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PD-AAM-771
ISA 29648

AID 1350/IX (8-63)

DEPARTMENT OF STATE
AGENCY FOR
INTERNATIONAL DEVELOPMENT

Worksheet Iss.

PAGE 1 OF 9 PAGES

O/T

PROJECT IMPLEMENTATION
ORDER/TECHNICAL
SERVICES

1. Cooperating Country
World-Wide

2. PID/T No. 931-17-521-570-
73-3104711

3. Project/Activity No. and Title
Research on the Safety of Contraceptive
Steroids - Southwest Foundation for
Research and Education

4. Appropriation Symbol
72-11X4111.1

5. a. Allotment Symbol & Charge
489-31-099-00-23-01

5. b. Funds Allotted to:
 AID/W Mission

6. Obligation Status

Administrative Reservation Obligation Sub-Obligation

7. Original or
Amendment No.:

8. No. of Technicians

9. Services to Start (Mo., Day, Yr.)
Between: 5-27-70 And: 6-30-70

10. Duration (Months)
a. Of Services 36 b. Of Financing 36

11. a. Type of Action

AID Contract Cooperating Country Contract Participating Agency Service Agreement Other

11. b. Authorized Agent

AID/Washington

Financing \$1.00 =	A. Previous Total	B. Increase	C. Decrease	D. Total to Date
12. AID Financing a. Dollars		912,792		912,792
b. U.S.-Owned Local Currency				
13. Cooperating Country Contributions a. Counterpart				
b. Other				

14. Mission
References

15. Objective for which the Technical Services are to be used (Describe)

Certain steroid hormones are the active agents in the widely used oral contraceptives and in other, as yet experimental methods using injection and implantation techniques. These methods form one of the major technologies for conception and population control. While their effectiveness and acceptability is proven, their safety in long-term use and in a variety of populations is not established, and the possibility of undiscovered hazards has received considerable attention. It is the purpose of this research program to examine these questions intensively and from a variety of perspectives, ranging from inquires as to the mechanisms of action, to metabolic fate within the body, and to effects on organ systems not directly involved in the contraceptive action.

16. Mission Clearances	Date	Mission Clearances	Date

17. Date of Original Issuance

18. Date of this Issuance
May 27, 1970

19. For the Cooperating Country
The terms and conditions set forth herein are hereby agreed to:

20. For the Agency for International Development

Robert J. O'Brien
Robert J. O'Brien, Contracting Officer

SIGNATURE

DATE

SIGNATURE
Contract Services Division

TITLE

TITLE

DEPARTMENT OF STATE
AGENCY FOR
INTERNATIONAL DEVELOPMENT Worksheet Issuance

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D/T

PROJECT IMPLEMENTATION
ORDER/TECHNICAL
SERVICESCooperating Country
World-widePIO/T No. 931-17-521-570-
73-3104711Project/Activity No. and Title
Research on the Safety of Contraceptive
Steroids - Southwest Foundation for
Research and Education

SCOPE OF WORK

21. Scope of Technical Services

A. Description

Under the direction of the principal investigator and his staff a 3-year program of scientific research is to be conducted by the Southwest Foundation for Research and Education

The major areas of study are:

1. The Metabolism of ethynyl estrogens.
2. Adverse Endocrine effects of contraceptive steroids
3. Effects on lipid and carbohydrate metabolism
4. Thromboembolic phenomena.

Methodology

The contractor will carry out this research in accordance with the specific methodology described in the Southwest Foundation 1 April 1970 proposal "A Multi-disciplinary Investigation into the Metabolic Alterations and other (cont. p. 5)

B. Technicians

(1) (a) Number

(b) Specialized Field

(c) Grade and/or Salary

(d) Duration
of Assignment
(Mon-Months)

SEE BUDGET ATTACHED

(2) Duty Post and Duration of Technicians' Services

N/A

(3) Access to Classified Information

None

(4) Dependents

 Will Will Not

Be Permitted to Accompany Technician

C. Financing Costs of Technical Services

(1) By AID - \$912,792

(2) By Cooperating Country -

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22. Equipment and Supplies (Related to the services described in Block 21 and to be procured outside the Cooperating Country by the supplier of these services)

A. (1) Quantity

(2) Description

(3) Estimated Costs

SEE BUDGET ATTACHED

B. Financing Costs of Equipment and Supplies

(1) By AID - \$

(2) By Cooperating Country -

23. Instructions to Authorized Agent

This PIO/T is for the purpose of entering into a level of effort contract for three years with

Southwest Foundation for Research and Education
P. O. Box 28147 (10,000 W. Commerce)
San Antonio, Texas 78228

Contacts: Harold Vagtborg - President
Joseph W. Goldzieher - Principal Investigator

24. Special Provisions

- A. This PIO/T is subject to AID contracting regulations.
- B. Except as specifically authorized otherwise by AID, all services authorized by this PIO/T must be obtained from U.S. sources.
- C. Except as specifically authorized otherwise by AID, purchase of all commodities authorized by this PIO/T, must be obtained from U.S. sources under Grographic Code 000.
- D. All references in the Project proposal to an annual conference and dissemination of information to news media are to be precluded from the contract.

AID 1350-1X (8-63) O/T	DEPARTMENT OF STATE AGENCY FOR INTERNATIONAL DEVELOPMENT PROJECT IMPLEMENTATION ORDER/TECHNICAL SERVICES	X <input type="checkbox"/> Worksheet <input checked="" type="checkbox"/> Issuance Cooperating Country World-wide Project/Activity No. and Title Research on the Safety of Contraceptive Steroids - Southwest Foundation for Research and Education	PAGE 4 OF 9 PAGES PIO/T No. 931-17-521-570- 73-3104711
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25. Reports by Supplier of Services (Indicate type, content and format of reports required, including language to be used if other than English, frequency or timing of reports and any special requirements)

The information required in Reports under Section 16 of General Provisions will be submitted in semi-annual and annual reports. A semi-annual report will be required for the first 6 months of each calendar year and should be submitted to AID July 15. The annual report will cover each full calendar year and should be submitted to AID/W on or about January 15. The first report will be due on or about January 15, 1971 and will provide the information for the period beginning from the date the contract is signed until the end of calendar year 1970. Annual reports for each of the project sections should include tabular and narrative information on research findings and significance of findings; methodology used and constraints encountered scientifically administratively and in other areas in obtaining research objectives.

26. Availability of Background Information (Additional information useful to Authorized Agent and Prospective Suppliers; if necessary, cross reference Block 21.D(3) above)

- Project Summary
- Project Proposal - plus Appendices and Indirect Cost Rate Proposal
- Action Memo to the Administrator
- Summary RAC's recommendations
- Letter dated April 27, 1970 from Spollacy - Dictated Reply from Dr. Goldzieher
- Single Source Justification

27. Relationships of Supplier to Cooperating Country and to AID.
A. Relationships and Responsibilities

B. Cooperating Country Liaison Official

AID Liaison Officials
G. Joseph Spaidel TA/POP/R

DEPARTMENT OF STATE
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Checklist Is Co

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CONTINUATION
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YMDOL

PIO/T

Indicate block
numbers.

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21.

Potential Hazards of Contraceptive Steroids" with the exception of 5.c.Ib and 5.c.V (Prospective studies of thromboembolic disease and Annual Symposium). This protocol includes the following methods:

I. Metabolism of Contraceptive Estrogens.

Since these compounds are of fundamental importance in all current oral contraceptive preparations, and since the compounds themselves or their metabolites may be involved in the alleged hazards of these agents, a thorough inquiry of their metabolism and its individual variation is imperative.

Radioactively labelled ethynyl estradiol and mestranol will be given concurrently, to women who are just starting on oral contraceptive therapy and others who have been on these agents for at least one year. In this way, a comparison of initial and "adapted" metabolism can be undertaken.

Using a silvered florisil column developed at the Southwest Foundation, urinary and plasma metabolites will be isolated. Their kinetics in the body will be established using synthesized metabolites.

II. Adverse Endocrine Effects of Contraceptive Steroids.

a. The relative effectiveness of ethynyl estradiol and mestranol as ovulation inhibitors is still an unsolved question. It is critically important at the present time, when efforts are being made to reduce the dosage of the estrogens to a minimum. Accordingly, a study will be carried out on volunteer patients (protected with IUDs) of the ovulation-inhibiting effect of various dose levels of the 2 compounds, with proof of ovulation-inhibition being obtained by the determination of plasma progesterone levels by the competitive protein binding method.

b. Examination of the hypothalamic-pituitary effects. Post-treatment infertility and amenorrhea, though uncommon, have been emphasized as adverse effects of contraceptive steroid therapy. This problem can best be explored by a study of the effects of various types of oral and injectable steroids on plasma levels of FSH and LH as determined by radioimmunoassay. In the past, such studies have been carried out on a limited number of patients. This has been the consequence of experimental designs which required the daily blood samples over 30 to 60 days. Volunteers for this type of experimentation are hard to find. This study will approach the problem by a cross-sectional rather than a longitudinal design, utilizing the very large numbers of patients available, both in San Antonio and Mexico City. By the accumulation of large numbers of samples from every stage of therapy, the pattern of FSH and LH levels throughout the treatment cycle will emerge. Similar studies will be carried out for injectable compounds such as medroxyprogesterone acetate

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Worksheet Memo

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21.

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to compare the on-treatment and off-treatment effects.

c. The adrenal effects of steroid hormones have been examined almost entirely by inspection of urinary 17-ketosteroids and corticoids. A few studies on cortisol secretion rate have been carried out, but not in numbers sufficient to establish the magnitude and consistency of effects; nor has it been examined in respect to estrogen alone versus estrogen-progestin combinations, which are likely to have substantially different effects. This question is important, in view of the possibility that plasma unbound, unconjugated cortisol may be elevated by these agents. Plasma cortisol levels may be involved in the alterations of carbohydrate metabolism which have recently come under scrutiny. The studies of adrenal cortical function will be integrated with the tests of glucose tolerance and lipid metabolism in patients with and without family histories of diabetes, in an effort to obtain a broader insight into the interrelations of these components.

d. The interaction of gonadal hormones and the adrenal has another potentially useful aspect. It is well known that there are interrelationship at the hypothalamic level between the regulation of ovarian function and the regulation of adrenal cortical activity. Further exploration may lead to useful application of these interactions for purposes of ovulation control by classes of steroids which might avoid some of the side-effects of estrogens. The action of dexamethasone and of estrogen in inhibiting or stimulating ovulation has been investigated, and there is evidence that other compounds, with fewer "adrenal" or "estrogenic" action may have similar effects. This area of investigation will include weak corticosteroids such as corticosterone, etc. and weak or relatively "inactive" androgens such as androstenedione and 11B-hydroxyandrostenedione. The experiments involve parenteral administration to PMS-primed immature rats, and also intrahypothalamic micro-injections into the ventromedial, preoptic and related hypothalamic nuclei.

III. Long-term Studies of Carbohydrate and Lipid Effects

The contraceptive clinic at the Southwest Foundation has at the present time some of the longest-term users of contraceptive agents anywhere in the world. Some of the patients have been under treatment for 10 years. Certain studies have already been carried out on these patients, and examination of their glucose tolerance, plasma insulin and growth hormone levels have been published in collaboration with Dr. William Spellacy of the University of Miami (Amer. J. Obstet. & Gynec. 106:173, 1970). Of particular interest is the difference between sequential and combination type oral contraceptives. The former produce much less change in carbohydrate metabolism than the latter. These differences need further confirmation in a larger groups, the program anticipates enlisting the aid of several other clinics (cont. p. 7)

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Research and EducationIndicate block
numbers.

21.

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(Mexico City, possibly the Tyler Clinic in Los Angeles) in carrying out retrospective studies on long-term users.

However, prospective studies are essential, and they must have an epidemiological aspect in view of the marked differences reported for various populations: the differences between British and American reports are particularly striking. These differences also appear to be marked in the case of lipid abnormalities reported for British and American populations. This point has not received the attention that it deserves, and in particular it has not been explored in a sufficient variety of populations. Therefore the program will include studies of plasma cholesterol, triglycerides and lipoproteins on patients using various types of oral contraceptives, and correlate these with the studies of carbohydrate metabolism, and with studies of adrenal function. The importance of lipoproteins rather than merely lipid levels is recognized, since the association of various types of lipoprotein disturbances may be related to the tendencies to atherogenesis. These studies of lipoprotein patterns will use electrophoresis as the basic methodology.

IV. Studies of Thromboembolic Disease

a. Investigations of vascular pathology. The nature of vascular lesions associated with clinical thromboembolic episodes of idiopathic character, and the relationship of such changes to the effects of estrogens and progestins is as yet obscure. Some animal experiments have demonstrated lesions produced by estrogens; nothing is known of the effect of progestins, or estrogen-progestin combinations. Human lesions, which vary from author to author, have been reported in a small number of publications. It is clearly urgent to examine human vascular pathology in relation to this problem, in a more intensive way than has been done to date. Comparisons with the effect of estrogens in pregnancy are vital, as this represents a common clinical high-estrogen exposure. However, autopsy material from pregnant individuals is relatively scarce and difficult to obtain. Therefore there will be a collaboration with Dr. M. Maqueo, chief of the pathology service of the First Obstetrical-Gynecological Hospital of Mexico City, which has one of the largest services in North America, and a wealth of autopsy material.

It is planned to review the reported pathological lesions and in particular, to see if any such lesions are found in autopsy material from pregnant women, particularly those who have or have not undergone thrombotic episodes. Lesions in toxemic patients will also be important, in view of the reports of hypertensive changes in some subjects on contraceptive medication. An effort will also be made to

(cont. p. 8)

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obtain autopsy material from various hospital, from patients dying of acute pulmonary embolism, but including patients using or not using contraceptives, and patients with or without determinable predisposing causes for thrombosis.

Results and Scheduling Works

The above studies are expected to produce (1) a systematic body of knowledge regarding the objective side effects of contraceptive steroids; including, specifications of any hazards, their frequency and the mechanisms by which these effects occur (2) methods for modifying or averting such hazards (3) dissemination of findings in scientific journals. Because of the nature of this research and the status of the literature, the contractor has the option to make changes in the detailed protocols for each study described in the proposal and in the following work schedule in order to pursue whichever findings promise to yield the most important and relevant information. Any change however in the nature of the individual studies will require prior approval of TA/POP.

I. Metabolism of Contraceptive Estrogens - to begin as soon as possible and continue for approximately 3 years.

II. Adverse Endocrine Effects of Contraceptive Steroids
Pituitary investigations will continue for three years. Adrenal investigations to be carried out in approximately 1½ years.

III. Long term Studies of Carbohydrate and Lipid Effects - to continue for 3 years - Patients to be checked every 3 to 6 months over this period of time.

IV. Studies of Thromboembolic Disease.
These pathology studies will dovetail with the studies in III above and will be carried out over a period of three years.

Should clinical studies of any synthetic materials or compounds be deemed necessary and of interest for this research at any time during the life of this project, the contractor may enter into sub-contracts or collaborative arrangements with individuals or institutions for these purposes, subject to obtaining the prior approval of AID/TA/POP for these sub-contracts or collaborative arrangements.

The contractor will assure that all clinical studies conducted under the contract in the U.S. by the contractor, a sub-contractor or other collaborative institutions or individuals meet the requirements of FDA and the Surgeon General's directive governing human trials.

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Clinical studies conducted in any country outside of the U.S. require approval of AID/TA/POP and if approved shall be conducted in accord with that country's practices and regulations governing such studies.

The contractor may enter into sub-contracts or purchasing agreements (1) for the production of synthetic materials or compounds developed under this contract by the contractor which are needed for clinical studies and (2) for the production of synthetic materials and compounds not developed by the contractor but which are needed to carry out the research under this contract provided such sub-contracts have the prior approval of A.I.D. and assures that the rights, data and results of the work developed under this contract remain in so far as possible within the public domain.

PROJECT SUMMARY

Project Title : Research on the Safety of Contraceptive Steroids
Currently in Use

Contractor : The Population Crisis Foundation of Texas in
Cooperation with the Southwest Foundation for
Research and Education

Principal Investigator : Joseph W. Goldzieher, M. D.

Duration : Three years

Estimated Cost : Total \$1,887,792
FY 70 1,887,792
FY 71 -
FY 72 -

926,364

Action Officer : TA/POP/R, J. Joseph Speidel, M. D.

1. Background

Certain steroid hormones are the active agents in the widely used oral contraceptives and in other, as yet experimental methods using injection and implantation techniques. These methods form one of the major technologies for conception and population control. While their effectiveness and acceptability is proven, their safety in long-term use and in a variety of populations is not established, and the possibility of undiscovered hazards has received considerable attention. It is the purpose of this research program to examine these questions intensively and from a variety of perspectives, ranging from inquiries as to the mechanisms of action, to metabolic fate within the body, and to effects on organ systems not directly involved in the contraceptive action.

To date most important studies of safety of these compounds have been carried out in the United States and Great Britain. Differences in the findings between these two countries and fragmentary evidence from the less developed countries suggests that there may be marked differences in health hazards of contraceptive steroids depending upon the population group where they are employed. One of the objectives of

this research program is to seek comparative data to help elucidate this question.

2. Description of Proposed Project

The major areas of inquiry are as follows:

1. Studies of the metabolism of ethynyl estrogens. These compounds are present in all oral contraceptives currently in use, and many of the complications such as thromboembolic disease, changes in carbohydrate metabolism, etc. are attributed to them.
2. Endocrine effects. (a) Prolonged infertility has been claimed as an undesirable after-effect. (b) Changes in adrenal function may be involved in the abnormalities of carbohydrate metabolism. The nature of these effects is inadequately understood.
3. Effects on carbohydrate and lipid metabolism. These are of particular importance since the diabetic trait is a common one; lipid changes are of great importance since certain abnormalities of plasma lipoproteins are related to the development of atherosclerotic changes in some way.
4. Thromboembolic phenomena. Although these complications are rare, they have received inordinate public attention. The available data are limited to studies of blood coagulation phenomena, which may or may not be relevant, and to retrospective case-control studies, none of which are completely satisfactory. Intensified pathological and prospective studies are needed, keeping in mind population variables and the need for an epidemiological approach. These studies will include (a) clinical pathology, (b) experimental studies of the effect of estrogens on vasculature and (c) epidemiological studies on the thromboembolic disease and on susceptible populations.

3. Significance of the Project to A.I.D. Objectives

In 1958, clinical studies indicated that orally-active steroid hormones were capable of providing effective and acceptable contraception. Their success is now history, and, recent experience suggests that their availability and continuing improvement is of increasing importance to the success of population programs in the less developed countries.

In various forms, whether as pills, injections or implants, they have proved effective and acceptable both in the highly developed and in the developing countries. An assessment of their short-term and long-term safety, the existence and the nature of any hazards, and a circumvention or solution of these hazards is a matter of the greatest

urgency. In the immediate past, an extensive and biased public airing of the imputed risks of these agents has impaired their acceptability in the United States and overseas. Unless this situation is resolved, and the nature and extent of any real risks clarified, their future is uncertain. At this late date, we can ill afford the loss of a highly effective contraceptive modality that might have an acceptable risk-to-benefit ratio, if the facts were known. The importance of establishing the future acceptability of these agents is of obvious importance to A.I.D. objectives.

Furthermore, the less developed countries have been hesitant to accept safety data relating to the U.S. and other developed countries. Some of these studies will provide comparative data from populations similar to those in the LDC setting which should serve to better define risks and possibly enhance the acceptability of these contraceptives in such a setting.

4. Relevance to Existing Knowledge

The estrogenic compounds in oral contraceptives have been linked to the only well established risk (thromboembolism) and other theoretical risks. Surprisingly, there is at the present time, virtually no information regarding the metabolism of the two estrogens, ethynyl estradiol and mestranol, which are included in all commercial oral contraceptive preparations.

The other studies on the adverse endocrine effects of contraceptive steroids, the long-term studies of carbohydrate and lipid effects or vascular pathology do not duplicate current work on these problems sponsored by NIH and the Food and Drug Administration. These agencies are supporting six different studies on the relationship between cancer and contraceptive steroids - investigation of this problem will not be undertaken by the proposed project.

5. Description and Evaluation of Methodology

The following investigations will be carried out:

I. Metabolism of Contraceptive Estrogens.

Since these compounds are of fundamental importance in all current oral contraceptive preparations, and since the compounds themselves or their metabolites may be involved in the alleged hazards of these agents, a thorough inquiry of their metabolism and its individual variation is imperative.

Radioactively labelled ethynyl estradiol and mestranol will be given concurrently, to women who are just starting on oral contraceptive therapy and others who have been on these agents for at least one year. In this way, a comparison of initial and "adapted" metabolism can be undertaken.

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c. The adrenal effects of steroid hormones have been examined almost entirely by inspection of urinary 17-ketosteroids and corticoids. A few studies on cortisol secretion rate have been carried out, but not in numbers sufficient to establish the magnitude and consistency of effects; nor has it been examined in respect to estrogen alone versus estrogen-progestin combinations, which are likely to have substantially different effects. This question is important, in view of the possibility

that plasma unbound, unconjugated cortisol may be elevated by these agents. Plasma cortisol levels may be involved in the alterations of carbohydrate metabolism which have recently come under scrutiny. The studies of adrenal cortical function will be integrated with the tests of glucose tolerance and lipid metabolism in patients with and without family histories of diabetes, in an effort to obtain a broader insight into the interrelations of these components.

d. The interaction of gonadal hormones and the adrenal has another potentially useful aspect. It is well known that there are interrelationships at the hypothalamic level between the regulation of ovarian function and the regulation of adrenal cortical activity. Further exploration may lead to useful application of these interactions for purposes of ovulation control by classes of steroids which might avoid some of the side-effects of estrogens. The action of dexamethasone and of estrogen in inhibiting or stimulating ovulation has been investigated, and there is evidence that other compounds, with fewer "adrenal" or "estrogenic" action may have similar effects. This area of investigation will include weak corticosteroids such as corticosterone, etc. and weak or relatively "inactive" androgens such as androstenedione and 11 β -hydroxyandrostenedione. The experiments involve parenteral administration to PMS-primed immature rats, and also intrahypothalamic micro-injections into the ventromedial, preoptic and related hypothalamic nuclei.

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The contraceptive clinic at the Southwest Foundation has at the present time some of the longest-term users of contraceptive agents anywhere in the world. Some of the patients have been under treatment for 10 years. Certain studies have already been carried out on these patients, and examination of their glucose tolerance, plasma insulin and growth hormone levels have been published in collaboration with Dr. William Spellacy of the University of Miami (Amer. J. Obstet. & Gynec. 106:173, 1970). Of particular interest is the difference between sequential and combination type oral contraceptives. The former produce much less change in carbohydrate metabolism than the latter. These differences need further confirmation in a larger group, the program anticipates enlisting the aid of several other clinics (Mexico City, possibly the Tyler Clinic in Los Angeles) in carrying out retrospective studies on long-term users.

However, prospective studies are essential, and they must have an epidemiological aspect in view of the marked differences reported for various populations: the differences between British and American reports are particularly striking. These differences also

appear to be marked in the case of lipid abnormalities reported for British and American populations. This point has not received the attention that it deserves, and in particular it has not been explored in a sufficient variety of populations. Therefore the program will include studies of plasma cholesterol, triglycerides and lipoproteins on patients using various types of oral contraceptives, and correlate these with the studies of carbohydrate metabolism, and with studies of adrenal function. The importance of lipoproteins rather than merely lipid levels is recognized, since the association of various types of lipoprotein disturbances may be related to the tendencies to atherogenesis. These studies of lipoprotein patterns will use electrophoresis as the basic methodology.

IV. Studies of Thromboembolic Disease

a. Investigations of vascular pathology. The nature of vascular lesions associated with clinical thromboembolic episodes of idiopathic character, and the relationship of such changes to the effects of estrogens and progestins is as yet obscure. Some animal experiments have demonstrated lesions produced by estrogens; nothing is known of the effect of progestins, or estrogen-progestin combinations. Human lesions, which vary from author to author, have been reported in a small number of publications. It is clearly urgent to examine human vascular pathology in relation to this problem, in a more intensive way than has been done to date. Comparisons with the effect of estrogens in pregnancy are vital, as this represents a common clinical high-estrogen exposure. However, autopsy material from pregnant individuals is relatively scarce and difficult to obtain. Therefore there will be a collaboration with Dr. M. Maqueo, chief of the pathology service of the First Obstetrical-Gynecological Hospital of Mexico City, which has one of the largest services in North America, and a wealth of autopsy material.

It is planned to review the reported pathological lesions and in particular, to see if any such lesions are found in autopsy material from pregnant women, particularly those who have or have not undergone thrombotic episodes. Lesions in toxemic patients will also be important, in view of the reports of hypertensive changes in some subjects on contraceptive medication. An effort will also be made to obtain autopsy material from various hospitals, from patients dying of acute pulmonary embolism, but including patients using or not using contraceptives, and patients with or without determinable predisposing causes for thrombosis.

b. Prospective studies of thromboembolic disease. Inherent difficulties in retrospective studies make it evident that prospectively-designed epidemiological investigations will have to be carried out to

obtain more definitive information about this problem. Certain studies along these lines are in progress in other institutions, but the populations studied may not be similar to those in the LDC's and the results are still in the future. On the other hand, experience may have already been gained with respect to the size of populations required, dropout rates, the emergence of subgroups with greater or lesser susceptibility, etc. Moreover, the experience of others may indicate where a well-designed prospective study could serve to obtain different or supplementary types of data which would converge with the investigations already under way. This program is therefore envisaged in several steps: (1) A state-of-the-field study, involving visits to investigators engaged in ongoing programs, with discussion and evaluation of their activities. On this basis (2) a feasibility analysis, involving delineation of objectives and methodology, and statistical analysis of the experimental design required, the number of subjects needed, the time of observation necessary, etc. Finally, (3) field trials will be initiated. Efforts will be made to make these studies as relevant to the LDC setting as possible.

6. Evaluation of Research Competence of the Investigators

The curriculum vitae of the senior investigators in this study Drs. Goldzieher, Hagino, Maqueo, Matthijssen, and Moses provides adequate evidence of their competence in this field. An experienced analytical steroid chemist and an experienced epidemiologist will have to be added to the senior staff. At the outset, the major collaborating centers to be used will be the Asociacion Pro-Salud Maternal and the Hospital Gineco-Obstetricia Numero Uno, IMSS, in Mexico City. Other collaborations, as for the various epidemiological studies, will be developed as the program develops.

7. Appraisal of Research Resources and Budget

The Population Crisis Foundation of Texas is an organization founded for the specific purpose of promoting goal-oriented research in the population control. For the purposes of this application, the Southwest Foundation for Research and Education will serve as its in-house capability. The laboratories of the Division of Clinical Sciences will be the site of these studies.

The Southwest Foundation for Research and Education has been intimately involved in the development, testing and study of steroidal contraceptive agents for over a decade. Nearly 70 publications attest to the extent of this involvement. With developing knowledge of the mechanism of action, which it has helped to elucidate, the area of competence have extended into synthetic steroid metabolism, into basic

and developmental studies utilizing primates, into neurophysiology, and more recently into collaborative clinical and experimental investigations of metabolic and pathological side-effects. The proposed multidisciplinary research is in every way a continuation and expansion of ongoing investigations; and will make use of these proven capabilities.

A summary of the budget is as follows:

<u>Topic</u>	<u>Year 1</u>	<u>Year 2</u>	<u>Year 3</u>
Metabolism of Contraceptive Estrogens	96,873	100,699	104,365
Endocrine Effects	106,035	110,559	114,757
Carbohydrate and Lipid Effects	72,401	75,170	77,080
Vascular Pathology	10,000	10,000	10,000
Epidemiology of Thromboembolic Disease	148,070	301,024	337,297
Equipment	24,100	-	-
Administration	<u>60,330</u>	<u>62,747</u>	<u>65,285</u>
	518,809	660,199	708,784

Three-year total = \$1,887,792

8. Technical and Scientific Review of Proposal

This proposal was reviewed and approved by the A.I.D.-Regional Research Committee on 18 March 1970 and by the Research and Institutional Grants Committee on 23 March 1970.

Outside review is in process and will be submitted to the RAC Population Subcommittee prior to the RAC meeting.

9. Summary Evaluation

This research program will attempt to provide answers concerning the existence and magnitude of potentially hazardous effects of steroidal contraceptive agents. This institution possesses the capability of providing this information which has great importance to A.I.D.'s population programs.