LUNG

Recent studies (108, 162) show that oral contraceptives and allied agents exert a variety of effects on the respiratory system. First, progesterone, through some unknown effect on the respiratory center, increases alveolar ventilation and produces decreases in the arterial pCO_2. This effect is seen during pregnancy and in the luteal phase of the menstrual cycle. The presence of an ethinyl group on the progestin prevents this effect. Second, contraceptive steroids cause an increase of bronchial resistance; early work suggests that this effect may be mediated by an increase in histamine, a potent bronchial constrictor. Third, estrogens alone appear to inhibit gas transfer to a small degree. Fourth, stilbestrol or ethinyl estradiol in large amounts will produce progressive pulmonary lesions characterized by an accumulation of macrophages in capillaries, migration of macrophages to the alveolar interstitium and diffuse interstitial pneumonitis. Last, fibrosis of the pleura and the interstitial tissue of the lung was shown to develop after several months of treatment.

The relation between these effects and those of oral contraceptives in women has not been elucidated.

CENTRAL NERVOUS SYSTEM

Ovarian steroids are known to be essential to production of normal expression of sexual behavior in female animals. In man evidence of the essential role of these substances in the control of sexual activity is still lacking. The few reported studies suggest that an increase in either sexual desire or sexual activity in women as well as Rhesus monkeys coincides with the days preceding ovulation, while the second half of the menstrual cycle is characterized by a decrease or lack of sexual interest.

One study (117) reports a reduction in male sexual behavior in subhuman primates attendant upon the administration to the female of both sequential

and combination contraceptive steroids, the effect being more pronounced with the latter. This remarkable effect is mediated through some unexplained mechanism, possibly an alteration in female sexual pheromones.

No definite conclusions can be drawn from data about the effect of oral contraceptives on human sexual behavior. One study (122) indicates that libido was reduced or lost in about one-third of patients receiving oral contraceptives. Other investigators (87, 88, 119, 176a), however, report an increased desire and greater satisfaction from sexual intercourse. In these situations it is difficult to separate the actual effect of the contraceptive steroid on sexual perceptivity from the effect brought about by an absence of fear of an unwanted pregnancy.

In lower species, progesterone is known to increase and estrogen to decrease the threshold for seizures induced by electric current (90, 164). The combination of agents used as contraceptives tends to lower the threshold, and the effect appears to be dependent on the ratio of progestin to estrogen. The recently reported increase in frequency of epileptic seizures in patients with documented epilepsy in the immediate premenstrual period implies that the observations made in lower species may be applicable to man (113, 176).

No information is available regarding the relation between contraceptive steroids and central nervous system excitability. Pregnanolone, a metabolite of progesterone, is a potent hypnotic; in the cat it is more effective as a hypnotic on the basis of weight than is pentobarbital. On the other hand, several synthetic progestins such as norethynodrel have minimal hypnotic properties.

The effect of contraceptive steroids upon thermoregulatory centers still remains to be elucidated. There is circumstantial evidence that at least progesterone increases body temperature by a central action. The exact mechanism is not known.

Depression has been identified as a side effect of contraceptive steroids, but its relative frequency varies markedly from study to study. Close examination of the data (7a, 62a, 69a) indicates that the depressive episodes encountered are usually not related to the pharmacologic effects of contraceptive steroids but are peculiar to the population under study. Brief periods of depression are not infrequent among young housewives with many small children.

Depression is more frequently associated with women of higher educational background. Thus, one investigator (87) studying a small population in a predominantly academic community in which the mean level of education was 15.4 years detected symptoms of depression in 34 per cent. In general, women who suffer from depression before and during the menstrual period seem more susceptible to depression while on contraceptive steroids. Recent observations (69a) indicate that depression and loss of libido are more likely to occur with compounds containing larger quantities of progestins and that the lowest incidence of these side effects is observed with the sequential preparations. The incidence in the former group was 28 per cent, whereas that in the latter was only 5 per cent. Another study (119) covering 72 clinic patients followed for 15 months reports no increase in depression attributable to the medication.

The incidence of headache among patients attributable to contraceptive steroids ranges between 3 and 11 per cent (129a). This kind of headache often has features associated with migraine, and changes in the pattern of pre-existing migraine headaches have been reported (180a). The tendency for migraine to occur when the concentrations of gonadal steroids change is well recognized. It is also known that women with pre-existing migraine headaches tend to develop their attacks while off medication, in contrast to patients without pre-existing headache who are more likely to complain of migraine headaches during the period of medication. It must be stressed that most studies have drawn their samples from selected populations, often with characteristics that make the evaluation of this side effect difficult if not impossible. Evidently, more studies are required to ascertain the true incidence of these phenomena.

SKELETAL MATURATION

In recent years there have been several reports of the use of estrogen to prevent excessive height in otherwise normal girls through the induction of premature epiphyseal closure. Both estradiol valerate (179, 180) and stilbestrol (177) have been used for this purpose, and the endocrinologic basis for this treatment has been reviewed (182). The effect is said to be mediated by direct

metabolic action of the agent on bone structure rather than through suppression of growth hormone (179).

Observations of this nature have led to concern over the possible effects of oral contraceptives on bone growth in young women in whom epiphyseal closure has not yet taken place. There is not yet any evidence on which to base this conclusion. First, the use of estrogen even in much larger amounts than those in oral contraceptives is not uniformly successful in inducing epiphyseal closure. Second, there is no evidence that the progestin in oral contraceptives has any effect on bone maturation. Third, in order to be effective at all the estrogen treatment of excessive growth must be started prepuberally, considerably earlier than the age at which oral contraceptives are ordinarily used.

SKIN

Oral contraceptives have been known for some time to produce chloasma, or melasma. Resnick (138) reported an extensive study of 212 patients, a high percentage of which developed melasma with both combination and sequential oral contraceptives. This condition differs from the melasma of pregnancy in that it does not seem to regress completely after medication is stopped. Eighty-seven per cent of Resnick's patients who developed melasma from oral contraceptives had had this condition during pregnancy, suggesting that a history of increased skin pigmentation during pregnancy may be used as an indicator for detecting susceptible individuals.

A more recent case report (155) describes a woman who developed exceptionally marked melasma as well as areas of increased pigmentation of other parts of her body, suggestive of the pigmentation seen in Addison's disease. The authors ruled out this condition to their satisfaction and concluded that the effect was due to activity of melanocyte-stimulating hormone.

It has been known for some time that oral contraceptives decrease sebum production, and that suppression of sebaceous gland activity can be directly correlated with improvement of acne (166).

Erickson and Peterka (52) reported a single case of sensitivity of the skin to sunlight as a result of oral contraceptives; repeated studies in the same patient showed that the effect appeared to be caused by the estrogen. Another effect of these agents on the skin was described by Krane (113), who showed, in rats, that both estrogens and progestins decrease the collagen content of skin and increase its turnover. Progesterone in particular interferes with the generation of cross linkage and the maturation of collagen. Comparable studies have not been carried out in women. Other observations (36) suggest that oral contraceptives may produce a male-type partial alopecia in certain patients. Here again, there is insufficient evidence to confirm this observation (2).

OTHER EFFECTS

Studies of the effects of oral contraceptives on the gastrointestinal tract are limited. Crean (39) reviewed the relation between endocrine secretions and gastric function and described the decrease in severity of peptic ulcer in women during pregnancy and during the administration of estrogens. Whether these effects occur with the administration of oral contraceptives is not known.

A related observation concerns acute colonic lesions in a few women on oral contraceptives (1, 91, 174). The authors postulate that these lesions may result from thromboembolic phenomena.

Goh (63) has reported a significant increase in chromosomal abnormalities, particularly breaks, in the peripheral lymphocytes of women on oral contraceptives. Comparable changes in lymphocytes from male subjects were induced by incubating the lymphocytes with the serum of women on oral contraceptives. These effects disappear on discontinuation of medication. These observations have not yet been confirmed, but they may be related to the findings by Carr (28) of chromosomal abnormalities in abortuses collected from women who became pregnant after taking such agents.

Other clincial phenomena that have been described in association with oral contraceptives include abnormal patency of the Eustachian tube (5), hypertrophic gingivitis (10), myalgia (43), and positive LE cell test without evidence of collagen disorders (151a). Only one isolated report of the possible exacerbation of systemic lupus erythematosus by oral contraceptives (131) has appeared.

EFFECTS ON THE FETUS

Several studies implicate oral contraceptive agents in masculinization of the external genitals of female fetuses during the first 16 to 18 weeks of inadvertent pregnancy. Masculinization varies with the compound, but is most pronounced with 19-nor compounds. Jacobson (81), who treated 385 pregnant women with norethindrone, observed maternal masculinization in 5.5 per cent of women and virilization in 23.7 per cent of female newborns. A comparison of the placental transfer of norethindrone dydrogesterone and medroxyprogesterone showed that norethindrone is the most rapidly transferred (40) ; this is the compound most frequently implicated in masculinization by oral contraceptives.

A report (24) of medroxyprogesterone therapy in 172 women in the first 12 weeks of pregnancy showed no evidence of genital tract alteration in male fetuses and slight masculinization in one female fetus; this observation may be related to the very rapid metabolism of medroxyprogesterone in the pregnant woman and fetus (17). Feminization of the male fetus from the estrogenic component of oral contraceptives has not been a problem. It was not observed among male fetuses whose mothers had estrogen therapy in the critical first 12 weeks of pregnancy (72).

The experiments of Wharton and Scott (178) studying the effects of oral contraceptives on fetal rhesus monkeys appear to be unequivocal. Norethindrone was given in large doses to pregnant monkeys (25 mg. per day for 5 days per week) from approximately the 30th day of pregnancy to full term. Eight of the ten fetuses were stillborn. All 5 females were virilized, and males showed a greater degree of cryptorchidism than expected. Six mothers treated with 50 mg. progesterone IM daily during the same period of pregnancy suffered no deleterious effects. All were delivered alive at term (3 males and 3 females) and none showed genital malformations. These observations indicated that progesterone was much less harmful than norethindrone, but clinical implications for women cannot be drawn because of the very large doses of norethindrone employed.

Deleterious effects of several contraceptive steroids on the ova of rabbits have been described (31, 34, 41). One author (150) described minimal abnormalities in external genitalia and infertility in female offspring of rats treated with a combination of norethynodrel and mestranol during pregnancy and lactation. Others (11) noted disturbances of meiosis and disorganized chromosomes in ova of rats given norethynodrel. Animals that received norethynodrel throughout pregnancy showed reduced litters. There are no comparable data on effects of contraceptive steroids on ova or chromosomes in the human being or on the eventual fertility of human fetuses exposed to such steroids *in utero*.

CONCLUSIONS AND RECOMMENDATIONS

Oral contraceptives are an important and effective means of fertility regulation and family planning. For certain women they are undoubtedly the most effective method currently available. Nevertheless, it is evident that preparations now in use have a multitude of effects on many organ systems and although it is not yet possible to draw definite conclusions about their effect on the health of women and infants, the use of these agents warrants close observation and surveillance. Effects of special concern include alterations in carbohydrate metabolism, the character and distribution of lipids, liver function, protein metabolism and the development of hypertension as well as alterations in endocrine function.

References

1. Anon. Colitis and contraception. New Eng J Med 278:452, 1968.
2. Anon. Oral contraceptives and alopecia. Brit Med J 1:593, 1968.
3. Alexander, R. W., and Marmorston, J. Effects of two synthetic estrogens on the level of serum PBI in men and women with atheroslcerotic heart disease. J Clin Endocr 21:243, 1961.
4. Allan, J. S., and Tyler, E. T. Biochemical findings in long-term oral contraceptive usage. I. Liver function studies. Fertil Steril 18:112, 1967.
5. Allen, G. W., Abnormal patency of the eustachian tube. JAMA 200:142, 1967.

6. Arturson, G., Beckman, L., and Persson, B. H. Alterations in serum naphthylamidase isozymes during treatment with oral contraceptives. Nature 214:1252, 1967.
7. Aurell, M., Cramer, K., and Rybo, G. Serum lipids and lipoproteins during long-term administration of an oral contraceptive (anovlar). Lancet 1:291, 1966.
7a. Bakker, C. B., and Dightman, C. R. Side effects of oral contraceptives. Obstet Gynec 28:373, 1966.
8. Balin, H., Wan, L. S., Steven, V., Franklin, R. R., and Goldzieher, J. W. Alterations of ovarian physiology subsequent to oral contraceptive therapy. Presented at ACOG, April 28, 1969.
9. Banks, A. L., Rutherford, R. N., and Coburn, W. A. Pregnancy and progeny after use of progestin-like substances for contraception. Obstet Gynec 26:760, 1965.
10. Barber, D. N. Oral contraceptives and dental care. Brit Med J 4:417, 1967.
11. Beaconsfield, P., and Ginsburg, J. Oral contraceptives and cell replication. Lancet 1:592, 1968.
12. Beck, P. Effects of gonadal hormones and contraceptive steroids on glucose and insulin metabolism. Salhanick, H. A., Ed. Conference on metabolic effects of gonadal hormones and contraceptive steroids. December 1–5, 1968.
13. Behrman, S. J. Which "pill" to choose? Hosp Prac 4:34, 1969.
14. Bell, E. T., and Loraine, J. A. Urinary steroid and gonadotrophin excretion in women following long-term use of oral contraceptives. Lancet 2:442, 1967.
15. Bengtsson, L. P. The effects of oestrogen and gestagen on the non-pregnant human uterus. J Obstet Gynaec Brit Comm 73:273, 1966.
16. Benjamin, F., and Cooper, D. J. Comparative validity of oral and intravenous glucose tolerance tests in pregnancy. Amer J Obstet Gynec 97:488, 1967.
17. Besch, P. K., Vorys, N., Ullery, J. C., Barry, R. D., and Couri, D. *In vivo* metabolism of H^3-medroxyprogesterone acetate in pregnant and nonpregnant women and in the fetus. Amer J Obstet Gynec 95:229, 1966.
18. Bialy, G., Layne, D. S., and Pincus, G. Some biological properties of a urinary norethynodrel metabolite. Proc Soc Exp Biol Med 118:862, 1965.
19. Birge, S. J., and Avioli, L. V. The effect of oral contraceptives on calcium absorption. Salhanick, H. A., Ed. Conference on metabolic effects of gonadal hormones and contraceptive steroids. December 1–5, 1968.
20. Bolognese, R. J., Piver, M. S., and Feldman, J. D. Galactorrhea and abnormal menses associated with a long-term progesterone. JAMA 199:42, 1967.
21. Bowman, J. A. The effect of norethindrone-mestranol on cervical mucus. Amer J Obstet Gynec 102:1039, 1968.
22. Brody, S., Kerstell, J., Nilsson, L., and Svanborg, A. The effects of some ovulation inhibitors on the different plasma lipid fractions. Acta Med Scand 183:1, 1968.
23. Brown, J. J., Davies, D. L., Doak, P. B., Lever, A. F., and Robertson, J. I. S. Plasma renin in normal pregnancy. Lancet 2:900, 1963.
24. Burstein, R., and Wasserman, H. C. The effect of provera on the fetus. Obstet Gynec 23:931, 1964.
25. Burton, J. L. Effect of oral contraceptives on haemoglobin, packed-cell volume, serum-iron, and total iron-binding capacity in healthy women. Lancet 2:978, 1967.
26. Burton, J. L., Loudon, N. B., and Wilson, A. T. Urinary coproporhyrin excretion and hepatic function in women taking oral contraceptives. Lancet 2:1362. 1967.
27. Cargille, C. M., and Ross, G. T. Oral contraceptives and follicle-stimulating hormone. Lancet 1:924, 1968.
28. Carruthers, M. E., Hobbs, C. B., and Warren, R. K. Raised serum copper and caeruloplasmin levels in subjects taking oral contraceptives. J Clin Path 19:498, 1966.
30. Carruthers, R. Chloasma and the "Pill." Brit Med J 3:307, 1967.
31. Chang, M. C. Effects of certain antifertility agents on the development of rabbit ova. Fertil Steril 15:97, 1964.

32. Chang, M. C. Effects of medroxyprogesterone acetate and of ethinyl oestradiol on the fertilization and transportation of ferret eggs. J Reprod Fertil 13:173, 1967.
33. Chang, M. C. Effects of progesterone and related compounds on fertilization, transportation and development of rabbit eggs. Endocrinology 81:1251, 1967.
34. Chang, M. C., and Yanagimachi, R. Effect of estrogens and other compounds as oral antifertility agents on the development of rabbit ova and hamster embryos. Fertil Steril 16:281, 1965.
35. Connell, E. B., Sedlis, A., and Stone, M. L. Endometrial enzyme histochemistry in oral contraceptive therapy. Fertil Steril 18:35, 1967.
36. Cormia, F. E. Alopecia from oral contraceptives. JAMA 201:635, 1967.
37. Craft, I. L., and Wise, I. Oral contraceptives and plasma amino-acids. Nature 222:487, 1969.
38. Crawford, J. S., and Hooi, H. W. Y. Binding of bromsulphthalein by serum albumin from pregnant women, neonates and subjects on oral contraceptives. Brit J Anaesth 40:723, 1968.
39. Crean, G. P. The endocrine system and the stomach. Vitamins Hormones 21:215, 1963.
40. Crist, R. A., Krantz, K. E., Warren, J. C. Transfer of synthetic progestogens. Obstet Gynec 25:89, 1965.
41. Daniel, J. C., and Cowan, M. L. Effects of some steroids in oral contraceptives on the cleavage of rabbit eggs *in vitro*. J Endocr 35:155, 1966.
42. Das, G., and Becker, M. Adrenocortical insufficiency related to oral contraception. JAMA 207:2438, 1969.
43. Davies, D. M., Lund, J. F. Myalgia and an oral contraceptive. Lancet 2:1187, 1965.
44. Dickey, R. P., and Dorr, C. H. II. Oral contraceptives: Selection of the proper pill. Obstet Gynec 33:273, 1969.
45. Diczfalusy, E. Mode of action of contraceptive drugs. Amer J Obstet Gynec 100:136, 1968.
46. Doar, J. W. H., Wynn, V., and Cramp, D. G. Studies of venous blood pyruvate and lactate levels during oral and intravenous glucose tolerance tests in women receiving oral contraceptives. Salhanick, H. A., Ed. Conference on metabolic effects of gonadal hormones and contraceptive steroids. December 1–5, 1968.
47. Dodek, O. I., and Kotz, H. L. Syndrome of anovulation following the oral contraceptives. Amer J Obstet Gynec 98:1065, 1967.
48. Dodek, O. I., Segre, E. J., and Klaiber, E. L. Effects of Enovid on cortisol metabolism. Amer J Obstet Gynec 93:173, 1965.
49. Dunn, H. P. Sterility following oral contraceptives. New Zeal Med J 66:261, 1967.
50. Eisalo, A., Jarvinen, P. A., and Luukkainen, T. Liver-function tests during intake of contraceptive tablets in pre-menopausal women. Brit Med J 1:1416, 1965.
51. Eisenfeld, A. J., and Axelrod, J. Evidence for estradiol binding sites in the hypothalamus—effect of drugs. Biochem Pharmacol 16:1781, 1967.
52. Erickson, L. R., and Peterka, E. S. Sunlight sensitivity from oral contraceptives. JAMA 203:178, 1968.
53. Flowers, D. E., Vorys, N., Stevens, V., Miller, A. T., and Jensen, L. The effects of suppression of menstruation with ethynodiol diacetate upon the pituitary, ovary and endometrium. Amer J Obstet Gynec 96:784, 1966.
54. Foglia, V. G., Schuster, N., and Rodriguez, R. R. Sex and diabetes. Endocrinology 41:428, 1967.
55. Food and Drug Administration: Report on oral contraceptives. 1966.
56. Frantz, A. G., and Rabkin, M. T. Effects of estrogen and sex difference on secretion of HGH. J Clin Endocr 25:1470, 1965.
57. Frieden, E., and Osaki, S. Serum copper and oral estrogen. Science 163:959, 1969.
58. Friedrich, E. R. Effects of contraceptive hormone preparations on the fine structure of the endometrium. Obstet Gynec 30:301, 1967.
59. Gall, S. A., Bourgeois, C. H., and Maguire, R. The morphologic effects of oral contraceptive agents on the cervix. JAMA 207;2243, 1969.

60. Gershberg, H., Hulse, M., and Javier, Z. Hypertriglyceridemia during treatment with estrogen and oral contraceptives: An alteration in hepatic function? Obstet Gynec 31:186, 1968.
61. Gershberg, H., Javier, Z., and Hulse, M. Glucose tolerance in women receiving an ovulatory supressant. Diabetes 13:378, 1964.
62. Gershberg, H., Zorrilla, E., Hernandez, A., and Hulse, M. Effects of medroxyprogesterone acetate on serum insulin and growth hormone levels in diabetes and potential diabetics. Obstet Gynec 33:383, 1969.
62a. Glick, I. D. Mood and behavioral changes associated with the use of the oral contraceptive agents. A review of the literature. Psychopharmacologia (Berlin) 10:363, 1967.
63. Goh, K. Personal communication.
64. Gold, E. M., Carvajel, J., Rudnick, P. A., and Gerszi, K. E. Insulin production in overt (maturity-onset) diabetes: Absence of hyperinsulinemia despite hyperglycemia induced by contraceptive steroids. Salhanick, H. A., Ed. Conference on metabolic effects of gonadal hormones and contraceptive steroids. December 1–5, 1968.
65. Goldsmith, N. F., and Baumberger, J. P. Mineral changes after norethynodrel. Lancet 2:567, 1967.
66. Goldsmith, N. F., and Goldsmith, J. R. Epidemiological aspects of magnesium and calcium metabolism. Arch Environ Health (Chicago) 12:607, 1966.
66a. Goldzieher, J. W., Bacerra, C., Gual, C., Livingston, Jr., N. B., Maqueo, M., Moses, L. E., and Tietze, C. A new contraceptive. Amer J Obstet Gynec 90:404, 1964.
67. Goldzieher, J. W., Rice-Wray, E., Shultz-Contreras, M., and Aranda-Rosella, C. A. Fertility following termination of contraception with norethindrone. Amer J Obstet Gynec 84:1474, 1962.
68. Goodrich, S. M., and Wood, E. J. Peripheral venous distensibility and velocity of venous blood flow during pregnancy or during oral contraceptive therapy. Amer J Obstet Gynec 90:740, 1964.
69. Goolden, A. W. G., Gartside, J. M., and Sanderson, C. Thyroid status in pregnancy and in women taking oral contraceptives. Lancet 1:12, 1967.
69a. Grant, E. C., and Pryse-Davies, J. Effect of oral contraceptive on depressive mood changes and on endometrial monoamine oxidase and phosphatases. Brit Med J 3:777, 1968.
70. Gregoire, A. T., and Ledger, W. J. The glycogen content of human ectocervical tissues of females receiving steroid contraceptive therapy. Fertil Steril 20:91, 1969.
71. Gregoire, A. T., Rankin, J., Johnson, W. D., Fakoff, A. E., and Adams, A. Alpha-amylase content in cervical mucus of females receiving sequential, nonsequential or no contraceptive therapy. Fertil Steril 18:836, 1967.
72. Hagler, S., Schultz, A., Hankin, H., and Kunstadter, R. H. Fetal effects of steroid therapy during pregnancy. Amer J Dis Child 106:96, 1963.
73. Harkavy, M., and Javitt, N. B. Effect of ethynyl estradiol on hepatic excretory function of the rat. Salhanick, H. A., Ed. Conference on metabolic effects of gonadal hormones and contraceptive steroids. December 1–5, 1968.
73a. Hazzard, W. R., Spiger, M. J., Bagdade, J. D. and Bierman, E. L. Studies on the mechanism of increased plasma triglyceride levels induced by oral contraceptives. New Eng J Med 280:471, 1969.
74. Hellman, L. M. Safety of oral contraceptives. Texas Rep Biol Med 25:318, 1967.
75. Helmer, O. M., and Griffith, R. S. The effect of the administration of estrogens on the renin-substrate (hypertensinogen) content of rat plasma. Endocrinology 51:421, 1952.
76. Hilliard, J., Croxatto, H. B. Hayward, J. N., and Sawyer, C. H. Norethindrone blockade of LD release to intrapituitary infusion of hypothalamic extract. Endocrinology 79:411, 1966.
77. Hollander, C. S., Garcia, A. M., Sturgis, S. H., and Slenkow, H. A. Effects of an ovulatory suppressant of the serum PBI and red cell uptake of radioactive triiodothyronine. New Eng J Med 269:501, 1963.
78. Horowitz, B. J., Solomkin, M., and Edelstein, S. W. The over-suppression syndrome. Obstet Gynec 31:387, 1968.

79. Houssay, B. A., Foglia, V. G., and Rodriguez, R. R. Production and prevention of some types of experimental diabetes by estrogens and corticosteriods. Acta Endocr 17:146, 1954.
80. Ingle, D. J. The relationship of diabetogenic effect of diethylstilbestrol to the adrenal cortex of the rat. J Physiol 138:557, 1943.
81. Jacobson, B. D. Hazards of norethindrone therapy during pregnancy. Amer J Obstet Gynec 84:962, 1962.
82. Javier, Z., Gershberg, H. and Hulse, M. Ovulating suppressants, estrogens and carbohydrate metabolism. Metabolism 17:443, 1968.
83. Jeffrey, J. d'A., and Klopper. A. I. Steroid contraceptives: A review. J Reprod Fertil Suppl. 4:81, 1968.
84. Johannisson, E., Tillinger, K. G., and Diczfalusy, E. Effect of oral contraceptives on the ovarian reaction to human gonadotropins in amenorrheic women. Fertil Steril 16:292, 1965.
85. Juchau, M. R., and Fouts, J. R. Effects of norethynodrel and progesterone on hepatic microsomal drug-metabolizing enzyme systems. Biochem Pharmacol 15:891, 1966.
86. Kaern, T. Effect of an oral contraceptive immediately postpartum on initiation of lactation. Brit Med J 3:644, 1967.
87. Kane, F. J. Psychiatric reactions to oral contraceptives. Amer J Obstet Gynec 102:1053, 1968.
88. Kane, F. J., Daly, R. J., Ewing, J. A., and Keller, M. H. Mood and behavioural changes with progestational agents. Brit J Psychiat 113:265, 1967.
89. Kappas, A., and Song, C. S. Sex hormones, the gastrointestinal tract and the liver: Introductory comments. Salhanick, H. A., Ed. Conference on metabolic effects of gonadal hormones and contraceptive steroids. December 1–5, 1968.
90. Kawakami, M., and Sawyer, C. H. Effects of sex hormones and antifertility steroids on brain thresholds in the rabbit. Endocrinology 80:857, 1967.
91. Kilpatrick, Z. M., Silverman, J. F., Betancourt, E., Farman, J., and Lawson, J. P. Vascular occlusion of the colon and oral contraceptives: Possible relation. New Eng J Med 278:438, 1968.
92. Kleiner, G. J., Kresch, L., and Arias, I. M. Studies of hepatic excretory function: II. The effect of norethynodrel and mestranol on bromsulfalein sodium metabolism in women of childbearing age. New Eng J Med 273:420, 1965.
93. Krane, S. Effects of estrogens and progestogens on collagen metabolism. Salhanick, H. A., Ed. Conference on metabolic effects of gonadal hormones and contraceptive steroids. December 1–5, 1968.
94. Labhsetwar, A. P. Studies on the mode of action of oral contraceptives: Effect of chlormadinone on pituitary FSH and LH contents of the female rat. J Reprod Fertil 17:101, 1968.
95. Landau, R. L., and Lugibihl, K. The effect of progesterone on the concentration of plasma amino acids in man. Metabolism 16:1114, 1967.
96. Landon, J., Wynn, V., Cook, J. N. C., and Kennedy, A. Effects of anabolic steroid methandienone on carbohydrate metabolism in man. Metabolism 11:501, 1962.
97. Laragh, J. H., Newton, M. A., Sealey, J. E., and Ledingham, J. G. G. Oral contraceptives and high blood pressure: Changes in plasma renin, renin substrate, and aldosterone excretion. Salhanick, H. A., Ed. Conference on metabolic effect of gonadal hormones and contraceptive steroids. December 1–5, 1968.
98. Laragh, J. H., Sealey, J. E., Ledingham, J., and Newton, M. Oral contraceptives, renin aldosterone, and high blood pressure. JAMA 201:918, 1967.
99. Larsson-Cohn, U. The 2 hour sulfobromophthalein retention test and the transaminase activity during oral contraceptive therapy. Amer J Obstet Gynec 98:188, 1967.
100. Larsson-Cohn, U. An appraisal of the clinical effect of three different oral contraceptive agents and their influence on transaminase activity. Acta Obstet Gynec Scand 45:499, 1966.
101. Laumas, K. R., Malkani, P. K., Bhatnagar, S., and Laumas, V. Radioactivity in the breast milk of lactating women after oral administration of ^{3}H-norethynodrel. Amer J Obstet Gynec 98:411, 1967.

102. Laurell, C. B., Kullander, S., and Thorell, J. Effect of administration of a combined estrogen-progestin contraceptive on the level of individual plasma proteins. Scand J Clin Lab Invest 21:337, 1968.
103. Lauritzen, C. On endocrine effects of oral contraceptives. Acta Endocr (Kobenhaven) Suppl. 124:87, 1967.
104. Layne, D. S., Meyer, C. J., Vaishwanar, P. S., and Pincus, G. The secretion and metabolism of cortisol and aldosterone in normal and steroid-treated women. J Clin Endocr 22:107, 1962.
105. Leach, R. B., and Margulis, R. R. Inhibition of adrenocortical responsiveness during progestin therapy. Amer J Obstet Gynec 92:762, 1965.
106. Littleton, P., and Fortherby, K. Metsbolites of norgestrel (Wyeth 3707) in humans. Acta Endocr (Kobenhavn) Suppl. 119:162, 1967.
107. Loraine, J. A., Bell, E. T., Harkness, R. A., Mears, E., and Jackson, M. C. N. Hormone excretion patterns during and after the long-term administration of oral contraceptives. Acta Endocr (Kobenhavn) 50:15, 1965.
108. Lyons, H. A. Respiratory effects of gonadal hormones. Salhanick, H. A., Ed. Conference on metabolic effects of gonadal hormones and contraceptive steroids. December 1–5, 1968.
109. Maqueo, M., Azuela, J. C., Calderon, J. J., Goldzieher, J. W. Morphology of the cervix in women treated with synthetic progestins. Amer J Obstet Gynec 96:994, 1966.
110. Margulis, R. R., and Leach, R. Effect of prolonged cyclic therapy with estrogen-progestin combinations on thyroid function. Amer J Obstet Gynec 99:168, 1966.
111. Marshall, S., Lyon, R. P., and Minkler, D. Ureteral dilatation following use of oral contraceptives. JAMA 198:782, 1966.
112. Martinez-Manauton, J., Giner-Velanquez, J., Cortes-Gallegos, V., Aznar, R., Rojas, B., Guitterez-Najar, A., and Rudel, H. W. Daily progestogen for contraception: a clinical study. Brit Med J 2:730, 1967.
113. Matsumoto, S., Sato, I., Ito, T., and Matsuoka, A. Electroencephalographic changes during long-term treatment with oral contraceptives. Inter J Fertil 11:195, 1966.
114. McGregor, M. S. Amenorrhoea after oral contraceptives. Lancet 1:643, 1968.
115. McNellis, D., and Sherline, D. M. The rabbit ureter in pregnancy and after norethynodrel-mestranol administration. Obstet Gynec 30:336, 1967.
116. Mestman, J. H., Anderson, G. V., and Nelson, D. H. Adrenal-pituitary responsiveness during therapy with an oral contraceptive. Obstet Gynec 31:378, 1968.
117. Michael, R. P., and Plant, T. M. Contraceptive steroids and sexual activity. Nature 222:579, 1969.
118. Moghissi, K. S. Cyclic changes of cervical mucus in normal and progestin-treated women. Fertil Steril 17:663, 1966.
119. Murawski, B. J., Sapir, P. E., Shulman, N., Ryan, Jr., G. M., and Sturgis, S. H. An investigation of mood states in women taking oral contraceptives. Fertil Steril 19:50, 1968.
120. Musa, B. U., Doe, R. P., and Seal, U. S. Serum protein alterations produced in women by synthetic estrogens. J Clin Endocr 27:1463, 1967.
121. Nicholls, R. A., and Board, J. A. Carbonic anhydrase concentration in endometrium after oral progestins. Amer J Obstet Gynec 99:829, 1967.
122. Nilsson, A., Jacobson, L., and Ingemanson, C. A. Side effects of an oral contraceptive with particular attention to mental symptoms and sexual adaptation. Acta Obstet Gynec Scand 45:537, 1967.
123. Ober, W. B. Synthetic progestagen-oestrogen preparations and endometrial morphology. J Clin Path 19:138, 1966.
124. Ockner, R. K., and Davidson, C. S. Hepatic effects of oral contraceptives. New Eng J Med 276:331, 1967.
125. O'Leary, J. A., and Spellacy, W. N. Zinc and copper levels in pregnant women and those taking oral contraceptives. Amer J Obstet Gynec 103:131, 1969.
126. Ostergaard, E., and Starup, J. Occurrence and function of corpora lutea during different forms of oral contraception. Acta Endocr 57:386, 1968.

127. Perlroth, M. G., Marver, H. S., and Tschudy, D. P. Oral contraceptive agents and the management of acute intermittent porphyria. JAMA 194:1037, 1965.
128. Peterson, W. F., Steel, M. W., and Coyne, R. V. Analysis of the effect of ovulatory suppressants on glucose tolerance. Amer J Obstet Gynec 96:484, 1966.
129. Peterson, et al. Estrogen and adrenocortical function in man. J Clin Endocr 20:495, 1960.
129a. Phillips, B. M. Oral contraceptive drugs and migraine. Brit Med J 2:99, 1968.
130. Pincus, G. Suppression of ovulation with reference to oral contraceptives. Mod Trends Endocr, 2nd series: 231, 1961
131. Pimstone, B. L. L. E. Cells after oral contraceptives. Lancet 1:1153, 1968.
132. Posner, N. A., Silverstone, F. A., Pomerance, W., and Baumgold, D. Oral contraceptives and intravenous glucose tolerance. I. Data noted early in treatment. Obstet Gynec 29:79, 1967.
133. Posner, N. A., Silverstone, F. A., Pomerance, W., and Singer, N. Oral contraceptives and intravenous glucose tolerance. II long-term effects. Obstet Gynec 29:87, 1967.
134. Preedy, J. R. K. The effects of gonadal hormones on water and electrolyte metabolism in the human. Salhanick, H. A., Ed. Conference on metabolic effects of gonadal hormones and contraceptive steroids. December 1–5, 1968.
135. Pulkkinen, M. O., and Willman, K. The effect of oral contraceptives on serum enzymes. Acta Obstet Gynec Scand 46:525, 1967.
136. Reaven, G. M., Lerner, R. L., Stein, M. P., and Farquhar, J. W. Role of insulin in endogenous hypertriglyceridemia. J Clin Invert 46:1756, 1967.
137. Reed, M. The effect of norethandrolone (Nilevar) on serum proteins in the female guinea pig. J Endocr 37:253, 1967.
138. Resnik, S. Melasma induced by oral contraceptive drugs. JAMA 199:601, 1967.
139. Rice-Wray, E., Arana-Rosell, A., Maqueo, M., and Goldzieher, J. Comparison of the long-term endometrial effects of synthetic progestin used in fertility control. Amer J Obstet Gynec 87:429, 1963.
140. Rice-Wray, E., Gonzalez, O., Ferrer, S., Arana-Rosell, A., Maqueo, M. and Munguia, H. Central evaluation of norethindrone acetate in fertility control. Amer J Obstet Gynec 93:115, 1965.
141. Rice-Wray, E., Goldzieher, J. W., and Arana-Rosell, A. Oral progestin in fertility control: A complication study. Fertil Steril 14:402, 1963.
142. Roland, M., Clyman, M. J., Dicher, A., and Ober, W. B. Classification of endometrial response to synthetic progestogen and estrogen compounds. Fertil Steril 15:143, 1964.
143. Roman, W., and Hecker, R. The liver toxicity of oral contraceptives: A critical review of the literature. Med J Aust 2:682, 1968.
144. Rooks, W. H. II, Kugler, S. L., and Dorfman, R. I. The relative expressed estrogencity of oral contraceptives. Fertil Steril 19:419, 1968.
145. Ryan, G. M., Craig, J., and Reid, D. E. Histology of the uterus and ovaries after long-term cyclic norethynodrel therapy. Amer J Obstet Gynec 90:715, 1964.
146. Ryan, G. M., Goss, D. A., and Reid, D. E. Pituitary gonadotropins during long-term enovid therapy. Amer J Obstet Gynec 94:515, 1966.
147. Salhanick, H. A., Kipnis, D., and Vandewiele, R. Metabolic effects of gonadal hormones and contraceptive steroids. Plenum Press, NYC, 1969.
148. Sandberg, A. A., Rosenthal, E., and Slaunwhite, Jr., W. R. Certain metabolic effects of estrogens. Salhanick, H. A., Ed. Conference on metabolic effects of gonadal hormones and contraceptive steroids.
149. Satterthwaite, A. P., and Gimble, C. J. Contraception control with norethindrone: Progress report at Puerto Rico. J Amer Med Wom Ass 17:797, 1962.
150. Saunders, F. J. Effects of norethynodrel combined with mestranol on the offspring when administered during pregnancy and lactation in rats. Endocrinology 80:447, 1967.
151. Schaffner, F. The effect of oral contraceptives on the liver. JAMA 198:1019, 1966.

151a. Schleicher, E. M. L.E. cells after oral contraceptives. Lancet 1:821, 1968.
152. Shearman, R. P. Amenorrhoea after oral contraceptives. Lancet 1:817, 1968.
153. Shearman, R. P. Investigation and treatment of amenorrhoea developing after treatment with oral contraceptives. Lancet 1:325, 1968.
154. Shokeir, M. Oral contraceptives and caeruloplasmin activity. Lancet 2:1192, 1968.
155. Sotaniemi, E., Kreus, K. E., Kaipainen, W. J. Pigmentation and oral contraceptives, Brit Med J 2:120, 1968.
156. Spellacy, W. N. The effect of ovarian steroids on glucose, insulin, and growth hormone. Salhanick, H. A., Ed. Conference on metabolic effects of gonadal hormones and contraceptive steroids. December 1–5, 1968.
157. Spellacy, W. N. A review of carbohydrate metabolism and the oral contraceptives. Amer J Obstet Gynec 104:448, 1969.
158. Spellacy, W. N., Birk, S. A., Noer, K. A., and Schade, S. L. Sedimentation rate in the normal menstrual cycle or with oral contraceptives. Minnesota Med 5:645, 1967.
159. Spellacy, W. M., and Carlson, K. L. Plasma insulin and blood glucose levels in patients taking oral contraceptives. Amer J Obstet Gynec 95:474, 1966.
160. Spellacy, W. N., Carlson, K. L. and Schade, S. L. Effect of sequential oral contraceptives on plasma insulin and blood glucose levels after 6 months' treatment. Amer J Obstet Gynec 101:672, 1968.
161. Starup, J., Sele, V., and Buus, O. Pituitary-adrenal function in oral contraception. Acta Endocr (Kobenhavn) 53:1, 1966.
162. Stein, M., Rarabeih, A., Yasutake, T., and Hirose, T. Effects of gonadal hormones and contraceptive steroids on respiration. Salhanick, H. A., Ed. Conference on metabolic effects of gonadal hormones and contraceptive steroids. December 1–5, 1968.
163. Stevens, V. C., and Vorys, N. The regulation of pituitary function by sex steroids. Obstet Gynec Survey 22:781, 1967.
164. Stitt, S. L., and Kinnard, W. J. The effect of certain progestins and estrogens on the threshold of electrically induced seizure patterns. Neurology 18:213, 1968.
165. Stoll, B. A., Andrews, J. T., and Motteram, R. Liver damage from oral contraceptives. Brit Med J 1:960, 1966.
166. Strauss, J. S., and Pochi, P. E. Effect of cyclic progestin estrogen therapy on sebum and acne in women. JAMA 190:315, 1964
167. Tallat, M., Habib, Y. A., Naby, S., Malek, A. Y., and Ibrahim, A. A. The effect of sex hormones on carbohydrate metabolism in normal and diabetic women. Arch Int Pharmacodyn 154:402, 1965.
168. Taylor, H. B., Irey, N. S., Norris, H. J. Atypical endocervical hyperplasia in women taking oral contraceptives. JAMA 202:637, 1967.
169. Tietze, C. Fertility after discontinuation of intrauterine and oral contraception. Int J Fertil 13:385, 1968.
170. Townsend, J. F., Hall, D. G., Cavazos, F., and Lucas F. V. Uterine peroxidase activity in abnormal human endometrium. Amer J Obstet Gynec 93:1013, 1965.
171. Tyson, J. E. A. Oral contraception and elevated blood pressure. Amer J Obstet Gynec 100:6, 1968.
172. Uhlarik, S., Hoffmeister, H., and Nooke, W. Studies of a possible direct effect of oral contraceptives on the rat ovary. Acta Endocr (Kobenhavn) Suppl. 119:166, 1967.
173. Varga, L., Tiboldi, T., Varga, G., and Hegedus, Z. Effect of six months oestrogen and progesterone treatment on the serum proteins and protein-bound carbohydrate compounds in rates. Med Pharm Exp 17:339, 1967.
174. Ward, G. W., and Stevensen, J. R. Colonic disorder and oral contraceptives. New Eng J Med 278:910, 1968.
175. Weidenfeld, J., Serr, D., and Finkelstein, M. Effect of 17 a-ethynyl-19-nor-testosterone on the urinary excretion of oesterone, oestradiol-171 and oestriol and of pregnanetriol in normal menstruating women and in oophorectomized patients. J Reprod Fertil 12:107, 1966.
176. West, J., and West, E. D. The electroencephalogram and personality of women with headaches on oral contraceptives. Lancet :1180, 1966.

176a. Westoff, C. F., Bumpass, L. and Ryder, N. B. Oral Contraception; Coital frequency and the time required to conceive. Soc Biol 16:1–10, 1969.
177. Wettenhall, H. N. B., and Roche, A. F. Tall girls assessment and management. Paed J 1:210, 1965.
178. Wharton, L. R., and Scott, R. B. Experimental production of genital lesions with norethindrone. Amer J Obstet Gynec 89:701, 1964.
179. Whitelaw, M. J., and Foster, T. N. Treatment of excessive height in girls: A long-term study. J Pediat 61:566, 1962.
180. Whitelaw, M. J., Foster, N. T., and Graham, W. H. Estradiol valerate: its effects on anabolism and skeletal age in the prepubertal girl. Endocrinology 23:1125, 1963.
180a. Whitty, C. W., Hockaday, J. M., and Whitty, M. M. The effect of oral contraceptives on migraine. Lancet 1:856, 1966.
181. Wied, G. L., Davis, M. E., Frank, R., Segal, P. B., Meier, P., and Rosenthal, E. Statistical evaluation of the effect of hormonal contraceptives on the cytologic smear pattern. Obstet Gynec 27:327, 1966.
182. Wilkins, L. Hormonal influences on skeletal growth. Annals NY Acad Sci 60:763, 1954.
183. Woods, J. W. Oral contraceptives and hypertension. Lancet 2:653, 1967.
184. World Health Organization Technical Report Series 386: Hormonal steroids in contraception, 1968.
185. Wynn, V., and Doar, J. W. H. Fasting serum triglyceride and cholesterol levels during oral contraceptive therapy. Salhanick, H. A., Ed. Conference on metabolic effects of gonadal hormones and contraceptive steroids. December 1–5, 1968.
186. Wynn, V., and Doar, J. W. H. Longitudinal studies of the effects of oral contraceptive therapy on plasma glucose, non-esterified fatty acid, insulin and blood pyruvate levels during oral and intravenous glucose tolerance tests. Salhanick, H. A., Ed. Conference on metabolic effects of gonadal hormones and contraceptive steroids. December 1–5, 1968.
187. Wynn, V., and Doar, J. W. H. Some effects of oral contraceptives on carbohydrate metabolism. Lancet 2:715, 1966.
188. Wynn, V., Doar, J. W. H., and Mills, G. L. Effect of oral contraceptives on serum lipid and lipoprotein levels. Lancet 2:720, 1966.
189. Zanartu, J., Pupkin, M., Rosenberg, D., Guerrero, R., Rodriquez-Bravo, R., Garcia-Huidobro, M., and Puga, J. A. Effect of oral continuous progestogen therapy in microdosage on human ovary and sperm transport. Brit Med J 2:266, 1968.

APPENDIX II

FDA

REPORT ON THE ORAL CONTRACEPTIVES

by the

ADVISORY COMMITTEE ON OBSTETRICS AND GYNECOLOGY

FOOD AND DRUG ADMINISTRATION • AUGUST 1, 1966

advisory committee on obstetrics and gynecology

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preface

IN submitting this report on the oral contraceptives the Advisory Committee on Obstetrics and Gynecology wishes to express its appreciation to the Commissioner of the Food and Drug Administration and to his staff for their helpful and ever ready cooperation in arranging its meetings, submission of data, and preparation of reference material. The Committee is deeply indebted to the drug industry for the preparation of a thorough survey of the literature on the oral contraceptives and for ready submission of their own data. It is grateful also for the cooperation that made possible a survey visit to each of the drug firms concerned and an "on site" appraisal of their respective procedures. By such cooperative efforts alone can the public be made fully aware of the status of these compounds now so widely employed.

contents

introduction

THE oral contraceptives present society with problems unique in the history of human therapeutics. Never will so many people have taken such potent drugs voluntarily over such a protracted period for an objective other than for the control of disease. These compounds, furthermore, furnish almost completely effective contraception, for the first time available to the medically indigent as well as the socially privileged. These factors render the usual standards for safety and surveillance inadequate. Their necessary revision must be carefully planned and tested, lest the health and social benefits derived from these contraceptives be seriously reduced. Probably no substance, even common table salt, and certainly no effective drug can be taken over a long period of time without some risk, albeit minimal. There will always be a sensitive individual who may react adversely to any drug, and the oral contraceptives cannot be made free of such adverse potentials, which must be recognized and kept under continual surveillance. The potential dangers must also be carefully balanced against the health and social benefits that effective contraceptives provide for the individual woman and society.

The oral contraceptives currently in use are probably not those that will be employed 10 or even 5 years hence. Drugs with even less potentially adverse effect, utilizable in smaller dosage, will undoubtedly be developed through continuing research. At present several such promising compounds are under investigation. The research essential to the development and testing of these compounds is carried out by the drug industry working in close cooperation with the medical profession. It would be indeed unfortunate were such research and testing to be stifled by unnecessarily complicated, unscientifically harsh, and inelastic administrative procedures. It is axiomatic that all drugs must be carefully tested on several species of laboratory animals under comparable conditions before they can be given to human volunteers. It is equally important that the results of such experimentation be appropriately interpreted in extending their application to human beings. Particularly in reproductive functions man differs from experimental animals and other primates. To deprive a population of drugs of great benefit by overattention to adverse effects based on animal data without due consideration of clinical experience is unjustifiable. Throughout this report various types of adverse experience will be discussed. Most of them, however, occur naturally, with a definite though low incidence in our population. The data necessary to demonstrate an increase in these naturally occurring phenomena among users of oral contraceptives are not available. Most adverse reactions, including deaths, have been reported as individual cases or small series. Except in carefully controlled studies, neither the total number of people exposed to the oral contraceptives nor the number of adverse reactions in any locality is known. The crucial data are the numerator (adverse reactions) and the denominator (users) and a control made up of nonusers having the same or a different number of adverse reactions. The difficulty of obtaining such data for the oral contraceptives makes unreliable any assumptions regarding a cause and effect relationship of drug and adverse reaction.

There are, however, several epidemiological approaches which can shed light on the problem. The simplest and most obvious method is a system of surveillance leading to the reporting by physicians of suspicious illness in their patients who are taking the drug. Such a system is essential because it can give the earliest warning of trouble in a situation where quick action may be imperative. It should, however, be recognized that when the physician reports a suspected adverse reaction to a drug he usually cannot know with any certainty that what he has seen is in fact an adverse reaction and not a coincidental happening. The major deficiencies of this system are:

(*a*) Incomplete reporting by physicians of adverse experience for medico-legal rea-

sons, inertia, and lack of interest or awareness of the value of such data.

(*b*) Selective or biased reporting of incidents which may reflect fashions in medical interest rather than the magnitude of a possible hazard.

(*c*) The lack of a denominator population to evaluate the incidence of a possible adverse reaction.

(*d*) The lack of control populations not exposed to the oral contraceptives to permit comparison of the incidence of possible complications in users and nonusers, to see if, in fact, any excess risk occurs in users.

(*e*) The inability to detect potential long-term effects which might first appear after discontinuation of the oral contraceptives or even in the progeny of users.

Of the more formal and reliable epidemiologic methods, the one selected should depend upon the type of suspected complication and its temporal relation to the use of the drugs. Prospective studies of users and nonusers are capable of testing for each type of complication; however, they are extremely difficult and costly to perform if the suspected complication is thought to be of rare occurrence or if it is expected to occur after a latent period of many years. The prospective method has the advantages that it permits simultaneous study of all possible complications, including those which are initially unsuspected, and that certain biases are avoided. However, it does not reduce the problem that the inferences must be based on observation rather than experiment; i.e., that differences in disease frequency between the groups of users and nonusers may result from differences in their initial composition dependent on whatever determines the employment of contraceptive methods.

Efficient approaches to the principal possible types of complications are as follows:

(*a*) *Thromboembolic disease.* Here the supposed complication is serious, readily recognized in at least some of its forms, and quite rare. It may presumably occur at any time while the drug is being used, but not after termination of use. A case-control (retrospective) approach is the most efficient; a series of cases, and of suitable controls, are chosen and the number of drug users in each group is determined in order to demonstrate association or independence between drug and disease.

(*b*) *Cancer.* Here the suspected complication is again serious and readily recognizable. The situation differs from (*a*) in two respects: The disease is common and only a small proportion of cases could be expected to be attributable to the drug; and more important, the latent period would be expected to be very long, frequently extending until after the termination of drug use. A prospective study would be best but would be rendered exceedingly difficult by the length of latency and variations in contraceptive methods employed by a woman over her reproductive lifetime. The case-control approach employed at serial intervals of calendar time would also give promise, but no method is really efficient.

(*c*) *Diabetes or minor physiologic alterations* such as have been discussed in this report. Serial observations on adequate-sized groups of users and nonusers, incorporating whatever laboratory methods are required, will be needed.

Many different compounds administered in slightly different fashions, constitute the available oral contraceptives. The basic mode of action of currently marketed compounds is similar, however, namely, the inhibition of ovulation and the initiation of periodic bleeding through withdrawal. The committee has therefore chosen to approach broadly the potential problems raised by the massive use of the whole group of effective estrogen-progestogen formulations. For this purpose, the committee has been divided into four task forces with specific assignments, each headed by a chairman, as follows:

Task Forces

1. Thromboembolic Disease
   N. J. EASTMAN, M.D., *Chairman*
   C. TIETZE, M.D.
   P. E. SARTWELL, M.D.
   A. MASI, M.D.
2. Carcinogenic Potential
   R. SCOTT, M.D., *Chairman*
   R. HERTZ, M.D.
3. Endocrine and Metabolic Effects
   E. DELFS, M.D., *Chairman*
   E. CARRINGTON, M.D.
4. Efficacy
   K. ADAMSONS, M.D., *Chairman*
   H. FULLER, M.D.

The report of each task force has been carefully reviewed and approved by the committee as a whole. A summary of each report constitutes the body of the final report, while the complete reports are included in the appendix. In addition to the task forces, the committee appointed Schuyler G. Kohl, to visit the seven drug firms that manufacture these drugs and to review with the responsible personnel their data on adverse effects, deaths, and other pertinent material. Dr. Kohl's report, after review by the committee, was incorporated into the section on thromboembolism. It appears in its entirety in the appendix. A special pilot study to test an epidemiological approach to thromboembolic disease has been designed and completed by Dr. Sartwell's group. It is summarized in the report and appears in the appendix.

utilization

The pharmaceutical industry has estimated the numbers of women taking oral contraceptives, based on the numbers of tablets distributed in the United States. The approach is straightforward: Since each user takes 20 tablets per cycle and the average woman has 13 cycles per year, the number of tablets sold, divided by 260, gives the average numbers of users during the year. The following estimates have been prepared by this method for the period 1961–65:

1961	408,000
1962	1,187,000
1963	2,235,000
1964	3,950,000
1965	5,000,000

Another estimation has been made by Westhof and Ryder [1] of Princeton University in the study to be published shortly. Using a carefully selected and distributed sample of about 5,600 married women living with their husbands and under the age of 45, they derived the following estimates:

Ever used:	
Using in late 1965	3,815,000
Used previously, may use again	1,341,000
Will not use again	1,232,000
	6,388,000
Never used:	
May use in future	4,676,000
Will not use	12,794,000
Never heard of it	787,000
	18,257,000

These estimates are in general agreement with those of the drug industry. The discrepancies in the two sets of data are accounted for largely by the group of women that uses the drugs for purposes other than contraception, the unmarried women, and those over 45. Another approach to utilization is furnished by investigations such as those of Dr. McEvilla in Lawrence County, Pa. Through the cooperation of the physicians, the pharmacists, and the medical society of the county, every prescription for drugs of all kinds has been placed on a computer program that is capable of yielding data on utilization and adverse reactions with hitherto unavailable precision. In 1965 these data indicate that 7.4 percent of women in Lawrence County between the ages of 15 and 44 had never used oral contraceptive compounds. This figure is somewhat lower than the estimated national average, probably because of the particular population sampled.

Finally, based on the following assumptions, a rough estimate of future use of the oral contraceptives in the United States can be made. Assuming (1) Series B population projection,[2] (2) 46 percent of each cohort of married women starting oral contraception at the same rate as the women who were under 25 years of age in 1965, (3) no further changes to orals by older women, and (4) about 60 percent of ever-users are current users, the following table is derived:

Projected Number of Women in Millions Using Oral Contraceptives in 1985

Year	Total women	Ever-users	Current users
1970	43.3	10	6
1975	46.9	13	8
1980	51.9	16	10
1985	56.4	19	12

[1] Westhof, C. F. and Ryder, N. Presented at the annual meeting of the Population Association of America on Friday, April 30, 1966, New York City.

[2] Current Population Reports, Series P–25, No. 329, March 10, 1966.

thromboembolic disease

There are divergent reports in the literature on the effects of the oral contraceptives on blood coagulation. Unfortunately, however, hypercoagulability cannot be measured. Although many of the factors in the blood concerned with clot formation may be ascertained, their elevation is not a measure of hypercoagulability. For example, although fibrinogen and factors VII–X are elevated in pregnancy, thromboembolism occurs most commonly in the puerperium, when the levels of these factors have returned to normal. The most recent work on the response of blood coagulation factors to oral contraceptives indicated no statistically significant effect.

Of greater concern are the deaths from thromboembolic disease. The deaths from idiopathic pulmonary embolism in women aged 15 to 44 in the United States appear to be of the order of 12 per million per year. The average annual death rate for women of the same age group from cerebral embolism and thrombosis is about 5 per million. From these data one might expect that, of the 5 million women estimated to be taking the oral contraceptives in 1965, there should be about 85 deaths from idiopathic thromboembolic disease. Kohl's report (appendix 6) disclosed 20 such cases from all causes, only 13 of which were idiopathic. There are two possible explanations for this apparent discrepancy: (1) The oral contraceptives are protective against thromboembolic disease; (2) there has been gross underreporting. The second possibility seems to be the logical explanation, for the reported deaths fail to show the increment expected with the fivefold increase in use of the oral contraceptives from 1962 to 1965.

The present system of reporting deaths and adverse reactions relies on either the cooperation of physicians or the haphazard filtering of rumors to detail men. The latter route is patently unreliable, and the former not much better. Physicians are becoming increasingly fearful of reporting deaths or adverse drug reactions because of possible legal reprisal.

The data derived from mortality statistics are not adequate to confirm or refute the role of oral contraceptives in thromboembolic disease. They do, however, suggest that if oral contraceptives act as a cause, they do so very infrequently relative to the number of users. The Committee believes, accordingly, that the only way this important question can be answered is through large, carefully designed epidemiologic studies, such as those detailed in the appendix of this report.

carcinogenic potential

The committee directed its attention specifically to those lesions which were presumably related to the problem, but did not exclude the possibility of a relationship to other lesions.

The available prevalence and incidence rates of cancer of the uterine cervix, cancer of the endometrium, and cancer of the breast were reviewed in order to establish the expected rates for these cancers in women. All of the published and submitted data on patients who have received any of the estrogen-progestogen combinations for contraceptive and therapeutic purposes over a period of time were reviewed. The animal and clinical studies published and some unpublished, using these hormones, or similar agents, as they relate to the production of cancer or of the influence on an existing cancer, were studied. The following observations were made and conclusions drawn:

Uterine Cervix:

Dysplasia, carcinoma in situ, and invasive cancer were considered. The importance of the geographic, socioeconomic, and ethnic factors of the population sampled was quite evident. For example, the prevalence of carcinoma in situ and invasive cancer in Puerto Rico was almost six times that of a metropolitan New York group composed of women, for the most part, from a higher socioeconomic level. Another important factor was the average age of women showing

these changes: Roughly 35 years for dysplasia, 40 years for carcinoma in situ, and 47 years for invasive cancer.

The data from the various study groups using contraceptive pills were difficult to analyze for the following reasons:

1. Patients with suspicious smears were admitted to the study or in other instances the initial cytologic status was not stated.
2. The various methods of collecting cytologic specimens and the subjective factors in reading and reporting any changes make standardization of data difficult.
3. The frequent failure to record histologic followup after suspicion has been created on cytologic examination.
4. The concentration of contraceptors in age group below 35 yields such a low incidence of malignancy that very large samples are necessary.
5. The relatively small number of patients followed regularly and thoroughly for 4 years or more.

It is to be emphasized that all known human carcinogens require a latent period of approximately one decade. Hence any valid conclusion must await accurate data on a much larger group of women studied for at least 10 years. Furthermore, there is not sufficient evidence to support the contention that contraceptive pills may protect against the development of carcinoma of the cervix.

One possibly significant study showed an appreciable increase of coccoid bacteria, trichomonads, and fungi in women using contraceptive pills. This alteration in the microorganisms of the genital tract might be related to the use of the pills and could account for some of the changes in cytologic reports.

Endometrial Malignancy:

Endometrial carcinoma is primarily a disease of postmenopausal women and only 5 to 8 percent of the cases of this cancer occur before the age of 40.

In the data submitted the paucity of endometrial biopsies as a routine followup procedure, the limited number of women more than 40 years of age, and the short duration, do not permit any conclusions relative to the effect, either adverse or beneficial, of these contraceptive pills on endometrial cancer.

There are numerous studies that suggest an effect of a preponderance of estrogen, either endogenous or exogenous, in women who subsequently develop endometrial adenocarcinoma. While a precise etiologic relationship has not been established, nevertheless, all women receiving estrogen therapy must be followed with care. Administration of a progestogen periodically to women receiving estrogen, in order to allow periodic "withdrawal" bleeding on the basis that it "prevents" endometrial cancer, is invalid both theoretically and on the basis of the very limited number of postmenopausal patients so treated. It must be remembered, furthermore, that carcinolytic agents may also be potentially carcinogenic. Recent reports indicate that progestational compounds may exert a palliative effect on cancer, and adenomatous hyperplasia of the endometrium. While this matter is under study at several centers, there is no evidence, at present, that these compounds are curative. It must be remembered, furthermore, that cancer-suppressing agents may also be carcinogenic.

Breast Cancer

The relationship of the oral contraceptives to breast cancer in the human being is unknown. The solution to this problem is made difficult for several reasons as follows:

(*a*) Contraceptors are predominantly in the lower age groups in which breast carcinoma is sufficiently infrequent as to necessitate very large samples for studies of early effects.

(*b*) There are few long-term followup studies and none of sufficient duration to overcome the long latent period necessary to produce cancer in the human being.

(*c*) Many studies simply do not state whether the breasts have been routinely examined.

There are data that give contributory, although not very strong evidence to both sides of the question.

For:

There is experimental and clinical evidence that indicate a relationship between both endogenous and exogenous estrogen.

There is experimental evidence that estrogens closely related to those used in the oral contraceptives currently marketed will, when continuously

given to dogs and other animals, produce breast carcinoma. In many, but not all experiments the dosage was large on the basis of human therapy.

Against:

Although estrongens have been increasingly employed for a long time and there has been increasing use of oral contraceptives for 6 years, there has been no increase in mortality from breast carcinoma.

The FDA files contain only one case of breast carcinoma occurring in a patient taking oral contraceptives.

Carcinoma of the breast is less prevalent in multiparous than in nulliparous women, although each pregnancy induces an elevation in endogenous estrogen.

All this evidence has been carefully considered by the committee.

At the present writing, it seems that if the oral contraceptives are at all carcinogenic for the human breast, they cannot be very potent and the occurrence of breast carcinoma from this cause must be extremely rare. Nevertheless, caution and prolonged surveillance are in order. Whenever the oral contraceptives are employed, not only the pelvic organs, but the breasts as well must be examined at periodic followup.

Other Cancers:

Malignant lesions in the pituitary, kidneys, ovaries and bone marrow have been found in animals after treatment with certain sex hormones, but at present there are no human corollaries.

Animal Studies:

Sex steriods, particularly estrogens, have been shown to produce malignant lesions and to affect adversely the existing tumors in the mouse, rat, rabbit, hamster, and dog. These neoplasms have occurred in various organs, such as the cervix, endometrium, ovary, breast, testicle, pituitary, kidney, and bone marrow. The observations in animals given progesterone and the newer progestogens have been contradictory; however, these agents alone and in combination with other sex steroids have promoted neoplasia or metastatic growth in a few instances. A recent example is a 52-week study of six dogs that received massive doses of a combination of mestranol and ethyneron (MK-665, an experimental progestogen). Four of the dogs developed mammary lesions; one was a carcinoma in situ with early invasion; the second was a carcinoma in situ; the third represented atypical hyperplasia; and the fourth was a benign intraductal papilloma. Animal studies in which certain susceptible strains and species are used and in which the dosage is excessive and continuous, cannot be directly transferred to human beings. There is, nevertheless, a warning that an altered endocrine environment in human tissues might result in an abnormal expression or potentiation of growth, as in experimental animals. In fact, there has always been the suspicion that experimental animal and human tissues follow the same biological laws in this regard, but conclusive data are not available. A great difficulty in obtaining a reliable answer involves the prolonged period of latency in human beings exposed to known carcinogens. Future epidemiologic studies must take full recognition of this fact.

Statistical Considerations

A substantial change in the incidence of certain diseases such as cancer may be difficult to detect even with very large samples. For example, in a study of the incidence of breast cancer with 4-year followup of women aged 20 to 39 years, a sample of about 15,000 to 20,000 women, or 60,000 to 80,000 person-years, would be required to have a reasonable (that is, 90 percent) chance of detecting (at the 95-percent probability level) a twofold increase in risk. Naturally a control group of almost similar size would have to be studied in order to detect this change. Changes in the incidence of cervical cancer could be detected with samples of about the same size; changes in the incidence of endometrial cancer would require samples about six to eight times as large as those for breast cancer. No studies approaching this magnitude have been reported. Since duration of exposure is a critical factor, only those women exposed for prolonged periods provide pertinent information. There are no scientific data to justify the imposition of a time limitation for the oral contraceptives.

endocrine and metabolic effects

Pituitary-Ovarian Function

A considerable number of studies indicate that the oral contraceptives inhibit ovulation by a block at the pituitary level, specifically by inhibition of synthesis or release of LH. During such inhibition, the ovaries tend to become smaller, and changes suggestive of cortical stromal fibrosis have been described. After cessation of the medication recovery is usually prompt, with ovulation resuming in 4 to 8 weeks in most cases. Occasionally, the reappearance of cyclic ovulation may be delayed for several months. Fertility appears to be normal immediately after cessation of the oral contraceptives although a small but unknown number of patients remain amenorrheic. The outcome of pregnancy has been reported to be about the same as in the untreated population with regard to abortion, prematurity, abnormality, and anomaly. There are, however, no prolonged followup studies to ascertain the growth and development of infants born after cessation of therapy. There is no evidence that prolonged suppression of ovulation in nulliparas or multiparas will impair future fertility. The effects of prolonged suppression of ovulation, however, are unknown and require further investigation.

Pituitary-Adrenal Function

Increased cortisol binding by serum proteins under the influence of oral contraceptives tends to obscure the block of the pituitary ACTH that occurs. Prolonged use of oral contraceptives reduces the response of metopirone but not to ACTH, indicating an inhibition of pituitary ACTH rather than of adrenocortical activity. Recovery of responsiveness occurs in 2 months after cessation of medication. Impaired reaction to stress has not been noted in women on oral contraceptives. There are insufficient data to ascertain the effect of these compounds on women with adrenal insufficiency.

Thyroid Function

Increased thyroxin-binding globulin has been noted in the majority of women on oral contraceptives. Most, but not all, investigators report a rise in PBI and a decreased T_3-RBC uptake. These changes occur rapidly and are maintained for the duration of medication, returning to normal pretreatment levels in about 2 months. The alterations are secondary to the increase in binding proteins produced by estrogens and are similar to those occurring in normal pregnancy. The level of PBI may be in the hyperthyroid range but there is no clinical evidence of hyperthyroidism. If TSH is blocked at the pituitary level, it may be masked by increased protein binding. No precise data are available on this point.

Carbohydrate Metabolism

Data regarding effects on carbohydrate metabolism in experimental animals and in women are contradictory. Recent studies in women taking oral contraceptives suggest a possible diabetogenic effect of these medications. Abnormal glucose tolerance tests have been observed in as many as 40 percent of women taking oral contraceptives; in women with diabetic family histories, abnormal tests were even more frequent. Plasma insulin levels are above normal in supposedly normal women on oral contraceptives. Some known diabetic women require larger amounts of insulin while on medication. All of these changes tend to regress after discontinuation, and are similar to those seen in normal pregnancy. Whether pregnancy itself is diabetogenic is by no means certain, although diabetes seems to be more prevalent in women of high parity. Whether oral contraceptives can induce diabetes in normal women or even in those predisposed is not known, nor is it clear to what extent the induced changes in carbohydrate tolerance are reversible.

Liver Function

Many women on oral contraceptives show abnormalities of some liver function tests, especially the BSP and transaminase. A few develop clinical jaundice and evidence of mild hepatic damage, demonstrated by biopsy. These lesions resemble cholestasis of pregnancy. In several women with previous history of cholestasis, these changes have been induced by the oral contraceptives. The abnormal liver function tests revert to normal after cessation of medication.

Effect on Lactation

Oral contraceptives in high doses (5 and 10 mg. of progestogen) tend to decrease or stop lactation in many women in the first or second cycle of use. These compounds appear in breast milk but in minimal amounts (0.004–0.1 percent of the administered dose). Despite the small quantities of the steroids appearing in breast milk, mammary enlargement may occur in nursing infants. Administration of the androgenic steroids to newborn experimental animals at crucial periods can affect sex differentiation and behavior and result in sterility. No data on human beings are available.

Masculinization

Oral contraceptives have not produced serious masculinization in women taking these agents although all large series have reported some individuals with mild masculinizing symptoms. The 19-nor-compounds appear to have somewhat more masculinizing effect than other synthetic progestogens. These effects are mild, including acne and hirsutism. These changes regress with cessation of medication. The effect on the fetus is of greater importance. Synthetic progestogens, in doses used in the treatment of threatened or habitual abortion, may produce superficial masculinization of the genitals of the female fetus. These anatomic abnormalities are correctable, but the effect upon subsequent reproductive functions and psychosexual development is unknown.

miscellaneous adverse experiences

Ophthalmologic Complications

There have been reports of blurring of vision and even blindness in patients taking the oral contraceptives. The majority of these effects are thought to be of vascular origin, although some may be on a neurological basis. Most of the reports are of single cases or small series in which the etiologic relation is uncertain, but in some cases vision improved when the drugs were discontinued. In several large series of patients on oral contraceptives "eye complaints" and abnormalities have occurred but not with an increased incidence. The question of possible adverse effects on vision is by no means completely solved, but there appears to be no reason for undue concern at this time. Long-range and carefully controlled studies should be undertaken.

Migraine

There are instances reported of migraine occurring for the first time as well as some with exacerbation of preexisting migraine in patients taking oral contraceptives. Studies show that women who have preexisting encephalographic changes characteristic of migraine tend to have these abnormalities brought out but not initiated by the oral contraceptives.

Psychological and Emotional Factors

Studies are in progress regarding the effects of oral contraceptives on human and animal behavior. At present no precise data are available.

efficacy

The following uses for which therapeutic efficacy has been claimed were reviewed:

A. Control of Fertility
B. Amenorrhea
C. Dysmenorrhea
D. Endometriosis
E. Functional Uterine Bleeding
F. Habitual Abortion
G. Miscellaneous Uses

A. Fertility Control

The efficacy of the combined agents is exceptionally high. The more recently introduced sequential regimens are also highly effective in controlling fertility, although to a slightly lesser

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degree. Present evidence indicates that the frequency of pregnancies occurring with the patients on sequential medication remained unchanged over the 2½-year period, thus supporting the contention that tolerance to or escape from the medication probably does not occur.

B. Treatment of Amenorrhea

The efficacy of oral contraceptives in the treatment of amenorrhea could not be readily ascertained from the material available to the Committee because of the endpoint used. Treatment was considered successful when uterine bleeding followed cyclic withdrawal of the medication. Such an endpoint does not specifically measure the efficacy in treating amenorrhea, since cyclic withdrawal bleeding and menstrual periods are different biologic phenomena. If efficacy in the treatment of amenorrhea is claimed, it must be based on evidence that menstrual cycles are maintained following discontinuation of drug therapy. Such information was not contained in the submitted material. If, however, the objective of the therapeutic effort is to produce cyclic withdrawal bleeding in the amenorrheic patient, the oral contraceptive drugs can be considered efficacious, since this result was achieved in 80 to 90 percent of treated patients.

C. Treatment of Dysmenorrhea

The comments pertaining to efficacy of the drugs in the management of patients with dysmenorrhea were similar to those cited in the previous paragraph. The situation was even more complicated because of the difficulty in quantitation of the principal variable. Dysmenorrhea is known to disappear spontaneously, and relatively high "cure rates" have been obtained with placebos. No followup data were available in the submitted material; the reports thus pertained to the evaluation of pain during cyclic withdrawal bleeding rather than during a menstrual period. Although the data suggest that in certain patients the progestational agent might be of value in the treatment of dysmenorrhea, additional information is required before the therapeutic efficacy can be proved. Statistically, the submitted material was considered unsatisfactory because of the small number of patients in the individual series. It was surprising to find that a very small sample had been utilized in the study of such a common phenomenon. The members were aware of the difficulties in designing controlled studies, since placebos do not provide contraception, a fact that cannot remain undisclosed to the patient.

D. Treatment of Endometriosis

In evaluating the material in which the diagnosis of endometriosis was established by histologic examination, the Committee finds continued and prolonged (6 to 12 months) progestational therapy valuable to conservative management of the affected patient. In the well-documented cases it is reasonable to expect a favorable response in 75 to 90 percent. It must, however, be pointed out that recurrence might be expected in an appreciable proportion of patients after cessation of medication. In contrast, the therapeutic efficacy in subjects in which the diagnosis of endometriosis had been made by physical examination or history alone, was uncertain. This population undoubtedly comprises a variety of diseases that should not be expected to improve during therapy with progestational agents.

E. Treatment of Functional Uterine Bleeding

The claims for therapeutic efficacy in treatment of functional uterine bleeding were met with criticism similar to that applied to treatment of dysmenorrhea and amenorrhea. The Committee considers the joining of a variety of conditions under the heading "Functional Uterine Bleeding" inappropriate because the individual diseases have specific and different causes. The index of general efficacy might not therefore reflect the favorable results achieved in certain categories, or conversely might create the impression of therapeutic merit in diseases that are not susceptible to therapy. Irregular menstrual periods will respond in a high percentage of cases to therapy if cyclic withdrawal bleeding is considered synonymous with menses, whereas menorrhagia might be and appears to be considerably more resistant to the advocated therapy. Patients with hypermenorrhea appear to have shorter periods and less loss of blood when placed on cyclic therapy with these compounds. Difficulty in constructing a meaningful endpoint for the various categories was evident since most of the conditions causing functional bleeding are known to be self-limiting.

F. Habitual Abortion

The Committee found no data to indicate that any of the oral contraceptives are effective in altering the natural history of patients with habitual abortion. Although the reasons for habitual

abortion are not known, it often results from a cytogenetic defect in the embryo. These cases would, therefore, not benefit from steroid therapy. Clearly those synthetic progestogens that are known to have androgenic properties should be avoided in the therapy of threatened abortion or hibitual abortion.

G. Miscellaneous Uses

The value of oral contraceptives in the treatment of conditions such as "menopausal syndrome", acne, chronic vulvar infections, and psychiatric disorders could not be ascertained because of the preliminary nature of the available reports.

recommendations

In making the following recommendations, the Committee has given careful consideration to this problem, which is unique because of the large number of healthy women taking the oral contraceptives over very long periods of time, the low incidence of serious side effects, the metabolic changes induced, the paucity of requisite statistical and scientific data, and finally, the health and social benefits to be derived. These factors have imposed the requirement for unprecedented standards of safety; they have demanded the detection of sequelae that are often remote and infrequent; they have opened to question the existing methods of surveillance and retrieval of data; and they have required the design of highly refined epidemiological experiments.

As our case is new and unique in the history of therapeutics, so have we had to think anew in framing these recommendations.

I. A large case-control (retrospective) study of the possible relation of oral contraceptives to Thromboembolism.

This study should follow the methods developed in a pilot trial described in appendix 7 (p. 71) to this report. In view of the results of the pilot trial, such a study becomes mandatory. This study must include a considerable number of hospitals, which should be of large size and high clinical standards and quality of medical records. The potential contributions of operations already existing in the Food and Drug Administration to maintain systematic, unified collaboration with such hospitals should be explored. Most important, the investigation should be under competent epidemiologic supervision.

II. Continuation and support of studies such as the ones being carried out by the Kaiser Permanente group in California and the University of Pittsburgh group in Lawrence County, Pa.

III. Support of additional controlled population-based prospective studies utilizing groups of subjects that are especially amendable to long-term followup, such as married female employees of certain large industries, and graduate nurses.

Although such prospective studies are difficult and require large populations, they may provide the only feasible method to answer the question of a relationship between the oral contraceptives and carcinoma, as well as the effect of these compounds on the growth and development of subsequent offspring.

IV. Continuation and strengthening of the present surveillance system of the FDA.

V. Review of the mechanism of storage, retrieval, and analysis of surveillance data.

If this system is to serve its prime purpose; namely, that of early warning, a much more efficient system of "feedback" will have to be instituted.

VI. A conference be held between FDA and the respective drug firms concerning uniformity and increased efficiency of reporting.

There is every evidence that the drug firms are willing and anxious to cooperate with FDA and with each other to achieve more efficient surveillance and more meaningful data.

VII. Priority be given to support laboratory investigations concerning all aspects of the hormonal contraceptive compounds.

VIII. Uniformity in labeling of contraceptive drugs.

IX. Discontinuance of time limitation of administration of contraceptive drugs.

There is no scientific justification for the present restrictions. They are often circumvented and serve only to penalize the large indigent populations.

X. Simplification of administrative procedures to allow reduction in dosage of already approved compounds.

Once safety has been established, reduction in dosage should require only minimal proof of efficacy, say 3,000–4,000 cycles without a pregnancy.

conclusion

The foregoing considerations have been brought together to direct the attention of the medical profession and the Food and Drug Administration to those aspects of our knowledge, as well as our ignorance, that seem pertinent to our evaluation of the safety and risks involved in the use of these compounds.

The committee finds no adequate scientific data, at this time, proving these compounds unsafe for human use. It has nevertheless taken full cognizance of certain very infrequent but serious side effects and of possible theoretic risks suggested by animal experimental data and by some of the metabolic changes in human beings.

In the final analysis, each physician must evaluate the advantages and the risks of this method of contraception in comparison with other available methods or with no contraception at all. He can do this wisely only when there is presented to him dispassionate scientific knowledge of the available data.

appendix

TASK FORCE REPORTS

August 1, 1966

Appendix 1

Report of the Task Force on Thromboembolic Disease

N. J. EASTMAN, M.D., CHAIRMAN

The activities of the Task Force on Thromboembolic Disease have been as follows:

1. To ascertain the effect, if any, of oral contraceptives on the factors responsible for blood coagulation.

2. To ascertain the incidence of fatal thromboembolic disease in the total female population of the United States of reproductive age, exclusive of cases associated with pregnancy or a surgical operation.

3. To ascertain the approximate number of women in the United States who have taken oral contraceptives, year by year, from 1961 through 1965.

4. To ascertain the incidence of fatal thromboembolic disease in women who had been users of oral contraceptives prior to death.

5. To specify and recommend for immediate development certain epidemiological studies which promise to establish the risks associated with the use of oral contraceptives, or the absence of such risks, much more effectively than is possible on the basis of the data now available.

1. Blood coagulation in women taking oral contraceptives has been the subject of many studies by competent investigators. Although the data on the behavior of individual coagulation factors are somewhat conflicting, no clear evidence has been advanced that these preparations significantly alter the coagulation behavior of the blood. Thus, in a recent and most meticulous investigation, Beller and Porges summarize their findings as follows: "Two different commercially available agents and a placebo were taken by a group of volunteers in a double blind study. There was no statistical difference in blood coagulation factors among the different groups." (In press, Am. J. Obstet. & Gynec.) But even if some of the blood coagulation factors had shown differences between users and nonusers, no blood-coagulation assay at the present time is considered a test for prediction or confirmation of the clinical diagnosis of thromboembolic disease. (Alexander, B.: Blood coagulation and thrombotic disease; Circulation, 25: 872, 1962. Wessler, S.: Stasis, hypercoagulability and thrombosis; Federation Proceedings, 22: 1366–1370, 1963.)

2. Estimates of the incidence of fatal pulmonary embolism among women, 15–44 years of age, not pregnant nor in the puerperal state, in the United States in 1963 are shown below:

Age (years)	*Deaths per million*
15–19	2
20–24	6
25–29	10
30–34	12
35–39	18
40–44	22
15–44	12

These estimates were obtained by including in the numerator deaths attributed to pulmonary embolism and infarction (ICD 465) plus the deaths assigned to antecedent causes which rarely lead to death except by pulmonary embolism (ICD 463, 464, 466) and including in the denominator only women who are neither pregnant nor in the puerperium.

The estimates shown above are necessarily rough because the total number of pregnancies is not known.[1] It is believed, however, that they represent the level and trend of mortality with sufficient accuracy for the purpose at hand.

Age-specific death rates from cerebral embolism and thrombosis (ICD 332) among women, 15–44

[1] It was assumed that one-sixth of all pregnancies in the United States or approximately 1 million were terminated by spontaneous fetal wastage, and the same number by illegal abortion.

years of age, in the United States in 1963 were as follows:

Age (years)	Deaths per million
15–19	1
20–24	2
25–29	2
30–34	4
35–39	9
40–44	15
15–44	5

It should be realized that mortality statistics for this group of conditions are probably unreliable. This is in part because the classification of causes of death is based upon what is considered the underlying cause. The certifying physician's judgment and the care which he takes in recording these underlying causes are variables which cannot at present be assessed. Thus, for example, we do not know how often he fails to record on the death certificate such underlying causes as surgery, the puerperium, trauma, heart disease, and hypertension when these are present.

In spite of the limitations of statistics based on death certification, it is pertinent to compare the reported number of deaths from thromboembolic disease among women taking oral contraceptives with the number that might be expected from the above statistics. If, among women taking steriod compounds, the reported number of deaths is significantly greater, a causal relationship is suggested.

3. The number of deaths attributed to diseases of the veins (ICD 460–468), most of which are deaths from pulmonary embolism, and the corresponding death rates among women of reproductive age in the United States increased substantially from 1950 to 1964. However, parallel increases of equal magnitude have occurred among males, suggesting that the upward trend reflects changes in diagnostic practice, death certification, or causes applicable to both sexes.

Death rates from cerebrovascular accidents (ICD 330–334) have increased among nonwhite women (fewer of whom use oral contraceptives than white women), but have not changed among white women.

4. The pharmaceutical industry has estimated the numbers of women taking oral contraceptives, based on the numbers of tablets distributed in the United States. The approach is straightforward: Since each user takes 20 tablets per cycle and the average woman has 13 cycles per year, the number of tablets sold, divided by 260, gives the average number of users during the year. The following estimates have been prepared by this method for the period 1961–65:

1961	408,000
1962	1,187,000
1963	2,235,000
1964	3,950,000
1965	5,000,000

5. Another estimate of the number of women taking oral contraceptives is based on the responses of a nationwide sample of about 5,600 married women, interviewed in late 1965 (Westof and Ryder, 1966). According to this survey, about 3,800,000 women were using oral contraceptives at the time of the interview and an additional 2,600,000 had been taking them previously but had stopped medication, with or without the intention to resume use at a later date.

The difference between the industry estimate (5 million in 1965) and the survey estimate (3,800,000) may be explained, at least in part, by the inclusion of several categories of women in the former but not in the latter. These are: (1) Married women over 45; (2) unmarried women; and (3) women for whom steroid compounds have been prescribed for therapeutic reasons but who do not know the nature of the medication. In addition, it is possible that the industry estimate is inflated by the growth of inventories in the hands of distributors and/or retailers. On the other hand, some of the women interviewed in the survey may have withheld the relevant information.

6. Oral contraceptives are much more widely used among younger than among older women. According to the 1965 survey, 26 percent of married women under 30 years of age were current users, compared with 8 percent of those over 30. Among the current users, two out of three were less than 30 years old and two out of five were less than 25 years old.

7. In August 1962, some 275,000 letters were sent by the G. D. Searle Co., makers of Enovid, to physicians, druggists, and other pertinent persons throughout the United States requesting that "any thromboembolic occurrence in women receiv-

ing Enovid be reported to us and to the Food and Drug Administration."[2] In the fall of 1965, a survey of the deaths so reported to the FDA indicated gross underreporting. Accordingly, in January 1966, arrangements were made for Dr. Schuyler Kohl, professor of obstetrics and gynecology at the Downstate Medical Center of the State University of New York, to visit all pharmaceutical firms marketing oral contraceptives and make a thorough investigation of the deaths reported and other pertinent facts.

Dr. Kohl's report, which is included in appendix 6 (p. 64) confirmed the earlier impression of the Committee in respect to underreporting of deaths. In fact, he found the magnitude of underreporting to be so great as to preclude drawing any conclusions from these data. The evidence was clear that the pharmaceutical firms concerned reported promptly any adverse reactions of which they were notified; the breakdown of this voluntary system of reporting was caused rather by the inadequate information about deaths on the part of physicians and other persons who were relied upon to report adverse reactions.

8. Taking into account the preponderance of young women among those using oral contraceptives, one would expect for each million users about 14 fatal cases of thromboembolic disease per year, including 10 deaths from pulmonary embolism and 4 deaths from cerebral embolism and thrombosis. Hence, the numbers of deaths expected in 1962 on the basis of the industry estimate of users (1,187,000) would be on the order of 12 and 5, respectively. It would seem prudent, however, to reduce these figures to, say, 10 and 4, respectively, to allow for a possible inflation of the estimated number of users.

According to the information obtained by Dr. Kohl, 20 deaths from all causes were reported to the manufacturers (and subsequently to the FDA) as having occurred among users of oral contraceptives in 1962. Of these, only 13 were due to "idiopathic pulmonary embolus"; that is, to an embolus without any demonstrable predisposing factor. This figure (*13*) is larger than the expected number of deaths from pulmonary embolism alone (*10*), but the difference is not statistically significant. This relationship of reported to expected deaths in 1962 is virtually the same as found by the Wright Committee which used the same or very similar basic data and a comparable procedure. (Report by the ad hoc Committee for the Evaluation of a Possible Etiologic Relation With Thromboembolic Conditions, submitted to the Commissioner of FDA, HEW).

9. It would appear, then, that the intense effort of 1962 produced about as many reports of fatal cases of pulmonary embolism among users of oral contraceptives as would be expected on the basis of the experience of the general female population of reproductive age. It will be noted, further, that the number of women taking oral contraceptives increased more than fourfold from 1962 to 1965. The survey estimate for the latter year (3,800,000 users) implies 38 expected deaths from pulmonary embolism. Acceptance of the industry estimate (5 million users) would raise this figure to 50 deaths.

Even without any causal relationship whatsoever it would be expected that the numbers of reported deaths among women taking oral contraceptives would augment proportionally with the increasing numbers of users. This, however, was not the case. The number of reported deaths due to unexplained pulmonary embolism in 1962 and 1965 were the same (*13*).

The data derived from mortality statistics are not adequate to confirm or refute the role of oral contraceptives in thromboembolic disease. They do, however, suggest that if oral contraceptives act as a cause they do so very infrequently relative to the number of users. The task force believes, nevertheless, that the only way in which this question can be answered definitively is through well-controlled epidemiological studies.

COPY OF LETTER FROM G. D. SEARLE & CO.

AUGUST 7, 1962.

IMPORTANT—DRUG CAUTION.

DEAR DOCTOR: We are addressing this letter to you in keeping with our policy of bringing to you all of the pertinent facts concerning our products and as a response to recent publicity dealing with the occurrence of thromboembolic phenomena coincident with women receiving Enovid.

Since its introduction there have been reported to us as of this date 28 cases of thromboembolic disease in the more than 1 million users of Enovid in the United States. Among these were 10 cases

[2] "Drug Caution" letter appended.

of pulmonary embolism, 5 of which were fatal. In addition, there are press reports of four cases, including one death from the United Kingdom.

In some of these one or more of the usually accepted inciting causes of thrombophlebitis were evident; in some they were not.

Reports to the manufacturer do not reflect the accurate incidence of reactions and the available statistics are not adequate to determine whether or not there is a causal relationship, but caution requires consideration of this possibility.

It must be remembered that pulmonary embolism can occur without discernible inciting cause and without preceding peripheral thrombophlebitis. Nevertheless, careful studies by investigators experienced in the measurement of the extremely complex factors involved in the clotting mechanism are continuing, including an evaluation of the role of fluid accumulation sometimes seen after Enovid administration. This will be reported in a technical bulletin at an early date. At the present time the available laboratory data neither prove nor disprove a causal relationship between Enovid administration and the occurrence of thrombophlebitis.

The cases of thrombophlebitis reported to us have usually occurred early in the course of Enovid administration and at the lower dosage level. Experience based on patients taking Enovid at higher doses has not demonstrated any dose response relationship.

Physicians should be as alert to the possible occurrence of thrombophlebitis in patients to whom Enovid is prescribed as they are in patients taking other medication.

The above facts should be given particular attention if Enovid is considered for administration to patients with thrombotic disease or a history of thrombophlebitis.

We request that any thromboembolic occurrence in women receiving Enovid be reported to us and to the Food and Drug Administration.

Sincerely yours,

(S) Irwin C. Winter,
IRWIN C. WINTER, Ph. D., M.D.,
Vice President, Medical Affairs.

Appendix 2

Report of the Task Force on Carcinogenic Potential

R. B. SCOTT, M.D., CHAIRMAN

The available prevalence and incidence rates of cancer of the uterine cervix, cancer of the endometrium, and cancer of the breast were reviewed in order to establish, as near as possible, the expected normal rates for these cancers in the human female.

All of the published and submitted data on patients who have received any of the estrogen-progestogen combinations for contraceptive purposes over a period of time were reviewed.

The animal experiments, published and some unpublished, using these hormonal agents, or similar agents, as they relate to the production of malignancy or the influence on an existing malignancy, were studied.

The following observations and conclusions were made:

Cancer of the Uterine Cervix

Dysplasia, carcinoma in situ, and invasive cancer were considered. The importance of the geographic location and of the socioeconomic level of the population sample were very evident: for example, the prevalence of carcinoma in situ and invasive cancer in Puerto Rico was almost six times that of a Metropolitan New York group composed of women, for the most part, from a higher socioeconomic level. Another important factor was the average age of women showing these changes: roughly 35 years for dysplasia, 40 years for carcinoma in situ, and 47 years for invasive cancer (tables 1–7).

The data from the various study groups using contraceptive pills were difficult to analyze for the following reasons:

1. Initial cytological status was not given in many instances and in others patients with suspicious or positive Papanicolaou cytology were admitted to the study.
2. The various methods of collecting cytological specimens and the personal equation in reading and reporting any changes make standardization of data difficult.
3. The frequent absence of histopathology after cytologic suspicion was found.
4. The preponderance of patients in the age group before 35.
5. The relatively small number of patients followed regularly and thoroughly for 4 years or more.

In the data submitted there is no evidence of any increased incidence of premalignant or malignant changes in the uterine cervix which could be attributed to the use of the contraceptive pills in this relatively short time interval (tables 8–13). Any valid conclusion must await accurate data on a much larger group of women studies for at least 10 years. Also, in the data, there is no evidence to support the statement which has been made—that the use of the contraceptive pills may have a protective effect against the development of malignancy of the uterine cervix.

One study, in need of supporting evidence from other investigators, may be significant. This study showed an appreciable increase of coccoid bacteria, Trichomonads, and fungi in women using contraceptive pills for a year or more compared to a matched control group. This alteration in the microbiological content of the genital tract might be related to the use of the pills and could account for some increase in such cytological reports as atypical cells or class 2 Papanicolaou.

Uterine Endometrial Malignancy

Endometrial carcinoma is primarily a disease of the postmenopausal years and only 5 to 8 percent of these occur before the age of 40.

In the data submitted the paucity of endometrial biopsies as a routine followup procedure, the limited number of women more than 40 years of age, and the short duration do not permit drawing any conclusions relative to the effect, either

adverse or beneficial, of these contraceptive pills on endometrial malignancy (table 14).

There are numerous studies which suggest a preponderance of estrogenic influence, either endogenous or exogenous, in women who subsequently develop endometrial adenocarcinoma. A cause-and-effect relationship has by no means been established. All women receiving estrogen therapy must be followed with the utmost care and thoroughly investigated at the slightest suspicion; the advice to administer a progestogen periodically to women receiving estrogen, in order to allow periodic "withdrawal" bleeding on the basis that it "prevents" endometrial cancer, is not valid either on a theoretical basis or on the basis of the very limited number of postmenopausal patients so treated.

The use of progestogens in the treatment of adenomatous hyperplasia and carcinoma in situ of the endometrium is under investigation in several centers. At the present time no conclusions can be drawn. There is clinical evidence of some palliative benefit, but not cure, from the administration of large doses of progestogens in about one-third of the patients with metastatic endometrial cancer.

Breast Cancer

The mortality rate of cancer of the female breast in the United States has remained remarkably stable since 1930 (table 15). The incidence of cancer of the breast rises with age. Inasmuch as contraceptors are in the younger age groups, very large samples will be necessary to detect an association if one exists.

In the published reports of women receiving contraceptive pills for variable periods of time there are no observed cases of breast cancer. The FDA files contain one recent instance of a woman, age 44, with a history of previous cystic disease of the breast, who was shown to have a scirrhous carcinoma of the breast after 7 months of cyclic estrogen-progestogen. In the limited data available, with the preponderance of relatively young women and the uncertainty as to the completeness of followup breast examinations, no conclusions can be drawn as to the relationship between the use of the contraceptive pills and cancer of the breast.

The animal studies, to be mentioned later, and certain clinical observations indicate the need for a high index of suspicion and continuing alert observation and studies. The acceleration of growth of certain existing breast cancers by the administration of estrogens has been noted. Many instances of breast cancer have been reported in males receiving large doses of estrogens for prostatic cancer; although this is not proof of the inciting of breast cancer by estrogens, it is strongly suspicious. Any relationship of progesterone or the progestogens to breast cancer is not clear. One recent clinical study of breast biopsies in a limited number of women on the contraceptive pills revealed an increase in the amount of intralobular and perilobular fibrosis as compared to controls. The significance of this is not certain and the finding needs confirmation to accept.

Other Malignancies

Malignant lesions in the pituitary, kidneys, ovaries, and bone marrow have been found in animal studies after treatment with certain of the sex hormones, but at the present time there are no human corollaries. The FDA files contain one instance of malignant melanoma found during the administration of contraceptive pills; this is favorably coincidental, but the alterations of melanin distribution during pregnancy and in some patients receiving contraceptive pills are well known and therefore a relationship cannot be entirely dismissed.

Animal Studies

Sex steroids, particularly estrogens, have been shown to produce malignant lesions and to adversely affect existing ones in the mouse, rat, rabbit, hamster, and dog. These neoplasms have been in various organs and organ systems such as the cervix, endometrium, ovary, breast, testicle, pituitary, kidney, and bone marrow. The observations in animals using progesterone and the newer progestogens have been contradictory; however, these agents alone and in combination with other sex steroids have promoted tumor formation or not prevented it in a few instances. A recent example is a 52-week study of six dogs which received massive doses of a combination of mestranol and ethynerone (MK-665—an experimental progestogen)—four of the dogs developed mammary lesions; one, a carcinoma in situ with early invasion; one, a carcinoma in situ; one, an atypical hyperplasia; and one, a benign intraductile papilloma. The decision of the FDA to discontinue clinical trials of this agent and advise further animal studies was a correct one.

Animal studies in which certain susceptible strains and species are used and the dosage, excessive and continuous, cannot be transferred exactly to human expectancy. Nevertheless, a warning is there and a so-altered endocrine environment in human tissues might result in an abnormal expression or potentiation of growth.

Recommendations

1. The more extensive use of dogs and nonhuman primates in the animal testing of these drugs.
2. To test the presently approved contraceptive pills, if this has not been done, for mammary effects in dogs.
3. Encourage research in long-term administration of estrogens and other sex hormones in low and intermediate doses to nonhuman primates.
4. Continue the study groups on contraceptive pills in order to obtain more long-term data. Assure that the patients in those study groups are regularly and adequately examined and tested and that abnormal findings are immediately reported.
5. Continue the warning that the contraceptive pills are contraindicated in the presence of genital or breast malignancy and to extend this contraindication to any suspicion of genital or breast malignancy.
6. To establish at least two long-term study groups: one on the contraceptive pills and at least one control group. The minimum number in each group should be 20,000 women and the term of study for each group no less than 10 years. These studies must be within a reasonably stable population and geographic area. These are the minimum number required to ascertain a 2x change of genital and breast cancer incidence rates with 5 percent acceptable risk rate.

Table I.—*Cervical carcinoma—Initial screening* [1]

		Number of women	Number of cancers	Rate per thousand	In situ	Invasive cancers
2	Mayo Clinic, Rochester, Minn	139, 503	987	7. 1	897 (6. 4)	90 (0. 7)
3	Ohio State University, Columbus, Ohio	113, 758	388	3. 4	213 (1. 9)	175 (1. 5)
4	Memphis, Tenn	108, 136	724	6. 7	393 (3. 6)	331 (3. 1)
5	Wisconsin State Laboratory, Madison	65, 163	548	8. 4	195 (3. 0)	353 (5. 4)
6	Mecklenburg County, N.C	48, 697	412	8. 5	290 (6. 0)	122 (2. 5)
7	San Diego, Calif	33, 746	336	10. 0	259 (7. 7)	77 (2. 3)
9	Honolulu, Hawaii	24, 182	134	5. 5	51 (2. 1)	83 (3. 4)
10	Strang Clinic	19, 462	48	2. 5	46 (2. 4)	2 (0. 1)
12	Floyd County, Ga	17, 761	84	4. 8	56 (3. 2)	28 (1. 6)
11	Los Angeles, Calif	19, 192	145	7. 6	97 (5. 1)	48 (2. 5)
14	Puerto Rico	8, 435	119	14. 1	67 (7. 9)	52 (6. 2)
8	Metropolitan Hospital, N.Y.—Sedlis	27, 226	123	4. 5	71 (2. 6)	52 (1. 9)
15	Tijuana, Mexico	2, 161	51	23. 6	25 (11. 6)	26 (12. 0)
13	Kansas—Hellwig	10, 197	96	9. 4	52 (5. 1)	44 (4. 3)
1	Vancouver, British Columbia	322, 352	2, 156	6. 7	1, 228 (3. 8)	928 (2. 9)
	Total	959, 971	6, 351	6. 6	3, 940 (4. 0)	2, 411 (2. 6)

[1] Adapted from Day, E, table 4, p. 1193, Clini. Obst. and Gynec., 4: 1183-1198, 1961, with additions.

Table II.—*Prevalence of dysplasia, carcinoma in situ and invasive cancer of the cervix uteri*

Age	Total	Percent	Dysplasia		Stage 0		Stage 1		Stage 2-4	
			Number	Rate	Number	Rate	Number	Rate	Number	Rate
20-29	2,107	8	14	6.6	5	2.4	1	0.5	0	0
30-39	6,322	24	48	7.6	34	5.4	7	1.1	0	0
40-49	6,585	25	23	3.5	32	4.9	9	1.4	5	.8
50-59	6,058	23	25	4.1	21	3.5	7	1.2	7	1.2
60-69	3,951	15	15	3.8	9	2.3	9	2.3	17	4.3
70 plus	1,317	5	4	3.0	4	3.0	5	3.8	5	3.8
Total	26,340		129		105		38		34	
Average				4.9		4.0		1.4		1.3

From Stern, E., in Cancer, 12: 933, 1959.

Table III.—*Results of rescreening of patients with carcinoma of the cervix uteri*

Study	Screening	Number of women	Carcinoma in situ		Invasive cancer	
			Number	Rate per thousand	Number	Rate per thousand
Memphis, Tenn	First	108, 136	393	3.6	331	3.1
	Second	32, 728	72	2.2	9	.3
Wisconsin State Laboratory, Madison.	First	65, 163	206	3.2	335	5.1
	Second	9, 111	10	1.1	4	.4
Floyd County, Ga	First	17, 761	56	3.2	28	1.6
	Second	4, 482	12	2.7	4	.9
Ohio State University, Columbus	First	113, 758	213	1.9	175	1.5
	Second	44, 009	40	.9	7	.2
	Third	16, 137	2	.1	2	.1
San Diego	First	33, 746	265	7.8	78	2.3
	Second	9, 725	34	3.5	2	.2
	Third	4, 213	6	1.4		
	Fourth	1, 654			1	.6

Reproduced from Day, E., table 5, p. 1194, Clin. Obst. and Gynec. 4: 1183-1198, 1961.

Table IV.—*Cervical cancer findings (as of June 30, 1965)*

[Screening]

Age	Total No.	Percent of all screened	Findings per 1,000 screened				
			Cervical cancer			Dysplasia	Other cancer
			Total	Invasive	In situ		
15 to 29	143, 851	46	3.8	0.5	3.3	7.4	0.1
30 to 44	93, 110	30	11.4	3.1	8.3	7.2	.4
45 to 59	41, 655	13	12.5	7.8	4.7	4.9	2.5
60 plus	30, 228	10	16.6	11.9	4.7	5.0	7.0
Total	[1] 309, 750		8.5	3.4	5.1	6.8	1.2

[1] Ages not given in some instances.

From data submitted by Harvey Geller, Chief, Operational Studies Section, Cancer Control Branch, Division of Chronic Diseases, DHEW, Public Health Service.

Table V.—*Cervical cancer findings (as of June 30, 1965)*

[1st year routine repeats]

Age	Total No.	Percent of all screened	Findings per 1,000 screened				
			Cervical cancer			Dysplasia	Other cancer
			Total	Invasive	In situ		
15 to 29	14,561	34	2.3	0.2	2.1	6.1	0.1
30 to 44	13,833	33	3.7	.8	2.9	4.6	.2
45 to 59	7,737	18	1.9	.6	1.3	3.4	1.2
60 plus	6,196	15	1.9	1.1	.8	2.7	2.4
Total	[1] 42,330		2.6	.6	2.0	4.6	.7

[1] Age not given in some instances.

From data submitted by Harvey Geller, Chief, Operational Studies Section, Cancer Control Branch, Division of Chronic Diseases, DHEW, Public Health Service.

Table VI.—*Age—Specific annual incidence rates for cancer of the uterine corpus plus unspecified uterine cancer*

[Rates per 100,000]

Age	Connecticut, 1960	Upstate New York, 1958-60	Age	Connecticut, 1960	Upstate New 1958-60
0 to 4	0.7		50 to	47.5	41.59
5 to			55 to	61.2	50.67
10 to			60 to	52.1	72.28
15 to		0.11	65 to	63.8	69.19
20 to	2.8	.82	70 to	88.1	65.60
25 to	1.3	1.36	75 to	106.1	60.56
30 to	4.5	1.99	80 to	57.9	67.33
35 to	6.1	5.17	85 and over	77.7	56.56
40 to	16.7	11.94	Age adjustment	18.7	15.73
45 to	39.9	20.18			

Prepared by John C. Ballar III, M.D., National Cancer Institute

Table VII.—*Average annual cancer incidence rates and expected numbers of cancers per 1,000 women followed 4 years, Upper New York State, 1958-60*

Age at beginning of study		Breast	Cancer of—	
			Cervix [3]	Corpus [3]
20 to 39 years	Average annual incidence rate per 100,000 [4]	23.96	31.08	3.45
	Expected cases per 1,000 women followed 4 years [1]	.96	1.24	.14
40 to 54 years	Average annual incidence rate per 100,000 [4]	112.88	52.32	29.73
	Expected cases per 1,000 women followed 4 years [1]	4.52	2.09	1.19

[1] No allowance is made for death or loss to followup among members of the sample; if deaths or losses occur they would decrease the expected numbers per 1,000 sample members and increase required sample sizes.

[2] Including carcinomas in situ. If such tumors are excluded, expected numbers per 1,000 sample members would be decreased. Required sample sizes would be increased moderately at ages 40 to 54 and substantially at ages 20 to 39.

[3] Includes all uterine tumors except those specified as cervical. If endometrial tumors alone are considered, expected numbers per 1,000 sample members would be decreased and required sample sizes increased.

[4] Weighted average with adjustment for advancing age during the followup interval.

Table VIII.—*Data on Papanicolaou smears during use of oral contraceptives*

Reference	Compound	Number women treated	Total cycles studied	Number smears treated women	Number smears control women	Number smears positive	Number positive expected
Pincus, 1959	Enovid	830	8,133	(1)		0	
Goldzieher et al., 1962	Ortho-Novum	210	6,232	(2)		0	
Rice-Wray et al., 1962	do	364	6,062	(2)		0	
Rice-Wray et al., 1963	Enovid	2,040	[3] 22,948	(2)		0	11.8
						Positive smears in treated women (percent)	Positive smears in control women (percent)
Pincus, 1961	do			412	[4] 11,664	0.2	1.1
Tyler, 1961	Enovid, Ortho-Novum	1,004	[5] 33,132			.4	.6
Tyler, 1964	Enovid, Ortho-Novum and other.			6,746	2,510	.77	1.23

[1] Number not stated.
[2] Number not stated; smear taken at annual pelvic examinations.
[3] Enovid and Ortho-Novum used in 85 percent of cycles.
[4] Data of Lee, for Puerto Rico.
[5] Calculated on basis of 31 months average duration of treatment.

From Drill, V. A., Pacific Medical and Surgical, 75: November–December 1964.

Table IX.—*Cases of cancer during use of oral contraceptives*

Reference	Compound	Number of women treated	Total cycles studied	Number of cases of cancer observed during treatment	
				Genital	Mammary
Pincus, 1959	Enovid	830	8,133	0	0
Cook et al., 1961	do	550	6,743	2	0
Pincus, 1961	do		20,442	1	0
Tyler, 1961	Enovid, Ortho-Novum	1,004	[1] 33,132	(2)	0
Goldzieher et al., 1962	Ortho-Novum	210	6,232	0	0
Rice-Wray et al., 1962	Ortho-Novum	364	6,062	0	0
Rice-Wray et al., 1963	Enovid, Ortho-Novum	2,040	[3] 22,948	0	0

[1] Calculated on basis of 31 months average duration of treatment.
[2] No cases reported based on physical examination, pelvic or biopsy.
[3] Enovid or Ortho-Novum employed in about 85 percent of cycles.

Table X.—*The rate of development of suspicious Papanicolaou smears in subjects with negative smears before the use of contraceptives*

Contraceptive used	Number of subjects	Number/1,000 with suspicious smears	Average number of years of use
Vaginal	208	72.1±18.0	1.3
Enovid	580	[1] *26.2*± 6.6	3.4
Ovulen	188	*21.3*±10.5	1.8
Orthonovum	105	28.6±16.4	1.6
Intrauterine devices	500	54.0±10.0	1.1

[1] *Italic* values differ significantly from those for vaginal contraceptives.

From data submitted by Dr. Gregory Pincus (Jan. 6, 1966).

Table XI.—*Cervical cytology*

[At the time of enrollment, 6,583/11,711 women had recorded Papanicolaou smears]

	Class I	Class II	Class III	Class IV, class V
At 25 months (percent)	79. 1 (5, 208/6. 583)	20. 4 (1, 343/6, 583)	0. 4 (26/6, 583)	0. 1 (6/6, 583)
At 30 months (percent)	87. 0 (2, 090/2, 402)	12. 5 (300/2, 402)	. 3 (8/2, 402)	. 2 (4/2, 402)
At 36 months (percent)	79. 9 (1, 094/1, 369)	20. 1 (275/1, 369)	0	0
At 42 months (percent)	88. 0	12. 0	0	0

Conclusion: The incidence of abnormal cytology was low in those women examined, and was not observed to increase with continued use (25 to 42 months).

From Planned Parenthood Federation of America—"25 Months Club."

Table XII.—*Papanicolaou smears*

	At enrollment or 1 year Rx			13 to 24 months			25 to 36			37 to 48			49 to 60			60		
	I-II	III	IV-V	I-II	III	IV-V	I-II	III	IV-V	I-II	III	IV-V	I-II	III	IV-V	I-II	III	IV-V
San Antonio, orals	1, 191	[1] 4	[2] 4	263	0	[3] 1	117	2	0	78	[3] 1	0	40	2	0	----	----	----
San Antonio, all others	479	5	0	94	0	0	77	0	0	79	0	0	56	0	0	348	0	0

[1] 3 cancers. [2] 4 cancers. [3] cancers.

From data submitted by Dr. Joseph Goldzieher.

Table XIII.—*Papanicolaou smears by cycles of treatment with various estrogen-progestin compounds*

Cycles	Number of smears	Results	Cycles	Number of smears	Results
Control smears before Rx.	6, 157	13 carcinomas of the cervix before Rx. (0.21 percent). [1]	From 37 to 48	279	Negative.
			From 49 to 60	108	Do.
			Over 60	57	Do.
From 4 to 12	1, 694	Negative.			
From 13 to 24	1, 730	Do.	Total	10, 752	Do.
From 25 to 36	727	Do.			

[1] The incidence of cancer of the cervix in Mexican women is 0.3 percent.

NOTE: 25 Papanicolaus were suspicious, 24 became normal following treatment of existing cervicitis, 1 was lost to followup for a year—at that time she had an invasive cervical cancer (undifferentiated cell).

Edris Rice-Wray, M.D.

Table XIV.—*Analysis of endometrial biopsies in enovid users*

II. "ABNORMAL" ENDOMETRIAL STATES[1]

Lunar years of use	Cystic and adenomatous hyperplasia	Percent with			
		Atrophy	Endometritis	Anaplasia	Carcinoma-in-situ
Premedication	5.0±0.49	0.9±0.21	8.6±0.63	0.14±0.08	0.09±0.07
1 to 2	*0.8±0.40*	0.6±0.35	*0.6±0.35*	0.0	0
3 to 4	*2.8±0.79*	0.9±0.45	*1.2±0.52*	0.20±0.22	0
5 to 9	3.5±1.15	1.9±0.85	*0.8±0.56*	0.40±0.39	0
Postmedication	6.0±2.06	1.5±1.05	*3.0±0.56*	0.40±0.39	0

[1] From Pincus, Gregory, Jan. 6, 1966.

Italic values significantly differ from premedication values.

Table XV.—*The epidemiology of breast cancer*[1]

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SUMMARY

A review of available data on the epidemiology of breast cancer indicated the following: (*a*) A remarkable stability of the trend of mortality from female breast cancer in the United States since 1930; (*b*) Japan has the lowest death rate for female breast cancer, and Japan and Finland for male breast cancer, in the world; (*c*) the logarithm of the age-specific death rates from female breast cancer can be resolved into two linear components with the slope of the rates prior to 40–50 years of age being greater than the slope of those after 40–45 years of age; a similar change of slope, although to a lesser degree was observed for males. It was noted that for females this age group corresponded to the time of menopause; (*d*) female patients with breast cancer were more frequently never married or, when married, married at a later age than women in general. Since female breast cancer patients more often gave a history of having had artificial menopause and single women had had artificial menopause less frequently than married women, it was hypothesized that the single-married differences may reflect the differences in frequency of artificial menopause among single and married women; (*e*) the inverse relationship between frequency and length of nursing with female breast is far from being conclusive; (*f*) studies show that females with benign breast disease have an excess risk of developing breast cancer, but more definitive studies are needed; (*g*) studies show the existence of familial aggregation of breast cancer among both males and females; (*h*) a study of male breast cancer patients indicated that a larger proportion of them had a history of orchitis, orchiectomy, therapeutic X-ray exposure and benign breast disease. These data were interpreted as suggesting the influence of hormonal factors as being of importance in the etiology of breast cancer, but more definitive and precise studies are needed. A program of epidemiological research was outlined emphasizing the need for integrating laboratory investigations with the field epidemiological studies.

[1] Presented at a symposium on "Epidemiology of Cancer" given at the annual meeting of the American Association for Cancer Research, Toronto, Canada, on May 23, 1963.

bibliography

1. ALVIZOURI, M. AND RAMIREZ DE PITA, V. Experimental carcinoma of the cervix, Am. J. Obst. and Gynec., 89: 940, 1964.
2. ANDERSON, R. K., GILMORE, C. E., AND SCHNELLE, G. B. Utero-ovarian disorders associated with the use of medroxyprogesterone in dogs, J. Am. Vet. Med. Assn., 146: 1311, 1965.
3. BEECHAM, C. T. AND ANDROS, G. J. Cervical conization in pregnancy, Obst. and Gynec., 16: 521, 1960.
4. BOYES, D. A. Personal communication from the Cytological Diagnostic Laboratory of Vancouver, British Columbia, Canada.
5. CAVANAGH, D., MCLEOD, A. G. W., AND FERGUSON, J. H. Carcinoma of the cervix among women in their twenties, J.A.M.A., 195: 146, 1966.
6. CHRISTOPHERSON, W. M. The risk of cervical cancer in teenaged girls, J.A.M.A., 194: 176, 1965.
7. CHRISTOPHERSON, W. M. AND PARKER, J. E. Relation of cervical cancer to early marriage and childbearing, New Eng. J. of Med., 273: 235, 1965.
8. CHRISTOPHERSON, W. M., PARKER, J. E., AND DRYE, J. C. Control of cervical cancer, J.A.M.A., 179, 1962.
9. COOK, H. H., GAMBLE, C. J., AND SATTHERTHWAITE, A. P. Oral contraception by norethynodrel: A 3-year field study, Am. J. Obst. and Gynec., 82: 437, 1961.
10. COPELAND, M. M. Treatment of mammary dysplasia with special reference to microcystic disease of the breast, Am. J. Surg., 106: 382, 1963.
11. DAY, E. Evaluation of exfoliative cytology as a screening method for pelvic cancer, Clin. Obst. and Gynec., 4: 1183, 1961.
12. DOCKERTY, M. B., SMITH, R. A., AND SYMMONDS, R. E. Pseudomalignant endometrial changes induced by administration of new synthetic progestins, Proc. Staff Meet. Mayo Clinic, 34: 321, 1959.
13. DRILL, V. A. Relationship of administered estrogen, progesterone, and oral contraceptives to cancer of the breast and genital organs of women, Pacific Med. and Surg. (West. J. Surg. Obst. and Gynec.), 73: November–December 1964.
14. ERICKSON, C. E., EVERETT, B. E., GRAVES, L. M., ET AL. Population screening for uterine cancer by vaginal cytology, J.A.M.A., 162: 167, 1956.
15. FERGUSON, J. H. Positive cancer smears in teenage girls. J.A.M.A., 178: 365, 1961.
16. FERGUSON, J. H. AND BROWN, G. C. Cervical conization during pregnancy, Surg. Obst. and Gynec., 111: 603, 1960.
17. FIDLER, H. K., BOYES, D. A., AUERSPERG, N., AND LOCK, D. R. The cytology program in British Columbia. 1. An evaluation of the effectiveness of cytology in the detection of cancer and its application to the detection of carcinoma of the cervix, Canad. Med. Assn. J., 86: 779, 1962.
18. FLOWERS, C. E., JR. Effects of new low-dosage form of norethynodrel-mestranol, J.A.M.A., 188: 1115, 1964.
19. FOOTE, F. W. AND STEWART, F. W. Comparative studies of cancerous versus noncancerous breasts, Ann. Surg., 121: 197, 1945.
20. GILBERTSEN, V. A. Survival of asymptomatic breast cancer patients, Surg. Obst. and Gynec., 122: 81, 1966.

20a. GOLDZIEHER, J. W. AND MAAS, J. M. Clinical evaluation of a sequential oral contraceptive, presented at the Sixth Pan American Congress of Endocrinology, October 1965, Mexico City.

21. GORE, H. AND HERTIG, A. T. Carcinoma in situ of the endometrium, Am. J. Obst. and Gynec., 94: 134, 1966.
22. HELLWIG, C. A. The fate of women with positive smears, J. Int. Col. Surg., 40: 465, 1963.
23. HOMBURGER-FISHMAN, Physiopathology of Cancer, Second Edition, 1959, Hoeber-Harper, New York.

24. KAMINETZKY, H. A. AND SWERDLOW, M. Sex steroids and experimental invasive atypia in mice, Am. J. Obst. and Gynec., 89: 716, 1964.
25. KAUFMAN, R. H. Cervico-vaginal cytology in the teenage patient, Acta Cytol., 9: 314, 1965.
26. KELLEY, R. M. AND BAKER, W. H. Effects of 17-alpha-hydroxy progesterone caproate on metastatic endometrial cancer, Conference on Experimental Cancer Chemotherapy-Monograph 9: 235, Bethesda, Md., National Cancer Institute, 1960.
27. KELLEY, R. M. AND BAKER, W. H. Progestational agents in the treatment of carcinoma of the endometrium, New Eng. J. of Med., 264: 1, 1961.
28. KENNEDY, B. J. A progestogen for treatment of advanced endometrial cancer, J.A.M.A., 84: 102, 1963.
29. KISTNER, R. W. Histological effects of progestins on hyperplasia and carcinoma in situ of the endometrium, Cancer, 12: 1106, 1959.
30. KISTNER, R. W., GRIFFITHS, C. T., AND CRAIG, J. M. Use of progestational agents in the management of endometrial cancer, Cancer, 18: 1563, 1965.
31. KISTNER, R. W. Oral contraceptives. Safety factors in prolonged use of progestin-estrogen combinations, pt. I, Postgrad. Med., 39: 207, 1966.
32. KISTNER, R. W. Hormonal treatment of premalignant lesions of the endometrium, in press.
33. LEE, HARRY A. Some effects of two oral contraceptive agents on the breast, in press.
34. LEIS, H. P., JR., 55 East 87th Street, New York, N.Y.—Personal communication.
35. LILIENFELD, A. M. The epidemiology of breast cancer, Cancer Res., 23: 1503, 1963.
36. LUNDIN, F. E., JR., ET AL. Morbidity from cervical cancer: Effects of cervical cytology and socioeconomic status, J. Nat. Cancer Inst., 35: 1015, 1965.
37. MAQUEO, M., ET AL. Endometrial histology and vaginal cytology during oral contraception with sequential estrogen and progestin, Am. J. Obst. and Gynec., 90: 395, 1964.
38. MARSHALL, C. E. Effect of cytologic screening on the incidence of invasive cancer of the cervix in a semiclosed community, Cancer, 18: 153, 1965.
39. MOYER, D. L., ET AL. Vaginal cytohormonal effects of long-term cyclic administration of synthetic progestins, Fert. and Steril., 15: 164, 1964.
40. MUSTACCHI, P. AND GORDAN, G. S. Frequency of cancer in estrogen treated osteoporotic women in Segaloff, A., Breast Cancer (the Second Biennial Louisiana Cancer Conf., New Orleans, Jan. 22–23, 1958), C. V. Mosby Co., 1958, p. 163.
41. NOBLE, R. L. Hormonal regulation of tumor growth, Pharm. Review, 9: 367, 1957.
42. PINCUS, G. Control of Fertility. Academic Press, New York and London, 1965.
43. PINCUS, G. AND GARCIA, C-R. Studies on vaginal, cervical, and uterine histology, Metabolism, 14: 344, 1965.
44. REAGAN, J. M. Presidential address, Acta Cytol., 9: 265, 1965.
45. RICHART, R. M. AND VAILLANT, H. W. Influence of cell collection techniques upon cytological diagnosis, Cancer, 18: 1474, 1965.
46. RUCH, T. C. Diseases of Laboratory Primates. W. B. Saunders Co., Philadelphia, 1959.
47. RUDEL, H. W., ET AL. The role of progestogens in the hormonal control of fertility, Fert. and Steril., 16: 158, 1965.
48. RUDEL, H. W. AND KINCL, F. A. The biology of antifertility steroids, to be published in Acta Endocrin.
49. SCHONBEEG, L. A., ET AL. Cancer of the cervix in a Mexican population, J.A.M.A., 191: 96, 1965.
50. SCOTT, R. B. External endometriosis. Postgrad. Med., 39:295, 1966.
51. SEDLIS, A., ET AL. Cytology screening for cervical cancer in a municipal hospital, Cancer, 17: 152, 1963.
52. SHAPIRO, S., STRAX, PHILIP AND VENET, L. Evaluation of periodic breast cancer screening with mammography, J.A.M.A., 195: 111, 1966.
53. SHIMKIN, M. B. Cancer of the breast. Some old facts and new prospectives, J.A.M.A., 183: 358, 1963.
54. STERN, E. Rate, stage, and patient age in cervical cancer—an analysis of age specific rates for atypical hyperplasia, in situ cancer, and invasive cancer in a well population, Cancer, 12: 933, 1959.
55. STERN, E. AND DIXON, W. J. Cancer of the cervix—A biometric approach to etiology, Cancer, 14: 153, 1961.
56. STERN, E. AND NEELY, P. M. Dysplasia of the uterine cervix, Cancer, 17: 508, 1964.
57. STEVENS, G. M. AND WEIGEN, J. F. Mammography survey for breast cancer detection, Cancer, 19: 51, 1966.

58. Symposium—Symposium on the Effects of Progestational Agents, Acta Cytol., 6: 278, 1962.
59. TORRES, J. E., ET AL. Histological findings in the genital tract of females with class III smears, Acta Cytol., 8: 284, 1964.
60. TOTH, F. AND SZONYI, I. The inhibiting effect of a norsteroid on tumor formation and on the metabolism of tumor cells, Am. J. Obst. and Gynec., 94: 518, 1966.
61. TYLER, E. T. Current status of oral contraception, J.A.M.A., 187: 562, 1964.
62. VARGA, A. AND HENRIKSEN, E. Clinical and histopathologic evaluation of effect of 17-alpha-hydroxy-progesterone caproate on endometrial cancer, Obstet. Gynec., 18: 658, 1961.
63. VARGA, A. AND HENRIKSEN, E. Histological observations on the effect of 17-alpha-hydroxyprogesterone-17-n-caproate on endometrial carcinoma, Obstet. and Gynec., 26: 656, 1965.
64. WALDROP, G. M. AND PALMER, J. P. Carcinoma of the cervix associated with pregnancy, Am. J. Obst. and Gynec., 86: 202, 1963.
65. WALLACH, S. AND HENNEMAN, P. H. Prolonged estrogen therapy in postmenopausal women, J.A.M.A., 171: 1637, 1959.
66. WALSH, H., HILDEBRANDT, R. J., AND PRYSTOWSKY, H. Candidial vaginitis associated with the use of oral progestational agents, Am. J. Obst. and Gynec., 93: 904, 1965.
67. WENTZ, W. B. Effect of a progestational agent on endometrial hyperplasia and endometrial cancer, Obstet. Gynec., 24: 370, 1964.
68. WHITE, T. T. Prognosis of breast cancer for pregnant and nursing women, Surg. Gynec. and Obst., 100: 661, 1955.
69. WEID, G. L. The meaning of class 3 of the Papanicolaou classification of specimens from the female genital tract, Acta Cytol., 8: 99, 1964.
70. WIED, G. L., ET AL. Statistical evaluation of the effect of hormonal contraceptives on the cytologic smear pattern, Obst. and Gynec., 27: 327, 1966.
71. WIED, G. L. "* * * personal submitted data from taped material of patients on contraceptive hormones for at least 2 years.
72. WILSON, R. A. The roles of estrogen and progesterone in breast and genital cancer, J.A.M.A., 182: 327, 1962.
73. WILSON, R. A. AND WILSON, T. A. The fate of the nontreated postmenopausal woman; a plea for the maintenance of adequate estrogen from puberty to the grave, J. Amer. Geriatrics Soc., 11: 347, 1963.
74. WILSON, R. A., BREVETTI, R. E., AND WILSON, T. A. Specific procedures for the elimination of the menopause, West. J. Surg. Obst. and Gynec., 71: 110, 1963.
75. WILSON, R. A. AND THE WILSON RESEARCH FOUNDATION, INC., 777 Third Avenue, New York, N.Y.—Personal communication.
76. WOMACK, N. A. Endocrine relationships between chronic cystic mastitis and cancer of the breast, Amer. Surg., 24: 618, 1958.

Appendix 3

Report of the Task Force on Metabolic Effects

E. M. DELFS, M.D., CHAIRMAN

Pituitary-Ovarian Function

The controversy as to whether oral contraceptives inhibit at the pituitary or at the ovarian level appears now to be resolved. Diczfalusy (1965) and his group present convincing evidence that these compounds inhibit at the pituitary level and that they interfere predominantly with the synthesis and/or release of LH rather than FSH. Similar results have been obtained by Lin (1964), Martin (1961), Taymor (1964 and 1965), and Ryan et al. (1966). The differences in these results and those obtained by Loraine and others are probably related to differences in methodology. Diczfalusy's group employed technics for estimation of LH and FSH individually whereas Loraine's conclusions that progestational compounds inhibit ovulation without affecting HPG excretion were based on a method for determination of total gonadotrophic activity. Furthermore, in Diczfalusy's study, oral contraceptive steroid combinations were administered simultaneously with courses of HMG or HHG followed by HGG. Results showed that administration of these compounds in dosages three times higher than those used for ovulation inhibition did not interfere with the ovarian reaction to exogenous gonadotrophins.

Available evidence indicates that resumption of ovulation after cessation of oral contraceptives is prompt, occurring in 4 to 8 weeks in most cases. In a few women, amenorrhea persists for 6 months or more. This is not unlike the occasional protracted anovulation following pregnancy or lactation. Fertility is the best indicator of adequate pituitary-ovarian function. Goldzieher (1962) reported 62 percent success in the first cycle in women discontinuing medication with intent of becoming pregnant, which compares favorably with the 34 percent conception in the first cycle after stopping mechanical or chemical contraceptives noted by Tietze (1959). Pincus (1964) found a pregnancy rate of 233 per 100 years of exposure after oral contraceptives were discontinued as compared with a rate of 17 before use in the same women. Pregnancy outcome was satisfactory with no significant increase in abortion, prematurity, abnormality, or developmental anomaly—Pincus (1964), Rice-Wray (1965).

Long-term effect (beyond 6 to 8 years) of oral contraceptives on the pituitary-ovarian interrelation, on normality and duration of ovarian function, and on fertility throughout the reproductive span is not known. Answers will require long-term physiological study and complex statistical control.

Pituitary-Adrenal Function

Oral contraceptives have been observed to produce increased cortisol-binding by serum proteins but urinary excretion data for 17 hyroxysteroids and 17 ketosteroids have been equivocal. Recent work seems to clarify the effect on pituitary-adrenal function. ACTH activity was studied during progestin treatment by Leach and Margulis

Table 1.—*Comparison of ACTH response during and after therapy*

Patient	During therapy		After therapy		Difference (mg.)	
	Control	ACTH	Control	ACTH	Before	After
E. J.	4.6	19.6	9.3	27.3	15.1	18.0
H. L.	5.9	9.1	4.4	14.5	3.2	10.1
A. D.	3.6	5.7	5.3	14.4	2.1	9.1
G. E.	2.0	8.6	8.8	28.6	6.6	19.8
H. L.	6.4	10.1	6.0	14.0	3.7	8.0
P. S.	5.9	9.3	7.5	23.0	3.4	15.5
J. W.	3.7	11.6	7.0	18.4	7.9	11.4
A. B.	8.1	10.2	6.1	31.4	2.1	25.3
C. H.	1.1	9.6	13.6	17.1	8.5	3.5
G. R.	3.0	17.5	7.7	19.7	14.5	12.0
A. K.	3.6	6.5	12.8	16.3	2.9	3.5
N. H.	2.6	10.5	5.6	17.9	7.9	12.3
Mean	4.2	10.69	7.8	20.2	6.4	12.38

From Leach and Margulis.

(1965). Patients had been on oral contraceptives for 2 years or more. The 17 hydroxysteroid excretion was determined during therapy and after metopirone, then after ACTH. A reduced responsiveness to metopirone was found during prolonged OC therapy but the response to administered ACTH was not affected. The authors inferred that the changes are related to inhibition of pituitary ACTH rather than altered adrenocortical activity. Responsiveness to metopirone increased significantly 2 months after medication was discontinued.

No reports were found in which suppression of adrenal activity resulted in impaired response to stress.

Thyroid Function

In women taking oral contraceptives there is some variability in response to thyroid function tests. The majority show increase in the blood of thyroxine-binding globulin (TBG) and PBI and decrease in T_3–RBC uptake test. The PBI is usually elevated 25–40 percent above pretreatment level but may rise into the hyperthyroid range. Hollander et al. (1963) showed that the PBI rises rapidly in the first 7 days after medication is started, reaches a plateau at about 20 days and remains stationary for the duration of medication. After medication is discontinued the tests return to normal levels in about 2 months. (Florsheim and Fairclothe—1964). Radioiodine studies are variable and inconclusive.

These thyroid effects are secondary to estrogen increase of the binding proteins. The changes seem to be comparable to those occurring in normal pregnancy and no clinical evidences of hyperthyroidism have been reported.

If TSH secretion is altered by oral contraceptives, this may be masked by the increased thyroxine binding. No data are available on this point.

Carbohydrate Metabolism

Data available for examination suggests that the effect of oral contraceptive agents on carbohydrate metabolism may be unpredictable. Mechanisms of actions described are contradictory and complex. On the one hand evidence indicates that estrogens hinder the genesis of experimental diabetes, reduce glycosuria and in humans, may reduce insulin requirement. The proposed mechanisms of action include (*a*) action on the pituitary causing reduction in growth hormone and (*b*) action on the pancreas causing islet cell hypertrophy and increased beta cell activity. Several reports indicate that estrogen lowers fasting blood sugar by approximately 20 percent in humans and the higher the initial value for blood glucose the greater the decrease with estrogen. Some diabetics, mostly maturity onset type, show lower insulin needs when estrogens are given.

On the other hand diabetogenic effects have been described with respect to estrogens. This may be an anabolic effect, the increased appetite, increased dietary intake being the causative factors. However, an increase in protein binding of insulin with a reduction in the percentage of biologically active circulating insulin has not been excluded. The relationship of estrogens to elaboration of binding proteins is well recognized. This is of course dependent upon an intact liver function. Estrogens may stimulate production of anterior pituitary ACTH and indirectly increase the production of adrenal diabetogenic steroids but again, increased cortisol binding could offset this effect. Kitay found that after gonadectomy female rats responded with an increase in body and pituitary weight and a decrease in adrenal weight. Treatment with estradiol caused an increased secretion of pituitary ACTH and an increase in adrenal weight.

In view of these opposing actions a case could be made for either a favorable or an unfavorable effect of drugs containing estrogens upon patients with a diabetic disthesis. It seems important to determine whether the balance of the sum of these bioloric effects is deleterious or favorable in women predisposed to diabetes.

Adverse effect of the progestins upon carbohydrate metabolism reported in several recent communications indicate a potentially serious problem, if valid. In contrast to less prevalent conditions in which cause and effect relationship to treatment is difficult to assess, diabetes is a common health hazard. Furthermore, the estimated prevalence rate in the United States for 1959 (Remein) was 16.9 per 1,000 with cases about equally divided between cases of known diabetes and cases previously unsuspected. The unrecognized group deserves particular attention. If the current concept of the genesis of diabetes is accepted, i.e., that a genetic predisposition is present from conception and that stress situations can precipitate its appearance or aggravate the existing condition, then individuals with a family history of diabetes, an obstetric

record suggestive of this disorder or laboratory evidence of reduced carbohydrate tolerance warrant special study.

Investigations to date reveal the following:

Javier found reduced glucose tolerance in 40 percent of women on ovulatory suppressants.

Gershberg and coworkers performed glucose tolerance tests in women taking Norethynodrel with mestranol, 47 of whom had no family history of diabetes and 12 had a positive family history for diabetes. The instance of abnormal glucose tolerance in each group was as follows:

Table II

[In percent]

History	Fasting	1 hour	2 hours
Negative	8	17	43
Positive	17	33	58

Spellacy is studying the plasma insulin levels and response to intravenously administered glucose loads. In a preliminary report on 25 normal women, the mean values were as follows:

Table III

Control			Drug Rxd				
F	1/4	1/2	2	F	1/4	1/2	2
Mean Glucose mg. %							
79	196	125	75	81	215	147	76
Mean Insulin u U/ml.							
18	52	39	16	25	76	52	23

The difference between the control and the treated groups show higher values for both glucose and circulating insulin at each time interval of the test but the differences are slight and the top normal values are not stated in the report. Diabetic suspects were not included.

Individual case reports (Paros) of patients with known diabetes have shown increased insulin demand while on oral contraceptives with return to previous insulin dosages after withdrawal.

There is urgent need for a detailed study of carbohydrate metabolism in a much larger group of normal women and in a group of genetically predisposed women before, during and after the use of oral contraceptives. The following questions need to be answered:

Are oral contraceptive agents capable of inducing diabetes in normal subjects or do the few instances in which a significant abnormality was found in the glucose tolerance of control subjects indicate a genetic predisposition about which the patient has no knowledge?

What is the incidence and the magnitude of reduced carbohydrate tolerance in genetically predisposed individuals after prolonged use of oral contraceptive agents as compared with the responses in genetically predisposed individuals during the same period of time if no oral contraceptives are administered?

If an abnormality is found in carbohydrate tolerance or in insulin activity in either the control or the treated predisposed group, is it of a temporary nature or can permanent diabetes be induced by prolonged use of these agents?

These areas have been studied with respect to the diabetogenic effects of pregnancy and similar technics should be applied to the diabetogenic effects of oral contraceptive agents.

The following study is proposed:

Subjects.—Study patients will include women with a family history of diabetes, an obstetric record of large or stillborn infants, an abnormal glucose tolerance test during pregnancy which returns to normal postpartum and those with a normal glucose tolerance test but abnormal cortisone glucose tolerance test in the nonpregnant state. These will be matched with a group of normal women in whom family histories and obstetric records are negative for diabetes and the standard glucose tolerance test during pregnancy or the cortisone glucose tolerance test in the nonpregnant state is normal.

Methods.—Pretreatment values for blood glucose and for circulating insulin will be determined in the fasting state and at 1, 2 and 3 hours after a 100 gm. glucose load. The Somogyi-Nelson method for blood glucose and the Grodsky and Forsham immunochemical assay for total extractable insulin will be used. The study patients will be divided into two groups. Oral contraceptive agents will be administered to one half the total number of study patients. An intrauterine device or, if they choose, no contraceptives will be used in the other half of the study group. Glu-

cose tolerance tests and insulin assays will be performed during the course of treatment at intervals corresponding to 3 months, 6 months, and 12 months. Tests will be repeated at 1 week and at 3 months posttreatment. All subjects in the control group will receive oral contraceptive agents.

Pretreatment, interval and posttreatment tests will be identical with those performed in the study groups.

Comment.—Based on experiences with the study of carbohydrate metabolism during pregnancy it is evident the study group requires a group oriented control. Some of the diabetic suspects with relatively minor derangements of the glucose tolerance curve during pregnancy have progressed to an overt diabetic state spontaneously. It is now known how important an influence pregnancy exerts in hastening the clinical appearance of the disease or whether it does so at all. It is quite possible that stress hyperglycemia may develop in either of the two groups of study patients. If permanent hyperglycemia or abnormal insulinogenesis should be induced in normal patients by the use of these agents, current concepts of "prediabetes" may need to be revised.

Liver Function

The question of oral contraceptives and the liver has been reemphasized by reports of Eisalo et al. on postmenopausal women who developed deranged function tests and (occasionally) jaundice on medication. Subsequently, Eisalo has made similar observations on younger women. A number of other workers in the past 2 years have reported altered liver function tests, especially the B.S.P. and serum transaminase. A few investigators have not corroborated these observations (tables 4, 5, 6). Thirteen cases of jaundice have been reported in women taking oral contraceptives in which the relationship to the medication seems clear (table 7). The clinical courses and laboratory findings were similar to cholestasis of pregnancy. Liver biopsy of several showed changes of cholestasis and some hepatocellular damage. A quarter of the jaundiced women had previously had cholestasis of pregnancy, which suggests an inborn metabolic error or sensitivity reaction.

In summary, there have been no hepatic deaths reported, but an occasional woman develops clinical jaundice associated with definite though mild liver damage. It seems likely that such cases are more frequent than have been reported. Some degree of liver stress is present in many women on oral contraceptives, as evidenced by deranged function tests. These derangements are an exaggeration of mild alterations seen in some pregnant women. They regress when medication is stopped. Women who have had cholestasis of pregnancy or who have familial, congenital, or acquired defects of biliary secretion are most vulnerable. This may be an acceptable degree of abnormality but would seem to warrant further sequential study and reporting of cases of clinical jaundice and a continuation of caution in labeling.

Lactation

Oral contraceptives in the higher doses (5 and 10 mg. of progestogen) tend to decrease or stop lactation in many women in the first or second cycle of use. (Satterthwaite & Gamble 1962; Rice-Wray 1963.)

Breast enlargement may occur in the nursing infants when the mother takes oral contraceptives. (Curtis, 1964.)

In experimental animals, administration of sex steroids to the newborn may affect the "female pattern" or "male pattern" of the development and result in sterility in the adult animal. The human infant appears to have better protective mechanisms and there is no evidence of such a sterility effect in the human at the present time.

Masculinization

There is clear evidence that the oral contraceptive agents can cause congenital malformations of the female genital tract when the fetus in utero is exposed to these drugs during the first 16 to 18 weeks of gestation. Anatomic effects have been demonstrated in the experimental animal and in the human.

Experimental production of genital lesions in the rhesus monkey (Wharton & Scott—1964) was unequivocal. Norethindrone was given in relatively large doses (25 mg. per day for 5 days per week) from approximately 30 days to term (160 days). Eight of the ten fetuses were stillborn. All five females were virilized; males showed a greater degree of cryptorchidism than expected. Six rhesus mothers treated with 50 mg. progesterone I.M. daily during the same period of pregnancy suffered no deleterious effects. All infants were delivered alive at term (three males and three females) and none showed genital malformations.

In the human, there is no evidence that progestins increase the risk of intrauterine death. There is considerable evidence for masculinization. Wilkins (1960–61) collected cases with masculinization, as follows:

Ethisterone	34
Norethindrone	35
Norethinodrel	1
Testosterone	15
Progesterone	2
Stilbestrol	4
No hormone therapy	10
Total	101

Jacobson (1962) treated 385 consecutive pregnant women with norethindrone and observed maternal masculinization effects in 5.5 percent and fetal virilization in 23.7 percent.

In summary:

Progestins exhibit potentiality for masculinization of the female fetus. Anatomic abnormalities are easily corrected surgically. Subsequent effect on reproduction in the human is unknown. If any synthetic progestin is to be used in treatment of threatened or habitual abortion, consideration must be given to its androgenicity for the fetus. The 19 noncompounds are contraindicated for such use.

Table IV.—*Incidence of abnormal results of liver-function tests*

Test (normal values)	Number of subjects	Number with abnormal results
SGOT (35 units)	243	14 (5.8%)
SGPT (35 units)	243	18 (7.4%)
Bilirubin (1 mg./100 ml.)	202	0
Thymol turbidity test (4 units)	202	22 (10.9%)
Alkaline phosphatase (8 units)	199	4 (2%)
B.S.P. retention test (<5% at 45 mins.)	12	5 (41.6%)

From Larson-Cohn.

Table V.—*Reports of altered liver function*

Author	Medication	Time used	Cases	Elevated B.S.P.	Elevated	
					SGOT	SGPT
Eisalo, et al	Lynestrenol	40 to 420 days	109	19% to 48%	4% to 18%	
	Volidan	20 days				
	Lyndiol	20 days				
Larsson-Cohn	Norethindrone-mestranol	6 to 8 months	243	(12) 42%	5%	7%
Borglin	Lynestrenol, Lyndiol	Months	36			16%
Knutsson	Lyndiol	1 to 2 months	10		20%	50%
Tyler	7 compounds	To 8 years	125	32%	Some abnormal.	

Table VI.—*Reports of normal liver function*

Author	Medication	Time used	Cases	Tests	Abnormalities
Swyer & Littel	Orthonovin, Enovid+ (9 preparations).	3 to 6 years	12	Ceph. Chol., T. T., PGOT, bilirubin.	0
Linthorst	Lynestrenol, Lyndiol	14 to 43 months	52	Alk. phos., T. T., SGOT, SGPT.	0
Swaab	Lyndiol, Conovid	6 months	60	SGOT (342 tests)	0
Rice-Wray	Lyndiol	3 to 12 months	56	SGPT (1 test each)	0

Table VII.—*Clinical jaundice with oral contraceptives*

Author	Medication	Time used	Cases	Previous pregnancy jaundice	Relapse on O.C.	Remarks
Carlstrom, et al	norethisterone-ethinytestradiol.		1			
Sotanlemi, et al	Volidan	6 to 15 days	1	epid. hep. at 10 yrs.		Biopsy-hepatocanal. cholestasis.
Fawcett, et al	Anovlar	4 months	1			
Wetterberg	Lyndiol	4 months	1			
Baines	norethindrone-ethinylestradiol.	1 month	1			
Larsson-Cohn	norethindrone-mestranol.		2	1		Biopsy-cholestasis and hepatocell. damage.
Holzbach	do	1 month	1	1	1X	Sister and mother had pregn. jaundice.
Cullberg, et al	Lyndiol	1 month	1			Biopsy—as above.
Tait	norethindrone-ethinylestradiol.	1 month	1		3X	2 different drugs.
Alderheuz, et al	do		3	1–x2, 1–x1X	3X	3 different drugs.
Totals			13	4	3	

bibliography

1. ALDERKREUZ & IKONEN. Oral contraceptives and liver damage, Brit. Med. J., 2: 1133, 1964.
2. ALEXANDER, R. W., AND MARMORSTON, J. Effect of two synthetic estrogens on the level of serum protein-bound iodine in men and women with atherosclerotic heart disease, J. Clin. Endocrinol., and Metab., 21 : 243, 1961.
3. BAINES, G. F. Jaundice in a patient taking norethisterone compound tablets, Lancet (Let.) 1 : 108–9, 1965.
4. BAKKE, J. Hepatic impairment during intake of contraceptive pills: Observations in postmenopausal women, Brit. Med. J., 1 : 631–32, 1965.
5. BESCH, P. K. ET AL. Some systemic effects of a progestational agent (Ethynodiol Diacetate and Mestranol), Metabolism, 14 : 387–397, 1965.
6. BONGIOVANNI, A., GEORGE, A., AND GRUMBACH, M. M. Masculinization of Female Infants Associated with Estrogenic Therapy Alone During Gestation, J. Clin. Endocrinol., 19 : 1004, 1959.
7. BORGLIN, N. E. Oral contraceptives and liver damage, Brit. Med. J., 1 : 1289–90, 1965.
8. BRYANS, F. E. Contraceptives. Canad. Med. Ass. J., 92–287–88, 1965.
9. CARLSTROM, H., HOGLUND, S., AND REIZENSTEIN, P. Oral contraceptives and liver damage, Brit. Med. J., 1 : 992, 1965.
10. CARRINGTON, E. R., AND MCWILLIAMS, N. B. Investigation of serum insulin activity during pregnancy in normal and in subclinical diabetic mothers, Am. J. Obst. & Gynec., In press, 1966.
11. CARRINGTON, E. R., AND MESSICK, R. R. Diabetogenic effects of pregnancy. A 10-year survey, Am. J. Obst. & Gynec., 85 : 669, 1963.
12. COBLEY, J. F. C. C., AND LANCASTER, H. O. Carbohydrate tolerance in pregnancy, Med. J. Aust., 42 : 171, 1955.
13. CULLBERG, G., LUNDSTROM, R., AND STENRAM, U. Jaundice during treatment with an oral contraceptive, Lyndiol, Brit. Med. J., 1 : 695–97, 1965.
14. CURTIS, E. Oral-contraceptive feminization of a normal male infant, Obst. & Gyn., 23 : 295, 1964.
15. DATTA, H., NATH, R., AND CHAUDHURY, R. R. Oral contraceptives and liver damage, Brit. Med. J., 2 : 476–77, 1965.
16. DOWLING, J. T., FREINKEL, N., AND INGBAR, S. H. Effect of diethyl-stilbestrol on the binding of thyroxine in serum, J. Clin. Endocrinol., 16 : 1491, 1956.
17. DOWLING, J. T., FREINKEL, N., AND INGBAR, S. H. The effect of estrogens upon the peripheral metabolism of thyroxine, J. Clin. Invest., 39 : 1119, 1960.
18. DRILL, V. A. Endocrine properties and long-term safety of oral contraceptives, Metabolism, 14 : 295, 1965.
19. EISALO, A., ET AL. Hepatic impairment during the intake of contraceptive pills: Clinical trial with postmenopausal women, Brit. Med. J., 2 : 426, 1964.
20. EISALO, A., JARVINEN, P. A., AND LUUKKAINEN, T. Liver function tests during intake of contraceptive tablets in premenopausal women, Brit. Med. J., 1 : 1416, 1965.
21. ELZINGA, K. E., CARR, E. A., BEIERWALTES, W. H. New Eng. J. Med. 36 : 125, 1961.

22. ENGSTROM, W. W., MARKARDT, B., AND LIEBMAN, A. Effect of estrogens on serum precipitable iodine, Proc. Soc. Exper. Biol. & Med., 81 : 582, 1952.

23. FAJANS, S. S., AND CONN, J. W. An approach to the prediction of diabetes mellitus by modification of the glucose tolerance test with cortisone, Diab., 3 : 296, 1954.

24. FAWCETT, J. W., AND PEDERSEN, D. L. Oral contraceptives and liver damage, Brit. Med. J., 2 : 755, 1964.

25. FLORSHEIM, W. H., AND FAIRCLOTH, M. A. Effects of oral ovulation inhibitors on serum protein-bound iodine and thyroxin binding proteins, Proc. Soc. Exp. Biol. & Med., 117–56–58 (October), 1964.

26. FREEDBERG, I. M., HAMOLSKY, M. W., AND FREEDBERG, A. S. The thyroid gland in pregnancy, New Eng. J. Med., 256 : 505–510 and 555, 1957.

27. GARCIA, R. AND PINCUS, G. Ovulation inhibition by progestin-estrogen combination, Int. J. Fertil., 9 : 95, 1964.

28. GERSHBERG, H., JAVIER, Z., AND HULSE, M. Glucose tolerance in women receiving an ovulatory suppressant, Diab. 13 : 376, 1964.

29. GOLDZIEHER, J. W., ET AL. Fertility following termination of contraception with norethindrone, Am. J. Obst. & Gyn., 84 : 1474, 1962.

30. HAMOLSKY, M. W., GOLODETZ, A., AND FREEDBERG, A. S. The plasma protein thyroid hormone complex in man, J. Clin. Endocrin., 19 : 103, 1959.

31. Hepatotoxicity of Drugs, Lancet, 1 : 1056, May 19, 1962.

32. HOLLANDER, C. S., GARCIA, A. M., STURGIS, S. H., AND SELENKOW, H. A. Effect of an ovulatory suppressant on the serum protein-bound iodine and the red-cell uptake of radioactive tri-iodothyronine, New Eng. J. Med., 269 : 501, 1963.

33. HOLZBACH, R. T., AND SANDERS, J. H. Recurrent intrahepatic cholestasis of pregnancy : Observations on pathogenesis, J.A.M.A., 193 : 542–44, 1965.

34. JACOBSON, B. D. Hazards of Norethindrone Therapy During Pregnancy, Amer. J. Obst. & Gynec., 84–962, 1962.

35. JAVIER, Z. C. The diabetogenic effect of estrogen, Diab., 14 : 458, 1965.

36. JOHANNISSON, E., TILLINGER, K. G., AND DICZFALUSY, E. Effect of oral contraceptives on the ovarian reaction to human gonadotropins in amenorrheic women, Fertil. & Steril., 16 : 292, 1965.

37. JONES, H. W., JR., AND WILKINS, L. The Genital Anomaly Associated with Prenatal Exposure to Progestogens, Fertil. & Steril., 11 :148, 1960.

38. KITAY, J. I. Pituitary-Adrenal function in the rat gonadectomy and gonadal hormone replacement, Endocrinol., 73 : 253, 1963.

39. KLEINER, G. J., KRESCH, L., AND ARIAS, I. M. Studies of hepatic excretory function II. : The effect of norethynodral and mestranol on bromsulfalein sodium metabolism in women of childbearing age, New Engl. J. Med., 273 : 420–23, 1965.

40. KNUTSSON, F., ET AL. Anovulatory effect of lynestrenol in combination with mestranol, Acta Obst. Gyn. Scand., 54 : 325–38, 1965.

41. LARSSON-COHN, U. Oral contraception and liver-function tests, Brit. Med. J., 1 : 1414–5, 1965.

42. LARSSON-COHN, U., AND STENRAM, U. Jaundice during treatment with oral contraceptive agents ; report of two cases, J.A.M.A., 193–422–26, 1965.

43. LEACH, R. B., AND MARGULIS, R. R. Inhibition of adrenocortical responsiveness during progestin therapy, Am. J. Obst. & Gynec., 92 : 762, 1965.

44. LIN, T. J., DURKIN, J. W., JR., AND KIM, Y. J. The control of reproduction and the function of certain endocrine organs as reflected by biochemical and biological assays, Curr. Ther. Res., 6 : 225, 1964.

45. LINTHORST, G. Liver function after long-term progestational treatment with and without oestrogen, Brit. Med. J., 2 : 920, 1964.

46. LORAINE, J. A. Hormone excretion patterns during and after the long-term administration of oral contraceptives, Acta Endocr., 50 : 15, 1965.

47. LORAINE, J. A. The effect of anti-ovulatory compounds on hormone excretion, Internat'l J. Fertil., 8: 155, 1964.

48. MARTIN, L., AND CUNNINGHAM, K. Inhibition of human pituitary gonadotropin output by 17-alpha-ethinyl, 19-nortestosterone in Human Pituitary Gonadotropins, Ed. A. A. Albert. Springfield, Thomas, 1961, p. 226.

49. PAROS, N. L. Side effect of oral contraceptives, Brit. Med. J., 1: 630, 1964.

50. PASCHKIS, K. E., CANTAROW, A., AND PEACOCK, W. C. The influence of estrogens on thyroid function as measured by uptake of radioactive iodine, Proc. Soc. Exper. Biol. & Med., 68: 485, 1948.

51. PINCUS, G. The control of fertility, New York and London, Academic Press, 267–268, 1965.

52. POCHIN, E. E. The iodine uptake of the human thyroid throughout the menstrual cycle and in pregnancy. Clin. Sc., 11: 441, 1952.

53. PROVEST: Med. Let.—Drugs & Ther., 7: 5–6, Jan. 15, 1965.

54. REMEIN, Q. R. A current estimate of the prevalence of diabetes mellitus in the U.S., Ann. N.Y. Acad. Sci., 82: 229, 1959.

55. RICE-WRAY, E. Oral contraceptives and liver damage, Brit. Med. J., 2: 1011, 1964. Comment on Eisalo, et al.: Ibid. August 15, p. 426.

56. RICE-WRAY, E., GOLDZIEHER, J. W., AND ARANDA-RUSSELL, A. Oral progestins in fertility control: a comparative study, Fertil. & Steril., 14: 402, 1963.

57. RICE-WRAY, E., GONZALEZ, O., FERRER, S., ET AL. Clinical evalation of norethindrone acetate in fertility control, Am. J. Obst. & Gynec., 93: 115, 1965.

58. RICE-WRAY, E., SCHULTZ CONTRERAS, M., GUERRERO, I., AND ARANDA-RUSSELL, A. Long-term administration of norethindrone in fertility control, J.A.M.A., 180: 355, 1962.

59. RYAN, A. M., JR., GOSS, D. A., AND REID, D. E. Pituitary gonadotrophins during long-term Enovid therapy, Am. J. Obst. & Gynec., 94: 515, 1966.

60. SATTERTHWAITE, A. P., AND GAMBLE, C. J. Conception control with norethinodrel. Progress report of a 4-year field study at Humaco, P.R., J.A.M.Wom.A., 17: 797, 1962.

61. SAUNDERS, F. A., AND DRILL, V. A. Some biological activities of 17 ethynyl and 17 alkyl derivatives of 17 hydroxyestrenones, Ann. N.Y. Acad. Sci., 71: 516, 1958.

62. SHERLOCK, S. Jaundice, Brit. Med. J., 1: 1359, 1962.

63. SHERLOCK, S. Jaundice due to drugs, Proc. Roy. Soc. Med., 57: 881–86, 1964.

64. SOTANIEMI, E., KREUS, K. E., AND SCHEININ, T. M. Oral contraception and liver damage, Brit. Med. J., 2: 1264–1265, 1964.

65. SPELLACY, W. N., AND GOETZ, F. C. Plasma insulin in normal late pregnancy, N. Eng. J. Med., 268: 988, 1963.

66. SPELLACY, W. N., AND SCHOELLER, K. L. Insulin and glucose changes in the blood of subjects taking oral contraceptives, Clin. Res., 13: 407 (Oct.) 1965; abstr.

67. STOLL, BASIL A., ET AL. Oral contraceptives and liver damage, Brit. Med. J., 1: 723, 1965: comment on Eisalo, et al. Aug. 15, p. 426, and Tyler, Nov. 14, p. 1264.

68. SWAAB, L. I. Oral contraceptives and liver damage, Brit. Med. J., 2: 755, 1964.

69. SWAAB, L. I. A field trial with Lyndiol and Conovid, Int. J. Fertil., 9: 107, 1964.

70. SWYER, G. I. M., AND LITTEL, V. Absence of hepatic impairment in long-term oral contraceptive users, Brit. Med. J., 1: 1412–14, 1965; edit. comment, Ibid, p. 1391.

71. TAIT, ALAN S. Oral contraceptives, Med. J. Australia (Let.), 1: 667, 1965.

72. TAYMOR, M. L. The effect of synthetic progestins on pituitary gonadotrophin excretion, J. Clin. Endocrinol., 24: 803, 1964.

73. TAYMOR, M. L., AND RIZKALLAH, T. Effect of norethindrone acetate upon gonadotrophin-induced ovarian function, J. of Endocr. and Metab., 25: 843, 1965.

74. TIETZE, C. Differential fecundity and effectiveness of contraception, Eugenics Rev., 50: 231, 1959.

75. TYLER, E. T. Eight years' experience with oral contraception and an analysis of use of low-dosage norethisterone, Brit. Med. J., 2: 843–47, 1964.

76. WALSER, H. C., MARGULIS, R. R., AND LADD, J. E. Effects of prolonged administration of progestins on the endometrium and the function of the pituitary, thyroid and adrenal glands, Int. J. Fertil., 9: 191, 1964.

77. WETTERBERG, L. Oral contraceptives and acute intermittent porphyria, Lancet (Let. to Ed.), p. 1178–79, 1965.

78. WHARTON, L. R., JR., AND SCOTT, R. B. Experimental Production of Genital Lesions with Norethindrone, Am. J. Obst. & Gyn., 89: 701, 1964.

79. WILKINS, L. Masculinization of Female Fetuses Due to Use of Orally Given Progestins, J.A.M.A., 172: 1028, 1960.

80. WILKINS, L., JONES, H. W., JR., HOLMAN, G. H., AND STEMPFEL, R. S., JR. Masculinization of the Female Fetus Associated with the Administration of Oral and Intramuscular Progestins During Pregnancy: Nonadrenal Female Pseudohermaphroditism, J. Clin. Enrocrinol., 18: 559, 1958.

Appendix 4

Report of the Task Force on Efficacy

K. ADAMSONS, M.D., CHAIRMAN

The following uses for which therapeutic efficacy has been claimed were reviewed:

A. fertility control
B. treatment of amenorrhea
C. treatment of dysmenorrhea
D. treatment of endometriosis
E. treatment of functional uterine bleeding
F. habitual abortion
G. miscellaneous uses

(Note.—With the exception of subject A the comments pertain only to combination preparations containing a progestational agent and an estrogen.)

A. Fertility Control

The efficacy of the older oral progestational agents in fertility control was considered exceptional when compared with that of other therapeutic agents used in medical practice, such as antibiotics, analgesics and tranquilizers. Even when all contraception failures are considered to represent drug failure rather than patient failure in proper administration of the drug, these compounds are almost invariably effective. The more recently introduced sequential preparations were also found highly effective in controlling fertility, although to a slightly lesser degree than the progestational agents. The frequency of pregnancies occurring while patients were receiving sequential preparations averaged approximately 1.2 per 100 women years. It was considered that a sufficient number of patients have been studied up to 2½ years to justify statistically valid conclusions. On the other hand, the group sizes representing patients that had been followed for up to 54 cycles were too small to offer anything more than general impressions. It is noteworthy that the frequency of pregnancies occurring while on medication remained unchanged over the 2½ year period, thus supporting the contention that tolerance to or escape from the medication probably does not occur. The Committee commented on the terms "unwanted" and "unplanned" pregnancies used in the submitted material. Since the individual circumstances under which the pregnancies occurred did not appear to be known to the investigator, the use of these terms did not seem to be warranted. From the statistical point of view, difficulties were encountered in the interpretation of "woman years" since the value of large numbers observed for a short period is not comparable to long term observations on a small sample. It was also pointed out that the high efficacy of oral contraceptives may not be entirely due to suppression of ovulation but may result from other mechanisms such as changes in cervical mucus and endometrium.

B. Treatment of Amenorrhea

The efficacy of oral contraceptives in the treatment of amenorrhea could not be readily ascertained by the material available to the Committee because of the endpoint used. Successful treatment was considered one in which uterine bleeding was accomplished following cyclic withdrawal of the medication. It was the opinion of the Committee that such an endpoint does not specifically measure the efficacy in treating amenorrhea, since cyclic withdrawal bleeding and menstrual periods are different biologic phenomena. If efficacy in the treatment of amenorrhea is being claimed it could be based only on evidence that menstrual cycles are established following discontinuation of drug therapy. Such information was not contained in the submitted material. However, it was pointed out that if the objective of the therapeutic effort is to produce cyclic withdrawal bleeding in the amenorrheic patient, the oral contraceptive drugs can be considered as efficacious since this endpoint was achieved in 80 to 90 percent of treated patients.

Additional information desired:

1. Followup data on amenorrheic patients after discontinuation of the cyclic therapy with oral contraceptives.
2. Comparison with the frequency of spontaneous resumption of menstrual periods in similar patient material.

C. Treatment of Dysmenorrhea

The comments pertaining to drug efficacy in the management of patients with dysmenorrhea were similar to those alluded to in the previous paragraph. The situation was even more complicated because of the difficulty to quantitate the principal variable. Dysmenorrhea is known to disappear spontaneously and relatively "high cure" rates have been obtained with placebo preparations. No followup data were available in the submitted material, and thus, in reality, the reports pertained to the evaluation of pain during cyclic withdrawal bleeding rather than during a menstrual period. The data suggests that in certain patients the progestational agent might be of value in the treatment of dysmenorrhea. However, additional information is required before the therapeutic efficacy can be considered as demonstrated.

From the statistical point of view the submitted material was considered unsatisfactory because of the small number of patients in the individual series. It was surprising to find that a very small sample had been utilized in the study of such a common phenomenon. The members were cognizant of the difficulties in designing controlled studies, since placebo preparations do not provide contraception, a fact that cannot be left undisclosed to the patient.

D. Treatment of Endometriosis

In evaluating the material in which the diagnosis of endometriosis was established by histologic examination, the Committee finds a high therapeutic value of continued and prolonged (6 to 12 months) progestational therapy in conservative management of the affected patient. In the well documented cases it is reasonable to anticipate a favorable response in 75 to 90 percent. It must be, however, pointed out that recurrence might be expected in an appreciable proportion of patients after succession of medication.

In contrast, the therapeutic efficacy in subjects in which the diagnosis of endometriosis had been made on grounds of physical examination or history only, was uncertain. Undoubtedly, this population contains a variety of disease entities such as residual pelvic inflammatory disease, adnexal pathology of noninflammatory nature, etc., which are not expected to improve during therapy with progestational agents.

E. Treatment of Functional Uterine Bleeding

The claims for therapeutic efficacy in treatment of functional uterine bleeding were met with similar criticism that applied to dysmenorrhea and amenorrhea. The Committee finds the pooling of a variety of conditions summarized under the heading of "Functional Uterine Bleeding" inappropriate because the individual disease entities have specific and different etiologies. Thus, an overall efficicacy index might not reflect the favorable results achieved in certain categories or vice versa, and create the impression of therapeutic merit for disease entities which are not susceptible to therapy.

Irregular menstrual periods are expected to respond in a high percentage of cases to therapy if cyclic withdrawal bleeding is made synonymous to a menstrual period, whereas metrorrhagia might be and appears to be considerably more resistant to the advocated therapy. Patients with hypermenorrhea appear to have shorter periods and less blood loss when placed on cyclic therapy with these compounds. Difficulty in constructing a meaningful endpoint for the various categories was apparent since most of the functional bleeding abnormalities are known to be self-limiting.

F. Habitual Abortion

The Committee found no data to indicate that any of the oral contraceptives are effective in altering the natural history of patients with habitual abortion. Although the reasons for habitual abortion are not known, it appears that in a considerable percentage of cases it is due to a genetic defect in the embryo. These cases, in all certainty, would not benefit from steroid therapy. It was pointed out that clear distinction should be made between synthetic progestins, some of which have known androgenic properties, and the native product progesterone when their use in the therapy of threatened abortion or habitual abortion is considered.

G. Miscellaneous Uses

The value of oral contraceptives in the treatment of conditions such as menopausal syndrome, acne, chronic vulvar infections, psychotic and emotional disorders could not be ascertained at present because of the preliminary nature of the available reports.

Summary

The efficacy of the older progestational agents in fertility control is exceptional and approaches unity. The more recently introduced sequential preparations are also highly effective in reducing the incidence of pregnancies although with not quite the same degree of certainty as the progestational compounds. Regarding other uses, the efficacy is less certain. Most studies lack control and followup data and, consequently, it is difficult to determine whether drug treatment resulted in a significant departure from the course expected from the natural history of these frequently self-limiting disorders. Consistently the phenomenon "Cyclic withdrawal bleeding" is confused with menstrual period which is unwarranted.

Pelvic endometriosis and hypermenorrhea, however, represent notable exceptions. In these disorders, prolonged therapy appears to offer excellent palliation and an occasional cure.

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bibliography

1. Clinical Reports to Ortho Research Foundation based on 80 U.S. Private Practice studies.
2. Clinical Reports to Ortho Research Foundation based on 25 Canadian Private Practices.
3. Clinical Reports to Ortho Research Foundation submitted by: Planned Parenthood Clinic, Los Angeles, Calif.; S. J. Behrman, M.D., Ann Arbor, Mich.; W. P. Hutcherson, M.D., Chattanooga, Tenn.; A. P. Satterth, M.D., Puerto Rico; Mt. Sinai Hospital, New York, N.Y.; Detroit Planned Parenthood Clinic, Detroit, Mich.; J. W. Goldzieher, M.D., San Antonio, Tex.
4. LIVINGSTON, N. The use of Medroxyprogesterone Acetate and estrogen to inhibit fertility, Internat. J. Fertil., 8: No. 3, July–Sept., 1963.
5. MOGHISI, K. The use of Provera Ethinyl Estradiol in conception control, Internat. J. Fertil., 8: No. 3, July–Sept., 1963.
6. GOULD, J. Control of ovulation with Medroxyprogesterone-estrogen, Internat. J. Fertil., 8: No. 3, July–Sept., 1963.
7. MARGULIS, R. R., ET AL. Report to the Research Division, Department of Clinical Investigation, Parke Davis & Co.
8. GOLDZIEHER, S. W., MOSES, L. E., AND ELLIS, L. T. A field trial with a physiological method of conception control, in Research in Family Planning, Clyde V. Kiser, ed., Princeton University Press, 1962.
9. GOLDZIEHER, J. W., MARTINEZ-MANAUTOU, J., LIVINGSTON, N. B., JR., MOSES, L. E., AND RICE-WRAY, E. The use of sequential estrogen and progestin to inhibit fertility, West. J. Surg., 71: 187, 1963.
10. Clinical data on file, Eli Lilly & Co.
11. GOLDZIEHER, J. W., ET AL. Study of norethindrone in contraception, J.A.M.A., 180: 359–361, 1962.
12. COWAN, L. Norethindrone and Mestranol tablets for endometriosis and other conditions. A clinical study of 98 cases, International Symposium on Ortho Novum 1st—Toronto, Canada, 1964.
13. LAPOINTE, R. Therapy of cyclic dysfunction, Applied Therapeutics, 6: 518–519, 1964.
14. Clinical data on file, Ortho Research Foundation.
15. TOMPKINS, M. D. Progestins and the uterus, Applied Therapeutics, 6: 523–525, 1964.
16. RIVA, H. L., WILSON, J. H., AND KAWASAKI, D. M. Effect of Norethynodrel on endometriosis, Am. J. Obst. & Gynec., 82: 109–118, 1961.
17. KISTNER, R. W. The treatment of endometriosis by inducing pseudopregnancy with ovarian hormones, Fertil. and Steril., 10: 539–556, 1959.
18. GOODMAN, L. S., AND GILMAN, A. The Pharmacological Basis of Therapeutics, MacMillan, 1965, p. 1560.
19. A.M.A. New Drugs, 1965, p. 343.
20. BRAUN, T. E. Progestational agents in clinical obstetrics and gynecology, Am. J. Med. Sci., 247: 133/739–141/747.
21. GOLD, J. J., BORUSHECK, S., SMITH, L., AND SCOMENGA, A. Synthetic progestins: A review, Internat. J. Fertil., 10: 99–114, 1965.

special reports

Appendix 5

An appraisal of certain problems involved in the use of steroid compounds for contraception

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The growing acceptance of various steroid compounds as contraceptive agents has been attended by extensive controversy.

Such controversy has been mainly concerned with the nature of the immediate and delayed effects of these preparations. This communication aims to identify certain questions which merit consideration and to appraise the currently available data bearing on these problems.

Such a discussion becomes all the more imperative because of piece-meal and inadequate treatment of these matters in the lay and scientific press and in official statements of responsible governmental agencies. Meanwhile, the distribution of steroid compounds as contraceptives has become an accepted function of numerous public health agencies despite the lack of appropriately designed epidemiologic studies concerning many of their important potential effects.

The following are selected for discussion:

1. Will the prolonged use of steroid contraceptives affect the incidence or the pathogenesis of such malignant tumors as cancer of the breast, endometrium, or cervix?

2. Do these substances increase the frequency or predispose to the occurrence of thrombophlebitis or thromboembolism?

3. Does the prolonged exposure of the ovarian ova to steroids alter their reproductive or genetic potential?

Three types of steroid contraceptive regimens are currently employed: (*a*) Estrogen-progestogen combinations given cyclically; (*b*) estrogen and progestogen given in sequence on a cyclic basis, (*c*) progestogens given continuously. Accordingly, it is imperative that we consider the properties of each of these classes of compounds when administered both singly and in combination.

For example, certain effects of the estrogen-progestogen combinations constitute characteristic responses to estrogen. These include: (*a*) A rise in thyroxin-binding and cortisol-binding protein in the plasma, (*b*) a tendency to fluid retention as manifested by varying degrees of weight gain and edema, (*c*) alteration in bromsulphthalein clearance by the liver (*4a*), (*b*), and (*d*) the subjective symptoms of nausea and malaise (*1–4*) and fullness of the breasts. These effects are not produced by even massive doses of progestogens and are readily reproducible with all varieties of natural as well as synthetic estrogens. Such effects clearly indicate that the estrogen administered exceeds normal endogenous estrogen production despite the presumed drug-induced suppression of endogenous estrogen formation. Moreover, available data concerning normal estrogen secretion rates in women (*5, 6*) show that the total endogenous estrogen would not equal in *biological activity* for man the estrogenic doses contained in currently employed contraceptive mixtures (*6a*). Hence the net biochemical and biological effect of such combinations is characteristic of hyperestrinism.

It is therefore highly pertinent to consider what is known about the relationship between the levels of endogenous and exogenous estrogen and various neoplastic processes both in man and in animals.

First, however, certain salient features of the carcinogenic response in man must be described. Of major importance is the fact that all known human carcinogens exhibit a prolonged latent period. Table I lists most of the agents which can be considered with some certainty to be capable of producing malignancies in man. It is especially

* The author is greatly indebted to Dr. John C. Bailar III for many of the statistical calculations presented here; however, he accepts sole responsibility for the interpretations offered.

noteworthy that most of these effects involve a latent period of about a decade. In most instances no detectable objective basis for anticipating the ultimate carcinogenic response is apparent during the period of latency.

It is also noteworthy that all known carcinogenic agents for man have been shown to be also carcinogenic in animals. Hence common pathogenetic factors are clearly involved in the development of cancer in man and in animals. Consequently, we cannot ignore the regularly observed length of latency and the known parallelisms in the genesis of cancer in man and animals in evaluating what is known to date about the carcinogenic potential of the steroid substances under discussion.

Estrogens and Breast Cancer

Ovariectomy induces remissions in 30 to 50 percent of young women with breast cancer (*7*). It is generally agreed that this ablative procedure exerts its favorable effects through a reduction of estrogen formation in the body (*8*). Moreover, urinary excretion studies show that the amounts of estrogen involved must be measured in microgram quantities (*8*). Less direct evidence indicates that in some women estrogen administration in doses comparable to those contained in the currently marketed oral contraceptives will transiently stimulate the metabolic activity of metastatic breast cancer, but such stimulation is not always related to an impairment in the clinical course (*9, 10, 11*). Accordingly, it is universal clinical practice to prohibit the use of such materials by young women with a known breast cancer. Paradoxically, this restriction is not applicable to older women with breast cancer since a substantial proportion of such older women, and less commonly certain younger women, experience regression of a preexisting breast cancer when given estrogens (*11, 18, 29*). It is therefore clear that both endogenous and exogenous estrogen will modify the activity of established cancer in women.

The proponents of the use of these agents state that these considerations pertain only to "preexisting" breast cancer. Such an inference is untenable in view of the fact that other malignancies in women, such as cancer of the cervix and endometrium, have a prolonged pathogenetic phase involving many years. Unfortunately, we have no direct knowledge of the preclinical or pathogenetic phase of breast cancer in young women, nor do we know the effects of exogenous estrogens upon this process. Indirect evidence from mammography studies indicates however, that the pathogenetic phase can occupy several years (*12a*). Hence it seems reasonable to consider whether or not the repeated induction of a hyperestrogenic state implies any risk of exacerbation of this occult phase of breast cancer since such agents can significantly alter the established disease process in some women.

It is frequently stated that although estrogens have been employed clinically for 25 years, the incidence of breast cancer in women has not materially changed and that only an extremely limited number of cases of breast cancer in women have been reported to be specifically associated with estrogen therapy (*13–17*). These generalizations ignore some serious limitations in our epidemiological knowledge over the past 25 years.

Firstly, past clinical experience relates almost entirely to the use of estrogens for the control of symptoms in women of menopausal or postmenopausal age. In addition, a very limited number of younger women suffering from artificially induced menopause, ovarian insufficiency, menstrual disorders, and other gynecological problems have also been treated. We know, however, from differences in response of established breast cancer to estrogen therapy in older women as contrasted with that seen in menstruating women, that it is not valid to equate a past experience in predominantly older patients with what should be anticipated in younger women, especially with respect to breast cancer. This difference in response is clearly reflected in the remarkable increase in estrogen-induced regressions in breast cancer with increasing age (*18*).

The study of Kennedy on the dual effects of estrogen on breast cancer in women aged 35 to 54 also emphasizes the critical role of both age and dosage in determining whether the response of breast cancer to estrogen administration will be exacerbation or regression (*11*). Thus, Kennedy states: "In premenopausal women with breast cancer or in patients in whom castration produced a regression of tumor, there is no doubt that small physiological doses of estrogenic hormone may stimulate the growth of cancer," and further: "It might, therefore, be postulated that the estrogenic hormone has a dual action: stimulation of cancer cell growth by small doses, and a more potent inhibitory effect on cell growth in large doses" (*11*).

Secondly, because of the absence of specific data

as to the duration of estrogen exposure of most of the women treated during the past 25 years, and because the relatively small number of younger women have with few exceptions received comparatively short courses of therapy, we have no basis for a direct evaluation of the current approval for continued medication for 4 years or more. Thus, we were able to find only four studies in the world literature in which the actual incidence of breast and genital tract malignancies during prolonged estrogen therapy is recorded (*19–21*, *21a*). These studies respectively include 120, 292, and 304 and 206 women. Two of these studies included respectively 58 and 27 women under 40 years of age and in the remaining study, all women studied were over 40 years of age. Thus the published data on cancer incidence available for the age group presently under consideration is limited to 85 patients. Such limited data fail to provide an adequate epidemiologic basis for the promulgation of a new public health practice affecting millions of women.

Of course, additional data reside in the individual clinical records of numerous institutions and private offices. However, offhand generalization from such uncontrolled clinical experience without appropriate followup is notoriously misleading. Even very extensive uncontrolled clinical accounts are not the equivalent of soundly developed epidemiological data. Our inadequate knowledge concerning the relationship of estrogens to cancer in women is comparable with what was known about the association between lung cancer and cigarette smoking before extensive epidemiologic studies delineated this overwhelming significant statistical relationship. In the absence of similarly extensive studies regarding the effect of exogenous estrogens on the incidence of breast cancer in women we are ill-advised to ignore the mass of observations clearly relating both endogenous and exogenous estrogen to the pathogenesis of this disease in both man and animals.

Endometrial Cancer

Endometrial cancer should also be considered in evaluating the consequences of steroid therapy. Thus, the observations of Hertig and Somers and of Gusberg clearly define the pathogenetic relationship between adenomatous hyperplasia resulting from excessive endogenous or exogenous estrogen and the ultimate development of adenocarcinoma (*22–25*). It is also clear from retrospective studies of successive endometrial biopsies that endometrial cancer may require many years for full development (*22*, *24*, *26*).

In addition, a number of cases of endometrial cancer are reported to have been closely related to protracted estrogen administration (*23*, *27*, *19*, *28*). This may stem in part from the frequent natural setting in which estrogens have been often utilized and in which endometrial carcinoma is uncovered, namely, in the older women with excessive menstrual bleeding of undetermined origin. The chance association of these two clinical features is to be anticipated in patients recently initiating treatment. However, when endometrial cancer arises following long-term estrogen therapy, the potential pathogenetic effect of the administered hormone should be considered. For example, Wallach and Henneman in presenting a statistical analysis of the long-term effects of estrogen administration for the treatment of osteoporosis in 290 women state: "The incidence of endometrial carcinoma in this group of patients is many times the normal incidence." (*19*) (table II). Similarily, Mustacchi and Gordan (*20*) found two cases of endometrial hyperplasia among 120 estrogen-treated osteoporotic women, and such hyperplasia is regarded by Gusberg (*24*) and by others as premalignant. Ostergaard (*28*) similarly describes 18 cases of corpus cancer following prolonged estrogen therapy among a series of 123 patients with this disease. To attribute any statistical significance to such scattered reports would be highly fallacious, but such observations do clearly indicate the necessity for more epidemiological study of this complex problem.

Moreover, such clinical data as we have are not directly applicable to what is to be expected in younger women. Marked age differences in endometrial response are readily noted. For example, the relative infrequency of estrogen-withdrawal bleeding in older women, namely 40 percent as opposed to more than 98 percent in normal younger women (*29*) clearly reflects this notable age difference. Hence one may anticipate such differences in the immediate and long-term endometrial response of the great numbers of menopausal women treated in the past, as compared with that of the normal younger women now being treated with contraceptive agents.

Kelly and Baker have reported that metastatic endometrial carcinoma will undergo regression under intensive treatment with progesterone (*30*).

In addition, Kistner has described the marked regression of the glandular elements of the endometrium in patients with endometrial hyperplasia or "carcinoma *in situ*" treated with various forms of progestationally active preparations (*31*). In evaluating the relationship of this finding to our immediate problems, we must recall that practically all known carcinolytic agents, such as X-ray and certain alkylating agents, are also carcinogenic. Hence, these findings further implicate the steroid hormones in the pathogenesis of endometrial cancer and underline the serious limitations of our knowledge of the actual role of these factors in the pathogenesis of these disease processes. One may therefore reasonably question the advisability of unnecessary derangement of such endocrinological relationships in completely normal young women.

These considerations become even more pertinent when one reviews the highly distinctive histological effects of the estrogen-progestogen mixtures on the endometrium. Notable among these effects is glandular atrophy (*1–4*). This appears to be a progressive or cumulative effect attaining its maximal degree after several months of cyclic medication (*1–4*). This change is reflected in progressively decreased menstrual flow during the initial months of therapy and in the failure of bleeding on withdrawal in 1 to 2 percent of the cycles during therapy. Such atrophic changes represent drug-induced pathology since no such phenomena are observed in the endometria of normal young women.

This glandular atrophy is accompanied by varying degrees of stromal modification and in some instances by active decidua formation, a phenomenon not normally observed in the absence of a recently fertilized ovum. Nor are such stromal changes an expected response to the naturally occuring progestogen, progesterone, unless accompanied by the stimulus of nidation. The degree of such decidualization varies substantially with the various dosage and temporal regimens more recently developed. Nevertheless, such tissue is not found in the uterus of a healthy, young, regularly menstruating woman. Its presence in the nongravid uterus is a distinct drug-induced abnormality.

Although the endometrium reverts to an entirely normal-appearing structure after cessation of therapy, (*1, 2*) this provides little assurance as to the future behavior of the previously altered endometrial elements which persist *in situ*—namely the epithelium and the stroma of the basal layers of the endometrium from which the more superficial layers are to be subsequently regenerated throughout the remaining life span. During the prolonged latent period of the action of substances known to be carcinogens in man, such as radioactive ores, X-rays, or aniline dyes, there are frequently no histological changes detectable (*32, 33*).

An instructive lesson regarding the importance of this silent, prolonged, latent period can be learned from studies of the effect of 19-norprogesterone on the ovaries of the mouse. Lipschutz and Iglesias (*31a*) described completely normal fertility after removal of pellets of 19-norprogesterone from Balb A mice after the pellets had been in place for 108 days. However, in a subsequent report these authors described ovarian tumors in 8 of 14 animals which had previously been reported to have had entirely normal ovarian function (*31b*).

We have already emphasized that a prolonged latent period of many years characterizes the behavior of most known carcinogens in man (*32, 33*). Since the longest exposure of any individual to oral contraceptives is 9 years and the greatest bulk of observations is for very much shorter periods of time and only a few years have elapsed since the close of treatment, no data concerning potential delayed effects are as yet available.

Estrogens and Cervical Cancer

The relationship of steroid hormones to the pathogenesis and progression of cancer of the cervix in man is poorly understood. However, the secretory and mitotic activity of the cervical epithelium is clearly responsive to the cyclic changes in ovarian hormone output as well as to exogenous steroid administration. Hence, alterations in these cellular functions are readily induced by the oral contraceptive agents. It is, therefore, universally considered essential that the status of the cervical tissue with respect to the presence of malignant and premalignant change be initially evaluated and closely followed.

In this connection, it is to be emphasized that when initial screening by Papanicolaou smear of a given population is subsequently repeated, the number of positive smears found on rescreening will be a small fraction of the number found initially. Thus, Christopherson *et al.* (*34*) working in Louisville showed that for carcinoma *in*

situ a yield of 3.7 per 1,000 on initial screening fell to 0.63 per 1,000 on the second annual screening of the same women. For invasive carcinoma the corresponding figures were 2.8 and 0.52. This spontaneous reduction on rescreening reflects the expected difference between prevalence and incidence figures and should not be confused with a presumed favorable effect of any intervening medication in such studies. It would, of course, be expected that all women started on oral contraceptives would have been given the benefit of a prior pelvic examination and Papanicolaou smear. Hence, the findings in such a population of prescreened women cannot be compared with the findings in the population group from which they are initially selected.

The prolonged pathogenetic period for cancer of the cervix is estimated to be from 7 to 10 years on the basis of the difference in the age distribution of carcinoma *in situ* versus invasive carcinoma (*12, 34*). Hence studies of the effect of any medication on this prolonged pathogenetic process should certainly exceed in duration this phase of the development of cervical cancer. Observations of this duration in significant numbers are not at hand.

Pincus and Garcia (*35*) have recently summarized their available data on the occurrence of invasive cervical cancer and certain associated cytological phenomena in a limited sample of women using either oral contraceptives, vaginal spermicides or intrauterine devices. They state: "The data give practically identical figures for the presence of carcinoma, anaplasia or negative tissues in the Enovid and vaginal contraceptive users." Also: "Obviously far more extensive data are required for definitive determination, but with an enlarged population for study we hope to have adequate information on carcinoma incidence." We agree that the data reported provide no sound statistical basis for assurance on this vital point.

More recently, Wied *et al.* (*35a*) among others have offered data indicating no significant effect of certain preparations on the course of initial cervical dysplasia over a 1 to 2 year period. Such data provide some assurance as to immediate effects on the initial phases of the pathogenetic process, but have only an indirect bearing on the ultimate response to chronic exposure to medication which may become apparent some years hence. Studies for much more sustained periods of time and after more prolonged exposure are clearly needed.

Statistical Considerations

A substantial change in the incidence of certain diseases such as cancer, may be difficult to detect even with very large samples. For example, in a study of breast cancer incidence with 4-year followup of women aged 20 to 39 years, a sample of about 15,000 to 20,000 women, or 60,000 to 80,000 person-years, would be required to have a reasonable (i.e., 90 percent) chance of detecting (at the 95 percent probability level) a two-fold increase in risk.

Changes in the incidence of cervical cancer could be detected with samples of about the same size; changes in the incidence of endometrial cancer would require samples about six to eight times as large as those for breast cancer. No studies approaching this magnitude have been reported. On the contrary, the initial approval of the administration of oral contraceptive agents for 4 years to young women was initially based on a 4-year experience in 400 cases properly documented with laboratory studies (*36*). Since duration of exposure is so critical a factor, only those women exposed for the actually approved period of 4 years provide any experience pertinent to this evaluation. Certainly, it is to be reasonably expected that a new public health practice would be predicated on a more soundly developed epidemiological basis.

Thrombophlebitis

Thrombophlebitis and thromboembolic phenomena following the use of oral contraceptive agents have been reported. Accordingly, in January of 1963 an "ad hoc" committee was established by the Commissioner of the Food and Drug Administration to determine if the use of one of the oral contraceptive preparations (Enovid) resulted in an increase in incidence of deaths from thromboembolic conditions.

This committee concluded that: "on the basis of the available data * * * no significant increase in the risk of thromboembolic death from the use of Enovid in this population group has been demonstrated" (*37*).

In concluding their report this Committee added: "Any firm reliance on the risks as calculated is tempered by the assumptions made. This Committee recommends that a carefully planned and

controlled prospective study be initiated with the objective of obtaining more conclusive data regarding the incidence of thromboembolism and death from such conditions in both untreated females and those under treatment of this type among the pertinent age groups" (*37*). Meanwhile, a statistically inadequate mass of scattered observations continues to direct our attention to this as yet unresolved problem.

Final evaluation of this aspect of the study of oral contraceptive preparations must therefore be deferred pending the outcome of such studies.

Studies of Carcinogenesis in Laboratory Animals

The initiation and current development of oral contraceptive agents are almost entirely based on initial findings in experimental animals (*38–40*; *47*, *48*). It is therefore pertinent to consider the results of extensive animal studies concerning the role of these and similar agents, in experimental carcinogenesis and in relation to other endocrinological functions.

The major significance of animal data has been recently emphasized by the finding of neoplastic changes in the breasts of dogs following the prolonged ingestion of Ethynerone, and this finding led to the officially approved cessation of clinical trials with this estrogen-progestogen mixture. The estrogenic component, mestranol, is chemically identical with that contained in most marketed mixtures. The progestogen content of this preparation differs from the marketed mixtures in specific chemical structure. However, all prior studies in this family of progestogens indicate that such structural variations provide only quantitative biological differences, unlike the qualitative changes induced by such structural changes in the corticoid series (*48a*). Hence it is clearly inconsistent to consider the animal data with the new mixture to be of more significance than the huge body of preexisting animal findings with a wide variety of synthetic estrogenic compounds in numerous species of animals, including the dog (*48b*). Either the presently marketed preparations are also to be condemned on the basis of almost certainly expectable animal findings or Ethynerone should not have been condemned.

The essential consideration is whether or not demonstrable carcinogenicity in animals is pertinent to the clinical problem. From a comparative physiological standpoint there is no validity in considering the recent results in dogs to be any more significant than comparable data in mice, rats, rabbits, and hamsters.

The vast amount of experimental data concerning the vital role of estrogens in the pathogenesis and progression of cancer of the breast, uterus, and cervix in numerous species is considered by some to have little or no pertinence to comparable processes in man. This view stems largely from the superficial interpretation of the clinical and epidemiological observations of the past 25 years already discussed. Also, disproportionate emphasis is placed on a few negative experiments (*41–44*), in which no malignancies were observed in monkeys treated for prolonged periods with estrogens or, in the case of one monkey, with estrogen and progesterone. These primate studies, which ranged in duration from 3 months to 10 years, involved a total of 25 Maccacus rhesus monkeys in all, with only 4 of the monkeys treated for 4 years or more. Although no actual malignancies were described, these monkeys almost uniformly did exhibit profound metaplastic changes in the cervix and endometrium and one of them showed a marked endometrial hyperplasia and polyposis (*45*, *46*).

Estrogen administration readily leads to a wide variety of neoplasms under varying experimental conditions in several species. These include tumors of the breast, cervix, endometrium, ovary, pituitary, testicle, kidney, and bone marrow produced in either rats, mice, rabbits, hamsters, and dogs (*49*). These experimental effects are easily and uniformly reproducible and, in view of their multiplicity, do not represent bizarre or rare biological effects. Rather, they are the readily reproducible responses seen in practically all sufficiently tested species of appropriate genetic constitution. However, the human population is so genetically heterogenous, that the role of the genetic factor in man's response to such agents is thus far unknown. From what is known experimentally, however, wide variation in the frequency of response in different genetic groups throughout the world is not improbable (*50*).

A considerable part of what has been stated above relates to estrogens when applied alone. However, we have also already considered the unique histological effects on the endometrium of the estrogen-progestogen combinations presently employed as contraceptives. The question naturally arises as to whether or not the combined use of these two hormonally active agents does not

alter what is to be expected from either agent alone. Extensive experimental observations indicate certain interactions between estrogen and progestogens. These phenomena include synergistic as well as antagonistic effects of these two agents on the endometrium, on deciduoma formation, on premalignant metaplastic changes in the cervical glands, on fibroid tumor formation in the uterus, on carcinogen-induced endometrial carcinoma, and on many other biological end-points (*51–54*). The complexity of these interactions, varying as they do with different dosage ratios and with the critical effects of the timing of the administration of each agent creates many as yet poorly understood features of the tissue responses obtained.

Moreover, the naturally occurring substance, progesterone, as already noted, when given either following estrogenization of the endometrium or when given simultaneously with estrogen only rarely induces the degree of stromal change observed in the uteri of women given estrogen-progestogen mixtures. Such tissue effects in women are supplemented by extensive observations concerning the unique and anomalous qualitative effects of these compounds in animals as compared with progesterone (*47*, *48*). Hence, it seems inadvisable to presume that the interaction of estrogen with these newer progestogens will necessarily parallel that which has been previously observed for progesterone itself, and the potentiality for substantially different long-term effects must be more completely analyzed by clinical as well as experimental observation.

Effects on Germ Cells

An unequivocal abnormality produced by estrogen-progestogen combinations is the suppression of ovulation itself. It is only reasonable to consider the ultimate fate of the ovum that would have been normally released from the ovary. We do not know whether this ovum dies or survives. If it survives, is it altered in any way? The only information we now have in this regard is that subsequent fertilization of some ova from the same ovaries readily occurs and that a limited number of newborn derived from such pregnancies appear normal at birth (*1–4*). The number of such infants thus far described in the literature is a minute fraction of that required to determine the relative frequency of congenital defects or related abnormalities of the newborn and no significant pediatric followup of these children is yet available. Statistical and clinical considerations indicate that for an adequate analysis of this problem a population of 100,000 children would be required. Moreover, the delayed clinical manifestations of many congenital abnormalities requires that these children be followed for 6 to 9 years in order to completely appraise any possible effect upon them. It seems unjustified to assume that the suppression of the normal ovulatory mechanism of the ovary for a 4-year period may not be reflected in the quality of the ova subsequently released even from an ovary in which the histological findings appear to be normal. Interpretation of such findings after years of deferral of pregnancy would, of course, have to include a full appreciation of the spontaneous increment in the frequency of congenital abnormalities with advancing maternal age.

The foregoing considerations have been brought together to direct the attention of the medical profession to these aspects of our knowledge as well as of our ignorance which seem pertinent to an evaluation of some of the risks involved in the use of estrogen-progestogen combination for purposes of contraception in the completely normal, healthy, young woman over a 4-year period.

Each physician must evaluate these risks with an appreciation of the many undetermined factors involved and with due regard for the merits of alternative methods available to him and to his patients.

In view of the serious limitations in our knowledge of the potential long-term effects of estrogen-progestogen combinations, it is mandatory that further clinical experience be gained under properly controlled conditions of observation and followup.

Table I.—*Latent period of some known carcinogens in man*

Carcinogen	Site of cancer	Range of latency (years)
X-rays	Skin	10–30
Radioactive paints	Bone	10–30
Radioactive ores	Lung	5–20
Thorium dioxide	Liver	10–25
Ultraviolet exposure	Skin	10–40
Aromatic mines	Bladder	2–20
Coal tar (shale oil)	Skin	10–25
Soot (chimney sweeps)	Scrotum	11–17

Drawn from data of Hueper, W. C., chapter 24 *in* Homburger-Fishman "Physiopathology of Cancer," Hoeber-Harper, New York, 1959.

Table II.—*Estrogens and breast cancer*

Authors	Number of patients	Number of menopausal patients	Number of patients 20–40 years old	Duration of treatment	Breast cancers	Genital tract cancers	Expected cancers [1]
Geist et al	206	Most	Few	½ to 5½ years	Not observed	None	Not stated.
Mustacchi et al	[2] 120	94	26	5	0	[3] 0	5 or 6.
Wallach et al	292	234	58	5.1	0	[4] 7	Not stated.
Wilson et al	304	304	0	7.8	0	0	20.

[1] As stated by authors.
[2] 5 with carcinoma eliminated from study; others with osteoporosis.
[3] Endometrial hyperplasia in 2.
[4] 94 had had genital organ removal.

bibliography

1. ROCK, J., GARCIA, C. R., AND PINCUS, G. Synthetic Progestins in the Normal Human Menstrual Cycle, Rec. Progr. in Hormone Res., 13: 323, 1957.

1a. PINCUS, G., GARCIA, C. R., ROCK, J., PANIAGUA, M., PENDLETON, A., LARAQUE, F., NICOLAS, R., BORNO, R., AND PAEN, V. Effectiveness of an Oral Contraceptive, Science, 130: 81, 1959.

2. GOLDZIEHER, J. W., RICE-WRAY, E., SCHULZ-CONTRERAS, M., AND ARANDA-ROSELL, A. Fertility Following Termination of Contraception with Norethindrone, Am. J. Obst. and Gynec., 84: 1474, 1962.

3. TYLER, E. T., AND OLSON, H. J. Fertility Promoting and Inhibiting Effects of New Steroid Hormonal Substances, J.A.M.A., 169: 1843, 1959, and Tyler, E. T., Current Status of Oral Contraception, J.A.M.A., 187: 562, 1964.

4. RICE-WRAY, E., SCHULZ-CONTRERAS, M., GUERRERO, I., ARANADA-ROSELL, A. Long-Term Administration of Norethindrone in Fertility Control, J.A.M.A., 180: 355, 1962.

5. MORSE, W. I., CLARK, A. F., AND MACLEOD, S. C. Size and Production Rate of Oestradiol and Oestrone Miscible Body Pool of a Healthy Woman, J. Endocrinol., 26: 25, 1963.

6. GURPIDE, E., ANGERS, M., VANDE WIELE, R. L., AND LIEBERMAN, S. Determination of Secretory Rates of Estrogens in Pregnancy and Nonpregnant Women From the Specific Activities of Urinary Metabolites, J. Clin. Endocrinol. and Metab., 22: 935, 1962.

7. BEATSON, G. T. On the Treatment of Inoperable Cases of Carcinoma of the Mammae, Lancet, 2: 104, 1896.

8. CURRIE, A. R. (Cf. numerous authors) in Endocrine Aspects of Breast Cancer; Conference at University of Glasgow, 1957. Livingstone Ltd., London, 1958.

9. PEARSON, O. H., WEST, C. D., HOLLANDER, V. P., AND TREVES, N. E. Evaluation of Endocrine Therapy for Advanced Breast Cancer, J.A.M.A., 154: 234, 1954.

10. HALL, T. C. Biological Activities of Steroids in Relation to Cancer, Pincus, G., and Vollmer, E. P., eds., p. 487, Academic Press, 1960.

11. KENNEDY, B. J. Massive Estrogen Administration in Premenopausal Women With Metastatic Breast Cancer, Cancer, 15: 641, 1962.

12. DUNN, J. E. The Relationship Between Carcinoma In Situ and Invasive Cervical Carcinoma, Cancer, 6: 873, 1953.

12a. GERSHON-COHEN, J., AND BORDEN, A. G. Ann. N.Y. Acad. Sci. 114: 783, 1964.

13. LIEBEGOTT, G. Mammacarcinom beim Mann nach Follikelhormonbehandlung, Klin. Wchnsh., 26: 599, 1948.

14. ALLABAN, G. R., AND OWEN, S. E. Adenocarcinoma of the Breast Coincidental With Strenuous Estrogen Therapy, J.A.M.A., 112: 133, 1939.

15. AUCHINCLOSS, H., AND HAAGEMAN, C. D. Cancer of the Breast Possibly Induced by Estrogenic Substance, J.A.M.A., 114: 1517, 1940.

16. LONBEJAC, A. M. Cancer de la Mama en la Mujer y Folliculina, Bol. Soc. cir. d. Uruguay, 15: 28, 1944.

17. PARSONS, W. H., AND MCCALL, E. F. The Role of Estrogenic Substances in the Production of Malignant Mammary Lesions With Report of a Case of Adenocarcinoma of the Breast, Surgery, 9: 780, 1941.

18. DE NOSAQUO, N. Androgens and Estrogens in the Treatment of Disseminated Mammary Carcinoma, J.A.M.A., 172: 1271, 1960.

19. WALLACH, S., AND HENNEMAN, P. H. Prolonged Estrogen Therapy in Post-Menopausal Women, J.A.M.A., 171: 1637, 1959.

20. MUSTACCHI, P., AND GORDON, G. S. Frequency of Cancer in Estrogen-Treated Osteoporotic Women. Second Biennial Louisiana Cancer Conference, New Orleans, pp. 163–169; Mosby, St. Louis, 1958.

21. WILSON, R. A., BREVETTI, R. E., AND WILSON, T. A. Specific Procedures for the Elimination of the Menopause, Western J. Surg. Obst. and Gynec., 71: No. 3, May–June 1963.

21a. GEIST, S. H., WALTER, R. I., AND SALMON, V. J. Am. J. Obst. and Gynec., 41: 29, 1941.

22. HERTIG, A. T., AND SOMMERS, S. C. Genesis of Endometrial Carcinoma. I. Study of Prior Biopsies, Cancer, 2: 946, 1949.
23. GUSBERG, S. B. Precursors of Corpus Carcinoma, Estrogens, and Adenomatous Hyperplasia, Am. J. Obst. and Gynec., 54: 905, 1947.
24. GUSBERG, S. B., AND KAPLAN, A. L. Precursors of Corpus Cancer, Am. J. Obst. and Gynec., 86: 662, 1963.
25. SPEERT, H. Cancer of the Endometrium in Young Women, Surg. Gyn. and Obst., 88: 332, 1949.
26. TE LINDE, R. W., JONES, H. W., JR., AND GALVIN, G. A. What Are Earliest Endometrial Changes To Justify Diagnosis of Endometrial Cancer, Am. J. Obst. and Gynec., 66: 953, 1953.
27. FREMONT-SMITH, M., MEIGS, J. V., GRAHAM, R., AND GILBERT, M. Cancer of the Endometrium and Prolonged Estrogen Therapy, J.A.M.A., 131: 805, 1946.
28. ØSTERGAARD, E. Estrogens in the Etiology of Cancer of the Corpus Uteri, Proc. Int. Congr. of Gyn. and Obst., Geneva, Switzerland, July 26, 1954, pp. 222–228.
29. KENNEDY, B. J., AND NATHANSON, I. T. Effects of Intensive Sex Steroid Hormone Therapy in Advanced Breast Cancer, J.A.M.A., 152: 1135, 1953.
30. KELLEY, R. M., AND BAKER, W. H. Clinical Observations on the Effect of Progesterone in the Treatment of Metastatic Endometrial Carcinoma. Biological Activities of Steroids in Relation to Cancer, pp. 427–439, Academic Press, New York, 1960.
31. KISTNER, R. W. Treatment of Carcinoma in situ of the Endometrium, Clin. Obst. and Gynec., 5: 1166, 1962.
31a. LIPSCHUTZ, A., AND IGLESIAS, R. Recovery of Fertility After Protracted Steroid-Induced Sterility in Mice. Nature, 190: 174, 1961.
31b. LIPSCHUTZ, A., IGLESIAS, R., AND SALINAS, S. Ovarian Tumors Induced by a Sterilizing Steroid, Nature, 196: 946, 1962.
32. HUEPER, W. C. Environmental Cancer, ch. 24, p. 919 in Homburger-Fishman, "Physiopathology of Cancer," second edition, Hoeber-Harper, New York, 1959.
33. HUEPER, W. C. Occupational Tumors and Allied Diseases. Chas. C. Thomas, Baltimore, 1942.
34. CHRISTOPHERSON, W. M., PARKER, J. E., AND DRYE, J. C. Control of Cervical Cancer; Preliminary Report on Community Program, J.A.M.A., 182: 179, 1962.
35. PINCUS, G., AND GARCIA, C. R. Preliminary Findings on Hormonal Steroids and Vaginal Cervical, and Endometrial Histology. International Union Against Cancer; Mexico City, Feb. 5, 1964 (manuscript available through courtesy of the authors).
35a. WIED, G. L., DAVIS, M. E., FRANK, R., SEGAL, P. B., MEIER, P., AND ROSENTHAL, E. Obst. and Gynec., 27: 327, 1966.
36. Official correspondence with Dr. Arthur Ruskin, Acting Director, Division of New Drugs, Bureau of Medicine, Food and Drug Administration, Washington, D.C., Feb. 4, 1964.
37. WRIGHT, I. S., ET AL. The Final Enovid Report. Journal of New Drugs, 3: 201, 1963.
38. HERTZ, R., TULLNER, W. W., AND RAFFELT, E. Progestational Activity of Orally Administered 17-alpha-ethinyl-19-nor testosterone, Endocrinology, 54: 228, 1954.
39. SANDERS, F. J., COLTON, F. B., AND DRILL, V. A. Progesterone-like Activity of a Series of 19-nor-testosterone, Proc. Soc. Exper. Biol. and Med., 94: 717, 1957.
40. TULLNER, W. W., AND HERTZ, R. Progestational Activity of 19-nor-progesterone and 19-nor-ethisterone in the Rhesus Monkey, Proc. Soc. Exper. Biol. and Med., 94: 298, 1957.
41. OVERHOLSER, M. D., AND ALLEN, E. Ovarian Hormone and Traumatic Stimulation of Monkey's Cervix to a Condition Resembling Early Cancer, Proc. Soc. Exper. Biol. and Med., 30: 1322, 1933.
42. HARTMAN, C. G., GEOCHICKTER, F., SPEERT, H. Effects of Continuous Administration in Very Large Doses, Anat. Rec., 79: Supp. 2, p. 31, 1941.
43. PFEIFFER, C. A., AND ALLEN, E. Attempts To Produce Cancer in Rhesus Monkeys With Carcinogenic Hydrocarbons and Estrogens, Cancer Research, 8: 97, 1948.
44. ENGLE, E. T., KRAKOWER, C., AND HAAGENSEN, C. D. Estrogen Administration to Aged Female Monkeys With No Resultant Tumor, Cancer Research, 3: 858, 1943.
45. OVERHOLSER, M. D., AND ALLEN, E. Atypical Growth Induced in Cervical Epithelium of Monkey by Prolonged Injections of Ovarian Hormone Combined With Chronic Trauma, Surg. Gynec. and Obst., 60: 129, 1935.
46. CROSSEN, R. J., AND SUNTZELFF, V. Endometrial Polyps and Hyperplasia Produced in an Aged Monkey With Estrogen Plus Progesterone, Arch. Path., 50: 721, 1950.

47. PINCUS, G., CHANG, M. C., ZARROW, M. X., HAFEZ, E. S., AND MERRILL, A. Studies of the Biological Activity of Certain 19-nor-steroids in Female Animals, Endocrinology, 59: 695, 1956.
48. PINCUS, G., ET AL. Effects of Certain 19-nor Steroids on Reproductive Processes in Animals, Science, 124: 890, 1956.
48a. DJERASSI, C. Science, 151: 1,055, 1966.
48b. JABARA, A. Aust. J. Exp. Biol., 40: 139, 1962.
49. GARDNER, W. V., PFEIFFER, C. A., AND TRENTIN, J. J. Hormonal Factors in Experimental Carcinogenesis, ch. 6, p. 152, in Homburger-Fishman "Physiopathology of Cancer," second edition, Hoeber-Harper, New York, 1959.
50. LITTLE, C. C. Genetics of Neoplasia. Ch. 5, p. 127, in Homburger-Fishman "Physiopathology of Cancer," second edition, Hoeber-Harper, New York, 1959.
51. LIPSCHUTZ, A. Steroid Hormones and Tumors, Williams and Wilkins, Baltimore, 1950.
52. GRIFFITHS, C. T., TOMIC, M., CRAIG, J. M., AND KISTNER, R. W. Effects of Progestins, Estrogens and Castration on Induced Endometrial Cancer in the Rabbit, Surg. Forum, 14: 399, 1963.
53. HISAW, F. L., AND LANDRUM, F. C. Squamous Metaplasia in the Cervical Glands of the Monkey Following Estrin Administration, Endocrinology, 20: 228, 1936.
54. YOUNG, W. C. Sex and Internal Secretions (Allen), Williams and Wilkins, Baltimore, Md., 1963.
55. HERTZ, R., WHITE, J. H., AND THOMAS, L. B. Progestational Effectiveness of 19-nor-ethinyltestosterone by Oral Route in Women, Proc. Soc. Exper. Biol. and Med., 91: 418, 1956.

Appendix 6

Review of the Procedures and Reports of the Pharmaceutical Companies Concerned With the Manufacture and Sale of the Oral Contraceptives.

S. G. KOHL, M.D.

During February and March of 1966 the seven pharmaceutical manufacturers marketing oral contraceptives were visited at the request of the Advisory Committee of the Food and Drug Administration. The charge was to collect and analyze the deaths in patients taking oral contraceptives which had been reported to the manufacturers and investigated by them. A further charge was to "look into how they keep records and conduct investigations of adverse reactions." This combination of a specific and general charge made the visits easy to arrange and instructive to carry out.

All visits were arranged through the medical directors of the manufacturers. In almost all instances the chief medical officer of each manufacturer was interviewed. Some of the detail work was carried out with his subordinates who were directly responsible for the activities in question. An observation concerning these physicians and medical scientists is unavoidable. I believe these men, almost without exception, to be competent and interested in their work. I am impressed that they are truly concerned about the safety of the medications their firms produce and/or market. They wish to "do a good job." They are aware of the potential dangers of prolonged usage of potent medications and they wish to discharge this responsibility in an intelligent and scientific manner. They appreciate the shortcomings of their present methods of surveillance.

The "medical departments" of the manufacturers are quite variable. Some are very sophisticated in approach and personnel and one occupies a "basement office" and is quite restricted in personnel and outlook. These characteristics are detailed in the attached reports which describe the procedures followed by each manufacturer.

Standardization of Records

It was anticipated, prior to the visits, that there would be a degree of uniformity in the records and investigations of reported deaths. This was not the case. The variability was marked and so was the feeling of responsibility and involvement. Some of the investigations of deaths were associated with repeated visits and telephone calls to physicians whose patients had died. Other investigations were quite cursory and reflected considerable concern over the company's image with the physician. "He cannot be irritated—it's bad for our business relationships." I was surprised that there are no standard forms in use. This is true for the reporting of both deaths and adverse reactions which do not result in death. Thus compilations, tabulations, and analyses are made unnecessarily difficult and awkward.

Some physicians and hospitals hesitate to release patient information to a commercial organization. In fact some refuse to do so. It is of more than passing interest to note that the U.S. Naval Hospital at Bethesda replied that they had filed a report with FDA and would release no information to the manufacturer. This action is in spite of the fact that FDA charges the manufacturer with responsibility for carrying out an investigation. FDA has supplied no report to the manufacturer on this death. My own hospital has refused to release data to manufacturer without the consent of the Corporation Counsel of the city of New York. I am not anxious to undertake the chore of pushing this request through the Department of Hospitals and the Corporation Counsel's Office.

In this general area, I submit the following recommendations:

1. Adverse reactions should be reported on a standard form, rather than in memoranda, to a

single office in FDA. These should be in the form of an initial alert on a postal card perhaps, and followed by the completed form when the investigation has been completed or carried on as far as possible by the manufacturer.

2. If copies of these reports are to be distributed to several branches of FDA this distribution should be by FDA and not by the manufacturer.

3. The present FD 1639 form is not adequate for the analysis of oral contraceptive adverse reactions.

4. The initial request for information in the investigations of an adverse reaction should be from FDA on official stationary and signed by a responsible medical officer. If followup and collection of data is to be the responsibility of the medical department of the manufacturer, the initial request should so inform the recipient.

5. The medical officers of the FDA responsible for monitoring adverse reactions, the medical personnel of the pharmaceutical manufacturer having similar responsibility and the appropriate members of the Advisory Committee should evolve adequate forms, requests, and standard procedures to be followed. At present each unit acts independently and with varying interpretations of what is required.

6. Such an organization would make pooling and exchange of information an easy and rewarding experience. An instrumentality for "feedback" would be in existence. Such activity is imperative if reliable and continuous scientific data are to be "fed-in".

7. The pharmaceutical manufacturers' medical departments are enthusiastic about the possibility of working with the Advisory Committee, for whom they have great respect. Perhaps some of the "police activities" required by statute, can be efficiently carried out through the Committee's scientific and consultative activities.

Investigational Patients

Each manufacturer has a number of "investigational patients" who have been under observation for a known period of time or are continuing under observation. These groups include several thousand patients, perhaps as many as 15,000–20,000. The records of adverse reactions are, in general, quite complete. These patients might give more adequate known numerators and denominators for study. The medical people at the manufacturers have indicated to me that they would consider pooling these data for analysis on an anterospective basis. At present, this is awkward because each drug has a different form for the registration of the patient and the collection of followup data. These records are quite variable. Some are very detailed and some are "skimpy." The followup procedures are variable in the rigor demanded in the collection of data. A basic uniform record which was precoded for easy machine handling might be of advantage to both the investigators and FDA. Additions might be made to such a base record to satisfy the individuality of manufacturers and/or investigators.

1. A working group similar to the one suggested in the previous section, could be established to create a basic investigational registration and followup record. These basic forms would be utilized for all oral contraceptive drugs under study. Additions might be made to the basic records to satisfy individual desires of manufacturer and/or investigators.

2. A manual should be prepared containing "guidelines" for the selection of investigators and patients in future studies to be undertaken. This manual should contain standard terms and definitions as well as instructions for completing the various forms. Again single copies should be transmitted to FDA and duplicated by the Agency for internal distribution.

3. There is no uniformity in the procedures to be followed in "closing a case." These should be developed. A decision is needed on the effort to be expended upon patients who "stop coming to the clinic." At present the efforts to follow such patients vary from "nothing" to rather extensive, time consuming, and expensive effort to keep the patient under followup. An important oversight is the lack of followup of patients who are dropped because of pregnancy. This group presents an opportunity for the collection of considerable data. These data might be of importance in both medical and epidemiological areas of interest. Almost without exception, there is a dearth of data on pregnancy outcome in patients who become pregnant while on oral contraceptive therapy. No single investigator has many such patients but the "pool" would make several hundred available for analysis.

4. A computer program, perhaps patterned after the one in use by Eli Lilly & Co., should be established for the recording, storing, and analysis of these data. A program should also be evolved

for analysis of "adverse reactions," if this activity is to be continued. In as much as each of these manufacturers has computer facilities available, their medical and computer people might be able to add to the program development. The programs evolved could be implemented in their own organizations and perhaps replace some of the naive statistical analysis now carried out.

Surveillance of Patients Under Oral Contraceptive Therapy

Conversations with Advisory Committee members, medical personnel of the manufacturers and FDA personnel revealed considerable concern over the long-range effect of these medications. A woman with three children who begins oral contraception therapy at age 28, may use the drug for 20 years. Modern epidemiological and biostatistical methodology make possible the surveillance of such patients so that adverse chronic reactions may be detected at the earliest possible point in time. Such surveillance is rarely necessary because rarely have so many patients taken so potent a drug, for so long a period of time. Whether true or not, one gets the impression that certain adverse reactions may be time related. It seems imperative that the answers to this type of question be available. I believe that the costs involved in this type of surveillance are peculiar to the drug and its mode of use. Therefore, it seems to me that the cost of such surveillance is an integral part of the total cost of production and distribution of the medication. At the present time these medications cost the private patient about $25 per year. Because of the large number of patients under therapy, a fractional increase in the cost would supply ample funds to carry out the indicated epidemiologic surveillance.

As suggested by Dr. Louis M. Hellman, certain "captive groups" might be enlisted for study. Examples are: Wives of armed service personnel; clients of the Indian Service; patients of the Kaiser Medical Group; H.I.P. and the Family Union Medical Plan of the Hotel Industry of New York.

In order to have a representative sample of the population at risk, patients in Family Planning Clinics of various kinds and private patients should be included.

The FDA, its Advisory Committee, and the industry should set up a conference with capable epidemiologists and biostatisticians to investigate the feasibility of such a program and the planning thereof. An organization may need to be established, an existing agency may be able to take on the responsibility or the activity may be contracted to one or more of the Schools of Public Health for maintenance of the surveillance. Such an organization could serve as a model for future similar projects or for the maintenance of investigational studies in the drug industry.

The Food and Drug Administration

I have carried out no investigation of the Food and Drug Administration. My only contact with FDA or its personnel was at the committee meeting on April 7, 1966. Therefore any observations about FDA are hearsay or are related to what I have seen at the pharmaceutical manufacturers.

1. There appears to be little feedback to the manufacturers of the data which they are required to collect and transmit to FDA. Some pooled data might be very helpful and useful in maintaining a high level of scientific and epidemiologic interest. It might stimulate such awareness where it does not now exist.

2. One is struck by the lack of "guidelines" as to how investigational activities are to be carried out. The FD 1649 form is a cogent example. One manufacturer did not know of its existence. The form had been required for about 6 months and they had never filed a single one. The responsible FDA branch should have corrected this shortcoming. The FD 1639 form is completed by manufacturers' personnel in some cases, by treating physicians in other cases and in still other cases is not filed at all. The manufacturer, in each case, quote conversations with FDA personnel as authority for their routine. Who is responsible for this situation is unimportant. The need for instructions and guidelines is clear. Some of the memorandums filed are voluminous and burdensome to handle because the manufacturer is "afraid" to leave anything out. Others use their own judgment and inasmuch as they hear no complaints, it is assumed that their procedure is acceptable. One manufacturer files a list of adverse reactions and elaborates only on those cases which his representative believes merit elaboration. Another manufacturer files copies (triplicate) of every piece of paper including notes on telephone conversations with "detail men."

3. Intraagency communication seems to be faulty. The 110 deaths examined and tabulated in this report were taken solely from the duplica-

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tion of material already submitted to FDA. This total, I am told, is at considerable variance with the number of deaths presented to the Advisory Committee by FDA.

4. The expressed desire of cooperation in carrying out the provisions of statutes and regulations should be accepted. It may be that enforcement will be easiest and most complete when the industry participates in policing itself. The medical personnel, recruitable by FDA and the medical departments of the manufacturers, will be improved by cooperation. This will permit the insinuation of scientific activity into the usual expending or receiving effects of the required "police activity."

Report of Deaths in Patients Taking Oral Contraceptives

A series of tables is appended to the report which lists the 110 deaths found in the files of the manufacturers. The tables also show a second listing of 65 deaths judged to be due to "idiopathic pulmonary embolus." These 65 deaths were from the total of 75 deaths caused by pulmonary embolization. For the following reasons 10 deaths were deleted:

Rheumatic heart disease with valvulitis.
Pancreatitis, hypertension, and renal disease.
Thrombophlebitis in a previous pregnancy (three patients).
Thrombophlebitis 3 months before therapy.
Postoperative cholecystectomy.
Postoperative hysterectomy (two patients).
Postoperative radical mastectomy.

The collected data were abstracted onto 80-column punchcards which have been turned over to the Committee. The coding was performed in accordance with the attached code sheet. The IBM facilities of the Downstate Medical Center were employed to prepare the punchcards and to sort them for the preparation of the tabulations.

It is not possible to draw statistically valid conclusions regarding deaths in association with the taking of oral contraceptives. There is no reason to believe that these reported deaths are either a complete or an incomplete recording. They are more likely to be incomplete. The fact that most of the deaths occurred within the first 4 months of administration may reflect the larger number of patients taking the drug for this period of time as opposed to any later time period. It may reflect the fact that if a patient dies after taking a drug for a short period of time, it is more likely to be associated as a possible causative factor and reported. It may reflect the impression of the physician that the drug taken for a long period of time is not likely to have an etiologic relationship with a death. It may even be that a drug taken for a long period of time is ignored in getting a medical history.

Another unusual finding is that over 80 percent of the deaths were known to have been submitted to autopsy. This suggests that the association with the oral contraceptives may be an after thought suggested by the pathologic findings.

I surely agree with the position taken by the Committee members who feel that the present study has added little to our knowledge of the relationship of oral contraceptives to death in the population at risk. I have detailed the type of data needed to cast light on the presence or absence of such relationship.

I wish to thank the Advisory Committee for having given me the opportunity to carry out the investigation. The medical departments of the pharmaceutical manufacturers were forthright and cooperative and they made copies of reports available and in some cases prepared special tabulations and listings. The study could not have been completed or even begun without the approval and support of the Commissioner and his staff. It was a rewarding experience for your reporter.

Respectfully submitted,

SCHUYLER G. KOHL, M.D.

Oral Contraceptive—Death Report

1	1. Searle 2. Ortho 3. Upjohn 4. Parke Davis 5. Mead Johnson 6. Eli Lilly 7. Syntex	2–3	Case number	12–13	Age at death
		4–8	Manufacturers identification number	14	Race 0—White 1—Negro 2—Yellow 3—Unknown
		9	Month of death		
		10–11	Year of death		

64

15 Autopsy
0—No
1—Yes
2—Yes, no report
3—Partial report
16–17 Months of use prior to death
18 Full term
19 Premature
20 Abortion
21 Living children
22 Previous vascular disease (prior to medication)
0—No
1—Yes
23 0—None
1—Enovid 10
2—Enovid 5
3—Enovid 2.5
4—Ortho 10
5—Ortho 2
6—Provest
7—Norinyl
8—Norlestrin
9—C-Quens
x—Oracon
24 (Other Contraceptive drug used) Same as Column 23
25 Cause of death
0—None listed below
1—Pulmonary embolus
2—Pulmonary thrombosis
3—Cerebral embolization
4—Cerebral hemorrhage
5—Heart disease
6—Thrombocytopenia
7—General thrombosis
8—Leukemia
9—Welch bacillus infection
x—Peritonitis
26 Cause of death (2)
27 Other diseases
0—None listed
1—Diabetes
2—Pancreatitis
3—Murder
4—Sarcoma
5—Hodgkins
6—Carcinoma
7—Pneumonia
8—Alcoholism
9—Asphysia (Aspir)
x—Renal disease
y—
28 Associated diseases (1)
0—None below
1—Peripheral thrombosis
2—Pelvic throbosis
3—Varicose veins
4—Varicose vein ligation
5—Mesenteric thrombosis
6—Hypertension
7—Arteriosclerosis
8—Carcinoma of the breast
9—Leukemia
x—Psychiatric
y—Carcinoma of the uterus
29 Associated diseases (2)
30 Source of report
0—Not stated
1—Detail man
2—Private physician
3—Hospital clinic
4—Patients family
5—FDA
6—AMA
7—Medical examiner
8—Family planning clinic
9—Other pharmaceutical manufacturers
x—Investigator
31–32 State of Residence

New England:
Maine 01
New Hampshire 02
Vermont 03
Massachusetts 04
Rhode Island 05
Connecticut 06

Middle Atlantic:
New York 11
New Jersey 12
Pennsylvania 13

East North Central:
Ohio 21
Indiana 22
Illinois 23
Michigan 24
Wisconsin 25

West North Central:
Minnesota 30
Iowa 31
Missouri 32
North Dakota 33
Nebraska 35
Kansas 36
South Dakota 34

Unknown State

Canada

South Atlantic:
Delaware 40
Maryland 41
District of Columbia 42
Virginia 43
West Virginia 44
North Carolina 45
South Carolina 46
Georgia 47
Florida 48

East South Central:
Kentucky 51
Tennessee 52
Alabama 53
Mississippi 54

West South Central:
Arkansas 61
Louisiana 62
Oklahoma 63
Texas 64

Mountain:
Montana 70
Idaho 71
Wyoming 72
Colorado 73
New Mexico 74
Arizona 75
Utah 76
Nevada 77

Pacific:
Washington 81
Oregon 82
California 83
Alaska 84
Hawaii 85

33 Hospital care
0—None
1—University
2—Affiliated
3—Voluntary (not affiliated)
4—Proprietary
5—U.S. Navy
6—U.S. Army
7—U.S. Public Health Service
34 Physician
0—None
1—M.D.-G.P.
2—M.D.-Ob. G.
3—M.D.-Other specialist
4—D.O.
5—Clinic
35 FD 1639
0—None
1—Treating physician
2—Other physician
3—
4—Mfg.-M.D.
5—Mfg.-Non M.D.
y—Unknown
36 Thrombo-embolic death
0—No
1—Yes
2—Unknown
37 Size of place of residence
0—
1—1,000,000 or more
2—500,000–999,000
3—100,000–499,999
4—50,000–99,999
5—25,000–49,999
6—10,000–24,999
7—5,000 or fewer
y—Unknown residence

38 Medical examiner case
0—No
1—Yes
2—Unknown

39 Oral contraceptive death
0—No
1—Yes
2—Not sure

40 On drug at time of death
0—Yes
1—None for 1 month
2—None for 2 months
3—None for 3 months
4—None for 4 months
5—None for 5 months
6—None for 6 months
7—None for 7 months
8—None for 8 months
9—None for 9 months or more
x—None for less than 1 month
y—Unknown

41 Indication for drug use
0—Contraception
1—Pregnancy test
2—Dysmenorrhea
3—Menorrhagia
4—Endometriosis
5—Irregular menses
6—Premenstral tension
7—Habitual abortion
8—Ulcerative colitis
y—Unknown

42 Obese
0—No
1—Yes
2—Border line
y—Unknown

Cause	Less than 1	1-4	5-8	9-12	13-18	19-24	25-36	37-48	50	60	Unknown	Total
None listed	1	3	1	1		3	1		1			11
Pulmonary embolus	7	38	17	2	3						8	75
Cerebral embolization		1										1
Cerebral hemorrhage		3	1								3	7
Heart disease	1	1				1		1		1	1	6
Thrombocytopenia				1	1						1	3
General thrombosis	2											2
Leukemia											1	1
Peritonitis							1					1
Unknown		3										3

Race

	All		T.E.	
	Number	Percent	Number	Percent
White	66	60.0	43	66.2
Nonwhite	17	15.5	6	9.2
Unknown	27	24.5	16	24.6
Total	110		65	

Age

	All		T.E.	
	Number	Percent	Number	Percent
15–19	3	2.7	2	3.1
20–24	34	30.9	24	36.8
25–29	19	17.3	10	15.4
30–34	19	17.3	12	18.5
35–39	19	17.3	9	13.9
40–44	7	6.4	4	6.2
45 and over	4	3.6	3	4.6
Unknown	5	4.5	1	1.5
Total	110		65	
Range	18–50		18–50	
Average	30.2		28.5	

Parity

Number	F.T.	Prem.	Abort.	L. Child.
0	17	78	63	17
1	12	2	11	12
2	18	0	1	18
3	11	0	0	11
4	8	0	3	10
5	6	0	2	6
6	5	0	0	4
7	1	0	0	2
8	0	0	0	2
9	2	0	0	0
10 or more	0	0	0	0
Unknown	30	30	29	30
Total	110	110	110	110

Nulligravidae—15.

Current Medication

	All		T.E.	
	Number	Percent	Number	Percent
No drug	6	5.5	1	1.5
Enovid—10 mg	21	19.1	11	16.9
Enovid—5 mg	37	33.6	27	41.6
Enovid—2.5 mg	6	5.5	5	7.7
Ortho—10 mg	1	.9	0	0
Ortho—2 mg	16	14.5	11	16.9
Provest	3	2.7	3	4.6
Norinyl	3	2.7	2	3.1
Norlestrin	8	7.3	2	3.1
C-Quens	7	6.4	2	3.1
Oracon	0	0	0	0
Unknown	2	1.8	1	1.5
	110	------	65	------

Parity

Number	F.T.	Prem.	Abort.	Lv. Ch.
0	13	49	43	13
1	7	1	5	7
2	13	0	1	13
3	6	0	0	6
4	2	0	1	4
5	5	0	1	5
6	2	0	0	1
7	1	0	0	0
8	0	0	0	1
9	1	0	0	0
10 or more	0	0	0	0
Unknown	15	15	14	15
Total	65	65	65	65

Nulligravidae—13.

Months of Use

	All		T.E.	
	Number	Percent	Number	Percent
Less than 1 month	11	11.5	5	8.3
1–4	49	51.0	35	58.4
5–8	19	19.8	16	26.7
9–12	4	4.2	2	3.3
13–18	4	4.2	2	3.3
19–24	4	4.2	0	------
25–36	2	2.1	0	------
37–48	1	1.0	0	------
50	1	1.0	0	------
60	1	1.0	0	------
Subtotal	96	100.0	60	100.0
Unknown	14	12.7	5	8.3
Total	110	------	65	------

Manufacturer

	All		T.E.	
	Number	Percent	Number	Percent
Searle	73	66.3	46	70.7
Ortho	17	15.5	11	16.9
Parke Davis	8	7.3	2	3.1
Eli Lilly	7	6.4	2	3.1
Syntex	3	2.7	2	3.1
Upjohn	2	1.8	2	3.1
Mead Johnson	0	------	0	------
Total	110	------	65	------

On Drug at Report

	All		T.E.	
	Number	Percent	Number	Percent
Yes	73	66.4	47	72.3
None-less than 1 month	17	15.5	10	15.4
None for 1 month	1	0.9	0	------
None for 2 months	4	3.6	1	1.5
None for 3 months	1	.9	0	------
None for 6 months	1	.9	0	------
None for 9 months or more	1	.9	0	------
Unknown	12	10.9	7	10.8
Total	110	------	65	------

Year of Report

	All		T.E.	
	Number	Percent	Number	Percent
1959	1	0.9	0	0
1961	6	5.4	5	7.7
1962	27	24.5	13	20.0
1963	23	20.9	16	24.6
1964	27	24.5	15	23.1
1965	20	18.2	13	20.0
1966	1	.9	1	1.5
Unknown	5	4.5	2	3.1
Total	110	------	65	------

Obesity

	All		T.E.	
	Number	Percent	Number	Percent
No	60	54.5	35	53.8
Yes	19	17.3	14	21.6
Borderline	11	10.0	5	7.7
Unknown	20	18.2	11	16.9
Total	110	------	65	------

Residence

	All		T.E.	
	Number	Expected	Number	Expected
New England	7	6.1	4	3.5
Middle Atlantic	14	19.7	5	11.5
East North Central	26	20.7	15	12.1
West North Central	7	8.6	5	5.0
South Atlantic	20	15.5	15	9.0
East South Central	2	6.9	0	4.0
West South Central	6	10.0	3	5.8
Mountain	6	4.3	5	2.5
Pacific	17	13.2	9	7.6
Unknown	1	------	0	------
Canada	4	------	4	------
	110	105	65	61

Indication for Drug Use

	All		T.E.	
	Number	Percent	Number	Percent
Contraception	79	72.0	49	75.3
Menorrhagia	6	5.5	2	3.3
Endometriosis	5	4.5	4	6.2
Irreg. menses	4	3.6	3	4.5
Premenst. tension	2	1.8	1	1.5
Habit. abortion	1	.9	0	------
Ulcer. colitis	1	.9	1	1.5
Pregnancy test	1	.9	0	------
Dysmenorrhea	1	.9	1	1.5
Unknown	10	9.0	4	6.3
Total	110	------	65	------

Thrombo-Embolic Etiology

	All		T.E.	
	Number	Percent	Number	Percent
Yes	75	68.2	65	100.0
No	30	27.3	0	------
Unknown	5	4.5	0	------
Total	110	------	65	------

Vascular Disease Prior to Drug

	All		T.E.	
	Number	Percent	Number	Percent
Yes	21	19.1	[1] 6	9.2
No	78	70.9	52	80.0
Unknown	11	10.0	7	10.8
Total	110	------	65	------

[1] H.C.V.D.-4; RH. Fev.-1; Varicose Vein Ligat.-1.

Associated Diseases (1)

	All		T.E.	
	Number	Percent	Number	Percent
Peripheral thrombosis	22	20.0	18	27.7
Pelvic thrombosis	36	32.7	31	47.7
Hypertension	11	10.0	4	6.2
Mesenteric thrombosis	5	4.5	3	4.6
Varicose veins	4	3.6	3	4.6
Arteriosclerosis	4	3.6	2	3.1
Diabetes	4	3.6	0	0
Psychiatric	3	2.7	2	3.1
Cancer of breast	2	1.8	1	1.5
Cancer of uterus	2	1.8	0	0

Autopsy

	All		T.E.	
	Number	Percent	Number	Percent
Not done	4	3.6	0	0
Complete	58	52.8	43	66.2
Yes-no report	7	6.4	2	3.1
Partial report	26	23.6	16	24.6
Unknown	15	13.6	4	6.1
Total	110	------	65	------

Medical Examiner's Case

	All		T.E.	
	Number	Percent	Number	Percent
Yes	21	19.1	12	18.4
No	81	73.6	51	78.6
Unknown	8	7.3	2	3.0
Total	110	------	65	------

F.D. 1639

	All		T.E.	
	Number	Percent	Number	Percent
None	87	79.0	50	76.6
Treating physician	9	8.2	6	9.5
Other physician	0	------	0	------
Manufacturer-medical doctor	0	------	0	------
Manufacturer-nonmedical doctor	14	12.8	9	13.9
Total	110	------	65	------

Source of Report

	All		T.E.	
	Number	Percent	Number	Percent
Detail man	30	27.2	23	35.3
Private M.D.	32	29.1	20	30.7
Hospital clinic	5	4.5	3	4.6
Family	3	2.7	2	3.1
FDA	8	7.3	4	6.2
AMA	1	.9	0	0
Medical examiner	6	5.5	5	7.7
Family plan. clinic	8	7.3	4	6.2
Other manufacturers	2	1.8	2	3.1
Investigator	9	8.2	0	0
Unknown	6	5.5	2	3.1
Total	110	------	65	------

Appendix 7

Pilot Study To Test Feasibility of Obtaining Valid Case and Control Data in Idiopathic Thromboembolic Disease

P. E. SARTWELL, M.D., A. T. MASI, M.D., AND J. W. LONG, M.D.

An epidemiologic pilot study was designed and conducted under contract with the Food and Drug Administration at the Johns Hopkins School of Hygiene and Public Health, Department of Epidemiology. A report of the completed pilot study and specific recommendations for the major study follows.

The primary objectives of the pilot study were:

(*a*) To define the problems inherent in testing the hypothesis that oral contraceptives serve as a causative factor in thromboembolic diseases in women not otherwise predisposed to these diseases.

(*b*) To develop the methods and procedures that could best meet the needs of the study performance.

(*c*) To test the validity and practicality of these methods, and to coordinate them for maximum yield of pertinent data.

(*d*) To evaluate the feasibility of the study design in its entirety.

(*e*) To interpret the results of the pilot phase and form conclusions upon which appropriate recommendations can be based for a definitive study if indicated.

Copies of the clinical record abstraction form and interview questionnaire which were developed during the pilot study and tabulations of the results follow.

Design of the Study

A. Final diagnosis of all patients discharged alive from the Johns Hopkins Hospital from 1963–65 were obtained.

B. After careful review, cases of idiopathic thromboembolism in married women were selected.

C. These were controlled with twice the number of carefully matched patients selected from a group whose discharge diagnoses would not remotely be related to thromboembolic disease.

D. Each of the selected patients was extensively interviewed with the objective to obtain in a casual but accurate fashion data regarding oral contraceptives.

Summary and Conclusions

This pilot study has demonstrated that the study design is feasible and can be expected to furnish valid case and control data necessary to achieve an acceptable answer to the hypothesis stated in the study proposal, and to do so within practicable limits of time and cost. It was possible to obtain satisfactory completion of interview questionnaires on all cases and controls selected.

It is desirable that the initial case selection for analysis be somewhat broader than the limited few that would be designated restrictively as "purely idiopathic"; the final case selection should be the result of deliberate and searching appraisal under supervision of the principal investigators. It is desirable to consider the opinions of an advisory group regarding the criteria to be used to define "idiopathic." Such a group should include experts in the fields of cardiovascular disease, peripheral vascular disease, hematology, endocrinology, and metabolic disease.

It is presently considered that if a main study is to be done it should draw cases and controls from approximately 20 large hospitals (the size of Johns Hopkins Hospital or larger), which it is estimated should yield about 200 cases and an equal number of controls. Such a study could possibly be completed in 2 years. The basis for this estimate is that the Johns Hopkins Hospital yielded 10 idiopathic cases, constituting about 1 case per 10,000 discharges for all cases, or 10 percent of the

total discharges that were medically reviewed.

The scope of the main study can and should include the opportunity for the use of epidemiologic methods to add to the knowledge of the natural history of thromboembolic disease, especially its "idiopathic" varieties; and, in so doing, to suggest direction for potentially fruitful research into some of the many clouded aspects of this problem. The experience gained in a study so oriented can serve to good advantage not only the immediate problem but future investigations involving other drugs and the application of similar epidemiologic methods to other possible instances of drug reactions.

Johns Hopkins Hospital—Food and Drug Administration Thromboembolism Pilot Study
(Cooperating Hospital Thromboembolism and Controls Study)

Name _____ (Last) (First) (Middle) S M SEP W D (Marital status—circle)

Maiden name _____ (Last) (First) Age last birthday _____ (On admission)

Race _____ (W, NW) Birthdate _____ (Month, Day, Year) Birthplace _____ (City/County) (State/Country)

*Address on admission _____ (Street) Telephone _____

_____ (City/County) _____ (State/Country)

Next of kin or responsible friend _____ (Last) (First name) (M. I.) Relationship or friend _____ (Specify)

Address _____ (Street) _____ (City/County) _____ (State/Country)

Name of spouse _____ Employer _____ Business telephone _____

Business address _____ (Street) _____ (City/County) _____ (State/Country)

Patient employed: No ____ Yes _____ (Employer) Social security No. _____

Business address _____ Business telephone _____

Hospital _____ (Name) (Code number) Hospital record No. _____

Dates: Adm. _____ Disch. _____ Blue Cross: No ____ Yes _____ (Specify number)

Admission service _____ If transferred to other service _____ (Specify)

Attending physician _____ Telephone _____

Address _____ (Street) _____ (City/County) _____ (State/Country)

At last observation: Living _____ Dead _____ (If dead, complete other side)

Reviewer _____ Date form completed _____

*If moved, enter new address below:

Last known address _____ (Street) Date _____ (Month, Day, Year)

_____ (City/County) _____ (State/Country)

Hospital code No. _____ Patient series No. _____

Religion: Not specified Catholic (Circle) Jewish Protestant Other (Specify)

Welfare: No _____ Yes _____ (Specify No.)

Pay status: Private Semiprivate (Circle) Ward/staff

Discharge diagnoses: _____ (Primary)

_____ (Secondary)

_____

_____

_____

_____

Date of death _____ (Month, Day, Year)

Place of death _____ (Hospital name or other) _____ (City/County) _____ (State/Country)

Cause of death _____

If autopsied, No. _____ Death certificate No. _____

Attending physician _____ Telephone _____

_____ (Street) _____ (City/County) _____ (State/Country)

MASTER CODE SHEET 1

Detailed Birthplace or Residence Code

Other than United States

00 Not specified
01 Far and Near East
02 Africa
03 Russia/Slavic/Balkan
04 Greece/Italy/France/Spain/Portugal
05 Scandinavia/Germany/other continents
06 England/Ireland/Scotland/Australia/New Zealand
07 South and Central America
08 Mexico/Puerto Rico
09 Canada

United States

New England:
11 Maine
12 New Hampshire
13 Vermont
14 Massachusetts
15 Rhode Island
16 Connecticut

Middle Atlantic:
21 New York
22 New Jersey
23 Pennsylvania

East North Central:
31 Ohio
32 Indiana
33 Illinois
34 Michigan
35 Wisconsin

West North Central:
41 Minnesota
42 Iowa
43 Missouri
44 North Dakota
45 South Dakota
46 Nebraska
47 Kansas

South Atlantic:
51 Delaware
52 Maryland
53 District of Columbia
54 Virginia
55 West Virginia
56 North Carolina
57 South Carolina
58 Georgia
59 Florida

East South Central:
61 Kentucky
62 Tennessee
63 Alabama
64 Mississippi

West South Central:
71 Arkansas
72 Louisiana
73 Oklahoma
74 Texas

Mountain:
81 Montana
82 Idaho
83 Wyoming
84 Colorado
85 New Mexico
86 Arizona
87 Utah
88 Nevada

Pacific:
91 Washington
92 Oregon
93 California
94 Alaska
95 Hawaii

MASTER CODE SHEET 2

Centimeter-Inch Conversion

Centimeter	*Inch*	*Centimeter*	*Inch*	*Centimeter*	*Inch*
150	59	164	65	178	70
151	59	165	65	179	70
152	60	166	65	180	71
153	60	167	66	181	71
154	61	168	66	182	72
155	61	169	67	183	72
156	61	170	67	184	72
157	62	171	67	185	73
158	62	172	68	186	73
159	63	173	68	187	74
160	63	174	69	188	74
161	63	175	69	189	74
162	64	176	69	190	75
163	64	177	70		

MASTER CODE SHEET 3

Kilogram-Pound Conversion

Kilogram	*Pound*	*Kilogram*	*Pound*	*Kilogram*	*Pound*
40	088	74	163	108	238
41	090	75	165	109	240
42	093	76	168	110	243
43	095	77	170	111	245
44	097	78	172	112	247
45	099	79	174	113	249
46	101	80	176	114	251
47	104	81	179	115	254
48	106	82	181	116	256
49	108	83	183	117	258
50	110	84	185	118	260
51	112	85	187	119	262
52	115	86	190	120	265
53	117	87	192	121	267
54	119	88	194	122	269
55	121	89	196	123	271
56	123	90	198	124	273
57	126	91	201	125	276
58	128	92	203	126	278
59	130	93	205	127	280
60	132	94	207	128	282
61	134	95	209	129	284
62	137	96	212	130	287
63	139	97	214	131	289
64	141	98	216	132	291
65	143	99	218	133	293
66	146	100	220	134	295
67	148	101	223	135	298
68	150	102	225	136	300
69	152	103	227	137	302
70	154	104	229	138	304
71	157	105	231	139	306
72	159	106	234	140	309
73	161	107	236		

Date: _____

Name _____
Last First Middle

Time: Start _____ Finish _____

Hospital record No. _____

Reviewer _____

Hospital name _____

Col.
1–3 Hospital code number
_____ _____ _____
1 2 3

4–5 Patient's series number in hospital
_____ _____
4 5

6–7 Month of onset
_____ _____
6 7

8 Year of onset
0—1960
1—1961
2—1962
3—1963
4—1964
5—1965

9 Hospital pay status
0—N.S.
1—Private specified
2—Semiprivate specified
3—Attending service
4—Ward or resident service

10 Discharge status
0—N.S.
1—Alive
2—Deceased—no autopsy
3—Deceased—autopsy

11–12 Age on admission (last birthday)
_____ _____
11 12

13 Race or ethnic groups
0—N.S.
1—White
2—Negro
3—American Indian
4—Puerto Rican
5—Asian (Oriental)
6—Polynesian, Hawaiian
7—Other _____ (specify)

14 Marital status
0—N.S.
1—Single
2—Married
3—Separated
4—Divorced
5—Widowed

15 Religion
0—N.S.
1—Catholic
2—Jewish
3—Protestant
4—Other _____ (specify)

16–17 Birthplace (code as per master code sheet No. 1)
_____ _____
16 17

18 Residence at time of onset
0—N.S.
1—Baltimore City
2—Maryland, other
3—U.S.A., other
4—Latin America
5—Russia/Slavic/Balkan
6—Mediterranean/France/Romance
7—Scandinavia and other Europe
8—Commonwealth/Ireland
9—Orient/Africa

19 Occupation
0—N.S.
1—Housewife
2—Secretary/office asst.
3—Store clerk/saleswoman
4—Teacher/supervisor/professional
5—Nurse/dental assistant/laboratory technician
6—Beautician/waitress
7—Seamstress/laundry/cleaner-presser/domestic
8—Light machine operator (other than 7)
9—Other _____ (specify)

20 Number of pregnancies
0—N.S.
1—1 pregnancy
2—2 pregnancies
3—3 pregnancies
4—4 pregnancies
5—5 pregnancies
6—6 pregnancies
7—7 pregnancies
8—8 or more _____ (specify)
9—Never pregnant

21 Pregnancies aborted/miscarried (less than 6 months)
0—N.S.
1—Abortion/miscarriage
2—Abortions/miscarriages
3—Abortions/miscarriages
4—Abortions/miscarriages
5—Abortions/miscarriages
6—Abortions/miscarriages
7—Abortions/miscarriages
8—Or more _____ (specify)
9—Never aborted/miscarried

22 Delivery of stillborn or living infant, 6+ months gestation
0—N.S.
1—1 delivery
2—2 deliveries
3—3 deliveries
4—4 deliveries
5—5 deliveries
6—6 deliveries
7—7 deliveries
8—8 or more _____ (specify)
9—Never delivered

23 Living children
0—N.S.
1—1 living child
2—2 living children
3—3 living children
4—4 living children
5—5 living children
6—6 living children
7—7 living children
8—8 or more _____ (specify)
9—None

24 Interval from last delivery to onset
0—N.S. or D.N.A.
1—Pregnant, undelivered
2—0 to <3 months
3—3 to <6 months
4—6 to <12 months
5—1 to <2 years
6—2 to <3 years
7—3 to <4 years
8—4 to <5 years
9—5+ years

25 History of allergy
0—N.S.
1—Negative
2—Skin (eczema, angio-edema, urticaria)
3—Respiratory (Al. Rhin. Asthma, Al. Bronch.)
4—Drug (include biologicals)
5—2+3
6—2+4
7—3+4

Col.

25 8—2+3+4
9—If none of the above, but other _____ (specify)

26 History of minor conn. tissue disease
0—N.S.
1—Negative
2—Arthralgia, synovitis capsulitis
3—Bursitis, tendonitis, epicondylitis
4—Myalgia, myositis, fibrositis
5—2+3
6—2+4
7—3+4
8—2+3+4
9—If none of the above, but other _____ (specify)

27 History of previous T–E disease
0—N.S.
1—Negative
2—Pulmonary embolism/infarction
3—Other arterial (CNS, coronary, etc.)
4—Venous
5—2+3
6—2+4
7—3+4
8—2+3+4
9—If none of the above, but other _____ (specify)

28 Non-thrombo-embolic vascular disease
0—N.S.
1—Negative
2—Hypertensive vascular disease
3—Peripheral arterial V.D. (C.T.D., diabetic, etc.)
4—Peripheral venous V.D. (varicosities, hemorrhoids, etc.)
5—2+3
6—2+4
7—3+4
8—2+3+4
9—If none of the above, but other _____ (specify)

29 Pelvic or vascular surgery
0—N.S.
1—Negative
2—Surgery causing infertility (tubal lig., oophorect., hysterect)
3—Other pelvic surgery

Col.

29 4—Varicose vein procedure/hemorrhoidectomy, other vascular
5—2+3
6—2+4
7—3+4
8—2+3+4
9—If none of the above, but other _____ (specify)

30 Past use of cigarettes (code maximum possible)
0—N.S.
1—Never smoked
2—Smoked once in a while
3—Less than ½ pack a day
4—½ to < 1 pack a day
5—1 to < 2 packs a day
2—2+ packs a day

31 Current use of cigarettes (code maximum possible)
0—N.S.
1—Never smokes
2—Smokes once in a while
3—Less than ½ pack a day
4—½ to < 1 pack a day
5—1 to < 2 packs a day
6—2+ packs a day

32 Current use of alcohol
0—N.S.
1—Never used
2—Occasional drink
3—1 or 2 beers/cocktail, whisky/wine a day—most days
4—1 or 2 beers/cocktail, whisky/wine a day—almost every day
5—3 drinks a day—frequent
6—3 drinks a day—constant
7—4+ drinks a day—habitual

33 Hormone intake within 2 months of onset
0—N.S.
1—Negative
2—Insulin/thyroid
3—Steroids/acth./estrogen
4—Oral contraceptives (specify trade name)
5—2+3
6—2+4
7—3+4
8—2+3+4
9—If none of the above, but other _____ (specify)

34 Other drug intake within 2 months of onset
0—N.S.
1—Negative
2—Sedatives/tranquilizers
3—Anorectics/diuretics
4—Antibiotics plus chemo RX

Col.

34 5—2+3
6—2+4
7—3+4
8—2+3+4
9—If none of the above, but other _____ (specify)

35 Postural influence within 1 month of onset
0—N.S.
1—Negative
2—Prolonged bed rest
3—Prolonged sitting/stooping/standing
4—Limb splint, cast/strap/brace
5—Use of crutches
6—Use of traction
7—Strenuous calisthenics
8—Other than above_____ (specify)
9—Combinations _____ (specify)

36 Infection within 1 month of onset
0—N.S.
1—Negative
2—Local infection at thrombus site
3—Organ/system infection
4—Generalized infection (bact., viral, ricket.)
5—2+3
6—2+4
7—3+4
8—2+3+4
9—If 3 or 4 positive code col. 37

37 Infection specified
0—N.S.
1—CNS
2—Respiratory tract
3—G–I tract
4—Hepatic/biliary tract
5—G–U tract
6—Skin
7—Viremia/bacter./septicem.
8—Other _____ (specify)
9—Combinations _____ (specify)

38 Hemodynamic/fluid imbalance within 1 month of onset
0—N.S.
1—Negative
2—Acute blood loss
3—Hypotension/syncope shock
4—Dehydration
5—2+3
6—2+4
7—3+4
8—2+3+4

Col.
38 9—If none of the above but other _____ (specify)
39 Minor trauma within 1 month of onset
0—N.S.
1—Negative
2—Thermal (burns, chill)
3—Contusion/strain/sprain (no skin break)
4—Laceration/abrasion/bite (skin broken)
5—2+3
6—2+4
7—3+4
8—2+3+4
9—If none of the above but other _____ (specify)
40 Minor surgery within 1 month of onset
0—N.S.
1—Negative
2—Excisions/extractions
3—Instrumentation
4—Cauterization
5—2+3
6—2+4
7—3+4
8—2+3+4
9—If none of the above but other _____ (specify)
41 Non-T-E CNS disease
0—N.S.
1—Negative
2—Intervertebral disc. syndromes
3—Epilepsy/convulsion
4—Stupor/coma _____ (specify cause)
5
6
7
8
9—Combinations _____ (specify)
42 Predisposing heart disease
0—N.S.
1—Negative
2—Congenital
3—Rheumatic
4—Primary myocardopathy
5—Coronary art. H.D.
6—Luetic H.D.
7—Conn. tissue H.D.
8—Other _____ (specify)
9—Combinations _____ (specify)
43 Precipitating cardiac events within 1 month of onset
0—N.S.

Col.
43 1—Negative
2—Arrythmias, significant
3—Decompensation
4—Recent myocardial inj.
5—2+3
6—2+4
7—3+4
8—2+3+4
9—If none of the above but other _____ (specify)
44 Major conn. tissue dis.
0—N.S.
1—Negative
2—Rheumatoid arthritis
3—S.L.E.
4—P-A. nod.
5—Scleroderma
6—Dermatomyositis
7
8
9—Combinations _____ (specify)
45 Metabolic disease
0—N.S.
1—Negative
2—Obesity, mild
3—Obesity, moderate
4—Obesity, severe
5—Diabetes, mild
6—Diabetes, moderate
7—Diabetes, severe
8—Gout
9—Combinations _____ (specify)
46 Hematologic disorders
0—N.S.
1—Negative
2—RBC abnormalities, significant (anemias, polycythemia)
3—WBC abnormalities, significant (leukemia, lymphoma)
4—Bleeding/coagulation disorders _____ (specify)
5—2+3
6—2+4
7—3+4
8—2+3+4
9—If none of the above but other _____ (specify)
47 Pelvic disease
0—N.S.
1—Negative
2—Ovarian Cyst(s)
3—Endometriosis
4—Fibromyomata
5—2+3
6—2+4
7—3+4

Col.
47 8—2+3+4
9—If none of the above but other _____ (specify)
48 Thyroid disease/liver disease/malignancy
0—N.S.
1—Negative
2—Hypothyroidism or Hyperthyroidism _____ (specify)
3—Liver disease_____ (specify)
4—Malignancy _____ (specify)
5—2+3
6—2+4
7—3+4
8—2+3+4
9—If none of the above but other _____ (specify)
49 Postop/postpartum/major trauma within 1 month of onset
0—N.S.
1—Negative
2—Postop. (major surg.)
3—Postpartum (pregnancy related)
4—Major trauma
6—2+4
5—2+3
7—3+4
8—2+3+4
9—If none of the above but other _____ (specify)
50 Interval between delivery, operation, or trauma and onset
0—N.S.
1—Less than 7 days
2—7–13 days included
3—14–20 days included
4—21–27 days included
5—1–<2 months included
6—2–<3 months included
7—3–<12 months included
8—1+ years_____ (specify)
51–52 Height in inches (see Master Code Sheet Number 2)
51 52
If N.S. use 00
53–55 Weight in pounds (see Master Code Sheet Number 3 for kgm. to lb. conv.)
53 54 55
If N.S. use 000

Col.
56 B.P. categories at time of admission
0—N.S.
1—Normal <140/90
2—Systolic 140–159
Diastolic <95
3—Systolic 160+
Diastolic <95
4—Systolic <160
Diastolic 95+
5—Systolic 160+
Diastolic 95+
LABORATORY (Cols. 57–67)
57 Admission
Hematocrit or Hemoglobin (Code one test only)
0—Not stated
Hematocrit:
1—Below 25-Spec_____
2—25–29
3—30–34
4—35–39
5—40+ Spec_____
Hemoglobin:
6—Below 7.5 Spec_____
7—7.5–9.9
8—10.0–12.4
9—12.5+ Spec_____
58 Platelet count (Code one value only)
0—Not stated
Counts
1—Less than 50,000
Specify _____
2—50–99,999
3—100–199,999
4—200–299,999
5—300–399,999
6—400,000+ _____
(specify)
Smears:
7—Low on smear
8—Normal on smear
9—Increased on smear
59 Blood test for syphilis
0—N.S.
1—Reagin—type test negative
2—Reagin—type test positive, T.P.I. or F.T.A. negative
3—Reagin—type test positive, T.P.I. or F.T.A. positive
4—Reagin—type test positive, no further tests done
60 Cholesterol
0—N.S.
1—Less than 160
2—160 to 199
3—200–239
4—240–279
5—280–319
6—320–359

Col.
60 7—360–399
8—400–439
9—More than 440_____
(specify)
61 Bilirubin total
0—Not done
1—<1.0
2—1 to 1.4
3—1.5 to 1.9
4—2.0 to 2.4
5—2.5 to 2.9
6—3+ _____
(specify)
62 Ceph. Floc.
0—Not done
1—1+
2—2+
3—3+
4—4+
9—Negative
63 Transaminase
0—Not done
1—<20
2—20 to 34
3—35 to 49
4—50 to 64
5—65 to 79
6—80+ _____
(specify)
64 LDH
0—Not done
1—<20
2—200–399
3—400–599
4—600–799
5—800–999
6—1,000–1,199
7—1,200–1,399
8—1,400–1,599
9—1,600+ _____
(specify)
65 Blood type
0—N.S.
1—O negative
2—A negative
3—B negative
4—AB negative
5—O positive
6—A positive
7—B positive
8—AB positive
66 Chest X-ray examinations
0—Not done
1—Negative
2—Positive (Specify)
_____
_____
67 Electrocardiogram
0—Not done
1—Negative
2—Positive (specify)
_____
_____

Col.
Case categories (cols. 68–74)
(if controls, skip to cols. (74–75))
68 Idiopathic arterial thrombosis/embolism/hemorrhage
0—Nonidiopathic
1—Cerebral hemorrhage
2—Cerebral thrombosis/embolism _____
(specify)
3—Other CNS thrombosis/embolism _____
(specify)
4—Retinal art. thromb/em.
5—Coronary art. thromb/em.
6—Pulmonary art. thromb/em.
7—Mesenteric art. thromb/em.
8—Extremity art. thromb/em.
9—Other _____
(specify)
If embolism
_____
(specify origin)
69 Idiopathic venous thrombosis
0—Nonidiopathic
1—Cerebral vein
2—Intracranial venous sinus
3—Retinal vein
4—Vena cava
5—Pelvic vein
6—Upper extremity vein
7—Lower extremity vein, superficial
8—Lower extremity vein, deep
9—Other or combination
_____
(specify)
70 Pulmonary embolism/infarction—clinical presentation
0—Negative
1—Presenting and idio.
2—Presenting and embolic from pulmonary art.
3—Presenting and embolic from heart
4—Presenting and embolic from idiopath. ven. throm.
5—Presenting and embolic from nonidio. ven. thromb.
6—Complicating plus No. 2
7—Complicating plus No. 3
8—Complicating plus No. 4
9—Complicating plus No. 5

80

Col.
71 Nonidiopathic arterial thromb./embolism/hemorr.
0—Idiopathic
1—Cerebral hemorrhage
2—Cerebral thrombosis/embolism ---------- (specify)
3—Other CNS thrombosis embolism ---------- (specify)
4—Retinal art. throm/em
5—Coronary art. throm/em
6—Pulmonary art. throm/em
7—Mesenteric art. throm/em
8—Extremity art throm/em
9—Other or combinations ---------- (specify)

72 Nonidiopathic venous thrombosis
0—Idiopathic
1—Cerebral vein
2—Intracranial venous sinus
3—Retinal vein
4—Vena cava
5—Pelvic vein
6—Upper extremity vein

Col.
72 7—Lower extremity vein, superficial
8—Lower extremity vein, deep
9—Other or combinations ---------- (specify)

73 Thromboembolic episodes (idiopath. plus nonidio.)
0—Does not apply
Idiopathic
1—One episode, one site
2—One episode, multiple sites
3—Recurrent, one site
4—Recurrent, multiple sites
Nonidiopathic
5—One episode, one site
6—One episode, multiple sites
7—Recurrent, one site
8—Recurrent, multiple sites
9—Indeterminate

74 Thromboembolic disease category

Col.
74 0—Indeterminate
Idiopathic
1—Arterial
2—Venous
3—Combination
Nonidiopathic
4—Arterial
5—Venous
6—Combinations

Control categories (cols. 75–76) individual diagnoses to be specified on a master list

00–09 Operations for acute conditions
10–19 Acute self-limited URI's
20–29 Acute pneumonitis and bronchitis
30–39 Acute enteritis
40–49 Other acute G.I. disorder
50–59 Sprains and simple fracture
60–69 Head injuries without skull fracture
70–79
80–89
90–99

Column	Comments

COVER SHEET

Date of Interview _____

Time started _____

Time terminated _____

Dates of return calls _____

Respondent's name _____

Address _____

Phone No. _____

Date of Hospitalization _____

Hospital Record No. _____

Series No. _____

Letterhead _____

_____

Interviewer

Interview Questionnaire
5-31-66

INTRODUCTION TO RESPONDENT

Hello, Mrs. Smith, my name is Miss _____ from Johns Hopkins. You will recall that you received a letter from us last week regarding this interview, and we arranged this time in our telephone conversation. We appreciate your allowing us a few minutes of your time to ask you some questions.

Before we start, however, let me explain a little of what we are studying. Actually, we have two purposes in mind: First, we want to learn more about the kinds of medications women are taking, and secondly, we would like to see how the general health of married couples influences their family planning. As you know, new medicines are being introduced all the time, and we would like to learn how some of these have been used over the past 3 years.

Your name was chosen from a list of all women who were hospitalized at Johns Hopkins Hospital since January 1963. We will be talking to a number of women throughout the Baltimore area, and afterward all the information we receive will be put into computers. This way, we will know the results of the study, but no individual can be singled out nor will any names be known. We'd like to again assure you that all the information you give us will be absolutely confidential to this office, and that your name and identity will not at any time be revealed.

Do you have any questions?

Fine. Let's then, start with a few general questions about your health.

Page 1

DRAFT QUESTIONNAIRE

Our records show that you were hospitalized at Johns Hopkins Hospital in _____ (month _____ and year)

1. Before your hospitalization, have you ever had any of the chronic conditions listed on this card which have bothered you over a period of several months? (Show Card No. 1)

   Yes _____ No _____

   Which conditions are they?

   Conditions _____

   _____

   _____

2. Have you found it necessary to take medicines of any kind over long periods of time in the past?

   Yes _____ No _____

   What kind of medicines were these?

   Medications used _____

   _____

   _____

In this study we are mainly interested in certain groups of medicines. Some of these can be bought in the drugstore without a prescription; others require a prescription from your doctor or can be given to you at a clinic.

We are interested primarily in the period of your hospitalization and about 2 years before, and we would like your answers to the next questions to relate to that time. This is just to give us a time period to look at, and these questions don't necessarily have to do with any treatment or medication that you required as part of your hospitalization.

Page 2

3. During the 2 years before and leading up to the time of your hospitalization, were you using any medicine for relieving pain, such as for headaches, arthritis, rheumatism, or similar conditions?

Yes _____ No _____ (skip to Q–4).

(INTERVIEWER: Use Table 1 for multiple medications.)

(*a*) For how long a time before your hospitalization had you been taking this medicine?

Irregularly _____
Less than 1 week _____
1–2 weeks _____
2–3 weeks _____
3–4 weeks _____
1–6 months _____
6 months–1 year _____
1–2 years _____
Over 2 years _____
Don't remember _____

(*b*) Do you recall the name of the medicine(s)?

Yes _____ No _____

(*c*) Why were you taking this medicine?

(*d*) Did you obtain this medicine:

With a prescription.
Without a prescription (skip to *f*).
At a clinic (skip to *f*).

TABLE 1

Time prior to hospitalization (*a*)	Medication (*b*)	Indications (*c*)	Rx/clinic (*d*)

Page 3

(*e*) Do you recall the name of the pharmacy where you bought this medicine?

Yes _____ No _____

(*f*) Do you recall the name of the doctor (or clinic) that prescribed this medicine?

Yes _____ No _____

(*g*) Did you stop taking this medicine for any reason?

Yes _____ No _____

(*h*) Was another medicine substituted for the discontinued one?

Yes _____ No _____

TABLE 1

Name of pharmacy (*e*)	Doctor or clinic prescribing (*f*)	Reason for stopping (*g*)	Medication substituted (*h*)

Page 4

4. During the 2 years before and leading up to the time of your hospitalization, were you using any kind of tranquilizers, medicines to calm your nerves, or to help you sleep?

Yes _____ No _____ (skip to Q–5).

(INTERVIEWER: Use table 2 for multiple medications.)

(*a*) For how long a time before your hospitalization had you been taking this medicine?

Irregularly _____

Less than 1 week _____

1–2 weeks _____

2–3 weeks _____

3–4 weeks _____

1–6 months _____

6 months–1 year _____

1–2 years _____

Over 2 years _____

Don't remember _____

(*b*) Do you recall the name of the medicine(s)?

Yes _____ No. _____

(*c*) Why were you taking this medicine?

(*d*) Did you obtain this medicine:

With a prescription.

Without a prescription (skip to *f*).

At a clinic (skip to *f*).

TABLE 2

Time prior to hospitalization (*a*)	Medication (*b*)	Indications (*c*)	Rx/clinic (*d*)

Page 5

(*e*) Do you recall the name of the pharmacy where you bought this medicine?

Yes_____ No_____

(*f*) Do you recall the name of the doctor (or clinic) that prescribed this medicine?

Yes_____ No_____

(*g*) Did you stop taking this medicine for any reason?

Yes_____ No_____ (skip to Q–5).

(*h*) Was another medicine substituted for the discontinued one?

Yes_____ No_____

TABLE 2

Name of pharmacy (*e*)	Doctor or clinic prescribing (*f*)	Reason for stopping (*g*)	Medication substituted (*h*)

Page 6

5. What is your present weight?

_____ lbs.

6. What is the most you have ever weighed when you weren't pregnant?

_____ lbs.

When was this?

_____ (year).

7. What is the least you have ever weighed since you were 21 years old?

_____ lbs.

When was this?

_____ (year).

8. Did you follow a plan to lose weight within 6 months of your hospitalization?

Yes _____ No _____ (skip to Q–10).

(*a*) When was this? (INTERVIEWER: Use table 3).

(*b*) What method did you use? (SHOW CARD No. 2).

(*c*) How many pounds did you lose?

(*d*) How long did it take you?

TABLE 3

	When (*a*) (*Mo.*) (*Yr.*)	Method (*b*)	Pounds lost (*c*)	Time period (months) (*d*)
1st time				
2d time				
3d time				

(INTERVIEWER: If R. indicates having used methods 4, 5, 6, and 7 from card, within time period, ask question 9. If not, SKIP to question 10.)

Page 7

9. If you followed a plan that included medicine to reduce your appetite or to get rid of water in your body during the 6 months before your hospitalization, do you recall the name of the medicine?

Yes _____ No _____

(INTERVIEWER: Use table 4 for multiple medications.)

(*a*) For how long a time before your hospitalization had you been taking this medicine?

Irregularly _____ 1 to 6 months _____

Less than 1 week _____ 6 months-1 year _____

1 to 2 weeks _____ 1 to 2 years _____

2 to 3 weeks _____ Over 2 years _____

3 to 4 weeks _____ Don't remember _____

(*b*) Name of medicine(s)?

(*c*) Why were you taking this medicine?

(*d*) Did you obtain this medicine:

With a prescription.

Without a prescription (skip to *f*).

At a clinic (skip to *f*).

TABLE 4

Time prior to hospitalization (*a*)	Medication (*b*)	Indications (*c*)	Rx/clinic (*d*)

Page 8

(*e*) Do you recall the name of the pharmacy where you bought this medicine?

Yes _____ No _____

(*f*) Do you recall the name of the doctor (or clinic) that prescribed this medicine?

Yes _____ No _____

(*g*) Did you stop taking this medicine for any reason?

Yes _____ No _____ (skip to Q–10).

(*h*) Was another medicine substituted for the discontinued one?

Yes _____ No _____

TABLE 4

Name of pharmacy (*e*)	Doctor or clinic prescribing (*f*)	Reason for stopping (*g*)	Medication substituted (*h*)

Page 9

10. During the two years before and leading up to the time of your hospitalization were you using any kind of medicine for high blood pressure or for a heart condition?

Yes _____ No _____

(INTERVIEWER: Use table 5 for multiple medications)

(*a*) For how long a time before your hospitalization had you been taking this medicine?

Irregularly _____ 1–6 months _____

Less than 1 week _____ 6 months–1 year _____

1–2 weeks _____ 1–2 years _____

2–3 weeks _____ Over 2 years _____

3–4 weeks _____ Don't remember _____

(*b*) Do you recall the name of the medicine(s)?

Yes _____ No _____

(*c*) Why were you taking this medicine?

(*d*) Did you obtain this medicine:

With a prescription.

Without a prescription (skip to f).

At a clinic (skip to f).

TABLE 5

Time prior to hospitalization (*a*)	Medication (*b*)	Indications (*c*)	Rx/clinic (*d*)

Page 10

(*e*) Do you recall the name of the pharmacy where you bought this medicine?

Yes _____ No _____

(*f*) Do you recall the name of the doctor (or clinic) that prescribed this medicine?

Yes _____ No _____

(*g*) Did you stop taking this medicine for any reason?

Yes _____ No _____

(*h*) Was another medicine substituted for the discontinued one?

Yes _____ No _____

TABLE 5

Name of pharmacy (*e*)	Doctor or clinic prescribing (*f*)	Reason for stopping (*g*)	Medication substituted (*h*)

Page 11

11. During the two years before and leading up to the time of your hospitalization, were you using any of the following hormones which I will mention?

Yes _____ No. _____ (skip to Q–12).

(INTERVIEWER: Use table 6 for multiple medications.)

(*a*) For how long a time before your hospitalization had you been taking this medicine?

Irregularly _____

Less than 1 week _____

1–2 weeks _____

2–3 weeks _____

3–4 weeks _____

1–6 months _____

6 months–1 year _____

1–2 years _____

Over 2 years _____

Don't remember _____

(*b*) Do you recall the brand name of the medication?

Yes _____ No _____

(*c*) Why were you taking this medication?

(*d*) Did you obtain this medicine:

With a prescription.
Without a prescription (skip to f).
At a clinic (skip to f).

TABLE 6

Time prior to hospitalization (a)	Medication (b)	Indications (c)	Rx/clinic (d)
	Thyroid. Cortisone or related. Insulin. Tablets for diabetes. Female hormones (Estrogens and Progestins).[1] If yes, show card for identification.	[2]	

[1] (INTERVIEWER: SHOW CARD #4 of O.C. tablets for positive identification.)
[2] (SHOW CARD #3 of indications for use.)

Page 12

(*e*) Do you recall the name of the pharmacy where you bought this medicine?

Yes_____ No_____

(*f*) Do you recall the name of the doctor (or clinic) that prescribed this medicine?

Yes_____ No_____

(*g*) Did you stop taking this medicine for any reason?

Yes_____ No_____ (skip to Q–12).

(*h*) Was another medicine substituted for the discontinued one?

Yes_____ No_____

TABLE 6

Name of pharmacy (*e*)	Doctor or clinic prescribing (*f*)	Reason for stopping (*g*)	Medication substituted (*h*)

Page 13

Now I would like to ask you some questions about your health and your husband's health since you have been married.

Our records show that you were married at the time of your hospitalization at Johns Hopkins Hospital in _____ (Month and year). Are you still married?

Yes _____ No _____

12. Had you ever been married before?

Yes _____ No _____ (skip to Q–14).

How many times had you been married before?

Number of previous marriages _____

When did your first marriage begin?

Year of first marriage _____

13. When did the marriage at the time of your hospitalization begin?

Year of marriage _____

14. When were you born?

Date of birth _____

15. How many pregnancies have you had altogether?

Number of pregnancies _____

(IF NONE) Did you and your husband plan to have any children?

Yes _____ No _____ (skip to Q–19).

16. How many of those were miscarriages?

Number of miscarriages _____

Page 14

Now we would like some information about *each* of your pregnancies, starting with the first.

17. (a) Did your first (2d, 3d, etc.) pregnancy end in a live birth, or did the baby die before delivery?

(b) About how long were you pregnant?

(c) When was the baby born? or When did the pregnancy end?

(d) Is that child now living here in this household?

	1st	2d	3d	4th	5th	6th	7th
a. Live-birth, miscarriage, still-birth.							
b. Length of pregnancy.							
c. Date of termination month and year.							
d. Living here?							

Total number of live births? _____

Total number of children in this household? _____

18. Did you and your husband plan to have any more children at the time of your hospitalization?

19. Was your husband in good health at the time of your marriage?

Yes _____ No _____ (skip to Q–21).

20. Has his health remained good?

Yes _____ No _____

21. What serious illnesses has your husband had within the year that you went to the hospital? That is, illnesses which caused him to seek medical attention repeatedly or go to a hospital?

HOSPITALIZATION

Illness	Year	Yes	No	Name of hospital

Page 15

22. Were *you* in good health at the time of your marriage?

Yes _____ No _____ (skip to Q–24).

23. Has your health remained good?

Yes _____ No _____

24. What serious illnesses have you had since you were married? That is, illnesses which caused you to seek medical attention repeatedly or go to a hospital? You don't have to repeat any hospitalization for pregnancies.

HOSPITALIZATION

Illnesses	Year	Yes	No	Name of hospital

25. Have you or your husband felt that any of these illnesses were serious enough to postpone having children or to prevent pregnancy at the time?

Yes _____ No _____

26. Have you ever had an operation that made it impossible to have any more children?

Yes _____ No _____

When was this?

Date _____

What kind of operation was it?

Kind _____

27. Has your husband ever had an operation or injury that made it impossible to have any more children?

Yes _____ No _____

When was this?

Date _____

Page 16

28. Sometimes for health reasons and sometimes for economic reasons, married couples will decide to space their children and plan their pregnancies to their best advantage. Have you or your husband used any method to prevent pregnancy in the past?

Yes _____ No _____ (skip to Q-31).

29. What type of method(s) of birth control have you used within the two years before your hospitalization? (SHOW CARD No. 5) Just read me the letter which corresponds to the method if you like?

(INTERVIEWER: If R. does *not* indicate O.C., use Table 7)
(NOTE: If R. does *not* indicate O.C. or appears vague and indefinite, ask:)
Have you *ever* used birth control pills for family planning? (If *NO*, skip to Q-31).

TABLE 7

Methods of contraception indicated	
A. _____	G. _____
B. _____	H. _____
C. _____	I. _____
D. _____	J. _____
E. _____	K. _____
F. _____	L. _____

*(INTERVIEWER: If R. *does* indicate O.C. use Table 8)

(*a*) When did you begin using this form of birth control?
(PROBE for exact year and month.)

(*b*) When did you discontinue this type of method?
(PROBE for exact year and month.)

(*c*) Do you recall the brand name?
(IF NOT) Do you remember if the tablets looked like any of these? (SHOW CARD No. 4)

(*d*) Why did you discontinue its use?

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TABLE 8

O.C. Use—Time Periods Used

	1st time	2d time	3d time	4th time
(a) When started				
(b) When stopped				
(c) Brand name				
(d) Reason stopped				

30. Did you consult your doctor or go to a clinic for advice on birth control pills?

Yes _____ No _____

Do you recall the name of the Doctor or clinic that prescribed this medicine?

Name _____

_____

31. About how many cigarettes a day were you smoking just before your hospitalization:

Occasionally.

Less than ½ pack.

½–1 pack.

1–2 packs.

Nonsmoker.

32. Were you working just before your hospitalization?

Yes _____ No _____

What kind of work were you doing?

Type _____

33. Was your husband working at that time?

Yes _____ No _____

What kind of work was he doing?

Type _____

Page 18

34. What was the highest grade of school you completed?

Elementary 1 2 3 4 5 6 7 8
High School 1 2 3 4
College 1 2 3 4 5+

35. What was the highest grade of school your husband completed?

Elementary 1 2 3 4 5 6 7 8
High School 1 2 3 4
College 1 2 3 4 5+

36. Is your religious preference Protestant, Catholic, Jewish, or what?

Religion _____

37. Is your husband's religious preference Protestant, Catholic, Jewish, or what?

Religion _____

38. What was your total *family* income at the time of your hospitalization? (SHOW CARD No. 6.) Just tell me the letter which corresponds to the income if you like.

Income _____

39. How much of the total family income was earned by your husband?

Income _____

Page 19

INTERVIEWER—FILL IN

Respondent is: White _____ Nonwhite _____

Respondent's cooperation was:

Very good _____

Good _____

Fair _____

Poor _____

NOTE ANYTHING ELSE ESSENTIAL TO THE INTERPRETATION AND UNDERSTANDING OF THIS INTERVIEW:

CARD #1

1. Asthma.
2. Any allergy.
3. Tuberculosis.
4. Chronic bronchitis or lung infections.
5. Emphysema.
6. Rheumatic fever.
7. Hardening of the arteries.
8. High blood pressure.
9. Heart trouble of any kind.
10. Stroke.
11. Trouble with varicose veins.
12. Hemorrhoids or piles.
13. Gall bladder or liver trouble.
14. Stomach ulcer.
15. Chronic intestinal or colon trouble.
16. Kidney stones or kidney trouble.
17. Arthritis or rheumatism.
18. Menstrual difficulties.
19. Cyst on ovary or tumor of womb.
20. Diabetes.
21. Thyroid trouble or goiter.
22. Epilepsy or convulsions.
23. Mental or nervous trouble.
24. Serious anemia or blood disorders of any kind.
25. Chronic or repeated infections.
26. Tumor or cancer.
27. Repeated miscarriages.
28. Unable to become pregnant.
29. Paralysis of any kind.
30. Birth defects.
31. Repeated back or spine trouble.

CARD #2

1. Reducing diet (cutting down on sweets and starches; counting calories).
2. Reducing diet and exercising.
3. Cutting down on liquids (along with dieting and/or exercising).
4. Also took medicine to keep from getting hungry (bought at drugstore, no prescription).
5. Medicine from doctor (or clinic) to control appetite.
6. Medicine (pills or shots) to remove water from body.
7. Thyroid pills.

CARD #3

1. To help regulate menstrual periods (make them come on time).
2. To cut down on heavy flow (make menstrual flow lighter).
3. To prevent painful cramps with period (make period more comfortable).
4. To prevent headaches, nervousness and bloating before periods.
5. To prevent pain in between periods.
6. To improve chances of becoming pregnant (to help have babies).
7. To treat condition called endometriosis.

CARD #4

Enovid 10	C-Quens
Enovid 5	Norinyl
Enovid E	Oracon
Ortho-Novum 10	Norlestrin
Ortho-Novum 2	Provest

CARD #5

A. Rhythm.	G. Birth control pills.
B. Abstinence.	H. Suppositories.
C. Rubber, condom, safe.	I. Foam tablets.
D. Withdrawal.	J. Sponge, tampon.
E. Diaphragm.	K. Jelly, creams.
F. Douche.	L. Another method not on this card.

CARD #6

A. Under $1,000.	G. $6,000–$6,999.
B. $1,000–$1,999.	H. $7,000–$7,999.
C. $2,000–$2,999.	I. $8,000–$8,999.
D. $3,000–$3,999.	J. $9,000–$9,999.
E. $4,000–$4,999.	K. $10,000–$14,999.
F. $5,000–$5,999.	L. $15,000 plus.

Table 1.—Female patients discharged from Johns Hopkins Hospital, 1963–65, with diagnoses of conditions selected for study

	Discharges in 3 years			Records found	Acceptable and considered "Idiopathic" [1]		Final case series
	White	Nonwhite	Total		Number	Percent	
Thrombophlebitis extremity	22	25	47	36	7	19	4
Thrombophlebitis and pulmonary embolism	7	8	15	13	2	15	1
Pulmonary embolism (? source)	3	7	10	8	1	12	1
Cerebral artery thrombosis	6	6	12	9	2	22	2
Cerebral artery embolism	2	0	2	2	0	-------	-------
Retinal vascular lesion	3	3	6	5	2	40	2
Myocardial infarction	2	5	7	7	0	-------	-------
Arterial thrombosis, other	6	0	6	5	0	-------	-------
Total	51	54	105	85	14	16	10

[1] Patients who were married, and record review did not provide evidence of sterility or of predisposing conditions.

Table 2.—Diagnoses [1] which yielded control subjects

	Number in file	Number sought	Number found and matched to cases
Tonsillectomy and adenoidectomy	230	25	4
Acute appendicitis and appendectomy	49	44	6
Acute cystitis	46	6	1
Infectious hepatitis	36	21	2
Acute gastroenteritis	22	15	1
Pilonidal cyst	19	19	1
Elastosis senilis	10	6	1
Sprains and strains of sacroiliac	8	8	1
Fracture upper extremity—closed	5	5	1
Concussion	3	3	1
Fracture clavicle—closed	1	1	1
Total	429	153	20

[1] Control diagnoses which were selected for study but did not yield any matches with the cases are omitted.

Table 3.—List of attributes on which matching of paired controls to cases was done (in addition to sex, marital status, hospital and time period, which were common to cases and controls)

Race
Age (within 5 years)
Religion (Catholic, Protestant, Jewish)
Hospital pay status

Table 4.—Cases selected, exclusions, and results of attempt to obtain interview

	Cases	Controls
Number selected from printout of discharges	105	226
Records found	85	127
Excluded because of:		
Marital status	29	107
Sterility	21	
Other diagnoses on index sheet	51	
Predisposing condition on record review	67	
Acceptable	10	20
Interviewed	7	19
Questionnaires mailed and self-administered	3	1

Table 5.—Selected findings from interview schedules

	Cases (10)		Controls (20)	
	Number	Percent	Number	Percent
Race:				
White	8	80	16	80
Nonwhite	2	20	4	20
Ages:				
18–19	0	------	0	------
20–24	1	10	3	15
25–29	3	30	6	30
30–34	2	20	5	25
35–39	2	20	5	25
40–44	2	20	1	5
Religion:				
Catholic	2	20	3	15
Protestant	8	80	17	85
Income:				
Under $5,000	3	30	3	15
$5,000–$10,000	6	60	11	55
Over $10,000	1	10	5	25
Education:				
Elementary	1	10	1	5
High school	5	50	10	50
College	4	40	9	45
Parity:				
0	2	20	1	5
1	1	10	4	20
2	1	10	9	45
3+	6	60	6	30
Children in household:				
0	2	20	1	5
1	1	10	4	20
2	1	10	8	40
3	3	30	4	20
4+	3	30	3	15
Birth control practiced	8	80	15	75
Smoker	8	80	11	55
Serious illness:				
Husband	0	------	3	15
Wife	0	------	4	20
Chronic conditions	6	60	14	70
Past medications	3	30	5	25

APPENDIX III

DEAR DOCTOR LETTERS

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
Washington, D.C., January 12, 1970.

DEAR DOCTOR: I am enclosing revised labeling for oral contraceptives to reflect the latest findings on safety and efficacy, as reported by the Obstetrics and Gynecology Advisory Committee in August 1969. An American study confirms previously reported studies in Great Britain which show a relationship between the use of oral contraceptives and the occurrence of certain thromboembolic diseases. These carefully designed retrospective studies show that users of oral contraceptives are more likely to have thrombophlebitis and pulmonary embolism than non-users. Studies in Great Britain also show increased risk of cerebral thrombosis and embolism in users of oral contraceptives. A British study found a hospitalization rate (an index of morbidity) in women age 20–44 to be 47 per 100,000 in users compared to five per 100,000 in non-users.

The American study, although not designed to evaluate differences between products, also suggests there may be an increased risk of thromboembolic disease in users of sequential products. This difference in risk cannot be quantitated, and further studies are needed to confirm the observation.

The British Committee on Safety of Drugs recently advised practitioners in that country that only products containing 0.05 mg. or less of estrogen should normally be prescribed because reports of suspected adverse reactions indicated there is a higher incidence of thromboembolic disorders with products containing 0.075 mg. or more of estrogen than with products containing the smaller dose. This finding has not been confirmed by other studies.

The FDA is planning studies that will determine, among other things, the thromboembolic effect of various products. You will be kept informed as results become available.

Other aspects being investigated in separate studies underway or pending are cervical cytology, carbohydrate metabolism, serum lipids, urinary tract function, blood coagulation, effects on endocrine function in adolescents, breast pathology, outcome of pregnancy, and cytogenetic effects.

In the United States during 1969 an estimated 8.5 million women took oral contraceptives monthly. The unsurpassed clinical efficacy of these products is well established. Although reported pregnancy rates vary from product to product, the effectiveness of sequential products appears to be somewhat lower than that of the combination products.

I strongly urge you to familiarize yourself with the labeling, particularly with the cautionary material contained in the sections headed Contraindications, Warnings, Precautions, and Adverse Reactions. As the prescribing physician, you are in the best position to determine the extent of your discussion of this material with your patient. In most cases, a full disclosure of the potential adverse effects of these products would seem advisable, thus permitting the participation of the patient in the assessment of the risk associated with this method.

I also request your assistance in continuing our assessment of the safety of oral contraceptives. Your reports of adverse reactions will help us to do this. A supply of the standard reporting form (FD 1639), shown in facsimile below, may be obtained from the Bureau of Medicine, Food and Drug Administration, Washington, D.C. 20204.

Sincerely yours,

CHARLES C. EDWARDS, M.D.,
Acting Commissioner of Food and Drugs.

Attachment:
Revised labeling

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

DRUG EXPERIENCE REPORT

BUDGET BUREAU NO. 57-R0004
Approval Expires December 31, 1970

DATE SENT TO FDA (Mo., day, yr.)

1. [ ] INITIAL REPORT
[ ] FOLLOW-UP REPORT

2. PATIENT INITIALS AND IDENTIFICATION NUMBER

3. ACCESSION NO. (For FDA use only)

SECTION I. PATIENT DATA

4. SEX [ ] M [ ] F

5. HEIGHT (ins.) WEIGHT (lbs.)

6. DATE OF BIRTH (mo. / day / yr.)

7. ORIGIN [ ] CAUC [ ] NEGRO [ ] ORIENTAL [ ] AMERICAN INDIAN [ ] OTHER

8. DATE OF REACTION ONSET (mo. / day / yr.)

9. SOURCE OF REPORT (Mfg., Hospital, etc.) (Name of reporting Physician is optional.)

10. ADDRESS OF SOURCE (Give Street, City, State, and Zip Code.)

11. DESCRIBE SUSPECTED ADVERSE REACTION(s) AND ANY POSSIBLE ASSOCIATION WITH THE DRUG(s) INVOLVED

12. OUTCOME OF REACTION TO DATE
[ ] ALIVE WITH SEQUELAE
[ ] RECOVERED
[ ] STILL UNDER TREATMENT
[ ] DIED (Give date and cause)

13. LIST ALL THERAPY IN ORDER OF SUSPICION (Manufacturer: List NDA or IND No.)

NAME OF DRUGS TRADE (Generic)	MANUFACTURERS CONTROL NO.	DOSAGE FORM (tab, cap, etc.)	TOTAL DAILY DOSE	ROUTE (po, im, IV, etc.)	DURATION OF THERAPY	DATES OF ADMINISTRATION	14. DISORDER OR REASON FOR USE OF DRUG

SECTION II. SUPPORTING SUPPLYING DATA

15. SUBSTANTIATING LABORATORY STUDIES (Clinical Laboratory, Autopsy, X Ray, etc.)
CLINICAL LAB [ ] DONE [ ] ATTACHED [ ] NOT DONE
BIOPSY/AUTOPSY [ ] DONE [ ] ATTACHED [ ] NOT DONE

16. LIST POTENTIALLY NOXIOUS OR ENVIRONMENTAL FACTORS (Include household products, industrial and agricultural chemicals)

17. EXISTING OR PRIOR DISORDERS AND PAST DRUG REACTION OR ALLERGIC HISTORY

PREVIOUS EXPOSURE TO SUSPECTED DRUG OR RELATED COMPOUND
[ ] YES [ ] NO

18. (a) IF FEMALE
GRAVIDITY [ ] PARITY [ ]
(b) IF PREGNANT
WEEKS OF GESTATION [ ]

19. MAY THE SOURCE OF THIS REPORT BE RELEASED TO THE ARMED FORCES INSTITUTE OF PATHOLOGY?
[ ] YES [ ] NO

FOR FDA USE ONLY

20. REACTION FACTORS (Check all applicable boxes)
[ ] DECOMPOSITION OF DRUG [ ] INTERACTION OF TWO OR MORE DRUGS [ ] DRUG NOT USED ACCORDING TO LABELING [ ] DRUG OUTDATED
[ ] DRUG MISUSED BY PATIENT [ ] OVERDOSAGE [ ] DRUG MISLABELED [ ] CONTAMINATION OF DRUG [ ] OTHER DRUG MISUSE (Specify)

FOR MFG USE ONLY

FORM FD-1639 (Rev. 8/67)

(Use additional sheet if necessary.)

ORAL CONTRACEPTIVE LABELING

DESCRIPTION

This section includes generic name, amount, chemical name and the structural formula of each active ingredient.

ACTIONS

Combination oral contraceptives: The mechanism of action is inhibition of ovulation resulting from gonadotropin suppression. Changes in cervical mucus and endometrium may be contributory mechanisms.

Sequential oral contraceptives: The mechanism of action is inhibition of ovulation resulting from gonadotropin suppression.

SPECIAL NOTE

Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision. Long term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATIONS

The Obstetrics and Gynecology Advisory Committee considered the following indications acceptable: contraception, endometriosis, and hypermenorrhea. These indications may be used in the labeling when efficacy has been demonstrated in each case. Any other claims will be evaluated on the basis of efficacy data available to support each.

CONTRAINDICATIONS

1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions.
2. Markedly impaired liver function.
3. Known or suspected carcinoma of the breast.
4. Known or suspected estrogen dependent neoplasia.
5. Undiagnosed abnormal genital bleeding.

WARNINGS

1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis and pulmonary embolism and the use of oral contraceptives. There have been three principal studies in Britain [1-3] leading to this conclusion, and one [4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll [3] was about seven-

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[1] Royal College of General Practitioners: Oral Contraception and Thromboembolic Disease. J. Coll. Gen. Pract., *13*:267–279, 1967.

[2] Inman, W. H. W. and Vessey, M. P. Investigation of Deaths from Pulmonary Coronary and Cerebral Thrombosis and Embolism in Women in Child Bearing Age, Brit Med J, *2*:193–199, 1968.

[3] Vessey, M. P. and Doll, R. Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. Brit Med J, *2*:651–657, 1969.

[4] Sartwell, P. E., Masi, A. T., Arthes, F. G., Greene, G. R., and Smith, H. E., Thromboembolism and Oral Contraceptives: An Epidemiological Case-Control Study. Am. J. Epidem. 90:365–380, (November) 1969.

fold, while Sartwell and associates in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users. The American study also indicated that the risk did not persist after discontinuaton of administration, and that it was not enhanced by long continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable. Retrospective studies in Great Britain have shown a statistically significant association between cerebral thrombosis and embolism and the use of oral contraceptives. This has not been confirmed in the United States.

2. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

3. Since the safety of * * * in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long range effect to the nursing infant cannot be determined at this time.

PRECAUTIONS

1. The pretreatment and periodic physical examinations should include special reference to breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals.

2. Endocrine and possibly liver function tests may be affected by treatment with * * *. Therefore, if such tests are abnormal in a patient taking * * *, it is recommended that they be repeated after the drug has been withdrawn for 2 months.

3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size.

4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated.

6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

7. Any possible influence of prolonged * * * therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study.

8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving * * * therapy.

9. The age of the patient constitutes no absolute limiting factor, although treatment with * * * may mask the onset of the climacteric.

10. The pathologist should be advised of * * * therapy when relevant specimens are submitted.

11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES

A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions:

Thrombophlebitis
Cerebral thrombosis
Pulmonary embolism

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions:

Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis

The following adverse reactions are known to occur in patients receiving oral contraceptives:

Nausea
Vomiting
Gastrointestinal symptoms (such as abdominal cramps and bloating)
Breakthrough bleeding
Spotting
Change in menstrual flow
Amenorrhea during and after treatment
Edema
Chloasma or melasma
Breast changes: tenderness, enlargement and secretion
Change in weight (increase or decrease)
Changes in cervical erosion and cervical secretions
Suppression of lactation when given immediately postpartum
Cholestatic Jaundice
Migraine
Rash (Allergic)
Rise in blood pressure in susceptible individuals
Mental depression

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted:

Anovulation post treatment
Premenstrual-like syndrome
Changes in libido
Changes in appetite
Cystitis-like syndrome
Headache
Nervousness
Dizziness
Fatigue
Backache
Hirsutism
Loss of scalp hair
Erythema multiforme
Erythema nodosum
Hemorrhagic eruption
Itching

The following laboratory results may be altered by the use of oral contraceptives:

Hepatic function: Increased sulfobromophthalein retention and other tests
Coagulation tests: Increase in prothrombin, Factors VII, VIII, IX, and X
Thyroid function: Increase in PBI, and butanol extractable protein bound iodine and decrease in T^3 uptake values
Metayrapone test
Pregnanediol determination

DOSAGE AND ADMINISTRATION

This section includes routine administration and specific instructions on handling problems such as breakthrough bleeding, amenorrhea, etc.

CLINICAL STUDIES (AN OPTIONAL SECTION)

If any clinical data are included, the following paragraph must be used: Different pregnancy and adverse reaction rates have been reported with the use of each oral contraceptive. Inasmuch as these rates are usually derived from separate studies conducted by different investigators in several population groups, they cannot be compared with precision. Furthermore, pregnancy and adverse reaction rates tend to be lower as clinical experience is expanded, possibly due to retention in the clinical study of those patients who accept the treatment regimen and did not discontinue due to adverse reactions or pregnancy. In clinical trials with * * * patients completed * * * cycles, and a total of * * * pregnancies was reported. This represents a pregnancy rate of * * * per 100 woman years. Please see the SPECIAL NOTE in this labeling.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
Washington, D.C., June 28, 1968.

DEAR DOCTOR: Since 1960, when the first oral contraceptive was marketed in the United States, these drugs have been prescribed in a volume which may exceed that of any other potent medication. According to current estimates, more than six million American women now use oral contraceptives. As the drugs have been used more widely, adverse reactions, not known at the time of original Food and Drug Administration approval, have become evident; the labeling of the drugs has been revised from time to time to include this new knowledge.

The most recent data developed in studies conducted in Great Britain confirms what had been suspected: *there is a definite association between the use of oral contraceptives and the incidence of thromboembolic disorders.* New labeling, which will be in use by July 1, 1968, contains excerpts from the British reports and appropriate revisions of prescribing information. The labeling is uniform for all drugs in this class, and is in the standard format recommended by the FDA for all drug labeling.

A copy of the revised uniform labeling is attached. We urge you to give careful consideration to the information under the various cautionary headings in the labeling.

We ask, too, for your assistance in monitoring adverse reactions by reporting all such reactions to the Food and Drug Administration. A supply of the standard reporting form (FD 1639), shown in facsimile on the reverse of this letter, may be obtained by writing to: Bureau of Medicine, Food and Drug Administration, Washington, D.C. 20204.

Sincerely yours,

JAMES L. GODDARD, M.D.,
Commissioner of Food and Drugs.

Attachment:
Revised uniform labeling

UNIFORM SECTION OF ORAL CONTRACEPTIVE LABELING

CHEMISTRY

This should include generic name, amount, chemical name and the structural formula of each active ingredient.

MECHANISM OF ACTION

(As presented in current package insert.)

INDICATIONS

The Obstetrics and Gynecology Advisory Committee considered the following indications acceptable: contraception, endometriosis, and hypermenorrhea. These indications may be used in the labeling when efficacy has been demonstrated in each case. Any other claims will be evaluated on the basis of efficacy data available to support each.

CONTRAINDICATIONS

1. Patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or with a past history of these conditions.
2. Patients with markedly impaired liver function.
3. Patients with known or suspected carcinoma of the breast.
4. Patients with known or suspected estrogen dependent neoplasia.
5. Undiagnosed abnormal genital bleeding.

WARNINGS

1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Studies conducted in Great Britain and reported in April 1968[1, 2] estimate there is a seven to tenfold increase in mortality and morbidity due to thromboembolic diseases in women taking oral contraceptives. In these controlled retrospective studies, involving 36 reported deaths and 58 hospitalizations due to "idiopathic" thromboembolism, statistical evaluation indicated that the differences observed between users and non-users were highly significant. The conclusions reached in the studies are summarized in the table below:

COMPARISON OF MORTALITY AND HOSPITALIZATION RATES DUE TO THROMBOEMBOLIC DISEASE IN USERS AND NON-USERS OF ORAL CONTRACEPTIVES IN BRITAIN

Category	Mortality rates		Hospitalization rates (morbidity)
	Age 20–34	Age 35–44	Age 20–44
Users of oral contraceptives	1. 5/100, 000	3. 9/100, 000	47/100, 000
Nonusers	0. 2/100, 000	0. 5/100, 000	5/100, 000

No comparable studies are yet available in the United States. The British data, especially as they indicate the magnitude of the increased risk to the individual patient, cannot be directly applied to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may be different.

2. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

3. Since the safety of * * * in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long range effect to the nursing infant cannot be determined at this time.

PRECAUTIONS

1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as a Papanicolaou smear.

2. Endocrine and possibly liver function tests may be affected by treatment with * * *. There, if such tests are abnormal in a patient taking * * *, it is recommended that they be repeated after the drug has been withdrawn for 2 months.

3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size.

4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginum, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginum, adequate diagnostic measures are indicated.

6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

7. Any possible influence of prolonged * * * therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study.

8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving * * * therapy.

[1] Inman, W. H. W. and M. P. Vessey, British Medical Journal 2 :193–199, 1968.
[2] Vessey, M. P. and R. Doll. British Medical Journal, 2 :199–205, 1968.

9. Because of the effects of estrogens on epiphyseal closure * * * should be used judiciously in young patients in whom bone growth is not complete.
10. The age of the patient constitutes no absolute limiting factor, although treatment with * * * may mask the onset of the climacteric.
11. The pathologist should be advised of * * * therapy when relevant specimens are submitted.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES

A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions:

Thrombophlebitis
Pulmonary embolism

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions:

Cerebrovascular accidents
Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis

The following adverse reactions are known to occur in patients receiving oral contraceptives (Consult the clinical section.)

Nausea
Vomiting
Gastrointestinal symptoms (such as abdominal cramps and bloating)
Breakthrough bleeding
Spotting
Change in menstrual flow
Amenorrhea during and after treatment
Edema
Chloasma or melasma
Breast changes: tenderness, enlargement and secretion
Change in weight (increase or decrease
Changes in cervical erosion and cervical secretions
Suppression of lactation when given immediately post-partum
Chloestatic Jaundice
Migraine
Rash (Allergic)
Rise in blood pressure in susceptible individuals
Mental depression

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted:

Anovulation post treatment
Prementrual-like syndrome
Changes in libido
Changes in appetite
Cystitis-like syndrome
Headache
Nervousness
Dizziness
Fatigue
Backache
Hirsutism
Loss of scalp hair
Erythema multiforme
Erythema nodosum
Hemorrhagic eruption
Itching

The following laboratory results may be altered by the use of oral contraceptives (see sections on clinical laboratory):

Hepatic function: Increased sulfobromophthalein and other tests
Coagulation tests: increase in prothrombin Factors VII, VIII, IX and X
Thyroid function: increase in PBI, and butanol extractable protein bound iodine and decrease in T^3 values
Metyrapone test
Pregnanediol determination

ANIMAL STUDIES

This should include results of acute, chronic toxicity and reproduction studies using the compounds present in the product. Significant laboratory and pathologic findings should be mentioned.
Endocrine and metabolic screening. State results on dose per weight basis.

CLINICAL DATA

Efficacy—This should include the number of cycles completed. Breakdown by number of patients completing a specific number of cycles should also be mentioned. State number of pregnancies in number per 100 woman years. Pearl's formula or life table technique should be used. The following statement is permitted if applicable: "Virtually 100% effective when used according to directions."

Adverse Reactions Clinical Laboratory Results—This should include liver, thyroid, renal functions, coagulation tests, endocrine function as well as routine hematology and cytology.

DOSAGE AND ADMINISTRATION

This should include routine administration and specific instructions on handling problems such as breakthrough bleeding, amenorrhea, etc.

AVAILABILITY

BIBLIOGRAPHY

Reference, not a complete bibliography.

May 10, 1968 / Food and Drug Administration / U.S. Department of Health, Education, and Welfare / Washington, D.C. 20204.

APPENDIX IV

ARTICLES

[From The New York Post, February 14, 1970]

SURVEY LINKS THE PILL TO CANCER

(By Barbara Yuncker)

A "significantly higher" number of very early cancers of the cervix has been found in a study of New York women who use oral birth control pills, compared with similar women who use diaphragms, The Post learned today.

The still-unpublished report, involving nearly 35,000 women, stresses that the finding provides no proof of cause and effect. Other factors, particularly involving patterns of sexual behavior, may be as likely as causes, if not more so. But this is not expected to avert a new, major debate on the pill's safety.

The details of the study have been presented privately to the contraceptive advisory committee of the Food and Drug Administration which has found "nothing to confirm or refute" a theory that "The Pill" might cause such cell changes. It has not suggested any new FDA warning on the basis of this or other related reports, and FDA Commissioner Ley and other officials are understood to concur in this view at this time.

EARLY FORM CURABLE

When "Pap smear" tests were done on all 35,000 (who were clients at Planned Parenthood clinics) and followup biopsies were done on suspicious cases, 266 "carcinomas in situ" were found. (This is the earliest, most curable form of cancer of the female reproductive organs.)

Matching the users of the two methods for age, ethnic background, childbearing history and economic status, the researchers found about twice as many cases of early cancer among the pill-users. Because they outnumbered those using diaphragms by about four to one, they were matched in one/one, one/two and one/three groupings, with slightly different results, but a consistent pattern.

A principal reason why cause-and-effect cannot be assumed from this study is that earlier research, cited in this report, has shown that cervical cancer is higher in women with early sexual experience on frequent intercourse or many partners, or repeated pregnancies. It is rare among nuns, relatively high among prostitutes.

But because of the kinds of women involved and the fact that they were volunteers from the clients of Planned Parenthood, it was not considered appropriate—or even particularly revealing—to investigate earlyest sexual experience or number of partners, beyond what could be deduced from marital and pregnancy histories.

VIRUS A CAUSE?

Another lively area of cervical cancer research, suggesting that a virus may be a causative factor, is not directly involved in this study but is given suggestive support because the diaphragm could be a barrier against such infection. It could also be a barrier if simple lack of hygience is involved, which other studies have indicated as a possibility.

The study was directed by Dr. Myron R. Melamed, pathologist at Memorial Sloan-Kettering Cancer Center, and Dr. Hilliard Dubrow, obstetrician and cancer research adviser to Planned Parenthood of New York City. He is on

the staff at Lenox Hill Hospital and is director of obstetrics and gynecology at Doctors Hospital.

Dr. Melamed could not be reached for comment. Dr. Dubrow would not discuss details of the report, on which statistical analysis was guided by computer experts from IBM, but acknowledged its existence and general outlines. He said he * * * "until it has appeared in a medical journal where other physicians, may evalute it in full.

AN EARLIER STUDY

It is tentatively scheduled for publication within a month in the Journal of the American Medical Assn. It and three parallel studies are referred to in an issue of Medical World News, a magazine for physicians, being distributed today.

That story cites a study by Dr. George Wied of the University of Chicago which reported an occurrence of this same early cervical cancer six times above expectation in a screening done in Chicago of a similar-sized group. But Dr. Wied's paper has been withdrawn, by him, from planned publication in a research journal to review statistical analyses.

An important technical point about the New York study is that it studies "prevalence" not "incidence." Using the same women plus those using other contraceptive devices the same team is also studying "incidence", but the figures are not due for at least a year. ("Prevalence" means how many have a disease at a certain point in time. "Incidence" refers to how many will get it over a period of time. They diverge widely in epidemic diseases but are closer in figures and importance in chronic diseases like cancer.)

Cervical and other uterine cancers hit 44,000 women a year in this country and are fatal each year to about 13,000. But carcinoma in situ is so early a stage that it is nearly 100 per cent curable.

All cases found in the Melamed-Dubrow study have been treated and are apparently cured. In fact Dubrow regards a frequent examination and Pap smear, as is recommended procedure with oral contraceptives, as more likely to pick up early cancer than diaphragms changed only after childbirth or at other long intervals, unless women getting them also get annual vaginal examinations.

Fifty-three per cent of the women in the study were Negro, 23 per cent white, 22 per cent Puerto Rican or of other "Spanish" background, and just under 2 per cent were of other racial groups. They ranged in age from the teens to the 40s with nearly two-thirds between 21 and 30. The group were predominantly low-income. Each woman had made her own choice of contraceptive method.

The study report clearly suggests that the personality and sex pattern may control the choice of contraceptive.

But despite the possibility of other factors and the fact that the FDA and physicians like Dubrow still approve The Pill, a storm of debate is expected upon official publication of these new studies.

[From the New York Times, January 17, 1970]

EDITORIAL—THE PILL PROBLEM

Disturbing questions about the pill and its possible consequences for the millions of women taking it have been raised in Washington this week. Up to the present, most concern about this form of chemical contraception has focused upon the fact that a tiny fraction of users have developed blood clot problems. Now some doctors and scientists are raising the possibility that the pill may be responsible for causing cancer, damaging genes, and harming the children of women who have conceived after they have ceased to use the potent hormones that prevent pregnancy.

Such unresolved questions as to the long-term effects on human beings of an extraneous influence are not confined to use of the pill, or to drugs for that matter. In modern man's increasingly synthetic environment, the air he breathes and the food he eats contain ever more additives about which similar questions can be raised. What is the long-term impact of the air pollutants to

which urbanites are exposed daily or of the antibiotics in meat, just to mention two of the most obvious examples?

Proponents of the pill—of whom there are many—tend to minimize the short- and long-run dangers described by its opponents. Those who favor the pill point to its high efficiency as a contraceptive, and argue that the potential gains outweigh the potential perils from the pill. It is useful, however, that questions about the pill are being ventilated in public, and that responsible Government officials and the medical profession are being forced to face them.

In the present era of widespread concern over the population problem, the utility of the pill is indubitable. But more answers are needed than are yet available about the societal and individual costs that may yet have to be paid for the convenience and near certainty of contraception the pill provides.

[From Family Health, January 1970, pp. 36–38]

COMMONSENSE ADVICE ON CONTRACEPTIVES

Dr. Louis M. Hellman, one of the nation's leading experts on birth control, answers questions by senior staff writer Judith Ramsey. Dr. Hellman, who heads the Food and Drug Administration's blue-ribbon advisory committee on oral contraceptives, is also chairman and professor of the department of obstetrics and gynecology at Downstate Medical Center, Brooklyn, N.Y.

Judith: It's generally agreed that there's no one contraceptive method suitable for everybody. How can a woman decide which is best for her?

Dr. Hellman: Her personal physician can help her make that decision. First, she must identify her own special needs. Does she want a temporary method until she and her husband are ready to have children? Is she undecided about whether she wants more children? Is her family completed? Then she must weigh the benefits and risks of each method. How safe is it? How convenient? Are there any specific risks for her? A contraceptive method is only effective and safe when properly used by a woman who can tolerate it.

Judith: Let's talk about some individual but typical cases. For example, what contraceptive method would you recommend for a woman in her mid-twenties who has had two children? She has years of fertility ahead of her, but she and her husband don't know whether they'll want another child. They definitely feel they can't afford one for at least two years.

Dr. Hellman: This woman is an ideal candidate for the Pill, provided that she doesn't have adverse reactions to it. Some women react with irregular vaginal bleeding, weight gain, headaches, or dramatic mood changes.

Judith: Could she safely take the Pill for an indefinite period of time?

Dr. Hellman. Chiefly, the problem with oral contraceptives is an increased, though still small, risk of thrombophlebitis, or clots in the vein. A survey of records from more than forty American hospitals shows that the risk of blood clotting is almost four and a half times greater among pill users than among other women of childbearing age who don't use the Pill. Unfortunately, at present there is no test to determine which women on the Pill will have clotting problems. Of course there are some clear early warning signs: headaches, visual symptoms, excessive weight gain. If these occur, a woman should stop taking the Pill immediately.

Weighted against the small risk of the oral contraceptives are their large benefits. They are nearly a hundred percent effective when taken as prescribed; they are very easy to use; and they don't intrude on the relationship between husband and wife. These are the reasons why about eight and a half million American women are now on the Pill.

As for the length of time a woman should stay on the Pill, there is no evidence that she can't continue as long as she wants. However, she should have a periodic checkup, including a Pap smear and breast examination every six months to a year.

Judith: What about a wife who wants to take the Pill but wonders whether it is worthwhile? Her husband is a salesman and is away for many months of the year. They have infrequent sexual relations. Should she take the Pill, and if so, all the time or just before her husband comes home?

Dr. Hellman: This problem is more common than you would suppose. I see no point in her taking the Pill, since she doesn't need the continuous protection it affords. She could very well use the diaphragm or perhaps the intrauterine device (IUD). If she does take the Pill, however, she must take it *all* the time.

Judith: Then there is the woman with the opposite problem. She and her new husband have frequent sexual intercourse. But they are both in their early twenties and want to wait a few years before having children.

Dr. Hellman: The Pill is ideal for her, since it is difficult to insert an intrauterine device into a woman who has not had a baby.

Judith: Does the fact that this woman has frequent sexual intercourse influence the type of oral contraceptive you would prescribe for her?

Dr. Hellman: Not at all. The combined pill—which contains two powerful drugs, estrogen and progesterone—is a little bit safer if a woman forgets and skips a pill. But the sequential pill—which consists of a series of pure estrogen followed by several tablets of estrogen and progesterone—is considered safe if taken according to instructions.

I, myself, give some of my patients the sequential pill because its effect comes closer to the natural female menstrual cycle and does not diminish the monthly period, which is worrisome to certain women. However, the latest government report on the Pill suggests that the sequential form may be associated with a slightly higher risk of blood clotting. This remains to be proved.

Judith: What about the woman who has been using a foam preparation for three years since the birth of her second child? Her friends keep telling her about the advantages of the Pill, but she is afraid of its side effects. Should she change methods?

Dr. Hellman: If the foam has worked well for her for the past three years, the chances are that it will work well for another three years. If she's satisfied with the method she is using, there is no reason for her to change.

Judith: What about Mrs. G.? She is twenty-five years old. She has two children and would like to have two more spaced over a period of four to six years. Is the Pill going to interfere with her fertility?

Dr. Hellman: There is no evidence that it does. But before trying to get pregnant, she would be wise to go off the Pill for a few months and in the interim use another method. Some doctors think that the first few ovulations off the Pill may not be completely normal.

Judith: Here are women with special problems. What contraceptives would you recommend for them? Mrs. F., aged twenty-six, has just got married. She and her husband want to wait two years before having a child. A routine gynecological checkup revealed that she has fibroids.

Dr. Hellman: She's making a mistake from the beginning. There's always a chance that the fibroids, which are benign tumors of the uterus, will grow larger and require surgical removal. She should have her family right away. If she still wants to wait, it would be advisable for her to use a diaphragm. The Pill is not recommended for women with fibroids. The estrogen that it contains tends to make them grow. The IUD would also be suitable in certain cases.

Judith: What are the other complications that can be caused by the IUD?

Dr. Hellman: The problem is that it doesn't always work very well. The IUD can bring on cramps and also bleeding. Sometimes it is expelled. In a few instances, it has perforated the uterus. It has also caused peritonitis. The death rate from complications caused by the IUD in the United States is probably around two per hundred thousand—close to that of the Pill.

Judith: The next case involves a very delicate situation. You are consulted by the parents of a sixteen-year-old girl who is promiscuous. Her parents have tried to be firm. They have even punished her, with no success. She is now seeing a psychiatrist, but she is still sexually promiscuous. Her parents are desperately afraid that she will get pregnant, but they don't want to do anything that will encourage her sexual activities.

Dr. Hellman: By all means, she should be given contraceptive aid. A pregnancy would just worsen an already troublesome situation. Unfortunately, the type of girl who is promiscuous is apt to be forgetful about the Pill. She certainly cannot be relied on to use a diaphragm, and her multiple partners are not to be trusted to do anything to prevent pregnancy.

I would try to fit this girl with an IUD. The insertion would probably have to be done under anesthesia, since insertion is likely to be painful. I might have to try one of several IUDs—which come in different shapes and sizes—to find one that fits satisfactorily.

Judith: Suppose this girl develops cramps and bleeding or one of the other problems you said were associated with the IUD. Would you give the Pill to someone that young? Is there any chance that it will stunt her growth?

Dr. Hellman: No, it does not. In the first place, the growth spurt takes place in the tenth to twelfth years among American girls. In the second place, the amount of estrogen necessary to inhibit growth is far larger than that contained in the Pill. The Pill certainly will have less effect on growth at this age than a pregnancy would have.

However, I should point out that there is one potential problem in giving the Pill to sixteen-year-old girls. In the early years of menstruation, the Pill can interfere with the establishment of the regular menstrual cycle. This is another reason why I would recommend the intrauterine device for this particular girl.

Judith: How would you prescribe for Mrs. H., whose maternal grandmother has diabetes? Is it all right for her to take the Pill?

Dr. Hellman: As long as she doesn't have diabetes. Some women may have heard that the Pill can cause a rise in their blood sugar. This is true, but the elevation disappears as soon as they stop taking the Pill. Of course, any woman who has diabetes in the family should have her blood and urine checked as part of the physical checkup she undergoes annually.

Judith: Would you give the same advice to a woman whose mother and aunt both had cancer?

Dr. Hellman: No, I would not, for this reason: although there is no evidence that the Pill causes cancer in women, it is possible that the estrogens contained in the Pill could speed up the growth of existing cancers. If a woman has a well-established family history of cancer, she would do better with another form of contraception. This case underscores the need for a complete medical checkup by a gynecologist. The woman should be sure to tell her doctor about any diseases she may have as well as any family history of diseases like diabetes or cancer, especially if several relatives have been affected.

Judith: How would you advise a woman who decides that after the birth of her second child by cesarean section that she doesn't want any more children?

Dr. Hellman: For those women whose childbearing is definitely completed, even without complications such as cesareans, the ideal method of contraception is tubal ligation, or tying off, which is both safe and permanently effective. A small incision is made in the abdomen while the woman is under anesthesia. Then the fallopian tubes are tied off so that no more eggs can pass into the uterus. Women who have bad previous cesarean operations and are due to have another one are often asked by their obstetricians if they plan to have more children; if not, the obstetrician can easily perform the tubal ligation at the time of delivery.

I prefer the term tubal ligation to sterilization because nothing is taken out. It doesn't alter a woman's hormonal balance or menstrual cycle. Most of my patients who have undergone tubal ligation have felt greatly relieved afterward. They were free of the threat of pregnancy and were able to enjoy sexual relations even more.

Naturally, a woman should not undergo this operation unless she's pretty sure that she doesn't want another baby. The tubes can be untied, but only thirty to fifty percent of these women are able to conceive afterward.

If the woman doesn't want to undergo tubal ligation, I would recommend the Pill, the IUD, the diaphragm, or a condom for her husband—in that order of decreasing effectiveness.