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932-0548

PROJECT STATEMENT

Date: April 18, 1972

A. PROJECT SUMMARY

932-0-548004301

1. Statistical

Project Title: Simplified Techniques of Fertility Control

43p

New or Extention: New

Contractor and Address: The Johns Hopkins Hospital and  
School of Medicine  
Johns Hopkins University  
Baltimore, Maryland 21205

Principal Investigator: Theodore M. King. M.D., Ph.D.

Duration: 3 Years

Total Estimated Cost: \$2,673,650

Funding by Fiscal Years: Current Year \$2,673,650

FY 73: 0

FY 74: 0

Project Manager:

J. Joseph Speidel, PHA/POP

2. Narrative

The objective of this research program is to establish a clinical unit for the development and evaluation of simplified fertility control techniques suitable for use in less developed countries. A secondary objective is to determine the undesirable side effects of drugs and techniques currently used in LDC fertility control programs and to seek ways of eliminating or minimizing these undesirable side effects. It is expected that this unit will allow the development and testing of new means of fertility control with regard to efficacy, simplicity, safety and patient acceptability of fertility control techniques. It will also serve as a facility for training LDC participants in the most up to date techniques of fertility control.

## B. EXPANDED NARRATIVE STATEMENT

### 1. Project Description and Background

The objective of this proposal is to establish a research program for development and evaluation of simplified post-conceptive fertility control techniques. A second objective is to delineate and eliminate the untoward effects of drugs and techniques used in fertility control. Research into multiple areas is proposed, including the development of improved pregnancy testing technology, the development of post-conceptive fertility control methods for menses induction and early termination of pregnancy, improved means of cervical dilatation, improved surgical equipment for clinical utilization in LDCs, the further perfection of second trimester pregnancy termination agents, and the elimination of untoward effects of presently employed fertility control agents and methods. Establishment of such a program will provide valid comparative results of the efficacy, safety, and patient acceptability of these fertility control techniques. It will also be available to trainees from LDCs at Johns Hopkins who participate in a variety of population programs.

### 2. Significance to A.I.D. Objectives

In March 1972, United Nations released a report confirming that the post-conceptive control of fertility by surgical termination of early pregnancy is the most important and frequently used means of fertility control throughout the world. Although prevention of pregnancy is desirable, it is well known that many individuals will only take action to control fertility after a pregnancy is suspected or established. With the passage of a liberalized abortion law in India in August 1971, surgical termination of pregnancy is now legal on reasonable indications for a majority of women in the less developed countries.

Research on improved post-conceptive means of fertility control is important for the following reasons:

1. A principal reason for this research is to develop techniques which can safeguard the health of women choosing post-conceptive means of fertility control. With abortion now more freely available in India, Pakistan, Mainland China, Malaysia, Singapore, Taiwan, and Korea, it is increasingly important that methods be developed which are as safe and practical as possible. Safety of the best current methods already compares favorably with means such as the pill and IUD, and is many times safer than continued pregnancy. In New York, the liberalized abortion law resulted in a significant decline in maternal death rates and out-of-wedlock births. Even so, improvement in methods of pregnancy termination

is important to maximize their safety and practicality in less developed countries where currently used techniques are frequently not as safe as those employed in the developed countries and in many countries, a sizeable percentage of Ob-Gyn beds in hospitals are occupied by incomplete, frequently infected, induced abortions.

2. Improved methods are needed to cope with the failures of currently used reversible contraceptives. For example, an IUD user may have only 3% chance of becoming pregnant in any given year, but over 25 years of sexual exposure the chance of an unwanted pregnancy may be very significant with failure to avoid unwanted pregnancy more likely than success over this time span.
3. The demographic impact of pregnancy termination is enormous. Changes in birth rates in Eastern Europe and Japan after liberalization of abortion laws have amply demonstrated both the demographic impact and latent demand for this means of fertility control. Official estimates in India placed the number of pregnancy terminations at 6 million annually--prior to the change in laws. The Indian Ministry of Health and Family Planning has recently held a conference to examine the best equipment and techniques for implementing the new law.

To date there has been little research to improve conventional pregnancy termination techniques. Since early terminations are safer than those carried out later in pregnancy, the development of simplified means of pregnancy testing and detection will be an objective of this project. Pregnancy testing is also a valuable public health measure for women desirous of more children in that it allows initiation of early prenatal care which is necessary to achieve the healthiest outcome for both mother and infant.

Although primarily a research program, it has become increasingly clear that moving the latest research findings into the hands of practitioners in less developed countries is often a slow and difficult process. Therefore, a component of this program will be to train LDC practitioners in a "model" fertility control clinic setting. The clinical research unit will be one part of this fertility control clinic--the other activities contributing to this clinic already in being at Hopkins.

With many countries moving to adopt a new "pregnancy centered" approach for family planning services (recently documented by UN Fund for Population Activities), family planning clinics will increasingly emphasize (1) the provision of quick and accurate diagnosis of pregnancy, (2) expeditious termination of any unwanted pregnancy, and (3) provision of the best methods for prevention of subsequent unwanted pregnancies, e.g., immediate IUD insertion or outpatient female sterilization, as well as ample

supplies of oral and other contraceptives. Trainees at Hopkins will receive instruction in a program offering this new pattern of family planning services and the latest techniques of fertility control which will facilitate their initiating such programs in their own countries. While an output of 40 clinical trainees in the first year of the program would not possibly solve the need for hundreds of thousands of such individuals throughout the world, nevertheless, the strategic placement of trainees in underdeveloped countries could lead to a secondary diffusion of the essential knowledge and skills in the field of population control.

### 3. Relation to Existing Knowledge

Research in three basic areas is proposed: (1) pregnancy testing, (2) pharmacologic means of pregnancy termination and (3) physical means of pregnancy termination. The relationship of current knowledge to each of these research topics is as follows:

1. Improved pregnancy testing technology - Current methods are limited by lack of sensitivity in early pregnancy. A test which could detect a pregnancy prior to the missed period would be invaluable in allowing selective application of menses inducers (such as prostaglandins). Improved reagents which are stable in tropical climates on long storage without refrigeration are needed, as are easy to read tests which minimize false positives and false negatives.
2. Pharmacologic means of post-conceptive fertility control - There are several potential approaches to this means of fertility control including: (a) prostaglandins and other direct stimulants of uterine musculature such as oxytocic agents, (b) agents which interfere with progesterone production by a direct effect on the corpus luteum, (c) agents which interfere with the hormones needed to maintain corpus luteum function such as anti-lutenizing hormone (LH) or anti-human chorionic gonadotrophin (HCG) and (d) agents with a direct toxic effect on the uterine contents.

Although these pharmacologic agents, particularly prostaglandins, are very promising when used in the first trimester, evacuation of the uterine contents is incomplete in a certain proportion of cases. Therefore criteria must be established as to when intervention is warranted, new means developed to determine when uterine evacuation is complete, and the best methods developed to handle incomplete terminations.

3. Physical means of pregnancy termination - Improved physical methods should stress simplicity and safety. The question of safety as it relates to pregnancy termination is complicated, and there has been no systematic approach with the goal of identifying and eliminating those factors which contribute to morbidity and mortality.

- a. Anesthesia - To be practical in less developed countries procedures must be done under local anesthesia which minimizes or eliminates some of the risks of general anesthesia, especially aspiration and its consequences. With local anesthesia, the uterine fundus remains normally responsive to oxytocic agents allowing maximum contraction of the uterine musculature with diminished risks of hemorrhage and perforation. This method of anesthesia has disadvantages, including drug toxicity related to the local anesthesia, or the sedative or tranquilizer usually required. Variable degrees of pain relief are experienced.
- b. Perforation of the Uterine Fundus - While uncommon, perforation of the uterine fundus is a serious complication of surgical termination. There has been no systematic approach to the problem of perforation with its goal the reduction of this complication to its irreducible minimum.
- c. Hemorrhage - There is little question that blood loss in suction curettage is less than that associated with the traditional D&C. Blood loss generally stops only after complete evacuation of the uterus, and the greater the time elapsed during the procedure, the greater the blood loss. There is no documentation of those parameters which influence blood loss, and there is therefore no systematic approach design to minimize this problem.
- d. Infection - This complication remains the most common of the serious sequelae of abortion. Following suction curettage or D&C, infection most commonly indicates incomplete evacuation of the uterus. There is no reliable method of determining when the uterus has been completely emptied. Most commonly, the operator simply continues until no further tissue is obtained, and assumes complete evacuation.

#### 4. Relation to Other Research

The question of safety as it relates to pregnancy termination is indeed complicated, and there has been no systematic approach with the goal of identifying and eliminating those factors which contribute to maternal morbidity and mortality. Such factors include anesthesia, both local and general, and a study of the relation to the morbidity of the various techniques of fertility control. Injury to maternal tissues, whether manifested by perforation of the uterine fundus, hemorrhage, or infection, is an area relatively unstudied. There has also been little research into the efficacy and safety of the abortion methods themselves. No work has been done to minimize blood loss during curettage, to establish with certainty the completion of an abortion, or to eliminate the more serious intra-abdominal damage complicating termination of pregnancy. As in the field of sterilization, it has not yet been ascertained if the

transfer of these surgical methods from the hospital to the clinics of lesser developed countries will allow continuance of the low incidence of complications and side effects.

A.I.D. has made a large investment in prostaglandin research. Prostaglandin studies in this program will be confined to work on side effects, studies needed to obtain comparative data and use of other drugs in conjunction with prostaglandins and cases for demonstration and training purposes. There is little clinical work on other pharmacologic post-conceptive means of fertility control.

A.I.D. has one project funded at \$170,000 per year with the Battelle Memorial Institute to develop improved electrical and non-electrical vacuum systems for suction curettage. This project will serve as a clinical testing facility for the equipment developed at Battelle. This project is a clinical research program whereas the Battelle program focuses on engineering development of equipment.

The proposing office is not aware of any other major research efforts in the area of the proposed research.

#### 5. Scope of Work

Research into the following areas is proposed:

1. Development of improved pregnancy testing technology, with specific focus on accurate and simple detection of the very early gestation.
2. Development of improved means of menses induction and termination of early pregnancy.
3. Development of improved means of second trimester termination of pregnancy.
4. Improved pharmaceutical and mechanical means of cervical dilatation.
5. Improved equipment for clinical utilization in surgical pregnancy termination.
6. The Clinical Research Unit and the other family planning services of Johns Hopkins will be used for training purposes.

#### 6. Research Methodology and Work Plan

Project I: Evaluation and Development of Improved Pregnancy Testing Technology

Objective: To improve the practicality and reliability of tests for the early detection of pregnancy. A method suitable for use in LDCs which

can be used by the individual at home will be sought.

The history of bioassays for HCG in the Department of Gynecology and Obstetrics in the Johns Hopkins Medical Institutions is well-recorded in the literature and was initiated by the invention of a quantitative assay for HCG in serum in 1941.

The history of immunoassays in the department began in 1961 when efforts were initiated to develop new immunological tests for pregnancy. Since that time the department has invented three entirely different pregnancy tests, two of which are now commercial products, some of which are on the market and others of which are still undergoing field trials. The institution has developed considerable experience in conducting large field trials of new pregnancy tests, both theirs and others.

Proposal: Based on the experience of this laboratory three approaches will be followed to meet the stated objective: (1) Invention of an entirely new pregnancy test; (2) perfection or completion of one of several tests which have been evolving in the laboratory; and (3) modification of existing tests and their adaptation to meet the needs of early diagnosis.

The project will stress the importance of the covalent bond in indicator binding, but will also investigate the possibility of new improved carrier indicator particles on which the binding will occur. Conjugation will be attempted with the newer, more highly purified preparations of antigen, namely pure preparations of HCG, which were not available five years ago. Specifically for this project, another batch of antibody to HCG will be developed using the newer preparations of HCG. Antibody purification will be effected. For storage stability and transport ability lyophilized (dried) reagents are envisioned as the most suitable but liquid preparations will be considered also if they can be packaged to produce similar results. Innovative ways of packaging to achieve the criteria as defined under laboratory and field testing reliability will be investigated.

The method developed will attempt to achieve the following criteria:

1. A sensitivity of at least 0.5 IU/ML with the performance of two tests instead of one.
2. An accuracy ranging from 95-99%.
3. A false-positive rate of 1% or less.
4. A false negative rate of 1% or less.
5. Absolute precision.

Storage conditions will be judged by satisfactory performance after one year at room temperature and six months at any temperature over 80° C. With such a test it would be possible to detect very early pregnancies, e.g., prior to the missed period, and it would be suitable for overseas use due to simple packaging and use, and stable reagents. The test will be evaluated as per routine in The Johns Hopkins laboratory using the same protocol which includes methods for collection, sampling, programming and analysis as performed for all other tests. Trials will be conducted in the actual settings in which they will be employed later, namely fertility control clinics which focus on termination of pregnancy or initiation of early prenatal care. The tests should also be made under the most adverse conditions, as might be experienced by individuals in developing countries, in comparison with an already well-established but less sensitive commercial test.

Project II: New Means of Menses Induction and Termination of Early Pregnancy

Objectives:

- I. To seek new means of menses induction and early pregnancy termination by systemic drug administration and to determine the best means of treating incomplete evacuation.
- II. To seek new means of endometrial shedding and early pregnancy termination by topical drug administration.

The study is designed to explore the possibility of inducing early abortion in such a way as to avoid those problems associated with currently used methods. Systemic drug administration and the topical application of drugs to the endometrium will be aimed at inducing shedding and therefore, evacuation of the uterine contents. Such methods would be directed at the endometrium and its contents rather than pregnancy per se and would, therefore, be **efficacious** even if implantation had not yet occurred. Routes amenable to self-administration, such as intravaginal, will be emphasized.

I. Systemic Drug Administration

A. Prostaglandins

Prostaglandins have been reported to induce menses when given up to a week or ten days after the missed menstrual period. This technique has only been tested in small series of women inadequately evaluated and followed. The potential use of prostaglandins as a self-administered, once-a-month contraceptive must be established by controlled investigation of their efficacy, safety, low teratogenicity in sub-marginal doses, tolerance and patient acceptability.

The following studies will be performed:

1. PGF<sub>2a</sub>:intravenous trials,
2. PGF<sub>2a</sub>:intravaginal trials,
3. PGE<sub>2</sub>:intravenous and intravaginal,
4. Prostaglandin analogues:intravenous and intravaginal.

Materials and Methods - Normally ovulating women, exposed to pregnancy, and two to 14 days past the first missed menses will sign informed consent and receive approval for therapeutic abortion. This study has already received approval from the Joint Committee on Clinical Investigation of The Johns Hopkins Hospital.

A series of 15 to 20 women will be treated with intravenous prostaglandin F<sub>2a</sub>, 50 ug<sub>m</sub>/minute for eight hours, with serial evaluation of serum progesterone, estrogens and HCG. Menstrual-like vaginal bleeding should result, but it is presently unknown whether the oxytocic effect of prostaglandin will be sufficient to interrupt an early implantation. Following infusion, patients will be discharged if stable, with followup HCG and pregnanediol determinations, and basal body temperature recordings. At approximately three weeks after the initial infusion, these patients will either have an endometrial biopsy or a dilatation and curettage, either to diagnose the presence of pregnancy, or to ascertain its complete termination. Tissue obtained will be sent for microscopic pathologic evaluation, as well as for karyotyping, tissue culture, and enzymatic analysis. The teratologic effects of the drug will therefore be evaluated, and an index of its efficacy gained.

If these preliminary results indicate that longer duration of exposure is needed to assure complete termination, daily infusions of intravenous medications will be evaluated. This is justified since the aim is to develop a self-administered, effective vaginal preparation, which might well be given over a longer period of time without added inconvenience to the patient. Thus, the first goal is to establish that the approach has merit; the second, to obtain information on the parameters of dose tolerance, efficacy, and needed duration of use. Therefore, the carefully controlled studies using intravenous administration are a necessary prelude to trials of PGF<sub>2a</sub> in the form of intravaginal suppositories or tablets. Drug tolerance and efficacy will be analyzed, and studies performed as described above.

Prostaglandin E<sub>2</sub>, and other prostaglandin analogues will be tested as they become clinically available, using FDA approved protocols. The mechanism for controlled experiments of drug tolerance, efficacy, and

patient acceptability will exist. In addition, the means will be provided to evaluate improved delivery systems for prostaglandins, including prostaglandin-impregnated plastics, and devices designed for insertion within the cervical os.

The pathophysiology of those patients without complete evacuation of the uterine contents will be studied. Techniques for assessing completeness of evacuation will be studied and a variety of regimens for treatment of the incomplete termination evaluated including use of forceps, curettage, suction, aspiration, and antibiotics. Indications for treatment such as bleeding and fever will be evaluated.

#### E. Immunologic Means

Immunologic means of fertility control are receiving a great deal of research interest, with only limited human utilization to date. Much of the research into these agents is being carried on in institutions that do not possess clinical population for appropriate testing. This project will provide both continuity between such A.I.D. supported institutions, and a clinical setting for the statistical comparison of these agents as to their efficacy in terminating human pregnancy. Anti-HCG and anti-LH are being prepared, and anti-trophoblastic sera is currently being tested in animals. Studies investigating these antisera will be performed in conjunction with other institutions involved in their development, as they become clinically available.

#### II. Topical Drug Administration

The aim of this project area is to determine if early termination of pregnancy can be performed in a simple, safe, inexpensive and efficacious manner by local application of drugs to the endometrium so as to induce shedding of the uterine lining and its contents.

The drugs selected for testing are those which might be expected to exert a specific or non-specific effect upon the endometrium resulting in shedding. Topical application can be expected to result in higher tissue concentration than could be achieved through systemic use. Therefore, drugs which might be toxic when given systemically, may prove both effective and safe when applied topically. Certain classes of drugs have been chosen based upon their specific pharmacologic actions. It is anticipated that as the project develops, some clues will be obtained as to which class of drugs will be most **efficacious**. Concentration of drugs will be varied. The following is a tentative list of drugs to be studied:

- a. Drugs which affect smooth muscle. These are chosen with the hope that they might be effective through the vasculature of the endometrium, and will include epinephrine, ergot alkaloids and oxytocins and prostaglandins.

- b. Drugs with non-specific effects upon protein. Included will be ethanol, rivanol, and acetic acid.
- c. Drugs which effect vascular permeability. These will include histamines, bradykinins, and seratonin.

Materials and Methods -

1. All animal studies will be carried out in Rhesus monkeys. The monkeys will be at least 3 1/2 years old, and when appropriate, will be introduced into the primate colony well in advance of the studies so as to insure a healthy and predictable population.
2. Uterine surgical specimens will be obtained through the cooperation of the Department of Gynecology and Obstetrics at The Johns Hopkins Hospital and the Department of Pathology. Surgical specimens will include only total hysterectomies done for benign disease and will be used to develop methods of introducing drugs into the uterine cavity.
3. Patients to be included in this study will consist of the following groups:
  - a. Those scheduled for laparotomy and/or abdominal hysterectomy will be utilized in the development of techniques for introduction of drugs into the uterine cavity.
  - b. Patients who are pregnant and requesting therapeutic abortion and whose duration of pregnancy is less than six weeks from the last menstrual period.

In all instances, each patient's participation in the project will be preceded by appropriate informed consent.
4. Tissue to be studied histologically will be immediately fixed in Hartman's solution and routinely prepared for hemotoxylin and eosin staining.
5. The Malmstrom intrauterine injector device such as routinely used for hysterosalpingograms will be utilized in the application of drugs in both the monkey and the human, alleviating cannula introduction through the Z-shaped monkey endocervical canal.
6. Pregnancy testing in the monkey will be carried out in the Gynecologic Endocrine Laboratory of the Department of Gynecology and Obstetrics.
7. Hematologic and blood chemistry tests in the monkeys will be carried out by the Department of Animal Medicine of the Johns Hopkins Hospital.

8. Hematologic and blood chemistry tests performed on the human will be carried out by the Department of Laboratory Medicine of the Johns Hopkins Hospital.
9. Animal surgery will be carried out under general anesthetic (Halothane) in operating facilities supplied by the Department of Animal Medicine of the Johns Hopkins Hospital.

Study Design - The project will be carried out in three segments:

Segment I - The testing of drugs on the endometrium of the Rhesus monkey.

Segment II - The development of techniques designed to achieve uniform delivery of the drug to the endometrial surface of the human.

Segment III - Testing of drugs in the human.

Segment I and II - of this program may be completed simultaneously.

Segment I

All drugs will first be tested in the Rhesus monkey utilizing both the non-pregnant and pregnant animal. The techniques for delivering the drug to the endometrium will be tailored to the unique characteristics of the monkey cervix and therefore, might be quite different from that eventually used in the human. While the precise methods used for drug application in the monkey must be determined as the project develops, it is anticipated that the technique will involve the use of a Malmstrum Uterine Injector, a device commonly used for the performance of hysterograms.

Experiments will be designed in such a way that following application of the test drug, its effects on the endometrium will be evaluated by sequential biopsies subjected to routine histologic preparation. In selected animals, the test drug will be administered with the animal under general anesthesia. At varying intervals, and under direct vision, biopsies of the endometrium will be obtained over a period of several hours to determine the immediate and early effects of the drug. In other animals, at varying intervals following drug application, the entire uterus, tubes and ovaries will be surgically removed for histologic examination. It is essential that these agents have minimal effects on the tubal epithelium.

Only in those instances where a drug produces a satisfactory endometrial response, i.e., shedding or sloughing of the endometrium, will more extensive studies be carried out. In those instances, animals will be subjected to experiments designed to test the systemic and long-term effects of drug application on the genital tract.

Systemic effects will be determined by application of drugs in an animal who has been prepared for appropriate monitoring of vital signs including

intra-arterial blood pressure, respiratory rate, pulse, electrocardiogram, and appropriate blood and urine sampling. In each experiment, under general anesthesia, the apparatus for drug application will be placed in a proper position in the animal prepared for monitoring. After complete recovery from the anesthesia, the drug application will be accomplished and monitoring will be continued over a period of approximately four to eight hours. Blood samples will be tested for hematocrit, white blood count, electrolytes, appropriate enzymes, and liver function tests. Urine samples will be analyzed for protein, sugar and formed elements.

Long-term effects will be tested on selected animals. These animals will be subjected to repeated drug applications during three separate early pregnancies. Approximately one to two months after the last drug application, selected animals will be subjected to total hysterectomy and the specimens grossly and microscopically examined. Other animals will be allowed to mate to test the reproductive capacity of the genital tract.

A drug will be considered for further testing if the following criteria have been met:

- A. Endometrial application of the drug results in reproducible shedding or sloughing of the endometrium and its contents.
- B. There is no adverse systemic effect demonstrated.
- C. The endometrium demonstrates its capacity for normal regeneration and maturation following recovery.
- D. The subsequent reproductive capacity of the genital tract has not been compromised by the drug application.

Drugs meeting these criteria will then be tested in Segment III.

#### Segment II

This segment of the project will involve the development of techniques designed to achieve uniform delivery of drugs to the endometrium of the human with the following objectives:

- A. The technique must be simple, rapid and inexpensive.
- B. Uniform distribution of drugs to the entire endometrial surface.
- C. There must be minimal or no spill into the uterine tubes or the peritoneal cavity.
- D. The introduction of drug must be accomplished through the undilated cervix in both nulliparous and parous patients.

Several techniques for drug application will be explored including the following:

- A. Application of drug by way of a small polyethylene catheter.
- B. Application of the drug by lavage utilizing a commercially available product (Gravelee Jet--Washer).
- C. Application of the drug in a form of a thick paste.
- D. Application of the drug with an endometrial brush.
- E. Application of the drug in a capsule which dissolves at body temperature.

The testing and development of these techniques will be carried out in two parts:

Part A - This part will make use of the human uterus removed as a surgical specimen for benign disease. Such specimens, when freshly removed, will be used to test the various techniques for their capacity to achieve uniform distribution of a drug through an undilated cervix. The test material in this part will consist of a readily-visualized dye such as methylene blue suspended in an appropriate solvent or vehicle. After application, the uterus will be opened and the distribution of the dye over the endometrial surface will be documented. Those techniques which achieve a uniform distribution of dye through an undilated cervix will then be further tested in Part B.

Part B - These tests will involve the use of volunteers who are scheduled for laparotomy and/or abdominal hysterectomy for benign disease. The test material will consist of an inert, readily-visualized dye such as indigo carmine suspended in an appropriate solvent or vehicle. With the patient under general anesthesia and after appropriate preparation of the vagina and cervix and immediately prior to laparotomy, application of the dye will be accomplished by one of the techniques being tested. At the time of laparotomy, careful inspection of the uterine tubes and pelvic cavity will be carried out to detect spill of the dye through the uterine tubes. After removal of the surgical specimen, the distribution of the dye will be carefully determined by appropriate examination of the uterine cavity and the uterine tubes when available.

Those techniques which accomplish uniform distribution of dye within the uterine cavity and are not associated with significant spill into the uterine tubes or peritoneal cavity will then be subjected to testing in Segment III.

### Segment III

Patients who are pregnant, requesting therapeutic abortion and in whom the duration of pregnancy is less than six weeks, will be considered candidates for study in this segment. Volunteers among such candidates will have a complete evaluation including history, physical examination, and laboratory screening to include hematocrit, white count, urinalysis, blood group and Rh and SMA-12. While the patient's vital signs are being constantly monitored, drug application to the uterine cavity will be accomplished by the techniques previously developed. The patient will then remain in the hospital for 24 hours or longer if clinically indicated. Following an appropriate time interval, patients will be discharged.

If, at the end of approximately three weeks, pregnancy is not interrupted as judged by persistently positive immunologic pregnancy tests and other confirmatory data, the pregnancy will be terminated by sharp curettage under local anesthesia. Tissue obtained from careful curettage will be subjected to enzymatic analysis, karyotyping, and histologic evaluation. Thus, the possible teratologic effects of such agents will be determined, as well as the efficacy and safety of the method studied by the diagnostic use of ultrasound.

### Project III: Development of Improved Means of Second Trimester Termination of Pregnancy

Agents active in the second trimester of pregnancy appear to fall into two distinct categories with a third group that overlays the first two. The first category (Group A) includes agents which are effective stimulants in the initiation of myometrial activity, and includes such drugs as prostaglandins or large pharmacological quantities of oxytocin. The second category (Group B) includes agents that are effective in causing death of the fetus, i.e., fetotoxic agents. An example of such an agent is the monamine oxidase inhibitor, Pargyline-Hydrochloride. The third category (Group C) includes the hypertonic solutions currently employed for second trimester terminations. The mechanism of action of hyperosmolar agents is probably related to a progressive loss of placental function and as a result, gradual evolution of uterine contractile activity culminating in abortion.

Problems exist in the utilization of all three categories of agents. These problems are in two spheres, (1) untoward effects with associated patient morbidity and occasional maternal death, particularly with use of the intra-amniotic hypertonic saline solution, and (2) inadequate evaluation by clinical trials of reportedly effective agents, such as synthetic oxytocins, monamine oxidase inhibitors, as well as the hypertonic agent, urea.

### Materials and Methods

The agents that will be studied in this project and their planned route of administration include:

<u>AGENT</u>	<u>ROUTE OF ADMINISTRATION</u>
<u>Group A</u>	
1. Oxytocin	Intravenous; Intra-amniotic
2. 4-threonine oxytocin	Intravenous; intra-amniotic
3. Ergonovine maleate	Intravenous; Intra-amniotic
4. Prostaglandins and analogs	Intravenous; Intra-amniotic
<u>Group B</u>	
1. Ergyline Hydrochloride	Intra-amniotic
<u>Group C</u>	
1. Urea 40%	Intra-amniotic
2. Dextren 40 and 75	Intra-amniotic
3. Mannitol	Intra-amniotic

Group A: Myometrial Stimulants

- Proposal 1. Studies in animals
- Proposal 2. Studies in humans

Proposal 1

Prior to human utilization of either 4-threonine oxytocin or ergonovine maleate, intravenous and intra-amniotic studies in the monkey will be required. 4-threonine oxytocin, synthesized in 1970, has been extensively tested in the rat, rabbit and chicken. This analog of oxytocin, in which the glutamine residue in the four position is replaced by a threonine residue, has strikingly increased oxytocic activity and relatively low antidiuretic activity, allowing dissipation of concern over water intoxication. The clinical utilization of intra-amniotic ergonovine requires evaluation in monkeys because of its commonly known influence on systemic blood pressure and the induction of cardiac arrhythmias. Therefore, the incidence of these untoward effects following intravenous and intra-amniotic injection will be documented prior to use in humans.

Oxytocin, 4-threonine oxytocin and ergonovine will be studied in second trimester pregnancies of the Rhesus monkey. In the planned intravenous studies the monkeys will be restrained throughout the period of drug infusion, while for the intra-amniotic studies the intrauterine catheter will be placed while the animal is anesthetized and exteriorized at the dorsum of the neck, and the remainder of the study will be completed with the monkey conscious. In both the intravenous and intra-amniotic series the physiological data that will be collected includes intra-arteriole blood

pressure, respiratory rate, pulse, electrocardiogram, hourly urine volumes and specific gravity. The uterine activity will be directly recorded. The time of onset of uterine activity, and total time required for termination will be determined. The quantitation of amniotic fluid volumes will assist in the determination of the human intra-amniotic dosages of the respective four drugs.

### Proposal 2

It is known that first trimester and mid-trimester uteri are relatively insensitive to oxytocin requiring as much as 30-32 mU. oxytocin per minute intravenously to evolve labor-like activity as compared to 3-6 mU. per minute in the term uterus. The clinical series where oxytocin has been employed have been relatively small and not well documented. The only report of direct uterine application has been in experimental animals in studies of induction of decidual reactions and no literature has been found documenting the utilization of oxytocin by intra-amniotic infusion.

The agents in Group A will be employed in a comparative clinical trial in 12 to 20 week gestations. Both intravenous and intra-amniotic routes will be tested, with dosage information predominantly obtained from the monkey studies described previously. I.N.D.'s will be required prior to employment of intra-amniotic oxytocin, ergotrate, and 4-threonine oxytocin. Prostaglandins have previously been demonstrated to be highly effective in second trimester terminations and will be employed as a comparative group in this trial. In addition, pretreatment with anti-euretic and anti-diarrheal agents will be explored to determine if they will minimize the occurrence of these two side effects of prostaglandin administration.

It is possible some of these myometrial stimulants will also be effective in the first trimester or can be used to make prostaglandins work more effectively at this time and in the second trimester.

Eight groups of 15 patients each will be recruited for the intra-amniotic and the intravenous administration of these four agents. A total of 120 patients will be employed for this project. In both the intravenous and intra-amniotic series, monitoring of the blood pressure, heart rate and hourly urine output will be essential. A previously placed intra-amniotic catheter will allow documentation of resting uterine time and magnitude of individual contractions. In these patients, time to termination, degree of completeness, and incidence of morbidity will be recorded.

### Group B: Monamine Oxidase Inhibitors

Koren et. al. gave intra-amniotic injections of 50-100 mg. of pargyline hydrochloride in 20 patients between three and 26 weeks of pregnancy. In

19 patients termination occurred without reported problems. This agent blocks the endogenous monoamine oxidase contained in the placenta and amniotic fluid where it has the function of protecting the fetus from the harmful effects of the vasoconstrictor amines of the placenta. The reported preliminary clinical study will be repeated and expanded to document the incidence of untoward effects and completeness of evacuation. An I.N.D. will be required for the use of this drug. Pargyline hydrochloride is employed for the treatment of hypertension. Untoward effects associated with its use are potentiated by foods with high content of tyramine and this drug should not be administered in the presence of other medication in order to prevent the possible occurrence of drug interaction.

#### Proposal

Pregnancies of 14 to 20 weeks will be employed for the intra-amniotic administration of 100 mg. of pargyline-HCL in 20 ml. of sterile saline. This medication will be administered via a properly placed intra-amniotic catheter. The elapsed time to fetal death and from injection to termination, the incidence of retained uterine placental fragments, and the incidence of morbidity will be determined. If this agent is effective and safe in the first series of 20 patients, a second series will be completed in which the dosage will be reduced to 50 mg. Once the minimal effective dose is determined, this agent could possibly be used for termination of pregnancies greater than 12 weeks duration on an outpatient basis, resulting in minimized cost of abortion.

#### Group C: Hyperosmolar Agents

Hyperosmolar agents other than saline have been relatively little explored for second trimester pregnancy termination. Intra-amniotic urea has been used effectively in pilot clinical trials, both alone and with oxytocin (pitocin). Craft and Musa in late 1971 reported successful induction using intra-amniotic urea and intravenous pitocin administered from time of injection. In this series, the mean injection-abortion interval was approximately 22 hours, and no significant side effects were observed. These results compare favorably with the 40-hour mean latent period for hypertonic saline. They reported a reduced duration of hospital stay, and the complete elimination of complications.

#### Proposal

Pregnant women between 16 and 20 weeks gestation who have already been approved for therapeutic abortion will be recruited for this study. The use of an investigational drug will be described and each patient will sign informed consent. No patient will be accepted who has had prior uterine surgery, including myomectomy, hysterotomy, Cesarean section, or therapy for an incompetent cervix. Patients with major systemic abnormalities, including diabetes mellitus, renal or hepatic disease will be excluded.

Baseline laboratory tests that will include Pap smear, hematocrit, Rh and type, STS, and urinalysis. Baseline hematologic, hormonal, urinary, and metabolic studies will also be collected. These will include a complete blood count, serum osmolarity, renal and liver function tests, hormonal assays, and urinalysis.

All patients will undergo a standard method of intra-amniotic urea administration. The abdominal skin will be prepared with an antiseptic solution, draped with sterile towels, and local anesthetic solution will be infiltrated through the abdominal wall at a site selected for puncture. A sterile 20 gauge Tuohy needle will be inserted into the amniotic cavity, and the needle stylette withdrawn. Following removal of 150-100 cc. of amniotic fluid, 200 cc. of a solution of Ureaphil (Abbott Laboratories) will be introduced. This solution will be prepared by adding 140 cc. of D5W to a bottle of Ureaphil containing 80 gm. urea. No antibiotics will be instilled. The catheter will then be withdrawn, and firm pressure exerted on the site of the puncture for five minutes.

The 45 patients participating in this study will be divided into the following three groups.

Patients in Group I will have an intravenous butterfly needle begun in the forearm, and will slowly receive an intravenous infusion of 500 cc. D5 0.2% saline. The drip will be administered with an IVAC pump over 12 hours and followed with additional solution as necessary.

Patients in Group II will receive 200 units of pitocin in 500 cc. D5 0.2% saline given in each 12-hour period.

Patients in Group III will receive buccal pitocin at regular intervals, determined by uterine response.

Patients will be monitored by vital signs taken every hour, careful recording of intake and output, electrocardiograms where indicated, and by emergency blood chemistries or hematology analysis as required. Patient acceptance of the method will be evaluated by non-directive questioning, and by observance of both subjective and objective side effects.

The first 10 patients of the series will be studied more closely. On each patient, a baseline complete blood count, serum urea nitrogen, serum electrolytes, serum osmolarity and urinalysis will be performed. These studies will be repeated at four hour intervals until termination has occurred, and **again** at time of discharge. In addition, each patient will have a baseline differential, white cell count, and platelet count performed, as well as renal and liver function tests, and serum creatinine. These studies will be repeated at 24-hour intervals until discharge. Selected patients will also be monitored by the use of an indwelling, open-end polyethylene catheter placed within the amniotic fluid to record uterine contractions on a polygraph.

Data collected will include the evaluation of the efficacy of urea as an abortifacient, the injection-to-vaginal bleeding interval, the injection-to-incomplete and -complete-evacuation interval, and the total duration of hospital stay. Side effects, both subjective and objective will be described and recorded as detailed. Uterine contractility studies will be monitored, and their results compared to contractility studies already performed in patients undergoing saline injection and prostaglandin termination.

While problems with urea-loading have not been reported, the patient with compromised renal functions might experience difficulty in clearance of this agent. Therefore, mannitol, dextran-40 and dextran-75 will also be investigated.

Dextran-40 and Dextran-75 are "low molecular weight" and "average molecular weight" preparations with colloidal properties and are used intravenously as plasma expanders. They would not be expected to cross the placental barrier and therefore should have only an indirect effect on the maternal organism. Mannitol, a reduced form of the sugar Mannose, is not metabolized to any appreciable extent when administered intravenously in humans as a plasma expander, and should not clear the placenta.

The hypertonic nature of these agents, the lack of metabolism, their inability to cross the placenta, their non-toxicity and their routine utilization intravenously in humans, make them attractive agents for intra-amniotic administration. Inadvertent injection either into the maternal vascular space or into the myometrium would have no undue effect.

Unlike hypertonic glucose, these agents would not serve as a culture medium, resulting in enhancement of growth of pathogenic bacteria.

<u>Agent</u>	<u>Concentration</u>	<u>Volume Employed</u>	<u>Weight of Agents In Grams</u>
Dextran-40	10%	200-300 ml.	20-30 grams
Dextran-75	6%	200-300 ml.	12-18 grams
Mannitol	20%	200-300 ml.	20-30 grams
	10%	200-300 ml.	10-15 grams

I.N.D.'s will be required for the utilization of these agents by the intra-amniotic route, and are currently in preparation. Extensive animal testing will not be required prior to utilization, although studies paralleling those completed in monkeys of intra-myometrial injection of hypertonic saline and prostaglandin F<sub>2a</sub> will be expanded to include urea, mannitol, dextran-40 and dextran-75.

It is hoped that the intra-amniotic administration of one of these four agents will be found to be totally safe, effective, possess a short latent period, and be free of all untoward effects. In this way, midtrimester terminations would be effectively managed as outpatient procedures with minimal costs and effective utilization of professional and para-professional time in the care of a larger volume of patients.

Project IV: Improved Pharmaceutical and Physical Means of Cervical Dilatation

Objective

1. To develop instruments capable of assessing work and force factors required to produce cervical dilatation;
2. To develop pharmaceutical means of increasing the ease of cervical dilatation;
3. To develop improved mechanical means of effecting cervical dilatation.

Introduction

It is important to improve efficacy and safety of currently available surgical (sharp curettage, suction curettage) and pharmacologic (hyper-osmolar agents, prostaglandins) means of pregnancy termination. In the gestation less than 12 weeks, the cervix represents the sole barrier to uterine evacuation. The undilated cervix in the contracting uterus is the single factor determining the duration of labor, length of hospital stay, and efficacy of the pharmacologic method to induce abortion.

Very little effort has been made to characterize the composition of the cervix, its smooth muscle and collagen components, and the physiologic changes which occur during normal pregnancy, labor and delivery. It is presently unknown if the composition of the cervix undergoes changes, and whether the protein molecules involved in its structure can be altered and made less cohesive.

The force and work necessary to dilate the nulliparous and parous cervixes in women 12 weeks of gestation or less is presently unknown. With knowledge of the forces involved, dilatating instruments may be developed with the specific goals of decreasing the necessary force, thereby reducing the necessity of cervical traction, and lowering the chance of uncontrolled dilatation with its attended cervical laceration and uterine perforation.

It is unknown to what extent the smooth muscle in the cervix can be made to contract or relax with pharmacologic stimulation. For instance, prostaglandin F<sub>2</sub> has been shown to produce contractions of cervical strips in vitro, whereas prostaglandin E<sub>2</sub> has been shown to produce relaxation of comparable strips. Obstetricians firmly believe that the injection of local anesthetics into the cervix promotes ease of dilatation during term labor. The utilization of hyaluronidase, or other injectable agents, might produce dissolution of some of the collagen or other proteins causing cervical cohesiveness, and thereby decrease the force necessary to effect dilatation.

Bromelain, a proteolytic enzyme mixture produced from the stems of mature pineapple plants, is similar in its proteolytic action to papain, but has the advantage of reduced odor and increased availability. During an investigation of the mucolytic properties of these proteolytic enzymes, it was found that introduction of bromelain in solution into the vagina resulted in relaxation of the internal cervical os within five minutes. Hunter and co-workers in 1957 published the first of four papers on this aspect, including convincing hystero-cervico-grams showing the appearance of the endocervical canal and internal os before and after administration of the enzyme. Enlargement, dilatation, and relaxation of the cervical canal were marked. Papain was tested in parallel, and was found to be effective, but with a decreased shelf-life, and a most disagreeable odor like organic sulfides. The action of these enzymes results in specific dilatation of the internal os. Food and Drug Administration approval has been obtained for the testing of the proteolytic enzyme bromelain.

The investigation of improved mechanical means of cervical dilatation is also essential. The design of currently used metal dilators might be improved to allow greater ease of dilatation. More appropriate would be the development of a single dilator, which would suffice for all diameters necessary for trans-cervical uterine evacuation.

A device designed at The Johns Hopkins Hospital proposes a new concept in cervical dilatation, that of from within, out. This device has an acceptable diameter for introduction within the endometrial cavity without the necessity for cervical dilatation, and with simple mechanical adjustment, can increase its diameter three-fold. Dilatation of the cervix from within allows more physiologic dilatation, avoids the necessity of transfixing the cervix for traction, and eliminates the hazard of uterine perforation.

Other means of cervical dilatation, such as the use of newly designed expanding laminaria, will be evaluated. The original "slippery elm" is an absorbent device which imbibed fluids from the surrounding area. The amount of fluid in the endocervical canal is limited, and predominantly exists in the form of mucoid cervical protein. Thus, the adaptation of design to that of a device increasing in size through some inducible chemical change would be attractive.

The Applied Physics Laboratory of The Johns Hopkins University with its coordinator, Dr. Joseph T. Massey, will collaborate in these projects, and will assist in the development of instruments and techniques to perform specific tasks required for cervical dilatation. They have suggested the development of a cervical dilatation device involving, instead of air expansion system, the utilization of water or some other such fluid within an expanding instrument. The design of such a self-contained unit utilizing malleable plastic that allows

controlled expansion was first completed by the staff of the Applied Physics Laboratory for their cardiovascular investigative programs.

Subproject I. Development of Work-Force Instruments. The Applied Physics Laboratory of The Johns Hopkins University will develop an instrument to give quantitative measurement of the force and work necessary to dilate the non-pregnant and pregnant, nulliparous and parous cervix. Such a device will be simple in design, and will be utilized to gain comparative data for evaluation of the influence of pharmacologic agents and the efficacy of specifically designed instruments to effect cervical dilatation.

Hegar and K-Pratt dilators will be compared as to the amount of work and force necessary to effect cervical dilatation. These dilators are commonly used throughout the world, and would provide essential comparative systems. The Hegar dilator, with a blunter end, appears to involve the greater use of force. The K-Pratt dilators are longer, and more slender, with a more gradually increasing diameter. Obstetricians think that these dilators allow greater ease of effecting cervical dilatation. The disadvantage of the K-Pratt dilator is that its length exceeds that of the Hegar, and in a smaller gestation, is more often associated with uterine perforation and other damage. Therefore, utilizing the instrument developed to measure the force of dilatation, designs of dilators can be improved.

Another advantage in such testing would be to provide precise data for improving methods of cervical transfixation for cervical dilatation. The presently used tenaculae are either single or double toothed, and tend to tear, or are thickened with a large broad ridge of metal, and tend to crush. In addition, the transfixation obtained by these instruments is poor, resulting in force applied in the wrong direction.

Subproject II. Pharmacologic Means of Cervical Dilatation. The following pharmacological agents will be employed to determine their influence on cervical dilatation.

SUBSTANCE

ROUTE OF ADMINISTRATION

Local Anesthetics

Carbocaine 1%, 2%  
Xylocaine, 1%, 2%

Intra-cervical  
Intra-cervical

Enzymes

Hyaluronidase  
Bromelain  
Papain

Intra-cervical  
Vaginal  
Vaginal

Other

Prostaglandin F<sub>2</sub> , E<sub>2</sub>                      Systemic

Pregnancies of four to 14 weeks duration will be utilized for these studies. Following local administration of these agents, the work required for cervical dilatation will be quantitated and the incidence of cervical laceration and total blood loss in association with the subsequent curettage will be determined.

If effective cervical dilatation occurs with the use of either bromelain or papain, the effectiveness will be quantitated with the use of cervico-hystero grams. These two agents will be administered in solution form into the vagina.

In instances of systemically administered prostaglandin F<sub>2</sub><sup>α</sup> and E, the ease of cervical dilatation will be similarly quantitated. In later studies, if use of the administered enzyme is found to be efficacious, they will be similarly used in combination with systemically administered prostaglandin in an attempt to reduce the total quantity of prostaglandin required and thereby effectively minimize abortion time, and associated untoward effects.

Subproject III. Development of Improved Mechanical Means of Cervical Dilatation. Through the cooperation of Dr. Joseph T. Massey, Coordinator of the Investigative Program of the Applied Physics Laboratory, the resources of that institution will be of assistance to this program.

The initial portion of this project will be completed in hysterectomy specimens delivered to the Gynecological Pathology Laboratory. The only pre-requisite will be that the cervix is normal and undilated.

The initial plans are to design and explore the utilization of the following types of cervical dilators, a number of which are solitary, self-contained units.

1. The Hopkins Cervical Dilator that is now capable of expanding three times its insertion diameter. This instrument will essentially effect cervical dilatation beginning at the internal cervical os, to subsequently include the endocervical canal and finally the external cervical os. This instrument, if effective, eliminates a requirement of cervical counter-pressure during dilatation.

2. Maleable plastics with self-contained water or fluid filled expansion systems.

The prototypes of such instruments have been developed by the Applied Physics Laboratory for use in their cardiovascular investigative program.

### 3. Hydrophilic laminaria.

If any or all of these devices are found satisfactory in pathology specimens, subsequent comparative clinical studies will be completed utilizing currently employed dilatation in 4 to 12 week pregnancies being terminated by curettage. The work required by any of these instruments to effect cervical dilatation will therefore be quantitated. The incidence of cervical laceration, blood loss and total time required for abortion will be determined.

#### Project V: Evaluation of Improved Clinical Equipment for Surgical Pregnancy Termination in Less Developed Countries

##### Objective

The objectives of this project are the development and clinical testing of surgical equipment for pregnancy termination that will meet the special requirements of abortion programs in less developed countries.

##### Introduction

With few exceptions, there has been little organized effort to improve instrumentation used in the performance of surgical interruption of pregnancy. In this and other well-developed countries, complication rates are already reasonably low. Furthermore, when complications do occur, large, modern and well-equipped hospitals with unlimited professional skills are available to assure that the outcome is satisfactory. Available statistics clearly indicate that uterine perforation in this country is often managed in such a way that the patient's major inconvenience is an extended hospital stay and reproductive capacity is usually unaffected. Similarly, unexpected hemorrhage in a large, modern hospital is rarely a serious challenge in management. In less developed countries, such complications can often be very serious.

It is also clear that those who are actively involved in carrying out such surgical procedures are usually ill-equipped through experience, time or motivation to develop improved instrumentation.

The present project is designed to develop instrumentation which takes into account a specific patient population, a specific level of professional skill, and the limited physical facilities which can be expected in less developed countries. Not only must simple equipment be developed, but it must be tested in such a way that its effectiveness will be proven prior to distribution. It is, for instance, imperative that instrumentation being distributed to less developed countries be tested by professional individuals whose skill and experience is similar to those using the equipment in the recipient country.

### Design of the Project

The program is organized in such a way as to consider the individual steps in a surgical abortion that require special instrumentation.

A. Surgical Exposure. Currently available instruments for this purpose include retractors of varying weights and sizes and specula of varying sizes. The operator chooses one instrument based upon the individual patient. The instrument developed for this program must have the following characteristics:

1. The diameter of the instrument must be flexible enough to meet the needs of the nulliparous as well as the parous patient.
2. The instrument must be long enough to reach the cervix but short enough so as not to interfere with traction on the cervix. It is abundantly clear that straightening of the uterine canal by traction is a cardinal safety feature in preventing perforation and this need therefore must not be compromised by the instrument.
3. The cervix must be clearly visualized and accessible.
4. The instrument must be self-retaining.
5. The instrument must be durable, inexpensive and easy to sterilize.

B. Stabilization and Traction of the Cervix. The instrument used for this purpose must have the following characteristics:

1. It must hold the cervix securely. Traction on the cervix allows for straightening of the uterine canal which is a major criterion for safety.
2. It must not cause damage to the cervix.
3. It must be simple, inexpensive and easy to sterilize.

One approach that will be explored is the use of a vacuum cup similar to that used in the Malstrom device currently available for hystero grams.

C. Dilation of the Cervix. The instrument developed for this purpose as described in Project IV will be utilized.

D. Uterine Cannula or Suction Curette. This instrument should have the following characteristics:

1. A diameter of 1 cm. or less.

2. It should be designed in such a way as to minimize the risk of perforation.

3. It should be maximally effective in evacuating uterine contents.

4. It should be simple, inexpensive and easy to sterilize.

Possible approaches to the development of this instrument will include the following:

1. The development of an instrument which, when introduced into the uterine cavity can be manipulated so as to form a flanged or bulbous end which will preclude or minimize the risk of perforation.

2. The development of a single unit which will include not only a device for stabilizing the cervix but also the dilator and the uterine cannula.

3. The device should be designed in such a way that its depth of insertion can be pre-determined so as to minimize the risk of perforation.

E. A Vacuum Source. This instrument will be developed with the following criteria:

1. The negative pressure developed must be adequate for evacuation of the uterine contents through a cannula of minimum diameter. Every effort will be made to develop a unit that will allow efficient evacuation of a 12-week pregnancy through a cannula with a diameter of 1 cm. or less.

2. Consideration will be given to the development of a vacuum-producing device that does not require electricity as a source of power. The program will evaluate the devices currently being developed by other research projects prior to initiating work on improved vacuum sources.

F. Local Anesthesia. An instrument will be developed for the application of local anesthesia to the cervix with the following objectives:

1. The application of local anesthesia must be uniformly effective in the relief of pain.

2. The device must be associated with a high degree of safety to the patient. This requires the precautions be taken to prevent intravascular injection and the total amount injected must be far less than the toxic dose of the drug.

3. The technique must be rapid and simple.
4. The instrument must be simple, sturdy and easily sterilized.
5. The use of the jet injector used for immunization programs will be evaluated.

The program outlined above will be carried out in two phases.

Phase I. Development of New Instrumentation to Meet the Criteria Outlined Above.

Collaboration with the personnel of the Applied Physics Laboratory will facilitate the development of prototypes of each of the required instruments. The instruments which will be improved include the vaginal speculum, the cervical clamp, cannulae, and suction curettes. The following system will be evaluated: an ultra-sound apparatus for emulsification of the uterine contents and a non-electricity-requiring vacuum pump. To assist with surgical exposure, a self-contained light source will be developed to eliminate the need for cumbersome lighting equipment. Such a source might be a modified miner's headlamp with battery pack.

As the initial approach to the evaluation of these instruments, surgical specimens will be employed. For completion of the patient testing of these instruments, the following observations will be completed:

1. Operative time.
2. Facility of use.
3. Quantitation of anesthesia or analgesia requirements.
4. Quantitation of blood loss.
5. Incidence of laceration and perforation.
6. Number of required personnel for effective use.
7. Patient acceptability.

The clinical testing of instruments under actual operating conditions will be carried out in the following steps:

1. The instrument will first be tested by senior members of the team having maximum skill and experience. If, under these conditions during the performance of surgical interruption of pregnancy the instrument meets the expected standards, it will then be subjected to testing at the next level.
2. The instrument will then be tested utilizing individuals with less skill and experience. If the instrument continues to meet the expected standards, it will then be subjected to testing at the next level.

3. The instrument will then be tested by those with the lowest level of skill and experience, for instance, those being introduced for the first time to the performance of surgical abortions.

Phase II. The Preparation of a Simplified Surgical Abortion Set for Distribution to Less Developed Countries.

Based upon experience with instruments developed and tested in Phase I, a surgical set will be developed that incorporates the following:

1. A device for achieving exposure of the cervix.
2. A device for stabilizing and applying traction to the cervix.
3. A single instrument to be used for dilatation of the cervix.
4. Two uterine cannula: one for the undilated cervix, and one for the cervix dilated up to 1 cm.
5. A device for delivering local anesthesia to the cervix.

Of equal importance will be the development of a carefully prepared and tested manual of instruction that outlines in a simple, step-wise manner the techniques for performing surgical interruption of pregnancy utilizing the simplified surgical abortion set.

In conclusion, probably in few surgical specialties has the individual operator's skill and clinical acumen been the most significant factor in determining a successful clinical outcome. For these reasons, the large-scale delivery of abortion services to populations of under-developed countries benefit from new instrument design based on knowledge accrued from instrumentation of other medical specialties.

Project VI: Training for LDC Participants

Objective

To provide clinical experience and training in a research/service setting offering all means of fertility control services in a model family planning clinic.

Proposal

Johns Hopkins has originated or contributed to several of the major advances in fertility control technology in recent years, particularly the Dalkon Shield IUD, the single puncture laparoscopic sterilization technique performed as an outpatient procedure under local anesthesia,

and pregnancy termination techniques (including prostaglandins) carried out on an outpatient basis. They are one of the few centers in the world where the complete array of modern fertility control techniques is available to the trainee.

With the change in policies in many countries, these superior fertility control technologies can now be initiated in a pregnancy centered family planning program. However, an adequate cadre of personnel is needed.

This training program will seek to provide physicians from underdeveloped countries with didactic and practical experience in modern fertility control techniques. In this program these physicians will be taught the use of the various techniques of female and male sterilization, termination of first and second trimester pregnancies, and the employment of all forms of contraception. With the cooperation of the faculty of the School of Public Health, information will be provided in demography, program construction, and the ethical and social factors of the countries of the participating student physicians. The emphasis of this program will be to transmit clinical skills that would enable the trainees to implement effective population control programs in their respective countries.

It is apparent that the clinical skills necessary for the effective utilization of existing fertility control techniques have not been taught in an organized, integrated fashion to physicians of such countries. This has been true for a host of reasons, including the lack of facilities within the United States having a large active patient program utilizing a full range of population control techniques coupled with a staff interested and experienced in the training of candidates from underdeveloped countries.

The Department of Gynecology and Obstetrics of the Johns Hopkins Hospital has provided tutorial training in techniques of sterilization, abortion and contraception for an average of ten candidates per annum from underdeveloped countries in the past, as well as concentrated three day seminars in surgical techniques of population control for American clinicians.

An active clinical service program is an essential component to meaningful training in fertility control technique. In the course of 1971, there were 1200 sterilizations, 1800 pregnancy terminations, and 1300 new patients entering the contraceptive program at the Johns Hopkins Hospital. Follow-up visits for patients active in the pregnancy spacing program now number 8000 per annum.

#### Program Description

The trainees of this four week program will be taught the following manual skills:

1. Abortion techniques

- A) First trimester termination - Sharp and vacuum curettage.
- B) Mid trimester termination
  - Prostaglandin utilization
  - Intra-amniotic Hypertonic solution techniques

2. Sterilization procedures

A) Female

- 1. Laparoscopic tubal cauterization
- 2. Culpotomy tubal ligation
- 3. Abdominal tubal ligation

B) Male

- 1. Vas ligation

3. Placement of Intrauterine Devices

Within this time interval the trainee should be technically proficient in the completion of these procedures.

Essential information for a fertility control program will be provided for the trainees and they will have participated in the delivery of the following types of patient services.

- 1. Pregnancy diagnosis.
- 2. Selecting of the appropriate abortion technique and the required patient counseling.
- 3. Selection of appropriate sterilization procedure to meet the individual and/or families needs.
- 4. Complete contraceptive services tailored to the individual patient's requirements.
- 5. Management of the medical and surgical complications of both first and second trimester abortion.
- 6. The trainees will have observed the completion of hysterotomies and pregnant hysterectomies, with attention to the specific details of surgical technique required in the presence of intact pregnancies.
- 7. Management of the incomplete abortion.

8. **Diagnosis and treatment of common infertility problems.**

Forty candidates will be trained in the first year of the program, with expansion in the second and third years of the program to 55 and 70 students respectively.

Location of Training Sites

1. The Woman's Clinic gynecological operating rooms will be used for completion of female sterilization procedures, first trimester abortion, and for the removal of retained products of conception in the mid-trimester abortion. These facilities will also be employed for demonstration of pregnant hysterectomies and hysterotomies.

2. The clinical research unit for fertility control will be available for the trainee to participate in the utilization of prostaglandin and hypertonic solutions in mid-trimester abortions and to observe all the experimental programs in progress. By being assigned night duty they will participate in the management of the complications of abortion as they are admitted to this unit.

3. The contraceptive program of the Woman's Clinic is newly located in a separate clinical facility designated as COFLAC, (Community Family Life Action Center) three blocks from the Hospital-Medical School complex. The trainee will attend the patient functions in this clinic.

This outpatient facility is designed for provision of all contraceptive services, early pregnancy diagnosis, abortion and sterilization counseling, and the completion of ambulatory abortions and sterilization procedures in an efficient and compassionate manner. Since this clinic is an arm of this department, the Woman's Clinic facilities serve as the back-up for any required hospital admissions. The professional staff of this facility is the full-time faculty of this department.

4. The department's associated clinical facilities.

The Department of Gynecology and Obstetrics is responsible for the professional staffing of State Health Department, county contraceptive clinics, as well as a number of the clinic sessions at the Baltimore Planned Parenthood Clinic. The faculty serving as clinical teachers for the trainee will utilize these sessions for discussion of the organization and structure of contraceptive clinics and the online delivery of such care.

5. The School of Public Health, specifically the Departments of International Health, and Population, will assist in the delivery of didactic material to the trainee.

Candidate for Training in the Fertility Control Program

It would be ideal for the prospective trainees to be either a functioning obstetrician and gynecologist or to be at least trained in surgical techniques. This is a requirement because of the purposeful emphasis of this training program on the surgical technique of fertility control.

Secondly it would be desirable to have these individuals functioning as clinical teachers in their home countries so that they would be in a position to teach others the techniques they have acquired.

Finally, it would be most appropriate if the trainee would be from countries that have evolving or established programs in population control that have ongoing interrelationships with either A.I.D. or the World Health Organization. Since most of these individuals will require support for equipment and consumable supplies on their return home if viable programs are to evolve or they must have the opportunity of returning to already established programs in their home countries.

It should be noted that the standard procedures and recommendations of the Office of International Training of A.I.D. will be followed with regard to trainee selection, trainee orientation, transportation and per diem costs and all required internal statistical reporting.

With the desired criteria met the ideal individuals to recruit trainees would be the population officers of A.I.D. missions. Other sources of candidates would be found in A.I.D. sponsored programs that include the International Fertility Research Program, as well as from the evolving A.I.D.-A.V.S. Program.

Additional training candidates would be sought from the International Planned Parenthood Federation, The Ford and Rockefeller Foundations, the Federation of Internal Gynecologists and Obstetricians.

Hopkins will arrange transportation and subsistence for each trainee. In the first year of the program, 40 candidates would be accepted with expansion to 70 in the third year of the program. This expansion in number of trainees would evolve with the continued expansion of the ambulatory fertility control center.

7. Protection of Human Research Subjects

A.I.D. Policy for Protection of the Individual as a Research Subject is as follows:

"Safeguarding the rights and welfare of human subjects involved in research supported by A.I.D. is the responsibility of the institution to which support is awarded. It is the policy of A.I.D. that no work shall be initiated under a grant, award, or contract for the support of research involving human subjects unless the research is given initial and continuing review and approval by an appropriate committee of the applicant institution. This review shall assure that (a) the rights and welfare of the individuals involved are adequately protected, (b) the methods used to obtain informed consent are adequate and appropriate, and (c) the risks and potential medical benefits of the investigation are assessed.

The institution must provide written assurance to A.I.D. that it will abide by this policy for all research involving human subjects supported by the A.I.D. This assurance shall consist of a written statement of compliance with the requirements regarding initial and continuing review of research involving human subjects and a description of the institution's review committee structure, its review procedures, and the facilities and personnel available to protect the health and safety of human subjects. In addition to providing the assurance, the institution must also certify to A.I.D. for each proposal involving human subjects that its committee has reviewed and approved the proposed research before any work may be initiated.

Since the welfare of the subject is a matter of concern to A.I.D. as well as to the institution, A.I.D. advisory groups, consultants, and staff may independently review all research involving human subjects, and prohibit research which presents unacceptable hazards. This provision, however, shall not derogate in any manner from the responsibility of the institution set forth herein.

All of the above provisions apply to any research involving human subjects conducted outside of the United States and in addition such overseas research, will conform to legal and other requirements governing human research in the country where they are conducted.

In addition to the procedures set forth above, studies with unmarketed drugs will be carried out in compliance with provisions applicable to such studies in the country where such studies are conducted. In the United States, the regulations of the Food and Drug Administration will be followed and evidence of such compliance provided to A.I.D.

Guidance on procedures to safeguard human subjects involved in research is found in the document "Institutional Guide to DHEW Policy on Protection of Human Subjects", U.S. Department of Health, Education and Welfare Public Health Service, Revised 16 June 1971. Compliance with these procedures except as modified above is required."

Johns Hopkins has agreed to adhere to A.I.D.'s policy and that all human studies will vigorously adhere to the regulations and ethical standards established by the Department of Health, Education and Welfare and the Food and Drug Administration for experimentation involving human research subjects. These regulations require appropriate animal work prior to seeking FDA permission for human testing. Full explanation of the proposed studies will be provided individual patients in language and terms that they understand in order to have an informed consent. Further, a fair explanation of the procedures to be employed, their possible benefits and attendant hazards and discomforts, and the reasons for pursuing the research and its general objectives will be given.

Permission for therapeutic abortion will have been obtained from the Johns Hopkins Hospital Committee on Abortion and for all experimental drug utilization by the Joint Committee of Clinical Investigation of the Johns Hopkins Medical Institutions. The additional precautions that will be utilized in all studies involving human subjects are listed below.

1. All patients in the proposed studies will be provided with the phone number of the fertility control unit to facilitate immediate reporting of any complications after discharge.
2. All patients will be informed of the complications associated with abortion procedures prior to therapy and immediately before discharge from the unit.
3. Follow-up clinic visits for all program patients will be seen in our gynecology out-patient area by the staff of the Fertility Control Unit.
4. There will be participation in this program by both service and private patients of the full-time faculty. The per cent participation of each will be approximately equal.
5. There will be weekly meetings of the clinical investigators with the participation of the head nurse of the clinical research unit to review the course of the patients treated within the succeeding week. One purpose of this meeting will be to review all encountered untoward reactions.

6. A complete summary of the medical course of each patient treated in the Fertility Control Unit will be kept on file for utilization in a prospective study of the characteristics of future pregnancy performance.

It should be noted that of the patients who will be studied, equal numbers are expected to be private paying patients and from ward services.

#### 8. Researcher Competence

Johns Hopkins Hospital has long been innovative in the field of fertility control and abortion research. Since passage of reformed legislation in 1968, the Department of Gynecology and Obstetrics, the Department of Pediatrics, and the School of Hygiene and Public Health have been involved in various phases of evaluation of this means of fertility control.

Saline abortion has been extensively evaluated at Johns Hopkins. Such innovative research as development of specific RhoGam doses necessary for RH negative abortion patients, the establishment of the incidence of disseminated intravascular coagulation associated with Saline terminations, and the determination of the efficacy and tolerance rates of dilatation and curettage in comparison to suction curettage have been completed. An on-going program evaluating prostaglandin as an abortifacient is in progress. In the past, the Department of Medicine, Surgery, Nuclear Medicine, Pediatrics and Psychiatry have all utilized clinical abortion material for research purposes.

Within the Department of Gynecology and Obstetrics, there is active interest in the hormonal support of pregnancy, amniotic fluid dynamics, and immunologic interruption of pregnancy.

Other important advances in the field of fertility control coming from Hopkins include the single incision outpatient laparoscopic sterilization technique and the Dalkon Shield IUD, now the most widely used in the U.S.

A self-contained 12 bed clinical unit will be available for the exclusive use of this program. Most procedures will be carried out on an outpatient basis; inpatient studies will be conducted as warranted.

A strong engineering backup will be provided by the Applied Physics Laboratory of Johns Hopkins University.

Complete facilities for blood chemistries and hormonal assays are available, as well as instrumentation to record physiologic data.

For those methods and studies requiring initial experimental work in animals, the Department of Animal Medicine of The Johns Hopkins University has both a primate colony with pregnant and nonpregnant Rhesus monkeys, and extensive laboratory facilities housing lower animals for research purposes.

The principal investigator will be Dr. Theodore M. King, who is Professor and Chairman of the Department of Gynecology and Obstetrics at The Johns Hopkins University School of Medicine.

In 1959 Dr. King received his Ph.D. in Physiology from Michigan State University and his M.D. from the University of Illinois. In the same year he also received the Sigma Xi Research Award, the Borden Foundation Award in Medicine, and appointment to Alpha Omega Alpha. Following an internship in Surgery at the Presbyterian Hospital of the Columbia Medical Center, he entered the residency in Obstetrics and Gynecology at the Columbia Presbyterian Medical Center. During this time, he was a visiting Fellow at the University Womens Clinic and Biochemistry Institute, Wurzburg, Germany, an American Cancer Society Fellow, and was chief resident in Obstetrics and Gynecology at the Columbia Presbyterian Medical Center in 1964-65. In 1966, he obtained a Macy Faculty Fellowship at the University of Missouri, and in 1967, was appointed a Markle Scholar in Academic Medicine. In July, 1968, he was promoted to Associate Professor in the Department of Obstetrics and Gynecology and Physiology of the University of Missouri School of Medicine, and in August of 1968, was appointed Professor and Chairman of the Department of Obstetrics and Gynecology at the Albany Medical College, Albany, New York. In November of 1971 he assumed the responsibilities of his present position at Johns Hopkins.

Dr. King is a Diplomate of the National Boards, of the American Board of Obstetrics and Gynecology, and a Fellow of both the American College of Obstetricians and Gynecologists, and the American College of Surgery. He is a member of many societies and professional organizations, and has served as Consultant to the New York State Health Department. His publications number over thirty.

Dr. King will serve as the principal investigator in this project. In addition to his duties as overall Administrator, he will have primary responsibility in Project III, Second Trimester Terminations. Also, with the Coordinator for Education who is to be appointed, he will have primary responsibility for the education program for trainees from underdeveloped countries.

Dr. Georgeanna Seegar Jones has enjoyed a long and prestigious career in Gynecology. She is an Associate Professor of Gynecology and Obstetrics, Gynecologist, Johns Hopkins Hospital, Director of Laboratory of Reproductive Physiology and Gynecologist-in-Charge of

the Gynecological Endocrine Clinic, Johns Hopkins Hospital. An acknowledged international expert in problems of infertility, Dr. Jones is a member of the FDA Obstetrics and Gynecology Advisory Committee and a former President of the American Fertility Society. She is the author of 80 publications, including three books.

In 1966, she was honored with the Rubin Award, and in 1971, received the Barron Foundation Award for meritorious service in the field of Gynecologic Endocrinology.

Dr. Jones will serve as Assistant Principal Investigator, and will devote primary interest to Project I, The Improvement of Pregnancy Testing. Her ongoing expertise in other areas of proposed research allows a broad perspective, and valuable critique in all areas of this program. She will be integrally involved in the study of the efficacy of prostaglandin in menses induction, and will aid in the interpretation of the hormonal data to be obtained.

Dr. Anne Colston Wentz graduated from Wellesley College and subsequently received her M.D. from Western Reserve University School of Medicine in 1966, having been awarded the Senior Research Prize. Following an Internship in Straight Medicine at the University of Maryland, she entered the residency in Gynecology and Obstetrics at the Johns Hopkins Hospital, completing this in 1971. She was appointed an Instructor in Gynecology and Obstetrics, and presently serves as Director of the Gynecologic Endocrinology Clinic at Sinai Hospital. Dr. Wentz will be appointed Assistant Professor of Obstetrics and Gynecology effective July 1, 1972. She is a Junior Fellow of the American Fertility Society, a Junior Fellow of the American College of Obstetricians and Gynecologists, and has passed Part I of the American Board of Obstetrics and Gynecology.

Dr. Wentz has been investigating the efficacy of prostaglandins in luteolysis, menses induction, and abortion for the past year. One publication has been accepted, two have been submitted, and five are in preparation.

Dr. Wentz will be the principal investigator in Project II, Menses Regulation and Termination of Early Pregnancy, and Project V, Improved Clinical Equipment for Surgical Termination of Pregnancy. As Director of the Clinical Research Unit she will be responsible to Dr. King for the maintenance of high standards of practice in the Fertility Control Center.

Dr. Lonnie S. Burnett graduated from the University of Texas Medical School in 1953, interned in Medicine at the Henry Ford Hospital, and was then trained in Internal Medicine at the Mayo Clinic and Foundation. He entered the residency in Gynecology and Obstetrics at the Johns

Hopkins Hospital, during which time he also had Fellowships from the Department of Pathology and from the Department of Microbiology. In 1964, he was appointed Assistant Professor in the Department of Gynecology and Obstetrics, and in 1965, in the Department of Microbiology. In 1970, he was promoted to Associate Professor. Dr. Burnett was appointed to the Alpha Omega Alpha Honorary Medical Society in 1963, and in 1965 became a Josiah Macey Jr. Foundation Scholar. He became a Diplomate of the American Board of Obstetrics and Gynecology, and a Fellow of the American College of Obstetricians and Gynecologists in 1969.

Dr. Burnett will serve as Assistant Director of the Clinical Research Unit and will have primary responsibility for Project II, Menses Regulation and Termination of Early Pregnancy, and Project IV, Improved Pharmaceutical and Physical Means of Cervical Dilatation. Dr. Burnett has contributed extensively to the Johns Hopkins University School of Medicine in the areas of administration, teaching, and research. His publications reflect his ongoing interests in the fields of Immunology, and radical pelvic surgery. Dr. Burnett will actively participate in the educational component of this program.

Dr. Lau graduated from the Johns Hopkins School of Medicine in 1958, completed his residency at Georgetown University Hospital, and was a National Institutes of Health Postdoctoral Fellow at Johns Hopkins from 1962-1964. He served as Assistant Director of the Gynecologic Endocrine Laboratories, and in 1970 was appointed Director. Dr. Lau has been primarily interested in the development and testing of immunologic means of pregnancy determination and has published extensively in this area. He will take primary responsibility with Dr. Georgeanna Jones of completing Project I, Evaluation and Development of Improved Pregnancy Testing Technology, and will serve as consultant for other projects requiring endocrine assays.

Dr. Wheelless will be involved in this project only through the teaching of surgical techniques for female sterilization to the trainees from underdeveloped countries. After receiving his M.D. from the University of North Carolina, he completed a residency in Gynecology and Obstetrics at the Johns Hopkins Hospital, and was appointed to Assistant Professor of Obstetrics and Gynecology in 1970. Dr. Wheelless has been instrumental in the utilization of the laparoscope for tubal sterilization, and has traveled extensively teaching the method, and establishing clinics capable of operative sterilization. Dr. Wheelless has organized a teaching course at the Johns Hopkins Hospital in "Surgical Techniques in Fertility Control" which has been well attended, and attracted physicians both from the United States and lesser developed countries. The Laparoscopic-Clip Sterilization Program will be completed in the Fertility Control Unit.

Dr. Hugh Davis was graduated from the Johns Hopkins University School of Medicine in 1953, completed the residency in Obstetrics and Gynecology at the Johns Hopkins Hospital, and was a Research Fellow at the Radium Stationen in Denmark until 1962. He was appointed Associate Professor of Gynecology and Obstetrics, Director of Out-Patient Services, and Assistant Professor of Population and Family Health, and Assistant Professor of International Health. Dr. Davis has been extensively involved with the development of the Dalkon Intrauterine Device, and instrumental in the establishment of the COFLAC Clinic, visualized to be a "one-stop" fertility control center. Dr. Davis will participate in this project as a teacher of Means and Techniques of Fertility Control. He will be involved in Project VI, Training of Personnel from Lesser Developed Countries.

The proposing office's evaluation of facilities and personnel is that they are of high quality and well suited for the proposed research.

9. Contribution to Institution Building

Johns Hopkins has an excellent international reputation in biomedical fertility control research and trains large numbers of LDC medical personnel. This program will strengthen their capacity to carry out such research and the scope of their training program.

10. Utilization Plans

New methods resulting from this work will be provided to A.I.D.'s field trials program (e.g., the International Fertility Research Program - University of North Carolina). New methods will be taught to LDC medical personnel receiving training at Hopkins and disseminated through the strong alumni associations of the Medical School and School of Public Health. Publications in scientific journals will also result from this program.

11. Budget Analysis

The proposing office has insisted on a continuous and careful review of this budget. This has resulted in judicious reductions in many items. The attached budget is therefore considered appropriate for the scope of work envisioned.

12. Internal and External Reviews

This proposal was reviewed with individual regional population officers and approved by the RIGC on 13 April 1972. In discussion, the RIGC sought and received assurance that (1) if adequate research on abortion and pregnancy termination was not being conducted under this proposal, additional projects would be initiated elsewhere by A.I.D. and (2) that this program did not overlay ongoing research.

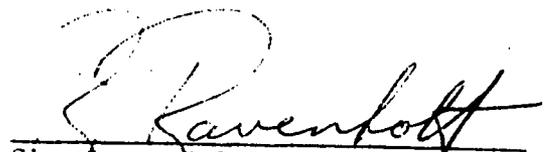
RIGC suggested the following changes which are now incorporated in this project statement, (1) emphasizes the contribution the project will make to maternal health and safety; (2) fuller description of research methodology; (3) recognition that Office of International Training Procedures would be followed; and (4) adequate description of procedures to protect human research subjects.

External review is in process and will be provided to RAC when completed.

13. Proposing Office General Evaluation

Research to improve the safety and effectiveness of currently used post-conceptive means of fertility control should have high priority. This means has a powerful appeal to individual women, with popularity exceeding all other methods. Its demographic impact has also proven to be very great. The research proposed is an applied clinical effort by an outstanding group of investigators at a leading institution. This work should serve to make safer the millions of pregnancy terminations now being carried out, as well as to develop more practical techniques for this means of fertility control. For these reasons, the proposing office gives this proposal high priority and approval is recommended.

  
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Signature of Monitor

  
\_\_\_\_\_  
Signature of Office Director

## BUDGET

<u>PERSONNEL-PROFESSIONAL</u>	<u>SALARY</u>			
<u>Position</u>	<u>% Effort</u>	<u>Year 1</u>	<u>Year 2</u>	<u>Year 3</u>
Principal Investigator (King)	10	0	0	0
Assistant Principal Investigator (Jones)	17	5,500	5,925	6,350
Director Clinical Research Unit (Wentz)	50	11,500	11,925	12,350
Assistant Director Clinical Research Unit	45	10,000	10,500	11,000
Clinical Research Unit Physician	50	10,000	10,500	11,000
Clinical Research Unit Staff (5 registered nurses, 3 licensed practical nurses, 3 nursing assistants, 2 unit clerks)	100	110,500	116,025	121,550
Bioengineer	50	10,000	10,500	11,000
Pharmacologist	50	10,000	10,500	11,000
Physiologist	100	20,000	21,000	22,000
Coordinator for Training	100	18,000	18,900	19,800
Coordinator x 2	100	18,000	18,900	19,800
Secretary x 2	100	14,000	14,700	15,400
Lab Technician	100	8,000	8,400	8,800
Statistician	25	5,000	5,250	5,500
<u>Salary Subtotal</u>		<u>250,500</u>	<u>263,025</u>	<u>275,550</u>
Fringe Benefits @ 13% Salaries		<u>32,565</u>	<u>34,193</u>	<u>35,822</u>
Indirect Costs @ 36.1% Salaries (excluding Clinical Research Unit Staff)		<u>50,540</u>	<u>53,067</u>	<u>55,594</u>
Hospital Overhead		<u>63,723</u>	<u>63,723</u>	<u>63,723</u>
<u>Operational Costs of Clinical Research Unit</u> (includes all hormone assays, blood chemistries, X-rays, pathology, and other hospital costs)		151,000	170,500	170,500
<u>Additional costs for each project</u> (includes experimental animal and bioengineering work)				
I. Improved Pregnancy Testing Technology		11,000	8,000	5,000
II. Menses Induction		20,000	15,000	10,000
III. 2nd Trimester Termination		15,000	15,000	10,000
IV. Cervical Dilatation		25,000	15,000	10,000
V. Improved Equipment		25,000	25,000	10,000
VI. Training (travel and subsistence for 40-70 trainees/yr.) See detail on page		<u>250,841</u>	<u>196,657</u>	<u>212,502</u>
<u>Project Subtotal</u>		<u>346,841</u>	<u>274,657</u>	<u>257,502</u>
Office Supplies		4,000	4,000	4,000

<u>Equipment</u>	<u>Year 1</u>	<u>Year 2</u>	<u>Year 3</u>
<u>Laboratory</u>			
Monitors, electronic equipment	5,100	0	0
Centrifuge, refrigerated	3,100	0	0
Freezer and freezer/refrigerator	2,000	0	0
<u>Office</u>			
Typewriter	450	0	0
Filing Cabinets	250	0	0
Desks/Chairs/Table	600	0	0
Calculator	175	0	0
Dictation Equipment	850	0	0
<u>Clinical Unit</u>			
Operating Room	10,500	5,000	5,000
Autoclave	2,600	0	0
Examining Table/Lamps	3,500	0	0
Airconditioners (5)	2,500	0	0
<u>Equipment Subtotal</u>	<u>31,625</u>	<u>5,000</u>	<u>5,000</u>
<u>Travel Expenses</u>	<u>1,000</u>	<u>1,000</u>	<u>1,000</u>
<u>Publications Expenses</u>	<u>1,000</u>	<u>1,500</u>	<u>1,500</u>
Total Project Cost	<u>932,794</u>	<u>870,665</u>	<u>870,191</u>
<u>3 Year Total</u>		<u>\$2,673,650</u>	