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from

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for

Simplified Techniques of Fertility Control

Proposal Submitted by

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TABLE OF CONTENTS

I. Summary

II. Introduction and Background

III. Aims and Objectives

IV. Significance to Agency of International Development Objectives

V. Detailed Description of the Study

A. Evaluation and Development of Improved Pregnancy Testing Technology

B. Menses Regulation and Termination of Early Pregnancy

C. Development of Improved Means of Second Trimester Termination of Pregnancy

D. Improved Pharmaceutical and Physical Means of Cervical Dilatation

E. Evaluation of Improved Clinical Equipment for Surgical Pregnancy Termination in Less Developed Countries

F. A Fertility Control Education Program for Physicians of Lesser Developed Countries

VI. Expected End Result

VII. Previous Work in the Area by the Investigators

VIII. Review of Pertinent Work by Other Investigators

IX. Scientific Personnel and their Qualifications

X. Facilities and Equipment

XI. Project Budget and Justification

SUMMARY

The objectives of this program are (1) to establish a clinical unit for the development and evaluation of simplified fertility control techniques, suitable for use in underdeveloped countries; and (2) to coordinate all of the required clinical components of a fertility control program to allow establishment of a education program which would effectively disseminate current knowledge of fertility control to participating physicians from lesser developed countries.

The aim of developing improved fertility control techniques would be implemented by the establishment of a clinical research unit where activities would be directed toward the control of fertility after conception has occurred. The clinical investigative areas of such a goal-oriented unit would include new methods of early pregnancy detection, new means of re-establishment of the menstrual cycle in the immediate post-conceptive period, improved pharmacologic and mechanical means of termination of established first and second trimester pregnancies, and finally improved equipment for clinical utilization in pregnancy termination. The goals of this clinical unit would be made relevant to the needs of underdeveloped countries by developing the most simplified, efficacious, safe and inexpensive techniques for post-conceptive fertility control.

The educational program will provide didactic and practical information on the most advanced techniques of sterilization, pregnancy termination, hormonal and intra-uterine contraception, and family planning clinic management. The emphasis of the educational program will be to transmit clinical skills that would immediately enable the trainees to implement or participate in population control programs in their respective countries. The faculty will make every effort to insure the relevancy of this educational program to the specific ountries of the selected trainees, and to provide technical assistance for their respective evolving fertility control programs.

In summary, the coordination of all of the clinical components of fertility control within one institution will assist in effective dissmeination of knowledge to individuals from lesser developed countries. The establishment of a related clinical research unit will allow continued evaluation and development of newer techniques of fertility control. The coordinated teaching program would include an exposure to the development and evaluation of such methods and allow acquisition of necessary competence in currently employed techniques in procedures of fertility control in an organized and integrated fashion for immediate clinical utilization.

INTRODUCTION AND BACKGROUND

An investigation of recent trends related to increased population pressure reveals that the incidence of both legal and illegal abortion is steadily mounting. In March, 1972, the 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 the 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. In many countries, a sizeable percentage of Ob-Gyn beds in hospitals are occupied by incomplete, frequently infected, induced abortions.

To meet these trends and take full advantage of the new advanced technologies, a well-organized effort to develop new types of fertility clinics and to disseminate them widely in the lesser developed countries is required. These clinics will be characterized by sophisticated technologies that can be applied in an outpatient setting capable of providing pregnancy diagnosis, giving contraceptive and sterilization counseling and servicing, along with safe, efficient and compassionate pregnancy termination services.

In seeking an optimum method for fertility control, whether this be by contraception, male or female sterilization, or abortion, the efficacy of the method is of foremost importance. Contraceptive techniques, including oral medication, use of the I.U.D., and others, have been fully evaluated as to their efficacy and related effects. Female sterilization is presently becoming a foremost method of fertility control, especially with the utilization of modern laparoscopic techniques under local anesthesia, which are adaptable to the needs of lesser developed countries. Vasectomy as a method of control is also currently being developed. However, 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 is essential. With many countries moving to adopt a new "pregnancy centered" approach for family planning services, 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 method for prevention of subsequent unwanted pregnancies, e.g., immediate I.U.D. insertion or outpatient female sterilization as well as ample supplies of oral and other contraceptives.

As one considers the optimum methods for pregnancy termination, besides efficacy, one must consider the following factors: (1) safety, (2) cost, (3) separation time, (4) time invested by professional and related medical personnel.

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. 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.

With the recent concern over population stabilization has come the realization that making research findings of efficacious and simple fertility control techniques available to practitioners in lesser developed countries is a slow and difficult process. Fragmentation of research efforts has led both to incomparability of data and lack of thorough evaluation of a method prior to its pragmatic utilization. New drugs are being proposed as abortifacients, new methods and techniques of sterilization and vasectomy are being developed, new instruments are being designed for all forms of fertility control, many without adequate means of providing valid, statistical and comparative results of their relative efficacy, safety, and patient acceptability.

While we await with interest and expectation the development of even more sophisticated techniques of population control, it is evident that the skills necessary for the effective utilization of existing techniques have not been taught in an organized, integrated fashion.

The hypothesis is that coordination of fertility control activities within one institution will assist in effective dissemination of knowledge to individuals from lesser developed countries. The establishment of a related clinical research program will allow continued evaluation and development of newer techniques of fertility control. The establishment of a coordinated teaching program would therefore include exposure to the development and evaluation of such techniques, but yet allow acquisition of necessary competence in currently employed techniques and procedures of fertility control.

AIMS AND OBJECTIVES

The overall objective is two-fold, first to establish a unit for development and evaluation of simplified fertility control techniques, and secondly, to coordinate family planning and population control activities into a model clinic setting for training of personnel from lesser developed countries.

The aim of developing improved fertility control techniques would be implemented by developing a simple method for the detection of pregnancy in the first 14 to 19 days following conception. Other studies would include the evaluation of new drugs as abortifacients. New and simplified drug delivery systems would be tested, including infusion pumps for medication delivery, and simplified vacuum pumps, neither of which would be dependent upon available electric supplies. New cervical and uterine instruments would be developed and tested, including mini-catheters for curettage, and mechanical instruments for the simplified production of cervical dilatation. A final and absolutely essential goal would be to delineate the untoward effects of abortifacient drugs and techniques. Efforts are required to establish means of early detection and effective treatment of medical problems associated with abortion in order to minimize or eliminate resulting maternal mortality.

In summary, then, goals of the fertility control unit would be directed toward the development of simplified fertility control techniques with (1) reduced morbidity and mortality, (2) reduced cost with maintenance of high, uncompromised quality of care, (3) minimal separation time, (4) minimal required professional time, and (5) establishment of medical criteria for quality of care applicable to lesser developed countries.

The second overall objective is to establish a model fertility control center. Such a unit would serve as a clinical training center for the teaching of the most advanced techniques of sterilization, pregnancy termination, hormonal and intrauterine contraception, and family planning clinic management to trainees from underdeveloped countries.

SIGNIFICANCE TO A.I.D. OBJECTIVES

This project should contribute to the overall objectives of the Agency for International Development in their related lesser developed countries by providing testing and evaluation of new fertility control techniques. There is obvious need for improved pregnancy testing, since development of simplified means of pregnancy detection would allow early, and hence safer, termination of unwanted pregnancies. Pregnancy testing is also a valuable public health measure for women desirous of children in that it allows initiation of early prenatal care which is necessary to achieve an improved outcome for both mother and infant. Improved methods of pregnancy termination are needed to cope with the failures of currently used reversible contraceptives. The demographic impact of pregnancy termination is enormous, e.g., official estimates in India place the number of pregnancy terminations at six million annually, prior to the liberalization of the abortion law. Improvement in methods of pregnancy termination is important to maximize their safety and practicality in lesser developed countries. Yet only in sophisticated medical centers is it possible to evaluate the efficacy, safety and tolerance of any new pregnancy termination procedures. This prior clinical evaluation would assure that only the simplest, safest, and most effective techniques would be transmitted to specific field operators, and the education of such trainees within the testing and development unit will insure continuity.

The establishment of a training center would contribute to the effectiveness of the Agency for International Development's population program by providing individuals trained in the full range of population control techniques. A shortage of individuals skilled in the application of modern techniques of conception control has undoubtedly contributed to delays in the implementation of effective overseas action programs. 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 stragic placement of trainees in underdeveloped countries could lead to a secondary diffusion of the essential knowledge and skills in the field of population control.

Finally, the establishment of such a program would increase the effectiveness of the Agency for International Development by providing liaison with other areas of concern. A.I.D. has interest in the development of improved mechanical devices for pregnancy termination, which at present have no setting for necessary clinical testing. Secondly, A.I.D. has established overseas population missions, without the availability of a training arm in the United States to provide the necessary cadre of clinically competent individuals, necessary for goal achievement.

DETAILED DESCRIPTION OF THE STUDY

The Clinical Research Unit will study techniques of abortion induction in four groups of patients. These include (1) those patients in whom post-conceptive methods of pregnancy termination are applicable, i.e., between two and fourteen days past the first missed menses; (2) those patients otherwise handled by routine suction or sharp curettage, i.e., two to twelve weeks; (3) those patients for whom no method of pregnancy termination is currently available, i.e., 12 to 16 weeks; and (4) those patients for whom saline injection is now routinely performed, i.e., 16 to 20 weeks gestation.

At present, between 160 and 175 patients are aborted at The Johns Hopkins Hospital each month. These are divided between private and resident service patients, and approximately 65% are handled by suction curettage, 25% by saline injection, and 10% by prostaglandin termination. Therefore, this A.I.D. program is not assisting in the initiation of a new required patient care service. It has been shown that over 8,000 Maryland residents a year obtain abortion services from out-of-State facilities.

All patients requesting termination of pregnancy will be channeled through a central coordinator for abortion services. All patients who "walk in" for instance, to the Gynecologic Clinic, the Obstetrical Clinic, or the Adolescent Unit, will be referred to a designated area in the Woman's Clinic Outpatient Department for initial history, counseling services, physical examination and screening laboratory tests. Following acceptance into the program, patients will then be scheduled by the central coordinator for admission to the Clinical Research Unit at a specified time. Patients who are not accepted into the experimental program or who are not agreeable to participation will be scheduled for termination by the residents of the Obstetrical service, or will be cared for by the full-time faculty. All patients calling into the Hospital, whether to the Clinics mentioned previously, or to the secretary of the Department, will be referred to the central coordinator for abortion services. They will then be handled by appointment as previously described. Private patients of full-time faculty will be encouraged to participate in the experimental program, and will be handled as described above. By having a single telephone line for abortion information, all patients are screened and evaluated with minimal delay.

Various agencies in the State of Maryland have cooperated with previous experimental pregnancy termination projects. Such agencies as Pregnancy Detection and Counseling, Planned Parenthood of Maryland, the Peoples' Free Clinic, the Maternal and Child Health Division of the Maryland State Health Department, have all referred appropriate patients in the past, and it is expected that they will continue to do so.

The Clinical Research Unit will be a self-contained area including interview office and record area, an operating room capable of performing procedures under local anesthesia, or for intensive monitoring of study patients, a two-bed

monitoring room in which intensive care can be performed, and two four-bed areas primarily to be used by patients in the process of abortion, or as a recovery room for patients who have undergone surgical methods of termination.

At all times, a physician will be in attendance in the Unit. The operative procedures will be performed by Board-eligible or Board-certified physicians, or the resident assigned to the Unit under supervision by a full-time faculty member. Complete 24-hour nursing care will be provided.

Followup on all patients will be assured by several mechanisms. The counsellors will provide each patient with a written description of the procedure done, including the appropriate telephone number for contacting the fertility control unit at any time, day or night. In addition, each patient, before discharge, will be given an appointment to followup clinic where she will be seen by the staff of the fertility control clinic. Contraception will have been discussed before termination, and will be re-emphasized prior to discharge, and at the followup clinic visit. A mechanism of contacting patients by means of telephone calls and letters will be initiated, and all patients will be specifically interviewed at the four-week followup appointment with respect to their understanding of the procedure accomplished, and the care and consideration given to them.

PROJECT I. EVALUATION AND DEVELOPMENT OF IMPROVED PREGNANCY TESTING TECHNOLOGY

PURPOSE

The aim of this project is to improve the reliability of tests for the early detection of pregnancy to meet the needs of contraceptive clinics in both developing and developed countries. The focus will be on early detection, which refers to the days before and immediately after the missed menstrual period. Early detection of pregnancy is important because it enables early and safer terminations of pregnancy. The provision of quick and accurate diagnosis for pregnancy by laboratory means will help fertility control clinics to emphasize their new "pregnancy center" approach.

DEFINITION AND APPROACHES

From the experience of our laboratory one can generate the techniques to meet the stated objectives in the following three ways. One can invent an entirely new pregnancy test; secondly, one can perfect or complete one of several tests which have been evolving in the laboratory; and finally, one can modify an existing test and adapt it to meet the needs of early diagnosis.

For clarity, the criteria for laboratory reliability are spelled out. Sensitivity refers to the calling of positive those urine or blood samples which are positive. For the early detection of pregnancy in this project, the term "early" refers to before the missed menses at a "sensitivity" of 0.5 IU HCG/ML of urine. Specificity refers to the calling of negative, those samples which are truly negative. The operational definition here implies that we will purify the antibody to an extent which eliminates the properties of FSH and LH-like activity to an extent possible at this time. The occasional cross-reaction with LH and FSH at mid-cycle can be minimized by the way in which the pregnancy tests are conducted and will be elaborated upon later. Precision refers to repeated estimations on the same sample with determinations of the variance. This will vary with batch lots, but can be minimized by quality control of reagents when materials are manufactured on a large scale. Accuracy refers to the nearness of the experimental result to the true result and can be ascertained by recovery experiments in which we add purified HCG to sample preparations.

PAST EXPERIENCES

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 by Eleanor Delfs of a quantitative assay for HCG in serum in 1941 and the greatly expanded use of this assay by Drs. Delfs and Georgeanna Seegar Jones since its inception. The chief

advantages and unique properties of this particular bioassay are its employment of serum (in contrast to most bioassays which are restricted to urine) and its continued, uninterrupted use since 1941 in this department with the same inbred colony of gray-hooded rats. This assay furnishes a comparative reference for all other pregnancy tests. The first experimental proof that HCG was elaborated from placental cells rather than pituitary cells also originated from this laboratory and was reported by Gey, Gey and Jones in 1941.

The history of immunoassays in the department began in 1961 when efforts were initiated to develop new immunological tests for pregnancy. The first was a complement fixation technique utilizing the classical method of complement fixation as described by Kabat and Mayer, which was compared against the Delfs' bioassay on a series of patients in which both the old and the new international standard preparations were employed. An advantage of this method was the great difficulty experienced in trying to force cross reactions with LH. Manually, the technique was not feasible for rountine use but is currently highly applicable in the automated devices issued by Technicon. Since that time we have invented three entirely different pregnancy tests,[1, 2] two of which are now commercial products, some of which are on the market and others of which are still undergoing field trials. As stated, we have developed considerable experience in conducting large field trials of new pregnancy tests, ours and others.

TEST APPLICATIONS AND FIELD PERFORMANCE

The "way" in which a pregnancy test is employed is important in determining the results achieved. The basic concepts which have evolved from our experience are that "two tests are better than one" and that "the selection and knowledge of the reagents employed are more important than the advertised claims of any test". A fuller discussion of the latter concepts can be found in Tice's Practice of Medicine,[3] which describes the pros and cons for designing tests at different sensitivities ranging from 0.3 IU HCG/ML to 5 IU HCG/ML and the properties of several commercial preparations in terms of earliest detection, accuracy, false positives and false negatives. The type and quality of the reagents determines the success of results obtained.

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1. Lau, H. L., et al. "Comparison of a New Covalent Indicator-Linked Immunochemical Assay for Human Chorionic Gonadotropin in Serum with the Delfs' Bioassay." The Johns Hopkins Medical Journal, Vol. 127, No. 5, pp. 247-253, 1970.

2. Lau, H. L., and Jones, G. S. "Immunoassay of Serum Human Chorionic Gonadotropin by Quantitative Complement Fixation and its Comparison with the Delfs Bioassay and Two International Standard Preparations." American Journal of Obstetrics and Gynecology, Vol. 92, No. 4, pp. 483-497, 1965.

3. Lau, H. L. "Tests for Pregnancy." Tice's Practice of Medicine. Hagerstown, Maryland: Vol. II, Chapter 29, 1970.

Immunological pregnancy tests are all relatively simple to perform but design of the package is important. Much can be done to reduce the number of steps employed and the number of simple tools needed, and thus reduce manual error in the field.

Design of the package to include two pregnancy tests at two different sensitivities can be beneficial in providing four times as much information as is provided by a single test. A single test leaves doubt: 1) as to whether that particular test falls into the 95% accurate or 5% inaccurate category; 2) as to the reliability of the reagent; 3) as to the reliability of the patient's estimate of the last menstrual period; and 4) as to the actual titer of HCG if HCG is present at all. The use of two tests instead of one can eliminate these four points of doubt.

METHODS AND MATERIALS

All methods employ the binding of either antigen molecules or antibody molecules to indicator particles to achieve macroscopic visualization of the antigen-antibody reaction. Commercial tests fall short of the criteria described to meet the needs of this project in that they are designed to meet consumer demands which do not stress the earliest possible detection of pregnancy and which are geared to fit ideal conditions as found in a private physician's office.

The first immunological test employed absorptive forces to hold antigen or antibody molecules to the surface of the indicator particle. The disadvantage of the absorptive type of binding was that the binding was loose and that a solution containing any appreciable amount of protein could not be used because the non-specific proteins replaced the specific antigen and antibody proteins on the surface of the particles. One solution to this problem is to replace the absorptive type of binding with a true covalent bond which has the additional advantage that a reaction strong enough to break the bond will also destroy the indicator particles. This destruction is visibly evident and no special tests for deterioration need be conducted.

Antibody purification has progressed considerably since the inception of immunoassays for HCG. Most commercial companies find it expedient not to purify the antibody to HCG to any considerable extent since they are working with relatively gross sensitivities of 1-5 IU/ML. We have found it advantageous to purify the antibody to HCG to a considerable extent.

The factor of humidity, which has great importance in transportability, has never been discussed or described previously and will be studied as an essential aspect of this project. Performance in the field should also take into consideration the various characteristics of the water supply available in underdeveloped countries, which in laboratory terms means a satisfactory test performance using water with a wide range of ionic concentrations.

Another direction of development includes improved packaging. One group of investigators, for example, has designed a simple plastic capsule containing reagents into one side of which has been impressed a hemispherical cup to simulate the lower most portion of a test tube, thus eliminating the test tube itself. Another group of investigators has entirely eliminated the need for a wooden stick to mix the reagents and the need for dropper bottles containing liquid reagents by incorporating lyophilized products onto an already formed slide on which the reagents can be mixed by simply tilting the slide back and forth. Another group of investigators has produced a slide in the form of a miniature pie pan on which one drop of urine is placed. Still another group of investigators has added a drop of fluorescein to their slide to aid visualization of the agglutination reaction, but this still requires liquid reagents for performance of the test. The general thesis is that every step and tool required in the procedure adds to the possible error of the method; therefore, reduction of steps and of tools is a necessity in simplifying new pregnancy tests.

In this project we 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. Second, we will attempt conjugation with the newer, more highly purified preparations of antigen, namely pure preparations of HCG, which were not available five years ago. Third, specifically for this project, we will develop another batch of antibody to HCG using the newer preparations of HCG. We will effect antibody purification in a manner previously described. For storage stability and transport ability, we envision lyophilized reagents as the most suitable to achieve these criteria, but reserve the right to resort to liquid preparations if they can be packaged to produce similar results. Lastly, we will experiment with innovate ways of packaging to achieve the criteria as defined under laboratory and field testing reliability. Ideas about new pregnancy tests have been constantly evolving and some of these ideas are in the laboratory stage, others are in the testing stage so that the three approaches as outlined at the beginning of this section will be employed.

In summary, the method would 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 would be judged by satisfactory performance after one year at room temperature and six months at any temperature over 80° C. The test will be evaluated as per routine in our laboratory using the same protocol which

includes methods for collection, sampling, programming and analysis as performed for all other tests. Trials should 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 by individuals in developing countries in comparison with an already well-established but less sensitive commercial test.

PROTECTION OF THE VOLUNTEER

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.

PROJECT II. MENSES REGULATION AND TERMINATION OF EARLY PREGNANCY

Background

A technique used for termination of unwanted pregnancy should have as its objectives:

a. A high degree of safety in terms of morbidity, mortality, and adverse long-term sequelae.

b. It should be 100% effective.

c. Technical simplicity which will preclude the need for complex and expensive equipment.

d. A minimum investment of time by professional and other skilled personnel.

e. A high degree of patient acceptance including a minimum investment of time by the patient.

f. It should be inexpensive.

It is clear from vast previous experience with therapeutic abortions that the single most important factor in achieving these objectives is the duration of pregnancy when a procedure is carried out. Nevertheless, even during early pregnancy, currently available techniques for interruption, the traditional dilatation and curettage, and suction aspiration, continue to be associated with various problems including the need for some type of anesthesia and the potential for serious complications. For instance, the introduction of rigid or semi-rigid instrument into the uterine cavity continues to carry a small but definite risk of perforation and the incomplete evacuation of the uterine contents continues to be associated with the potential for hemorrhage and infection. Furthermore, as abortion is accomplished at an earlier and earlier period of gestation, there is some concern that there is a risk of a diminishing rate of effectiveness in that the pinpoint implantation site might be missed by the curette.

The present 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 effacacious even if implantation had not yet occurred.

Objectives

1. To seek new means of menses induction and early pregnancy termination by systemic drug administration.

2. To seek new means of endometrial shedding and early pregnancy termination by local drug administration.

I. Systemic Drug Administration

A. Utilization of Prostaglandins

Introduction. Prostablandins have been reported to induce menses and early pregnancy termination in small series of women inadequately evaluated and followed.[1, 2] 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_{2a}: intravenous trials,

2. PGF_{2a}: intravaginal trials,

3. PGE_2: 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_{2a}, 50 ugm/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 on 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.

From evaluation of results of the preliminary trials, we may find that dose appears adequate and pregnancy is terminated, thus allowing continuation into Phase II, the intravaginal trials. However, we may find that longer duration of exposure is essential, and may have to evaluate daily infusions of intravenous medication. 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.

The intravenous trials will be followed by trials of PGF_{2a} in the form of intravaginal suppositories or tablets. Drug tolerance and efficacy will be analyzed, and studies performed as described above.

Prostablandin E_2, and other prostaglandin analogues will be tested as they become clinically available, using F.D.A. 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.

B. Utilization of Immunologic Means of Fertility Control

At the time of this writing, 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. The establishment of this unit 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. To date, immunologic preparations have been tested in but a handful of patients. 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

Aim: The aim of this project 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.

Introduction. Studies in the primate that are pertinent to this project and its stated objectives have not been reported. Shelesnyak (1957)[4], using rats, has demonstrated that decidual cell response and ovum implantation can be inhibited by the introduction of various drugs into the uterine cavity including antihistamines, oxytocin, epinephrine and various ergot alkaloids. With the

exception of the ergot drugs, systemic injections were either ineffective or the effectiveness was markedly reduced. It has been postulated that the efficiency of local over systemic application of drug is related to the higher tissue levels achieved with the former. The ergot alkaloids, on the other hand, have been shown to inhibit decidualization and implantation in the rat through a systemic effect apparently mediated through the hypothalamus with suppression of luteotrophic hormones and therefore, progesterone.[5-12] These studies, while elegant and certainly pertinent to our fundamental understanding of nidation in the rat, are of limited value with respect to the project. The inhibitory effects of the drugs described above are temporarily restrictive to the period preceeding implantation and furthermore, it is not possible to transfer information relating to nidation from one species to another.

Of somewhat more pertinence were the control studies carried out by Shelesnyak in which he induced destruction of the endometrium by various drugs referred to as "irritants" and including acetic, formic, and phosphotungstic acids; acetone, chloroform, benzine, xylene, turpentine, methanol, and ethanol. These drugs introduced into the uterine cavity, produced tissue damage and sloughing in varying degrees related to the concentrations used. He did not, however, determine the regenerative capacity of the endometrium following the tissue injury.

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. It should be kept in mind that 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. Some examples include the following:

A. Drugs which affect smooth muscle. These are chosen with the hope that they might be effective through the vasculature of the endometrium.

B. Drugs which affect vascular permeability.

C. Drugs which exhibit a non-specific but toxic effect upon proteins.

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.

10. Drugs to be Tested.

It is anticipated that as the project develops, some clues will be obtained as to which class of drugs will be most effacacious. Concentration of drugs will be varied. The following is a tentative list of drugs to be studied:

a. Drugs with non-specific effects upon protein. Included will be ethanol, rivanol, and acetic acid.

b. Drugs which effect smooth muscle. These will include epinephrine, ergot alkaloids and oxytocins and prostaglandins.

c. Drugs which effect vascular permeability. These will include histamines, bradykinins, and seratonin.

Study Design. The project will be carried out in three phases:

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

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

Phase III - Testing of drugs in the human.

Phase I and Phase II of this program may be completed simultaneously.

PHASE 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 followed 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 on the genital tract of drug application.

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, 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 Phase III.

PHASE II

This phase 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 Phase III.

PHASE III

Patients who are pregnant, requesting therapeutic abortion and in whom the duration of pregnancy is less than six weeks, will be considered as candidates for study in this phase. 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 a persistently positive immunologic pregnancy tests and other confirmatory data, the pregnancy will be terminated by a 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, and the efficacy and safety of the method studied as well. Completeness of termination if it occurs spontaneously will be ascertained by the diagnostic use of ultrasound, which has shown to be of considerable advantage in diagnosing incomplete abortions.[13]

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PROTECTION OF THE VOLUNTEER

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.

PROJECT III. DEVELOPMENT OF IMPROVED MEANS OF SECOND TRIMESTER TERMINATION OF PREGNANCY

Objective

To develop effective myometrial stimulants and other techniques for use in the second trimester abortion.

Introduction

Agents active in the initiation of the abortion process in this 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, which convert the previously viable pregnancy to that similar to the naturally-occurring missed abortion. An example of such an agent is the monamine oxidase inhibitor, Pargyline-Hydrochloride.[1] The third category (Group C) includes the hypertonic solutions currently employed for the induction of mid-trimester abortion. Delivery of a live fetus commonly occurs following the administration of hypertonic glucose[2] and is not a rare occurrence following hypertonic saline injection, particularly in twin gestations. Therefore, 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.[3,4]

Problems exist in the utilization of all three categories of agents. These problems are in two spheres, (1) untoward effects with associated patient morbidity[5,6,7] and occasional maternal death, particularly with use of the intra-amniotic hypertonic saline solution,[8] and (2) inadequate evaluation by clinical trials of reportedly effective agents, such as synthetic oxytocins,[9] monamine oxidase inhibitors,[10] as well as the hypertonic agent, urea.[11]

Materials and Methods

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

AGENT	ROUTE OF ADMINISTRATION
Group A	
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
Group B	
1. Pargyline Hydrochloride	Intra-amniotic

Group C

1. Urea 40% — Intra-amniotic
2. Dextran 40 and 75 — Intra-amniotic
3. Mannitol — Intra-amniotic

Group A: Myometrial Stimulants

Proposal 1. Appropriate animal studies
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,[12] has been extensively tested in the rat, rabbit and chicken.[13,14] 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[15] and the induction of cardiac arrhthymias.[16] 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 abortion 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.

The clinical utilization of oxytocin has been reported in the induction of elective abortion[9,17] and in the management of missed abortions.[18] 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 to evolve labor-like activity as compared to 3-6 mU. per minute in the term uterus.[17,19] The clinical series where oxytocin has been employed have been, to date, relatively small and not well documented.[9] The only report of direct uterine application has been in experimental animals in studies of induction of decidual reactions[20] and no literature could be 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. Finally, prostaglandins will be employed as a comparative group and to document whether pre-treatment with anti-emetic and anti-diarrheal agents will minimize the occurrence of these two side effects.

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, the time of fetal death, time to abortion, the degree of completeness of abortion and incidence of morbidity will be recorded.

Group B: Monamine Oxidase Inhibitors

Introduction

The effectiveness of monamine oxidase inhibitors in producing fetal deaths in rats and mice has been well documented.[1,21] Koren et. al.[10] gave intra-amniotic injections of 50-100 mg. of pargyline hydrochloride in 20 patients between three and 26 weeks of pregnancy. In 19 patients abortion occurred without reported problems. This agent blocks the endogenous monamine 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 uteri evacuation. Filing of 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 abortion, 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

Introduction

The recent publications from England reporting the effective utilization of intra-amniotic 40% urea in mid-trimester abortion illustrates the relatively limited exploration of available hyperosmolar agents.[11,22,23,24] Greenhalf and Diggory pioneered the work with intra-amniotic injection of urea, published early in 1971.[11] In a pilot study of 10 patients receiving intra-amniotic Ureaphil, they were unable to demonstrate any side effects, but only achieved a mean latent period of 50 hours. The shortest inpatient stay was four days, the longest nine days, and the mean six days.

Following this article, an additional 50 terminations of pregnancy with urea in mid-trimester were performed, this time with the supplementary use of oral oxytocin. With this regimen, the interval was not significantly reduced.[22] Pugh, Khunda and Baldwin[23] then reported on the induction of abortion in 50 patients, with the supplementary use of intravenous oxytocin. They reported no decrease in latent period with pitocin begun 24 hours after urea instillation. Craft and Musa, in late 1971[24] reported on the successful induction of abortion 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 be obtained 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 150-200 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 abortion 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-abortion interval, and the total duration of hospital stay. Side effects, both subjective and objective will be described and recorded as detailed. Evaluation of the hematologic, chemical and hormonal data will be performed. Uterine contractility studies will be monitored, and their results compared to contractility studies already performed in patients undergoing saline injection and prostaglandin termination.

Besides urea, which has been reported to be effective in induction of midtrimester abortion, it would be important to investigate mannitol, dextran-40 and dextran-75. No problems with urea-loading have been encountered but the patient with compromised renal functions might experience difficulty in clearance of this agent.

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.

The experimental protocol for these agents would parallel that described for urea. Depending on gestational duration, the following concentrations and amounts will be utilized intra-amniotically.

Agent	Concentration	Volume Employed	Weight of Agents In Grams
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 we have completed in monkeys of intra-myometrial injection of hypertonic saline and prostaglandin F_{2a} 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 tis way, midtrimester abortions 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.

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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.

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 with 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 cervices 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_{2a} has been shown to produce contractions of cervical strips in vitro, whereas prostaglandin E_2 has been shown to produce relaxation of comparable strips.[1, 2] 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.[3, 4] Enlargement, dilatation, and relaxation of the cervical canal were marked. Papain was tested in aprallel, 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 evaculation.

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 cervica 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 maleable plastic that allows controlled expansion was first completed by the staff of the Applied Physics Laboratory for their cardiovascular investigative programs.

Project 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.

Project 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%	Intra-cervical
Xylocaine, 1%, 2%	Intra-cervical
Enzymes	
Hyaluronidase	Intra-cervical
Bromelain	Vaginal
Papain	Vaginal
Other	
Prostaglandin F_{2a}, E_2	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 cercival dilatation occurs with the use of wither bromelain or papain, the effectiveness will be quantitated with the use of cervico-hysterograms. These two agents will be administered in solution form into the vagina.

In instances of systemically administered prostaglandin F_{2a} 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.

Project 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 Gyn e cological 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.

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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.

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 expected to be catastrophic and would in many instances serve to jeopardize an entire abortion program.

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 lesser 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 lesser developed countries be tested by pofessional 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 hysterograms.

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.

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.

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. It, 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 instrumetn 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 underdeveloped countries benefit from new instrument design based on knowledge accured from instrumentation of other medical specialties.

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PROJECT VI. A FERTILITY CONTROL EDUCATION PROGRAM FOR PHYSICIANS OF LESSER DEVELOPED COUNTRIES

The objective of this training program is 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 exercised leadership in research, training and service in the population field for more than a decade. The Department 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.

A suggested outline for the four week tutorial and preceptorship program in Fertility Control Techniques is given below. 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.

Tutorial discussions are indicated by *, the remainder of the meetings are clinical teaching sessions with models, experimental animals (i.e. rabbits for beginning laparoscopy) or patients.

INTENSIVE FOUR WEEK TUTORIAL OUTLINE

WEEK 1

Mon.	2-3 P.M.	* History of Fertility Control.
	3-4 P.M.	* Course Outline and Assignments of Required Reports.

Tues.	9-11 A.M.	* Clinical Physiology of Human Reproduction.
	11-12 A.M.	Pelvic Model Drill - for completion of bimanual examination and recognition of abnormal pelvic findings.
	1-4 P.M.	Contraceptive Clinic.
Wed.	9-10 A.M.	* Pregnancy Termination Techniques.
	10-12 A.M.	* Intrauterine Devices.
	1-3 P.M.	* Systemic Methods of Contraception.
	3-4 P.M.	Pittsburgh Carrels - selected self-educational audio-visual materials in fertility control, clinical obstetrics and gynecology and reproductive biology.
Thurs.	9-10 A.M.	* Laboratory Procedures - i.e. Hematology, urine analysis, and pregnancy testing.
	10-12 A.M.	Laboratory Drill - To gain proficiency in the completion of these required patient care tests.
	1-4 P.M.	Pittsburgh Carrels - Self-education materials in fertility control techniques.
Fri.	8-11 A.M.	Suction Abortion Procedures.
	11-12 A.M.	* Abortion Attitudes - Influence of patient, physician, and cultural attitudes.
	1-4 P.M.	Contraceptive Clinic.

WEEK 2

Mon.	8-11 A.M.	Suction Abortion Procedures.
	11-12 A.M.	* Patient Counseling in Fertility Control.
	1-3 P.M.	* Permanent Methods of male and female fertility control.
	3-4 P.M.	Pelvic Model Drill.
Tues.	8-11 A.M.	Laboratory Laparoscopic Procedures - Monkey demonstration with rabbits for individual trainees.
	11-12 A.M.	Construction of Fertility Control Program.
	1-3 P.M.	Clinic for Intrauterine Device Techniques.
Thurs.	8-12 A.M.	Saline Abortion Procedures.
	1-3 P.M.	Contraceptive Consultation Clinic - Uncommon patient problems.
Fri.	9-4 P.M.	Completion of Female Sterilization Procedures.

WEEK 3

Mon.	9-11 A.M.	Post Partum Interviews for Choice of Fertility Control Techniques.
	11-12 A.M.	* Ethical Considerations of Fertility Control Techniques.
	1-4 P.M.	Maryland Planned Parenthood Clinics.
Tues.	8-11 A.M.	Completion of Patient Laparoscopic Procedures.
	11-12 A.M.	* Social Considerations in Selection of Fertility Control Techniques.
	1-4 P.M.	Operating Room Demonstration of pregnancy Hysterectomies and Hysterotomies.
Wed.	8-11 A.M.	Suction Abortion Procedures.
	11-12 A.M.	Demography.
	1-4 P.M.	* Seminar by Participant Trainees with Presentation of Unique Problems of Individual Countries by the Students of the Specific Countries.
Thurs.	8-12 A.M.	Saline Abortion Procedures.
	1-3 P.M.	Male Sterilization Procedures.
Fri.	9-4 P.M.	State Health Department County Fertility Control Clinics.

WEEK 4

Mon.	9-11 A.M.	Post Partum Interviews for Choice of Contraception.
	11-12 A.M.	* Maternal-Child Health as Influenced by Fertility Control.
	1-4 P.M.	Prenatal Clinic.
Tues.	8-11 A.M.	Completion of Laparoscopic Procedures.
	11-12 A.M.	* Gynecologic Cancer Control.
	1-4 P.M.	Contraceptive Clinic.
Wed.	8-11 A.M.	Suction Abortion Procedures.
	11-12 A.M.	* Further Demographic Considerations.
	1-4 P.M.	* Continued Seminar by Participants of Individual Countries Problems.
Thurs.	8-12 A.M.	Saline Abortion Technique.
	1-3 P.M.	Contraceptive Clinic.
Fri.	9-12 A.M.	Examination - Course Critique.
	12-2 P.M.	Luncheon - Graduation.

Night duty of trainees will be in the clinical research unit for fertility control, every fourth night, observing the problems and required treatment of these patients.

It should be recognized that these trainees will not be licensed to practice medicine in the United States, thus this clinical preceptorship program must be formally approved by the State of Maryland Bureau for Medical Licensure. Therefore, each trainee must be completely supervised by the assigned preceptor in all instances of patient contact. These preceptors will be full-time faculty members of this department and are either Board-certified or Board-eligible specialists in obstetrics and gynecology. Every precaution will be taken to avoid any opportunity for patient injury, particularly during the trainees operative experiences.

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.

   This clinical facility has evolved because of the persistant interest of our director of Family Planning and Contraceptive Services, Dr. Hugh J. Davis. A genuine effort is being made such that only the most current technology in fertility control will be employed. It is planned that this facility will allow clinical testing of new procedures as they evolve and would therefore result in the reduction of the lag time from experimental clinical observations to clinical utilization for any given fertility control technique. In the three years of this A.I.D. program it is hoped that this clinical facility will evolve as a prototype for outpatient fertility

control services. This A.I.D. sponsored educational program will accelerate the evolution of the total educational capacity of this clinic.

This facility has at this time one operating room for outpatient procedures. Since the patient service function should be self-supporting, such service derived monies will assist in the expansion of the number of operating rooms, and in enlargement of the recovery area spaces. This outpatient facility should reduce patient cost by minimizing hospital utilization. More than 8,000 Maryland women per annum are currently seeking abortion outside the state and we have more than 1,000 women registered for sterilization.

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

A. Characteristics

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.

B. Selection of Trainees

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.

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 our ambulatory fertility control center.

BUDGET OF THE EDUCATIONAL PROGRAM

		Year 1	Year 2	Year 3
Personnel				
Principal investigator (King)		-	-	-
Coordinator for Training (see primary budget)		-	-	-
Clinicians x 3	50%	48,000	48,000	48,000
Nurse Specialist	100%	12,000	12,000	12,000
Secretary	100%	7,500	8,000	8,500
Trainee Program Administrator	100%	8,500	9,000	9,500
Salary Subtotal		76,000	77,000	78,000
Fringe Benefits @ 13%		9,880	10,010	10,140
Indirect Costs @ 36.1% of Salaries		27,436	27,797	28,158
Operational Costs of Educational Unit, to include: leasing of space, provision of teaching materials, laboratory animals, preparation of texts, etc.		15,000	9,950	5,904
Equipment				
Clinical		67,200	1,000	1,000
Office		2,325	-	-
Publication Costs		100	100	100
Travel to Lesser Developed Countries		2,500	1,500	1,000
Trainee Costs				
Travel	40 Students @ 1,000	40,000		
	55 Students @ 1,000		55,000	
	70 Students @ 1,000			70,000
Room	40 Students @ 50/mo.	2,000		
	55 Students @ 50/mo.		2,750	
	70 Students @ 50/mo.			3,500
Food	40 Students x 30 x 7.00	8,400		
	55 Students x 30 x 7.00		11,550	
	70 Students x 30 x 7.00			14,700
TOTAL Education Program Cost		250,841	196,657	212,502

3 Year Total 660,000

DETAIL OF TRAINING PROGRAM EQUIPMENT

	Year 1	Year 2	Year 3
Clinical			
Suction Machines x 4 @ $2,800	11,200	0	0
Laparoscopic Sets x 3 @ 3,500	10,500	0	0
Operating Tables x 4 @ 2,500	10,000	0	0
O.R. Lights x 4 @ 1,200	4,800	0	0
Instrument Sets x 12 @ 180	2,160	0	0
Examining Tables x 2 @ 600	1,200	0	0
Recovery Beds x 12 @ 600	7,200	0	0
Desks x 6 @ 350	2,100	0	0
Rolling Steel Tables x 4 @ 250	1,000	0	0
Rolling OR Stools x 4 @ 110	440	0	0
O.R. Sinks x 4 @ 1,200	4,300	0	0
Autoclave x 1 @ 4,800	4,800	0	0
Pittsburgh Carrel x 1 @ 3,400	3,400	0	0
Furnishings and Miscellaneous	3,600	1,000	1,000
TOTAL	67,200	1,000	1,000
Office			
Typewriter	450	0	0
Filing Cabinet	250	0	0
Desk/Chair/Table	600	0	0
Calculator	175	0	0
Dictation Equipment	850	0	0
TOTAL	2,325	0	0

BUDGET JUSTIFICATION

Personnel

The principal investigator does not require support for his teaching contribution. The coordinator for training, who will be the director of the education program is funded for $18,000 in the budget of the main program.

Three part-time clinicians and one full time nurse-specialist will be required to maintain the ratio of one trainee to one faculty member. Thus, one-half of the clinicians support is requested for this teaching function. A secretary and an administrator will be required for the processing of applications, arrangement of travel, and room reservations.

Operational Costs of this Education Unit

This unit is educationally a unified program that is composed of several components. These moneys are required for leasing of additional space required for the teaching program, preparation and provision of educational materials for each individual student as well as for purchase of experimental animals for training in laparoscopy and sterilization procedures. The surgical demonstrations will be completed on monkeys by the instructors, while each trainee will utilize rabbits.

Equipment

This equipment is required for the additional operating rooms that will essentially serve as a teaching laboratory for the trainees. The Pittsburgh Carrels are educational units that will contain the latest audio-visual materials in fertility control technique, appropriately selected obstetrical and gynecological information and materials on reproductive biology necessary for understanding of the fertility and infertility problems of man.

Office Supplies

These represent large items required for the establishment of the educational program office.

Publications

It is hoped that sufficient data is collected to warrant communication to journals in the discipline of obstetrics and gynecology.

Travel to Lesser Developed Countries

This will be undertaken by the program director in an effort to ensure relevancy to the specific countries of the selected trainees and after training of individuals from a given country to provide technical assistance for their evolving fertility control programs.

Trainees Travel, Room and Board

For each trainee $1,000 would be required for transportation. Fifty dollars per trainee would be required for a double room in the Johns Hopkins Medical Student Dormatory and seven dollars a day has been allocated for food costs.

PROTECTION OF THE VOLUNTEER

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.

EXPECTED END RESULT

The end result of establishment of the proposed project would be the development of a clinical testing unit for fertility control techniques which has the required sophisticated facilities to bridge the gap between design, development, and clinical applicability of such techniques for lesser developed countries.

It is expected that four to six months will be required to re-locate into the existing facilities, and to establish State-wide patient recruitment programs. With decreased facility costs, patients who now elect to go out of State for pregnancy termination will be recruited for the Johns Hopkins clinical program. During the first six months, while the program is being established and fully implemented, the ongoing evaluation of prostaglandins will continue, and the studies of hyper-osmolar drugs initiated.

During the first three months, the organization, including facilities, equipment and personnel to implement the training program will be acquired. In the succeeding nine months, the initial trainees will be accepted into the program, and will begin to rotate through the established facilities. The program as designed includes both didactic and clinical preceptorship experiences and will involve the use of all departmental facilities, including the Clinical Research Unit for fertility control techniques, COFLAC Clinic, the Johns Hopkins gynecological operating room, clinics of Planned Parenthood of Baltimore, and State Health Department's county contraceptive clinics. Didactic sessions provided by the faculty of the School of Public Health will be presented in their own facilities.

Also in the second six months, the early results obtained from testing of the prototype mechanical devices for cervical dilatation and uterine evacuation will become available. In this early stage, reliance upon the Johns Hopkins University, Applied Physics Laboratory, for the supply of design and devices will be necessary, and continued feedback is expected throughout the project with the additional input of a part-time Bioengineer. The early phases of these studies will include work with excised hysterectomy specimens for the design and adaptation of instruments and devices specifically for cervical dilatation and uterine evacuation. Close cooperation between the Applied Physics Laboratory the the Department of Gynecology and Obstetrics will be assured, and the proximity of the Agency for International Development will allow immediate communication of all promising ideas.

At the end of one year, evaluation of hypertonic agents for second trimester termination will be approximately 50% completed. Parallel efficacy and tolerance studies will be in progress, and the inferior hyperosmolar methods of pregnancy termination will be eliminated. The investigation of endometrial shedding and menses induction will be approximately 50% completed, and drug screening will be continued.

The investigation of cervical physiology should be well in progress, with the input of the uterine-cervical physiologist and the bioengineer as well as via the continued assistance of the Applied Physics Laboratory.

By the end of year one, the educational program will be fully established, with increasing attention directed toward improved techniques of education. It is expected that the routine handling of up to 55 trainees in the second year will present no problem. If extended training of any one individual appears to be of value a mechanism should be provided for this.

In the second year, follow-up studies to assess the results of training will begin. The anticipated plan is to send one or two observers from the Unit into a country from which there has been a trainee within the last six months. The efficacy and relevance of the teaching program will be evaluated by ascertaining whether or not practical as well as didactic information has been utilized and disseminated. If there has been the establishment of fertility control centers within the trainee's own country the observers could serve as program consultants.

In the second year the investigative program in the evaluation of new pregnancy testing, oxytocic agents, and locally applied abortifacients will continue. It is hoped that there will be continued development in all of the investigative programs.

Only experience can dictate the success of any projected project design, and it is expected that improvements by modification of the structure of the unit, its component staffing and personnel, projects and protocols to be run, and teaching input will be made continually. In the third year of the program 70 trainees will be accepted.

Progress reports, and lists of publications, will be reported yearly.

PREVIOUS WORK IN THE AREA BY THE INVESTIGATORS

The Johns Hopkins Hospital has long been innovative in the field of abortion research. Since passage of the reform legislature 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.

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 following hypertonic saline administration, and the determination of the efficacy and tolerance rates in comparison to suction curettage have been completed. An ongoing program evaluating prostaglandins as abortifacients is in progress. In the past, the Departments 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.

During the past two years, eight teaching sessions of four days duration, entitled "Surgical Techniques of Fertility Control", have been held for physicians from lesser developed countries and from the United States. Extremely well-attended, these courses have emphasized contraception, female sterilization, and abortion techniques.

Important advances from the Department of Gynecology and Obstetrics in the field of fertility control have included the single incision outpatient laparoscopic technique, and more recently, the initiation of a research program in the development of a tubal clip. This particular research project will be continued in the proposed clinical Research Unit.

Development of the Dalkon Shield I.U.D., now the most widely used in the United States, was headed by Dr. Hugh Davis of the Department of Gynecology and Obstetrics. Dr. Davis has recently published a book on intrauterine contraception, reviewing all aspects of contraception and including the design and management of contraceptive clinics and fertility control centers. The development of a "one-stop" fertility control center is in progress. All techniques of fertility control will be provided under one roof, and this unit will become one of the main teaching components of the training program.

The luteal phase defect was originally investigated and defined by Dr. Georgeanna S. Jones of the Department of Gynecology and Obstetrics. Understanding this entity is crucial to comprehension of the concept of luteolysis, as applied to prostaglandins, and to generalized techniques of fertility control.

Dr. Lorrin Lau, Director of the Endocrine Laboratories, and member of the Department of Gynecology and Obstetrics, has long been influential in the development of improved pregnancy testing. Immunologic techniques have been extensively compared and improved in his laboratory, and his is one of only two laboratories in the country performing the Delfs-Jones bioassay for human chorionic gonadotrophin.

The Applied Physics Laboratory of the Johns Hopkins University has long been interested in bio-medical engineering. Primarily, they have been involved in cardiovascular research, the development of intravascular pumps to be used to occlude large vessels, and production of instruments designed to test force and work. They have designed and developed all manner of delivery systems, and have extensive experience with all phases of bioengineering research.

Following is a list of pertinent publications completed by the faculty who will be included in this program.

PERTINENT DEPARTMENTAL PUBLICATIONS

CONTRACEPTION

Davis, H. J. and Israel, R.: Uterine cavity measurements in relation to design of intra-uterine contraceptive devices. Excerpta medica, Amsterdam, No. 86, 135-141, 1965.

Davis, H. J.: Evaluation of contraceptive techniques for demographic population control. The Social Responsibility of Gynecology & Obstetrics. Barnes, A. C., Ed. Johns Hopkins Press, Baltimore, 1965, pp. 15-23.

Davis, H. J.: Status of intrauterine devices in clinical practice. Curr. Med. Diag. 33: 10-15, 1966.

Davis, H. J.: Effect of intrauterine contraceptive devices on the endometrium. J.A.M.A. 195: 764-768, 1966. (with Israel, R.)

Davis, H. J.: The shield intrauterine device, a superior modern contraceptive. Amer. J. Obstet. Gynec. 106: 455-456, 1970.

Davis, H. J. and Lesinski, J.: Mechanism of action of intrauterine contraceptives in women. Obstet. Gynec. 36: 350-358, 1970.

Davis, H. J.: The IUD - Intrauterine Devices for Contraception. Williams & Wilkins, Baltimore, 1971.

Davis, H. J. and Lerner, I. S.: Experience with a shield design accommodative intrauterine device. Advances in Planned Parenthood - VI, Excerpta Medica International Congress Series No. 224, 89-92, 1970.

Davis, H. J.: Intrauterine contraceptive devices: Present status and future prospects. Amer. J. Obstet. Gynec. In Press.

Davis, H. J. and Trimble, F. I.: Clinical efficacy of loop and shield intrauterine contraceptive devices. J.A.M.A. In Press.

Davis, H. J., Liu, P. T. and Chow, L. P.: A comparative study of five intrauterine contraceptive devices. Amer. J. Pub. Hlth. In Press.

Davis, H. J.: The shield intrauterine device: Results in nulliparous women. Adv. Planned Parenthood. In Press.

Pertinent Departmental Publications

ABORTION

Johnson, J. W. C., Cushner, I. M. and Stevens, N.: Hazards of using hypertonic saline for therapeutic abortion. Amer. J. Obstet. Gynec. 94: 225-229, 1966.

King, T. M., Friedman, J. and Steer, C. M.: Electrolytic changes following transabdominal intra-ovular injection of hypertonic saline. A preliminary report. Symposium on The Mechanisms of Labor, Wurzburg, Germany, 1963.

King, T. M.: Hypofibrinogenemia and intrauterine fetal death. Amer. J. Obstet. Gynec. 19: 914, 1964. (with Phillips, L. L. and Skrodelis, V.)

Wentz, A. C., Cushner, I. M., Austin, K. and Shams, M.: Intra-amniotic administration of prostaglandin F_{2a} for abortion. Amer. J. Obstet. Gynec. In press.

Wentz, A. C.: Myometrial necrosis in therapeutic abortion. Obstet. Gynec. In press.

STERILIZATION

Wheeless, C. R.: A rapid, inexpensive, and effective method of surgical sterilization by laparoscopy. J. Reprod. Med. 5: 65-69, 1969.

Wheeless, C. R.: Outpatient tubal sterilization. Obstet. Gynec. 36: 208-211, 1970.

Wheeless, C. R.: Anesthesia for diagnostic and operative laparoscopy. Fertil. Steril. 22: 10, 1971.

Wheeless, C. R.: Outpatient sterilization by laparoscopy - A report of 666 cases. Obstet. Gynec. 38: 912, 1971. (with Thompson, B. H.)

Wheeless, C. R.: Elimination of second incision in laparoscopic sterilization. Obstet. Gynec. 39: 134, 1972.

PERTINENT ENDOCRINOLOGY

Jones, G. S., Gey, G. O. and Gey, M. K.: Hormone production by placental cells maintained in continuous culture. Bull. Johns Hopkins Hosp. 72: 26, 1943.

Jones, G. S., Delfs, E. and Stran, H. M.: Chorionic gonadotropin and pregnanediol values in normal pregnancy. Bull. Johns Hopkins Hosp. 75: 359, 1944.

Jones, G. S.: An evaluation of the hogben pregnancy test. Amer. J. Obstet. Gynec. 50: 691, 1945. (with Foote, E. C.)

Pertinent Endocrinology, Cont.

Jones, G. S.: Endocrine patterns in abortion. Obstet. Gynec. Survey 3: 680, 1948. (with Delfs, E.)

Jones, G. S. and Delfs, E.: Endocrine patterns in term pregnancies following abortion. J.A.M.A. 146: 1212, 1951.

Jones, G. S.: The filter paper electrophoretic identification of urinary chorionic gonadotrophin. Bull. Johns Hopkins Hosp. 93: 51, 1953. (with Stran H. J.)

Jones, G. S.: The gynecological aspects of adrenal hyperplasia and allied disorders. Amer. J. Obstet. Gynec. 68: 1330, 1954. (with Jones, H. W. Jr.)

Jones, G. S., Woodruff, D. J. and Moszkowski, E.: The inadequate luteal phase. Amer. J. Obstet. Gynec. 83: 363, 1962.

Jones, G. S.: The immunoassay of serum human chorionic gonadotrophin by quantitative compliment fixation and its comparison with the Delfs' bioassay and two international standard preparations. Amer. J. Obstet. Gynec. 92: 483, 1965. (with Lau, H. L.)

Jones, G. S.: Endocrine functions of the placenta. Intrauterine Development, Barnes, A. C., Ed., Lea & Febiger, Philadelphia, 1967, Chapter 3.

Jones, G. S.: The aluteal cycle - A severe form of the luteal phase defect. Amer. J. Obstet. Gynec. 103: 1059, 1969. (with Ruehsen, M. D., Burnett, L. S. and Baramki, T. A.)

Jones, G. S. and Madrigal-Castro, V.: Hormonal findings in association with abnormal corpus luteum function in the human: The luteal phase defect. Fertil. Steril. 21: 1-13, 1970.

Jones, G. S.: Comparison of a new covalent indicator-linked, immunochemical assay for human chorionic gonadotropinin serum with the Delfs' bioassay. Johns Hopkins Med. J. 127: 247, 1970. (with Lau, H. L., Ferraz, E. and Butler, M.)

Jones, G. S.: Corpus luteum abnormalities. Progress in Infertility, Behrman and Kistner, Ed., Little ,Brown & Co., 1968.

Jones, G. S.: Novak's Textbook of Gynecology. Williams & Wilkins, Baltimore, 1970. (with Novak, E. R. and Jones, H. W. Jr.)

King, T. M.: The influence of chronic distention on myometrial contractile protein. Amer. J. Obstet. Gynec. 105: 1082, 1969. (with DeClue, J. W. and Comfort, G. D.)

Pertinent Endocrinology, Cont.

King, T. M.: Observation on uterine growth effected by mechanical distention. Amer. J. Obstet. Gynec. 105: 517, 1969. (with DeClue, J. W.)

King, T. M.: Estrogen receptor in human endometrium during the menstrual cycle and early pregnancy. Amer. J. Obstet. Gynec. 111: 1064, 1971. (with Limpaphayom, K., Lee, C. and Jacobson, H. I.)

Lau, H. L.: A new simple immunoassay for human chorionic gonadotropin. Amer. J. Obstet. Gynec. 109: 29, 1971.

Lau, H. L., et al: Comparison of a new covalent indicator-linked immunochemical assay for human chorionic gonadotropin in serum with the Delfs' bioassay. Johns Hopkins Med. J. 127: 247, 1970.

Lau, H. L. and Jones, G. S.: Immunoassay of serum human chorionic gonadotropin by quantitative complement fixation and its comparison with the Delfs' bioassay and two international standard preparations. Amer. J. Obstet. Gynec. 92: 483, 1965.

REVIEW OF PERTINENT WORK BY OTHER INVESTIGATORS

I. Introduction

In 1970, Malcolm Potts of the International Planned Parenthood Federation stated: "The termination of pregnancy is one of the oldest and one of the commonest forms of fertility control. No human community has ever showed a marked fall in the birth rate without a significant recourse to induced abortion and it is unlikely that...contraceptive procedures alone will provide a sufficient measure of population control..."

In spite of the widespread current use and need for abortions, the provision of needed abortion services for the populations of either the well-developed industrial nations or for the agrarian societies of lesser developed countries is less than ideal. There is associated with all currently employed abortion techniques an incidence of maternal morbidity and mortality and while this is decreasing, it is far from totally eliminated. Late sequellae of abortion procedures have been demonstrated to have an ill effect on subsequent pregnancies with the resulting occurrence of impaired fertility. Because the currently employed abortion techniques that are surgical in nature require utilization of either hospital or clinic facilities with their associated professionals and para-professional personnel, abortion costs to individual patients and to specific populations are excessive. This problem is compounded because of the required multitude of surgical approaches predicated on the duration of pregnancy of the individual patient. Therefore, the large-scale delivery of abortion services is currently wed to the delivery of general medical services with its own problems of costs, and mal-distributions superimposed on a base of pregnancy termination knowledge that is lacking the ideal abortifacient for all patients.

For these reasons there must be continued search for an abortifacient that may be self-administered and productive of total uterine evacuation with restoration of the menstrual cycle. It must be free of immediate sequellae and without influence on future reproductive capacity.

The review of abortion literature demonstrates that man's interest and concern in this area dates from antiquity. The techniques and agents employed range from the ludicrous to the most sophisticated procedures and agents that our current civilization can conceive. This review has been primarily directed toward areas that may assist in the continued search for the ideal abortifacient.

II. Post-Conceptive Anti-Fertility Agents

A. Pharmacological Agents

Substances designed to act after fertilization has occurred may prevent continuation of pregnancy by (1) inhibition of implantation; (2) prevention of embryonic growth; (3) production of endometrial shedding. Although the mechanism would differ in each instance, such substances would not be considered post-coital in nautre, but rather post-conceptive, implying actions during the interval after fertilization. They would be administered either at a defined time during each cycle, or when menses is missed. They should have 100% efficacy, no toxicity, maximal simplicity of administration, maximal patient acceptability, and, in marginal doses taken at inappropriate times, not be teratogenic.

At the present time, the only substances which can serve as post-coital contraceptives are estrogens. Their utilization may interfere with tubal transport, with endometrial development, or with some factor essential for early embryonic growth. There are multiple reviews on the use of estrogens as post-coital agents or post-conception inhibitors.

For agents primarily active at or just following implantation, anti-progestational activity appears to provide a common denominator. The inhibition of endometrial development necessary for normal implantation would appear to establish a condition analagous to the luteal phase defect seen clinically in humans. This is secondary to reduced progesterone output from the corpus luteum, either because of inadequate gonadotropin preparation or stimulation, or because of an intrinsic enzymatic defect within the corpus luteum, therefore, the luteal phase defect is associated with poor implantation, and early abortion because of inadequate hormonal support.

Multiple non-specific embryotoxic agents have been investigated. While estrogens will disrupt the established implantation in rodents, this has not been observed in primates. There are, however, cytotoxic agents with anti-trophoblastic or anti-zygotic activity. Most of these have high maternal toxicity and are potentially teratogenic when given in marginal doses or at a marginal time.

Morris [1970], in searching for improved anti-fertiliyt agents, included the following agents that act in the peri-implantation period: (1) M-xylohydroquinone (mXHQ); (2) ergotoxine (ergocryptin, ergocornine, ergocrystin); (3) estrogens and anti-estrogens; and (4) other hormones. To this list, one would have to add the prostaglandins, particularly as luteolytic agents.

1. Anti-Progestational and Luteolytic Agents

a. Progesterone. Progesterone secretion by the corpus luteum is essential for the maintenance of the early pregnancy in the human. The luteal phase defect is associated with infertility, because of the common occurrence of early abortion.

Clinical symp nology may simply be that of a delayed menses with a somewhat heavier period than normal when it does occur. There is the possibility, then, that anti-progestational agents might be used to induce a controlled luteal phase defect, and therefore effect early pregnancy termination. Such an approach to pregnancy control has barely been explored. There is no means presently available to eliminate corpus luteum function, either by immunologic or drug therapy.

b. M-xylohydroquinone (mXHQ). M-xylohydroquinone (mXHQ), originally isolated from the oil of the field pea, has provoked considerable interest because of the persistent claim that it is a potent oral contraceptive [Sanyal, 1960]. In 1953, Sanyal reported that mXHQ caused resorption of fetuses in the first trimester in rats, but did not cause abortion in such animals once pregnancy was further advanced. Batra and Hakim, in 1956, performed further experiments in mice and rats in which mXHQ did indeed produce abortion. However, Thiersch, in 1956, found no delayed mating, no failure of implantation, or abortion. On the basis of earlier experiments with rats, the anti-fertility effect claimed for this agent was thought to be related to interference with the peripheral action of progesterone resulting in an endometrium unprepared for implantation. However, the anti-proge sterone effect of this agent could not be substantiated by Banik and Chakravarty. Pincus, in 1956, observed in rats a delay in mating, and reduction in the number of fetuses. Yet Prahlad and Kar showed that the administration of mXHQ on the third and sixth days of pregnancy had no effect on the number of implantations in rats, and provides direct evidence against any anti-progesterone or anti-estrogen effect of mXHQ. This agent has been tried in humans, two doses of 300-350 mg. of the compound was administered on the 16th and 21st days of the menstrual cycle and reportedly caused 50% reduction in fertility. However, on the basis of animal experimentation, and the poorly controlled human study, one would conclude that this agent is not effective as either a contraceptive or abortifacient.

c. Prostaglandins. There is great interest in the use of prostaglandins for fertility control in early pregnancy. The presence of a luteolysin was originally postulated to explain the phenomenon of prolonged corpus luteum function following hysterectomy in sheep [Bland and Donovan, Loeb]. Pharriss et al. in 1968 proposed that the life span of the corpus luteum is critically regulated by local blood flow and demonstrated that a common venous pathway exists in those animals which exhibit a local influence of the uterus on the corpus luteum. It was then postulated that a substance released by the uterus could regulate ovarian blood flow by its vasometer activity. That prostaglandins played the role of a luteolysin was demonstrated by Pharriss and Wyngarden in pseudopregnant rats, by Blatchley and Donovan in the guinea pig, by Johnston and Hunter in the hamster, and by McCracken et al. in the sheep.

The concept that luteolysis may be employed as a mechanism of early pregnancy termination effected by prostaglandin appears clear in many laboratory animals in which their placentas are not steroidogenic. The evidence is conclusively summarized by Pharriss [1971]. However, the situation is far from clear in the primate where both the corpus luteum and the placenta are steroidogenic, and thus the mechanism of pregnancy termination remains obscure.

Kirton et al. (1970b) injected PGF_2 subcutaneously in monkeys and demonstrated decreased progestin levels in 24 to 48 hours. In the monkey, progestins measured in a normal cycle show a secondary rise beginning about Day 11 of the cycle, and this second peak is rapidly abolished by protaglandin administration in pregnant monkeys during the period of placental dominance (after 40 days' gestation) does not appreciably decrease progestin levels (1970a).

In the human, work is in progress on the luteolytic effect of prostaglandins. It has been suggested by Karim (1971) and others that intravenous, intrauterine, and intravaginal administration of prostaglandin can cause menses in the late luteal phase and can induce early abortion (Bygdeman and Wiqvist, 1970). Wiqvist et al. (1970) has shown that administration of PGF_{2a} to the early pregnant female produces no significant drop in progestin levels during the infusion before abortion. Using eight-hour infusions of PGF_2 in six women, just after ovulation, they showed no suppression of luteal function. All females had subsequent menses at the expected time, but two did bleed three to five hours after beginning the infusion. Bygdeman and Wiqvist stated that the corpus luteum was probably not affected by the infusion, as only a slight transient drop in peripheral progestin was measured. However, the vasculature of the corpus luteum is not well-established until at least Day 20, and possibly infusions just after ovulation may be too early to affect corpus luteum function. Karim (1971) administered prostaglandin intravaginally to 12 women of proved fertility who had passed their day of expected menses, 11 of the 12 bled, and eight of these patients ultimately proved to be pregnant.

Henzl et al. administered PGE_2 intravenously to four volunteers on three consecutive days and measured serum progesterone levels before and after the infusion. No effect on cycle length was noted with prostaglandin administered soon after ovulation. However, administration on Day 23-24 was followed by premature bleeding on Day 25, but without a decrease in basal body temperature. No consistent change in serum progesterone levels was seen in this preliminary study. The infusion of PGF_{2a} on various days of the luteal phase has neither shortened the menstrual cycle, decreased the duration of the rise of basal body temperature, decreased serum progesterone levels, or decreased urinary pregnanediol output. It would appear at the present time that prostaglandins do not exert a luteolytic effect in the human female (G. S. Jones, personal communication).

Interest in the luteolytic effect revolved around the whole concept of prostaglandins as menses inducers. At the present time, attempts are being made to infuse women two to ten days past the first missed menses, to ascertain if pregnancy would be interrupted at this stage by myometrial contractions whether or not a luteolytic effect exists. Preliminary data from Scandinavia shows that of seven women so treated, three apparently aborted, and four went on to require termination by surgical methods (Wiqvist, 1971). In the United States, a few sporadic reported cases have shown similar results (Wentz, unpublished).

At the present time, the luteolytic effect appears unlikely and the reliability of menses induction in very early gestation is uncertain. The possibility of prostaglandin analogues performing such functions will be explored as they become

available. It is possible that preliminary attempts to induce menses have used sub-optimal doses for inadequate duration. It remains to be demonstrated that prostaglandins offer an advantage over suction curettage.

d. Ergocornine and Its Derivatives...as inducers of endometrial shedding, primarily for the development of pseudopregnancy.

Shelesnyak (1954) reported that the systemic administration to rats of ergotoxine (Ergocornine) prevented the development of deciduomas and this effect could be reversed by progesterone administration. Evidence of the direct action of ergotoxine on the hypothalamus had previously been presented by Buchanan and co-workers (Buchanan and Roberts, Roberts et al.) The inhibition of the decidual reaction could be caused by disturbing the estrogen-progesterone ratio by the resulting hyperthalamic suppression. Shelesnyak (1955) went on to show that ergotoxine administration disturbed the regularity of the estrus cycle, terminated pseudo-pregnancy, and produced abortion within 3 days of administration, however, this latter effect was limited to the first 7 post-coital days which in the rat, includes the implantation period. No teratogenic effect was seen in those rats receiving ergotoxine after the 7th post-coital day. Shelesnyak (1956) then showed the administration of progesterone to rats given ergotoxine on the 4th through the 6th day after copulation inhibited the gestation terminating action of ergotoxine. In 1963, Shelesnyak and Barnea administered ergocornine directly to the ovary, uterus, and pituitary gland of pregnant and pseudopregnant rats. Ergocornine, in local administration, did not always induce the usual response, and in no instance did estrus reappear or pregnancy terminate. It was concluded that the action of ergocornine (ergotoxine) was not mediated by direct contact between the drug and the target site. Varavudhi and co-workers showed that after the administration of ergocornine, the availability of progesterone was reduced, and that blastocysts were unable to nidate. The authors speculated that either ergocornine interferred with the secretion of luteotropic hormone, or with the secretion of progesterone by the ovaries. They favored the interpretation that ergocornine acts by way of the central nervous system, specifically via the hypothalamus.

In the rat, maintenance of gestation depends on the steroidogenic function of the corpora lutea which can be maintained only by continuous luteotropic stimulation. Initially, pituitary gland insures the secretion of this luteotropin. However, during the course of gestation, the placenta becomes the source of these luteotropic factors, although the exact time that the placenta acquires this particular endocrine function in the rat is obscure. Kisch and Shelesnyak in 1967, showed that ergocornine administration failed to interfere with pregnancy after implantation, even in the absence of the fetus. Data support the concept that ergocornine acts to suppress the pituitary luteotropic hormone, without modifying the capacity of the ovary to respond to trophic stimulation. When placentas had matured sufficently to produce enough luteotropic substances, the ergocornine activity was drastically inhibited, and pregnancies were maintained. Unpublished studies from Israel have shown no such effect in the human but the drug has not been investigated in early human pregnancies.

2. Estrogens

Numerous early observations have suggested that, in the rat and other species, various steroids can not only prevent conception, but can also interrupt established pregnancies. In 1966, Morris and Van Wagenen showed that estradiol-17B, stilbesterol, ethinyl estradiol, and mestranol would not only prevent implantation, but when given in early gestations, result in placental separation and death of the rabbit fetus. They commented that it was obvious that in the human, administration of estrogens had no effect incompatible with continued development of the fetus. This work resulted in continued use of diethylstilbestrol as a post-coital agent, effect in preventing implantation in the human if taken within 72 hours of coitus.

Hill and Pierson, in 1958, reported that intramuscular diethylstilbestrol was an abortifacient in 80% of heifers pregnant less than 150 days. Greenwald (1961, 1963) reported 100% abortifacient efficacy of intramuscular estradiol in the rabbit and rat. Morris et al., in 1967, investigated other synthetic estrogens and anti-estrogens, including clomiphene (Lerner et al., Prasad et al.), ORF-3858, and others. Clomiphene had previously been found to interfere with implantation of the ovum in the rat (Segal and Nelson, Barnes and Meyer, Chang). It was found to have no effect on preventing pregnancy in primates, or to have any deleterious effects on the developing fetus (Morris, 1967). Clomiphene is now employed as an effective ovulation induction agent in humans. ORF-3858 was shown to be a potent anti-fertility agent in rabbit and rat. In the primate, it was slightly estrogenic, and when given after documented matings, no pregnancies have occurred (Morris, 1967).

Bacic et al. in 1970 reported on the failure of large doses of ethinyl estradiol to interfere with early embryonic development in humans. Ethinyl estradiol was administered for seven days during early pregnancy in daily doses of 1 mg. to 20 women, and in daily doses of 5 mg. to 6 women. Abortion did not occur, and with present awareness of the correlation between diethylstilbestrol administration during pregnancy and the subsequent development of vaginal adenocarcinoma in female pregnancy, one would have to avoid the administration of any estrogen in early gestation (Herbst et al.).

It is now established that estrogens in the primate and human may effectively act as post-coital contraceptives when given within a narrow time range, but have no effectiveness in the post-implantation period. Their use in early gestation is restricted because of the development of vaginal adenocarcinoma in female offspring.

3. Cortisone

Wagner in 1971, reported on the induction of abortion in the rabbit by hydrocortisone acetate injections. The threshold for oxytocin response of the uterus was found to have been lowered after cortisone injection. In sheep premature labor can be induced by the administration of either ACTH, dexamethasone, or cortisol. It is thought that this resulting steroid effect is mediated via alteration of placental activity.

4. Miscellaneous Steroids

Naqvi and Warren in 1972, introduced the concept of "interceptives", drugs interrupting pregnancy after implantation. They administered oxymethalone and durabolin to pregnant rats and observed that oxymethalone caused resorption of pregnancy in 87.5% of the animals, probably due to an anti-gonadotropic effect of the agent. Durabolin, on the other hand, caused fetal resorption with only placental fragments remaining, and was thought to act either by interference with synthesis of progesterone in the corpus luteum, or acted competitively with progesterone at some uterine site necessary for the maintenance of pregnancy.

Cholesterol was shown by Selye et al., to have no effect on pregnancy interruption, while dihydroepiandrosterone, triamcinolone, prednisolone and dexamethasone have some limited ability to interrupt pregnancy in the rat.

5. Immunological Agents

The utilization of immunologic methods for fertility control is currently in the developmental stage. Tissues of the reproductive system as well as its hormones are, or can be made, antigenic. Actively induced auto-antibodies and passively-induced hetero-antibodies may have profound influences on the processes of reproduction.

Approaches to abortion induction by immunologic means would center on antibody production against: (1) the egg and embryo; (2) protein and steroid hormones; and (3) placenta, trophoblast and fetus.

Little information on antibody formation to eggs or embryos has appeared, but some intriguing preliminary work has been done. Chang in 1949 discovered a serum factor which, in some species, produces lysis of eggs and embryos, the active factor may be anti-lysosomal (Edwards). Tyler identified "fertilization" on the surfaces of certain eggs, an antibody which can block egg cleavage. Blastokinin, identified in rabbit uterine fluid, appears to be necessary for embryonic development (Daniel). Blastokinin is antigenic, and suppression of implantation would likely result from antibody administration. Theoretically, antisera might be prepared against any antigen expressed on cell surfaces of cleaving ova and blastocysts and impair progressive development.

Protein hormones are antigenic and the actions of these antibodies have been investigated. It has been demonstrated in rats that antibodies to luteinizing hormone (LH) can inhibit the estrous cycle (Laurence and Ichikawa, 1968). These actions may be of prolonged duration. Loewit and Laurence demonstrated that rabbit anti-bovine LH serum administered to pregnant rats produced resorption of fetal implants up to the 12th day of gestation. Termination of pregnancy after neutralization of endogenous LH is probably due to interference with continued functioning of the corpus luteum (Loewit et al.). Antibodies to LH may interfere specifically with in vivo steroidogenesis, and it appears that both estrogen and progesterone synthesis may be inhibited.

Spies and Quadri have investigated rabbit anti-ovine LH antiserum administered to pregnant rabbits and produced regression of corpora lutea and interruption of pregnancy. Pregnancies remained intact in animals treated with either estrogen or progesterone in the presence of the antiserum indicating that the primary mechanism was an inhibition of endogenous LH function. Although this approach has promise, it is not yet adaptable to human clinical trials.

The actions of human gonadotropins have been inhibited by an extract from pooled urine of children, appropriately called gonadotropin-inhibiting factor (GIF) [Davis et al., Soffer et al.). Administration of GIF to mice at various stages of pregnancy produced infertility, presumably by interferring with implantation (Landau et al.)

Antibodies to follicle stimulating hormone (FSH) have induced anestrous, lack of mating behavior, infertile matings, and resorption of implants in rats and rabbits (Talaat and Laurence). The histological patterns of ovaries from treated animals varied, but a constant finding was the prevention of normal follicular maturation.

Steroid hormones coupled to proteins are antigenic. Ferin et al (1968) demonstrated that antibodies specific to estradiol-17B (E_2) can inhibit the biologic effects of exogenously administered E_2, as well as endometrial stimulation and vaginal cornification due to endogenous hormone. The ability of specific antibodies to block ovulation, and its restoration by diethylstilbestrol provides direct evidence for the existence of a positive feedback role of estrogens in the release of leutinizing hormone (Ferin et al., 1969). Besides elucidation of reproductive mechanisms, anti-E_2 will have important therapeutic possibilities. Clinical testing is not yet feasible.

Antibodies to progesterone have been produced but these too are not yet ready for clinical trials. An attractive possibility would be the induction of a luteal phase defect and poor progesterone support of an early gestation.

In view of the anti-genicity of the embryo, and the immunologic competence of the maternal organism, it is a reasonable approach to attempt termination of pregnancy by immunologic techniques. In 1967, Kirby reported that all attempts directed specifically to immunize the maternal organism against paternal transplantation antigens present in the fetus had proved ineffective. Using an immune serum produced in rabbits by intravenous injection of living mouse thymocytes, Kirby produced involution of the corpora lutea and immediate termination of pregnancy in mice. The action was reversed by the simultaneous administration of progesterone. Serum given soon after mating prevented egg implantation, even after exogenous progesterone administration, and it was postulated that the serum had interferred with the mechanism by which the blastocyst initiates the decidual response in the mouse. A non-specific action, as an example, damage of the uterine tissues, was not ruled out.

Brent (1967) immunized rabbits with placental extract, and used the pooled sera for injection into pregnant rats. The antisera produced embryonic death, fetal growth retardation, and malformation. Similar results were obtained with rat kidney antiserum (Brent, 1961).

As immunologic techniques have become more refined, the antigenicity of the trophoblastic cells has been demonstrated. Gross in 1970, stated that there was no evidence of antigenicity of trophoblast. However, Koren et al. in 1969 demonstrated in vitro proof of the antigenicity of trophoblastic cells as indicated by a fluorescein technique, this was later confirmed by Douthwaite and Urbach. The problem is not one of lack of antigenicity, but rather lack of expression of antigenicity. Under normal physiologic conditions, the trophoblast may be incapable of manufacturing or expressing on the cell surface histacompatability antigens. It has also been suggested that although histacompatability antigens are present on trophoblastic cells, they are prevented from reaching and sensitizing the maternal host by a layer of surrounding fibrinoid material (Avery and Hunt, Currie et al.). However, the absence of this fibrinoid layer in other than hemochorial placentas argues against its general immunologic significance (Koren et al, 1969).

Koren et al. (1970) compared the biologic and immunologic activity of placental antigens prepared from whole placental homogenates, and placental cell suspension, primarily trophoblasts. Both preparations appeared to be antigenic in rabbits, and the immunologic and biologic activities were equal. When pregnant mice were treated with rabbit anti-placental sera, pregnancies were rapidly interrupted, but significant abnormalities were found in the maternal liver, kidney, and uterus. Prominent foci of coagulation necrosis and associated inflammation existed in the liver, and proliferative glomerular changes and tubular degenerative changes suggestive of glomerular nephritis were found. Koren indicated that fractionation of whole sera drastically reduced the pathologic changes in the kidney. The possibility exists of producing a "pure" trophoblast antigen capable of stimulating formation of a specific placental antibody.

Gusdon has reported on the possibility of immunologic destruction of placental or fetal tissue. Antibody activity directed against preparations of human placental lactogen (HPL), has been found primarily in postpartum patients (Gusdon et al.). A possible reason for survival of the placental allograft may occur by immunologic enhancement. Although antibodies develop against host antigens, the very presence of these antibodies which are not capable of tissue destruction, prevent rejection by the host lymphocytes. Antigenic sites are covered by antibody, which protect the tissue from sensitized lymphocytes primarily responsible for the rejection mechanism. Antibody to HPL may play such a role. In 1972, Gusdon treated pregnant rats with anti-HPL rabbit serum. Implantation occurred without complication in these gestations, but, after a short period of time, destruction of fetal tissue commenced. Within a month, normal estrous cycling recurred. It was suggested that the elucidation of this anti-fertility mechanism might lead to an effective, immunologically-induced method of contraception.

The evidence cited clearly indicates that reproductive processes can be controlled or modified by immunologic techniques. The problem at present is to develop adaptability to the human, such that normal reproductive function returns after such treatment.

6. Metals and Ions

Early attempts to study induced abortions utilized solutions of metallic ions.

In 1925, Bell showed that lead had a peculiarly selective action on the chorionic cells of rabbits producing abortion without affecting the maternal organism. Colloidal suspensions of metallic lead produces coagulation necrosis of the trophoblastic cells, beginning at the growing edge of the fetal ectoderm. The specific action of lead, a known abortifacient, had not previously been demonstrated. Datnow, in 1926, investigated the abortifacient activity of multiple substances, including cadmium, lead, and thelenium. The intravenous route of administration was used in rabbits and all products of conception were examined. Coagulation necrosis was produced by all preparations containing lead. Intraplacental hemorrhage was caused by cadmium, thelenium, and lead in large doses. In no instance was death of the embryo the primary cause of abortion.

The most significant modern work on the contraceptive efficacy of metallic ions was carried out by Zipper, Medel and Preager. They compared the effects of zinc, copper, tin, silver and magnesium in rabbits noting that copper had outstanding anti-conceptive properties. The work has now been extended to humans, comparing a T-shaped device of polyethylene plastic with and without a covering of copper wire. The copper ion in very low concentrations is an effective enzymatic inhibitor, and it is possible that fertilization occurs normally while implantation and embryonic growth are inhibited.

There is no evidence at present that intrauterine instillation of metallic solutions would be effective as an abortifacient in the human.

7. Cytotoxic Drugs

A remarkable volume of literature has appeared concerning the use of various nucleo-toxic and cytotoxic drugs as abortifacients. A partial listing of those agents studied include:

1. Anti-metabolites, such as aminopterin, 6-mercaptopurine, and aza uridine;
2. Alkalating agents such as nitrogen mustard, chlorambucil, and cyclophosphamide;
3. Anti-mytotics, including podophyllotoxin, colchicine and its derivatives, urethane, and actinomycin-D;
4. Other agents, including the alkaloids vinblastine and ergocornine.

In 1948, Thiersch and Phillips reported that administration of the folic acid antagonist, 4-amino-pteroylglutamic acid (aminopterin) destroyed litters of mice, rats, and dogs when given in the first trimester of pregnancy. A direct toxic action on the embryonic mesenchyme of the fetus appeared to be the mechanism, as the decidual and placental tissue appeared to be unaffected. In 1952, Thiersch began controlled studies of orally administered aminopterin to induce therapeutic abortion in women with cancer, tuberculosis or other serious illnesses. A dose of 6 to 12 mg. of aminopterin were administered over a period of two to five days in women who were scheduled to undergo surgical termination of pregnancy. Fetal death and spontaneous abortion resulted in 10 women after 18-20 days of treatment, but in two instances, the drug failed to induce fetal death and surgical evacuation was required. Live fetuses were found with malformations including hydrocephalus, cleft palate and meningocoeles. Subsequently, Thiersch reported an additional 12 cases of women administered aminopterin, daraprim, or azaserine. Aminopterin failed to induce abortion in six of the twelve women, and the results of the other drugs were inconclusive. Thiersch concluded from this work that unless folic acid antagonists were administered at the appropriate time in pregnancy, from two to six weeks, their action was unreliable and would lead in some instances to the delivery of malformed infants. Later studies have substantiated the unreliability of aminopterin as an abortifacient (Goetsch, 1962).

In this interval of time there have been multiple reports of patients who either took or were given aminopterin to induce ilicit abortion. Warkany et al., Emerson, Meltzer, Shaw, and Steinbock all have reported infants exhibiting anomalies including facial, skull and central nervous system defects, and associated appendage anomalies. Undesirable maternal effects have been similarly reported in association with aminopterin. One must conclude that aminopterin is an inappropriate agent for use as an abortifacient.

Didcock et al. in 1956 investigated the effects of colchicine, podophyllotoxin, demecolcin, and other nucleotoxic compounds on pregnancies of mice and rabbits. These substances, given orally or by injection, differ considerably in their ability to interrupt pregnancy. The most active are the spindle poisons, podophyllotoxin and the colchicine derivatives, which are consistently capable of interrupting pregnancy in doses not toxic to the mother. The chromosomal poisons are less active, and only produce an effect at levels which are also lethal to the mother. The anti-metabolites, 6-mercaptopurine, d-glucosamine, and 4-amino-methylglutamic acid, were almost completely inactive when given to mice between the 11th and 13th days of pregnancy, but were more effective at the time of implantation, the seventh to eight day of pregnancy. The main contribution of this work was to show that the intra-amniotic injection of such nucleotoxic substances provides a simple and reliable method of testing drugs for such properties.

Jackson et al. in 1959 employed 6-diazo-5-oxo-L-norleucine (DON) in pregnant mice. In mice, DON will interrupt pregnancy at all stages of gestation with doses which are only a fraction of the LD_{50}. The evidence suggests that

DON has direct toxic activity on the embryo, since progesterone administration did not prevent abortion. Two important findings limit serious consideration for clinical utilization. First, when DON is administered at mid-term, the fetus dies, but intact placentas may be found following fetal absorption thus providing a source of infection and hemorrhage. Secondly, sub-fetotoxic doses decrease the average weight of the surviving newborn mice, suggesting the existance of long-term effects in the surviving offspring. In view of the high therapeutic ratio of DON, the authors conclude that it may be possible to produce complete abortion in every instance.

Sanders et al. in 1961 reported that 6-azauridine was an oral agent which might control human pregnancy with minimal toxic effects. These workers established the optimum time for drug administration, its efficacy, and its dose-dependent toxicity. They showed that at abortifacient doses, 6-azauridine has no effect on the unfertilized ovum, the fetus in late pregnancy, or on the mother.

Vojta and Jirasek treated 15 pregnant women with intravenous 6-azauridine and performed surgical termination 24 hours to eight days afterwards. Most cases demonstrated marked degenerative changes of the trophoblast, except those in which the pregnancy was relatively advanced.

In 1967, Morris et al., investigated a number of compounds in an attempt to find a useful, non-toxic, effective post-coital anti-fertility agent. The alkaloids employed had variable anti-fertility effects in the rabbit. Ergocornine was ineffective, and vinblastine appeared to be teratogenic. Colcemide produced complete zygote-destruction after implantation in the rabbit, but there was no detectable effect on the primate fetus. Three anti-metabolites, a pyrimidine, a ribonucleoside, and a purine were also studied. 5-fluorouracil had little effect on the rabbit fetus, but 6-mercaptopurine and 6-azauridine produced litter destruction in early pregnancies and marked teratogenesis in mid-gestation. 6-mercaptopurine did not inhibit pregnancy when administered in the luteal phase on days 28 to 30 in monkeys.

Sasena and Chaudhury tested an orally active synthetic derivative of 6-azauridine, and showed that, in rats, the drug had relative lack of toxicity and increased efficacy as an abortifacient at large doses.

In 1970, Van Wagenen et al. reported on the abortifacient and teratogenic effects of triacetyl-6-azauridien in the monkey. In 14 pregnancies, treatment at different dosages induced 13 delayed abortions between the 36th and 131st day. However, one pregnancy carried to term, and hysterotomy revealed a malformed male infant. The drug was then administered on days 27 to 30 of 50 menstrual cycles, and with an expected conception rate of at least 10, only three pregnancies were identified. The observed pregnancies terminated in spontaneous abortion on days 23, 24, and 30. This abortifacient effects in the monkey was achieved with doses that produced no maternal evidence of toxicity. With such low toxicity and apparent abortifacient efficacy, it was suggested that this compound should undergo controlled investigation as an abortifacient in humans.

The number of anti-mitotic and anti-metabolic drugs is large, as enumerated by Nicholson. The observed toxicity, the potential teratogenic effect on surviving fetuses and the unknown effects on future pregnancies limit, at this time, the clinical utilization of cytotoxic agents.

B. Physical Techniques

Ionizing Radiation

Rapidly dividing tissues is quite sensitive to ionizing radiation. Gilman and Beatjer in 1904 exposed fertilized eggs to x-rays and reported the production of various anomalies. Between 1920 and 1930 multiple workers established that radiation during late pregnancy in animals could cause pregnancy termination (Schinz), that radiation produced direct fetal injury and was not mediated through damage of the corpus luteum (Driesen), that alterations could occur in the mitotic activity of the developing brain (Regaud et al.), and that embryo of rodents were more sensitive in early than in later stages of gestation (DeNobele and Lams). In 1929, Goldstein and Murphy studied 75 children irradiated while in utero, and showed that 37% manifested mental and physical abnormalities thought due to the irradiation.

In 1936, Mayer et al., encouraged by the favorable reports of Ganzoni and Widmer in 1925 and Stern in 1928, reported on a ten-year experience of 200 therapeutic abortions induced by irradiation. A uniform technique was used, with 60% of a skin erythema dose (600 r measured in air) given to the center of the uterus usually by two opposing ports, on two successive days. Abortion followed in 96% of the cases, three to 150 days after treatment with an average of 33 days. In over 50% of the women over 25 years of age, permanent amenorrhea and menopausal symptoms resulted. At least five of these patients had subsequent normal pregnancies.

The mechanism of abortion appeared to be radiation-induced fetal death rather than by effects on the ovaries or placenta. No damage to the uterine musculature, parametrial tissues, or placenta was documented. In actuality, these cases were excellent examples of missed abortion, that is, fetal death probably occurred some 14 days after treatment, and uterine contractions were initiated sometime thereafter. The pregnancy was never permitted to continue to term, and radiation was repeated after four weeks if the fetus was still alive.

Multiple articles have since appeared on the teratogenic effect of irradiation (Greim; Uchida; Schull and Neel). The article by Mayer is one of few expousing this technique as a means of abortion induction. The utilization of ionizing radiation as a means of inducing abortion is inappropriate because of the known carcinogenic and potential genetic risks.

Ultrasound

Ultrasound has quite recently been employed as a valuable tool in

obstetrics. In a review by Sunden in 1964, various characteristics of the medium were described. Ultrasound can cause a rise in temperature in a medium due to absorption of sound energy and its subsequent conversion to heat. It can cause destruction of cells and cell groups, and has been used to treat malignant tumors. Sachs and Wagener in 1950 produced resorption and stillbirth in pregnant rabbits, and similar experiments were performed by Thiele in guinea pigs and mice. However, other workers were unable to confirm these findings, (Fierz and Denecke, Mohr and Reiter, Bruschke, and Bobrow et al.).

Kamoxsay and Gy.O. gave ultrasound treatment to 150 women in the second and third months of pregnancy, without resultant abortion. The dosage frequency and intensity employed was far below that used to achieve abortion in animals, and not greatly increased above that which is used diagnostically in obstetrics.

There are now multiple reports demonstrating that, at intensities adequate for diagnostic work, no deleterious cell effects or chromosomal abberrations will occur (Loch et al., Fischer et al., Bernstine). In contrast to the 20-30 milliwatts per square centimeter intensity used for diagnosis, intensities of 50-100 watts per square centimeter can produce isolated, precise, and repeatable tissue damage (Ballantine et al.). Loch et al. reported that therapeutic intensities of 0.05-3 watts per square centimeter interfere with cell proliferation in tissue culture, and resulted in growth retardation.

The science of ultrasonic diagnosis and therapy is still in its infancy. Animal experiments have demonstrated that conception interruption is possible. The concept of utilizing ultrasound therapy as an abortion technique remains to be explored.

Imrie in 1971 reported on three women receiving short wave pelvic diathermy during pregnancy. Abortion occurred in the single case treated in the prei-ovulatory period and despite a subsequent positive pregnancy test, no fetus was ultimately found.

The possibility of diathermy as a means of abortion induction has not been explored. One might expect the method to be unreliable, and extensive animal studies would first have to confirm its safety to adjacent tissues.

III. First Trimester Abortifacients and Techniques

A. Pharmacological Agents

1. Malucidin

Malucidin, an extract of brewer's and baker's yeast, was originally prepared by Parfentjev, who was investigating its therapeutic effect on various animal infections. An anti-fertility activity was suspected and studies in dogs indicated that resorption of fetuses occurred after intravenous administration. Such treated dogs demonstrated rapid respiration, diarrhea, hypotension, weakness and dizziness (Whitney, 1959, 1960). Small doses given for several days prior to definitive treatment appeared to desensitize the animal and reduce the observed side-effects. Pathologic examination of the dogs uteri revealed necrotic placentas and hemorrhagic decidual areas, and the embryos were reabsorbed. No mechanism of action was postulated. Administration to cats and ewes produced embryo resorption, but an effect on rat or rabbits pregnancies was not noted.

Van Wagenen administered malucidin intravenously to two pregnant Rhesus monkeys and failed to demonstrate an abortifacient activity. In 1969, Levi reported on malucidin administration to pregnant mice. Administration of six and eight mg. of malucidin resulted in complete resorption of the fetal products, but at the eight mg. dose approximately one-third of the animals died. Larger doses than eight mg. were consistently lethal. These observations indicated that a rapid lysis and resorption of the fetus occurred suggesting activation of a proteolytic enzyme system. Mechanisms of action might include (1) activation of a pro-enzyme or a precursor; (2) inactivation of proteolytic enzyme inhibitors which are known to be elevated during normal pregnancy; (3) changes in permeability leading to the release of intracellular enzymes; and (4) premature release of active enzymes known to increase postpartum and thought to be responsible for the involution of the postpartum uterus. No further publications have appeared concerning this agent.

Studies have not been carried out to the extent that clinical application in humans might be considered. Utilization in early monkey pregnancies might be appropriate if locally administered to observe its effectiveness in producing endometrial shedding. If locally active, its untoward effects may be effectively curtailed.

2. Potassium Permanganate

Potassium permanganate ($KMnO_4$) is an oxidizing agent which, when in contact with moisture, is reduced to potassium hydroxide and maganese dioxide (Lammert and Scott). It is a systemic poison which causes hemolysis and release of potassium from damaged red blood cells (Jetter and Hunter). Smooth muscle is stimulated by direct contact with a 0.2-1% solution of $KMnO_4$. In pregnant guinea pigs oral administration causes death of the embryos. Similarly, abortion may be effected in pregnant mice (Cabaniss and Clark).

Potassium permanganate as an abortifacient is ineffective, despite lay

opinion to the contrary. Carney in 1953 reported on the use of vaginal $KMnO_4$ in 20 cases, of which only 12 were subsequently proven to be pregnant; in no instance did abortion occur. Of 45 cases reported from Charity Hospital, only five terminated in abortion (Johnson). Of nine cases reported by Lammert and Scott, only one aborted. In 1964, March and Webster reviewed 105 cases in the literature and reported 23 of their own. Only nine of these were known to have aborted. Complication of use of potassium permanganate included severe vaginal hemorrhage, chemical burns of the vagina, shock, and pelvic peritonitis (Shull, Kobak and Wishnick; Wanamaker; O'Donnell; Bookrajian and Wagner; Miller; Brudenell). It would appear that potassium permanganate is ineffective as an abortifacient and is an exceedingly toxic agent.

B. Mechanical

The previous sections of this review, the post-conceptive abortifacients, pertains to the first two weeks of the first trimester of pregnancy. However, many of the approaches to pregnancy termination descrived may be applicable to the remaining weeks of the first trimester pregnancy. The present section is devoted to techniques of abortion and abortifacients that are or appear to be applicable to the management of the fully established first trimester pregnancy.

1. Dilatation and Curettage

Surgical evacuation of the uterus is presently the method of choice for pregnancy termination at 12 weeks gestation or less (Nathanson). Vacuum methods have superceded sharp curettage because of ease, speed and decreased blood loss (Nathanson, Kerslake and Casey). Outpatient procedures now predominate, eliminating the necessity of utilizing hospital in-patient beds. Local anesthesia and systemic analgesia have replaced general inhalation techniques with a decrease in the risk inherent in usage of the latter.

However, despite the obvious improvements that have been made in the techniques, the procedure is still primarily a surgical one, and hence has an inherent morbidity and mortality (Nathanson; Kerslake and Casey; Pakter et al.; Brody).

While uncommon perforation of the lower uterine segment or uterine fundus is a serious complication of surgical termination, the incidence of uterine perforation ranges between 1.4 to 2.5 per 1000 patients (Nathanson; Pakter et al.; Brody). Approximately 30 to 50% of such patients require exploratory laparotomy. Surgical exploration is mandatory if a suspicion that intestinal injury has occurred as when a perforation has extended into the broad ligament with its attendant uterine artery or vein laceration. Most would agree that uterine perforations occur when the operator is inattentive to the position of the uterus, of to the location of the uterine cavity, when there is failure to maintain traction in the uterine cervix, when the uterus remains in a relaxed condition, or when the uterus is relatively large and the operator is inexperienced.

Hemorrhage and infection are complications not restricted to surgical termination but which adds to the morbidity of the dilatation and curettage. Both

of these complications commonly indicate incomplete evacuation of the uterus. Retained products of conception frequently require repetition of the surgical evacuation for the control of either bleeding or associated infection. The incidence of this requirement varies between 2.9 to 3.5 per 1000 patients (Nathanson; Pakter et al.). An infection rate of 15 per 1000 and hemorrhage rate of 2.1 per 1000 in association with curettage is experienced (Nathanson).

Surgical termination of the first trimester of pregnancy has been effectively provided for large populations. Currently the approach to the first trimester abortion is more satisfactory than that for the mid-trimester abortion (Brody). A research however should continue for a self-administered agent that would free the abortion patient from established medical services.

IV. Mid-Trimester Abortifacients and Techniques

A. Pharmacologic Agents

1. Hypertonic Solutions

Of the hypertonic solutions employed for the induction of abortion, sodium chloride is most commonly used in both this and other countries. Of 72,988 abortions reported to the Joint Program for the Study of Abortion (JPSA) 14,690 or 21.1% were accomplished by the use of hypertonic saline (Tietze and Lewitt). A rough estimate of the total number of saline abortions carried out in this country is derived from a consideration of data collected by the Communicable Disease Center of the Department of Health, Education and Welfare which indicates that approximately 200,000 to 235,000 legal abortions were performed in 1970. If 21% (the figure given by JPSA) were accomplished by hypertonic saline, this means that in 1970 alone there were from 44,000 to 49,350 such terminations.

Although the concentration of sodium chloride used for this purpose has ranged from 10 to 35%, the vast majority of cases are completed with 20% solutions. The volume of hypertonic saline employed has also varied; most reports described the removal of as much amniotic fluid as possible and the replacement with an equal volume of 20% sodium chloride up to a maximum of 200 ml, success has been reported with as little as 30 ml. Many of those using this technique express the opinion that the volume of hypertonic solution injected should not significantly exceed the volume of fluid removed (Menzies and Hawkins). Others routinely inject about 200 ml even though considerably less has been withdrawn. Although isolated instances of severe complications and even deaths tend to suggest that the total amount of salt injected is an important factor in determining complications, there is a paucity of controlled data to support any definitive conclusions.

All would agree that the optimum amount of sodium chloride is the minimum quantity that gives consistently good results, yet there has been no systematic approach to determine a minimum effective dose based upon the duration of pregnancy.

Experience with hypertonic solutions of glucose, usually 50% solutions, has come largely from other countries although sporadic use has been reported in the United States (Brosset, Olsen et al., Wood et al., 1962) The amounts used have been variable although most recommend 200 cc. of 50% solution to replace an equal volume of aspirated amniotic fluid. Because of several reported instances of severe sepsis and death, often from clostridial infections (Briggs, MacDonald et al.), the employment of this agent has been largely abandoned.

Duration of Pregnancy

All would agree that the termination of unwanted pregnancies to the twelth week of gestation is best carried out by surgical means such as vacuum aspiration. The use of hypertonic solutions was introduced as an alternative to the more complicated and risk-associated hysterotomy when the size of the uterus has progressed to the point that interruption by curettage or vacuum aspiration is no longer safe. Hypertonic solutions have been used to induce abortion as early as 12 weeks and as late as 28 weeks (Jaffin et al.).

Several considerations are important in determining the appropriate time for carrying out the procedure. For instance, the transabdominal introduction of a needle into the amniotic sac is exceedingly difficult prior to the 14th week and the chance of failure remains high until the 16th week after which the likelihood of success exceeds 95%. While there are probably many reasons for the difficulties encountered prior to the 16th week, the most pertinent ones relate to the small size of the amniotic sac, the pelvic location of the uterus and the observation that fetal membranes generally become fused with the uterine wall only after the 16th week of gestation. For these reasons, those using hypertonic solutions for induction of abortion prior to the 16th week have often turned to a transvaginal approach with introduction of the solution either into the amniotic sac or into an extra-ovular position (Ruttner). Wagner et al. have described a transvaginal approach with injection through the anterior lip of the cervix into the amniotic sac. The use of extra-ovular hypertonic saline for the induction of abortion was first reported by Svane, who introduced the solution through a transcervical catheter. The amount of solution introduced depended upon the duration of pregnancy beginning with 50 ml for a pregnancy of 12 weeks and increasing to 90 ml at 16 weeks of gestation.

Resulting Amniotic Fluid Changes

Using 200 cc. of 20% NaCl, Turnbull and Anderson found that amniotic fluid sodium concentrations rapidly decline from a peak value of approximately 2,500 MEQ/l to about 500 MEQ/l per liter after 12 hours. Simultaneously, there is a marked increase in urinary sodium excretion and, assuming a normal kidney function, there is usually little or no increase in serum sodium concentrations. The same authors reported a rise in serum sodium of about 10 MEO/l although others have reported no significant change. By the time abortion has occurred approximately 60 to 70% of the salt load has been cleared in the urine.

The chloride concentration in amniotic fluid has been measured by Kovaks following injection of hypertonic saline into one sac of a twin gestation. Chloride concentrations in the amniotic sac receiving the saline increased from a pre-injection level of 114 MEQ/l to an immediate peak value of 1776 MEQ/l. Three hours post-injection the concentration in the amniotic fluid had fallen to 800 MEQ/l and at the time of abortion it was reported as 200 MEQ/l.

Following introduction of hypertonic saline into the amniotic sac, the amniotic fluid volume increases over the next few hours by approximately 30 to 50% and then remains stable. This increased volume of fluid is from plasma water. The amniotic fluid is usually isotonic at the onset of uterine activity.

Uterine Activity

Studies by Bengtsson and Csapo indicate that following intra-amniotic injection of hypertonic saline the resting amniotic pressure averages 30 mm. Hg. This activity continues to increase with time and progresses to 70 to 90 mm. Hg. during active labor. They further showed that this spontaneous progression of uterine activity could be blocked at least for limited periods by the use of various progestational agents which resulted in a delay in completion of the abortion.

Maternal Changes

Assuming a healthy patient with normal kidneys, there is a marked increase in urinary sodium excretion and consequently no significant increase in serum sodium following the use of intrauterine hypertonic saline. Plasma volume does decrease and patients frequently complain of thirst.

Various coagulation factors have been measured in normal patients who have received intrauterine hypertonic saline. Stander et al. reported that 2 to 6 hours post-injection there is an increase in circulating fibrin and at 10 to 20 hours there is a decrease in platelets with a minimum value of 91,000. An accelerated euglobulin hysis time occurred in one of three patients beginning at 25 hours post-injection and spontaneous proteolysis was also present in one of the three patients. Factor II decreased in two of four observed patients. In general, all of the observed changes occurred before abortion had been completed and following abortion all factors were observed to return to normal values. The patients studied by Stander were all normal and at no time exhibited any clinical manifestation of coagulation abnormalities. Clinically significant coagulation abnormalities with severe bleeding has also been reported and will be described under complications.

There remains some controversy concerning the urinary excretion of placental hormones associated with intra-amniotic hypertonic saline. Csapo and Bengtsson and Stormley, have reported a significant fall in pregnanediol excretion after saline injection and before the increase in spontaneous uterine activity. Klopper et al., on the other hand, found pregnanediol excretion to remain unchanged until placental separation was complete. Estriol excretion falls sharply immediately after the injection of hypertonic saline (Klopper et al., Csapo, 1970).

Placental Changes

Bengtsson and Stormby have determined placental changes associated with intra-amniotic hypertonic saline; the placenta is grossly edematous and microscopically shos a necrotizing placentitis most marked immediately beneath the fetal membranes.

Fetal Changes

Fetal death usually ensues within a few hours following injection of hypertonic solution as demonstrated by cessation of fetal movements and the absence of the fetal heart by ultrasound. However, fetal death is not necessary for the occurrence of abortion. Bengtsson and Stormby report small red spots scattered over the fetal skin; histologically these consist of dilated cutaneous and subcutaneous vessels filled with blood. There is usually maceration and peeling of the skin and except for autolysis the internal organs have been described as normal.

Success Rate

The major cause of failure with this method is the inability to introduce a needle into the amniotic sac. Prior to the 16th week of pregnancy such failures are relatively common but after the 18th week success is virtually assurred (Gochberg and Reid). All would agree that in the absence of a free flow of amniotic fluid, injection of saline should not be accomplished because of the risk of intravascular injection. If a minimum of 100 ml of 20% NaCl is introduced into the amniotic sac induction of abortion is almost certain (Millar and Harvey, Pathak). Gillmer et al. reported a 100% success rate in 102 successive patients where infusion of saline was successful.

Injection-Abortion Interval

In the 102 cases reported by Gillmer et al., the interval between injection and abortion ranged from 11 to 98 hours with a mean of 39.7 hours. They found no correlation between the injection-abortion interval, and the duration of pregnancy, or the parity of the patient. Gochberg and Reid in their series of 23 cases reported a mean interval from injection to abortion of 36.5 hours. The routine use of intravenous oxytocin following saline injection has been demonstrated to shorten the interval between injection and abortion. Lauersen, in a controlled study demonstrated that with the routine use of intravenous oxytocin the interval could be shortened from a mean of 40 hours to one of 15.3 hours.

Complications

The Joint Program for the Study of Abortion has reported an overall complication rate of 27.5% with major complications occurring in about 2.7% of the cases. Their figures clearly indicate the increased rate of complication in the non-private patient population. Fever has been reported to occur in eight

of forty-two cases by menses and in four of 102 cases reported by Gillmer et al. Thirty-one of 102 patients reported by Gillmer et al. required evacuation of the placenta under general anesthesia; the incidence of retained placental fragments was lowest in those abortions performed after the 16th week. Hemorrhage sufficient to require transfusion occurred in 3 of 323 outpatient saline abortions described by Schulman; 4 out of 102 patients described by Gillmer et al. required transfusions.

Catastrophic reactions including shock, generalized abdominal pain and even cardiac arrest have been described in occasional patients either during or immediately following the injection of the hypertonic solution (Wagatsuma). Experimental studies on dogs by Johnson and Cushner indicate that such reactions probably result from the inadvertant intravascular injection of the hypertonic solution and are mediated at least in part by reflex receptors located in the pulmonary vessels (Agarwal et al.).

Serious delayed reaction occurring several hours after the injection of hypertonic saline have also been described and include such symptoms as headache, lethargy, coma, intense thirst and seizures (Cameron, Frost, and Weiss). Such reactions are often associated with severe degrees of hypernatremia and in several instances the outcome has been fatal. It therefore appears that in such patients there is an unusually rapid transfer of sodium into the maternal circulation but there have been few clues to indicate why this occurs (Sotos et al.)

Several patients following intra-amniotic infusion of hypertonic saline have been reported to show coagulation defects of serious proportions and these have been associated with hemorrhage. Beller et al. reported three such patients who demonstrated a decrease in platelet number, fibrinogen concentration and factor V activity and an increase in fibrinolysis breakdown products. Patients undergoing such changes are often first identified by the occurrence of vaginal bleeding followed by bleeding from needle puncture sites. Following completion of the abortion, the coagulation changes have generally returned to normal.

Following the use of intra-amniotic hypertonic glucose there have been isolated reports of overwhelming infection usually with clostridial organisms and usually with a fatal outcome (Briggs, MacDonald). For this reason, glucose utilization has been largely abandoned.

It would appear that many of the serious complications following the use of intra-amniotic hypertonic saline result from the inadvertent intravascular injection of the solution or leaking of the solution into the maternal circulation following the injection. Amris and Jepsen, using hypertonic saline labelled with Vitamin B12 and T-1824-albumin found significant amounts in the maternal circulation in eight of 14 patients. The maternal infusion usually occurred simultaneously with the intra-amniotic injection and was also associated with significant but sub-clinical degrees of hemolysis.

Hypertonic saline injection has been demonstrated to be an effective mid-trimester abortifacient. Unfortunately, associated with its use is an incidence of catastrophic complications that can cause death in the occasional patient. Therefore it is not the ideal mid-trimester terminating agent.

2. Prostaglandins

Only a few years have passed since the first report of the stimulatory effect of prostaglandins on uterine contractility under in vivo conditions (Bygdeman et al., 1968). Results of the initial clinical trials of prostaglandins as abortifacients appeared in 1970 (Karim and Filshie, Roth-Brandel et al.). The efficacy of prostaglandins in the induction of abortion at any stage of gestation has been amply demonstrated. Five routes of administration have now been tested, including the intravenous, intrauterine extra-ovular, intra-amniotic, intravaginal, and oral.

Intravenous administration of PGF_{2a} effects at least 70% abortion induction, usually complete at gestations greater than 16 weeks. The observed side effects include diarrhea, nausea and vomiting, headache, fever, flushing and emotional depression, however all are transitory in nature. A local inflammatory reaction at the needle site is noted in many patients, dependent upon the duration of administration and the concentration of the infusion (Karim; Hillier and Embrey, 1962; Wiqvist et al., 1971).

Intravenous administration of PGE_2 and PGE_1 is about 80% effective in abortion induction, with somewhat fewer side effects, but its use is associated with an increase in the incidence of venous erythema (Hendricks et al., Karim and Filshie, 1970).

The intravenous route of administration of prostaglandins for abortion induction appears to be complicated by side effects and by the unreliability of the method. At the present time, intravenous prostaglandin can be used to stimulate uterine activity in patients with failed saline terminations and in patients failing to abort using other routes of administration.

Intrauterine extra-ovular route of prostaglandin administration has been evaluated in several centers. The chief advantage is the almost complete elimination of side effects, but the disadvantages include a lower efficacy rate, the necessity for frequent drug administration, and an increased incidence of infection secondary to the transcervical indwelling catheter (Roberts et al.; Wiqvist and Bygdeman; Embrey and Hillier).

The intravaginal route of prostaglandin administration has been tested by Karim and Sharma who has reproted three failures in 20 cases using intravaginal PGF_{2a}, and one failure in 40 cases using PGE_2. The average abortion interval was approximately 18 hours, and side effects were reported to be markedly decreased. Results from the United States have not borne out this decrease in side effects (Wentz, unpublished). Vomiting, diarrhea and fever are all increased, although the method is certainly efficient in abortion induction.

The oral route has been limited by the unpalatability of the medication and by its induction of severe gastro-intestinal side effects. No extensive series has appeared (Karim, 1971; Karim, 1970).

The intra-amniotic route of administration appears the most favorable at the present time (Toppozada et al.; and Bygdeman et al., 1971). In more than 54 cases aborted at the Johns Hopkins hospital, there were but four failures, and the average time to abortion was approximately 18 hours. Side effects were greatly decreased, diarrhea and fever essentially eliminated, and vomiting occurred in less than 50% of the patients (Wentz, in press).

One would look with favor upon the development of analogues that would decrease side effects, and increase efficacy and acceptability of the method. Prostaglandins appear to be an effective abortifacient. The untoward effects are transitory in nature and fatalities have not been reported.

3. Oxytocin

There has been general acceptance and widespread utilization of synthetic oxytocin for the induction of term labor. When properly employed oxytocin has been demonstrated to be effective and safe for both the fetus and the maternal organism. Commonly encountered untoward effects when oxytocin has been inappropriately employed includes uterine dehiscence, tetanic uterine contractions, water intoxication, and transitory hypotension.

It is generally accepted that the first trimester and mid-trimester pregnant uterus is insensitive to physiologic quantities of administered oxytocin. Several investigators have employed macroinfusions of oxytocin to terminate both first and second trimester pregnancies (Loudon, 1959; Kumar and Russell, 1961; Jaffin, et al., 1962; and Toaff and Ayalon, 1962). These studies have not included large groups of patients. The duration of intravenous administration of oxytocin was excessive. In review of the literature no series of patients treated with intra-amniotic oxytocin could be found. The continued synthesis of oxytocin analogues have provided a new preparation, 4-threonine oxytocin that has relatively low antidiuretic activity (Sawyer and Manning, 1971; Manning and Sawyer, 1970; and Anderson et al., 1965). The incidence of water intoxication with the administration of this agent should be suitable for administration in large quantities intravenously. This agent has not been employed in humans.

4. Serotonin (5-Hydroxytryptamine) and Monamine Oxidase Inhibitors

In 1960, Poulson and co-workers studied the effects of 5-hydroxytryptamine (5-HT) on the pregnancy of mice. This agent interrupted pregnancy in both early and late stages, and the presumed mechanism of its action was the production of marked hemorrhage that occurred in the placenta. The hemorrhage and disorganization of the placenta leading to the death of the mouse fetus was produced as early as one-half hour after the subcutaneous administration of 1 mg. of 5-HT. In the study of rabbit pregnancies, similar results were obtained. Therefore it would appear that the placenta is extremely sensitive to 5-HT resulting in marked vascular change and hemorrhage.

Astrom and Samelius had previously demonstrated that the vasomotor action of 5-hydroxytryptamine (5-HT) in the human placental preparation is about 10 times greater than that of adrenalin and is antagonized by anti-adrenalin compounds.

Koren and co-workers discovered minute amounts of serotonin in human amniotic fluid at delivery, and postulated that production of serotonin starts in neonates in thehours following delivery. In 1962, Brezezinski and co-workers showed that degradation of serotonin occurs in amniotic fluid but not in urine. Hence, circumstantial evidence of monamine oxidase activity in amniotic fluid was presented.

In 1963, Lindsay and co-workers showed that 5-hydroxytryptamine and the monamine oxidase inhibitor, HR-1325 would interfere with the development of the decidual reaction in mice and that this effect could be reversed by the simultaneous administration of progesterone. Hence, it was hypothesized that these drugs were interferring with the endocrine function of the ovary, either directly or indirectly via the pituitary. Further, the administration of 5-HT to mice had a deleterious effect on all stages of pregnancy. The effect of 5-HT in early pregnancy could be antagonized by progesterone and prolactin, but in late pregnancy, little or no reversal of this toxic action was seen. It was felt that in early pregnancy, 5-HT interferes with the hormonal mechanisms responsible for the maintenance of gestation, while in later pregnancy its main toxic effect was exerted directly on the uterine contents. Under these conditions, gross pathological changes were observed in the placenta, including hemorrhage and dissruption of the normal histologic pattern. It was unknown how 5-HT produced these changes, whether primarily by affecting the caliber of the vessels, or acting directly on the endothelium. When 5-HT was given at critical stages of pregnancy, a high percentage of surviving fetuses showed congenital anomalies. The lethal and teratogenic effect of 5-HT appeared secondary to its actions on placental function. These studies therefore substantiated the findings of Poulson et al.

Sadowsky and co-workers showed that habitual abortion was associated with high serotonin production, which might be directly related to the cause of abortion. High levels were seen during periods of both psychological and physical stress.

Fahim and co-workers showed that in rats, the fetal level of 5-HT increased throughout pregnancy, the placental level increased throughout most of pregnancy, but fell to a lower level just before the onset of labor. After treatment of the mother with various monamine oxidase inhibitors, the levels of 5-HT in the uterine contents and maternal blood were measured. Iproniazide caused a delay in parturition and raised in the placental 5-HT level at parturition. HP-1325 in high doses caused resorption of the fetuses, and lower doses raised only the maternal blood levels of 5-HT.

In 1966, Robson and Sullivan showed that 5-HT injected into the mother did not produce constriction of the umbilical vessels, and local application to the

cord likewise did not produce any effect. It was suggested that the effect of 5-HT in producing fetal death is a consequence of the reduction in the transfer function of the placenta. This was shown by experiments investigating the passage of sodium-22 from the maternal circulation into the placenta and fetus. Following 5-HT injection, transfer of sodium-22 from mother to placenta was completely inhibited, and in the fetus, early deterioration of cardiac function and cessation of spontaneous movements occurred. Therefore, the lethal action of 5-HT on the fetus seems dependent on an interference with fetal nutrition. In 1967, Honey and co-workers investigated the mechanisms by which 5-HT produces lethal effect on the fetus. They substantiated that 5-HT markedly reduced placental transfer. It was suggested that 5-HT might have two partially independent effects to reduce placental blood flow and to reduce the permeability of the membranes separating the maternal and fetal circulations.

5. Monamine Oxidase Inhibitors

The efficacy of monamine oxidase inhibitors in producing fetal deaths in rats and mice has been well documented. These agents apparently are effective in blocking endogenous monamine oxidase contained in the placenta and amniotic fluid. The fetus is then no longer protected from the harmful effects of the active vasomotor amines such as 5-HT that is produced by the placenta. In a clinical study reported by Koren et al. intra-amniotic injections of 50-100 mg of pargyline-hydrochloride was completed in 20 patients between 8 and 26 weeks of pregnancy. In 19 patients abortion occurred within four days of drug administration.

6. Histamine

In 1926, Hofbauer, investigating the pathology of toxemia of pregnancy, observed that in premature separation of the human placenta, the decidual vessels were dilated into enormous, thin-walled sinuses. He then observed that after systemic administration of histamine, marked dilatations of uterine vessels occurred, associated with conspicuous hemorrhage. A striking feature was the marked edema, separating the uterine muscle bundles. Following acute histamine poisoning in pregnant guinea pigs, a number of changes have been observed which are highly suggestive of premature separation of the normally implanted placenta as it is seen clinically: the separation of the placenta itself, dilatation of the vessels of the uterus and broad ligament, uterine spasm, hemorrhage into various organs, marked shock, and the histologically observed degenerative changes of both the liver and kidneys.

In 1949, Wicksell observed that histaminolytic activity is greatly increased in pregnant women, and raised the questions if histamine might in some way be involved in the normal or pathologic processes of pregnancy. He found that no changes take place in the histamine content of plasma, the placenta, or urine during parturition.

In 1962, Kameswaran and co-workers concluded that histaminase activity, in the rat, functioned to protect maternal tissues from the effects of excess histamine present in pregnancy. The rat fetus forms histamine at an increased rate from the 11th to the 12th day of gestation, and reaches a maximum level at the sixteenth day. This is associated with a parallel rise and fall in uterine and placental histaminase activity. Histamine therefore may exert a dilating action on the umbilical and placental blood vessels which are without innervation, and thus may assist in the maintenance of adequate perfusion of the fetus until term. The most potent of the anti-histamine drugs tested (abrobit) in low doses, produces abortion, probably by antagonizing the vaso-dilator action of histamine on the placental vessels. Abrobit is at least 100 times more toxic to the fetus than to the mother.

7. Pastes

Medicated pastes were utilized for abortion induction in Germany in the early 1930's. During the next two decades, a lively controversy appeared in the literature debating the merits and safety of the utilization of such material [Theobald, D'Amour and Kiven, Weilerstein].

Interruptin is described as a fatty paste containing (1) ethereal oils of a number of substances - aloes, eucalyptus, rosemary, myrrh, crocus and camphor -- which are reputed to have an abortifacient action when given orally in toxic doses; (2) thymol; and (3) iodine [Theobald]. Provocol or Provocal was used in ointment form, with a soap base containing olive oil, cocoa butter, potassium iodine and thymol [Barns]. At least four similar preparations were available in 1932 and the ingredients common to all were soap and iodine. All additives were carefully mixed with a fat base which did not liquify at body temperature, so that prolonged contact with the uterine mucosa could be assured.

These pastes were administered either under general anesthesia, or with only pre-medication, through the undilated cervical canal into the uterine lumen. Depending on the duration of pregnancy, quantities varying between 15 to 50 ml. were slowly injected. Intravenous or buccal oxytocin was administered if uterine contractions had not ensued within 24 hours.

These pastes were utilized by practicing gynecologists, as well as by illicit abortionists. At that time, it was considered that the simplicity of the technique was its greatest danger, because of its use by the lay abortionist.

The action of Interruptin appeared to depend upon damage to the ovum in situ. Similar damage to the endometrium served as a stimulant for uterine contractions, obviously the paste produced necrosis of the endometrium, and an inflammatory reaction in the myometrium. It was said to be absorbed into the blood and cleared in the urine [Theobald].

Up to 1932, there had been 25 fatalities reported in the literature following administration of intrauterine paste [Williams et al]. Englemann in 1932 reported 12 deaths due to fat embolism, and five deaths due to air embolism. In 1932 the Federal Minister of the Interior in the German government prohibited the use of provocol in Germany except by a physician's prescription.

In 1938, the American Medical Association issued warnings against the use of intrauterine pastes. Weilerstein in 1944 reported a number of case histories illustrative of the complications of the use of such pastes in the United States. Those complications were as classified:

1. Systemic Effects
   a. General hemolysis, if severe resulting in death, or if mild, resulting in jaundice;
   b. Pulmonary embolism, sometimes fatal;
   c. Generalized septicemia, not uncommonly fatal.
2. Local Effects
   a. Inflammation, with sequelae such as sterility due to tubal occlusion, and necrosis of the uterine wall;
   b. Bleeding, either a severe acute hemorrhage or protracted genital bleeding.

Barns, in 1947, found that the morbidity in terms of pyrexia was no higher with intrauterine pastes than in cases aborted by other methods. In 1955, Williams et al. from Swansea, reported on 32 cases, 21 of which were uneventful. The other 11 cases experienced severe complications that included widespread pelvic infection, pulmonary embolism, and apparent gram negative shock. Lachlin and Burgess in 1968 reported on 182 terminations, between nine and 20 weeks' gestation, in whom abortion was satisfactorily completed in every case. Length of hospital stay ranged from three to 16 days, with a mean of 5.6 days, and only 7% of patients suffered pyrexia. The method replaced hysterotomy in their unit.

In 1971, Sood reported on 83 patients, with two failures, 12 patients with fever, three cases of septicemia, one of perforation and at least one case of pelvic peritonitis. Because of the incidence of severe and even fatal complications, it was concluded that the method had proved unsatisfactory and should be abandoned.

One would have to agree that now there is no indication for the utilization of such pastes as abortifacients. Probably a simple mechanical stimulation of the uterus was sufficient to induce uterine contractions, and the various compounds served no beneficial purpose. The introduction of thymol and iodine might have some antiseptive quality, but were unlikely contributors to the abortifacient activity.

B. Mechanical

1. Extra-Amniotic Injection of Solutions: Rivanol, Saline

Another method of mechanical stimulation of the uterus currently popular in Japan is that of the introduction of solutions into the extra-ovular space. Rivanol or acrinol has been the agent most frequently utilized [Manabe, 1969a, 1969b] although there are reports of the extra-ovular administration of hypertonic glucose or saline [Gustavii, Kovacs], isotonic saline [Shinizu, Yunoki], and sodium fluoride [Ishii].

The technique involves the introduction of a soft sterile catheter through the internal cervical os into the space between the uterine wall and the fetal membranes. 30 to 50 cc. of 0.1% rivanol solution warmed to body temperature is introduced with a syringe. Excessive amounts are not utilized to avoid leakage of the solution through the fallopian tubes. Merits of the technique reportedly include simplicity of the method, no cervical dilatation required, decreased chance of placental damage or inadvertent rupture of the membranes, and decreased infection because of the antiseptic nature of the solution. In a series of 796 patients treated with rivanol, 96.5% aborted, and the reported incidence of infection was minimal. Manabe states that intravenous injection of 0.1% of rivanol is pharmacologically safe, and a concentration between 0.05 and 0.2% has been used as a disinfectant for many infectious diseases. Thus, there would be minimal danger from intravenous spill and no report that this concentration causes any subsequent impairment of uterine or fallopian tube function.

Nabriski et al. from Israel corrobates the reports from the Japanese literature. Of 52 patients, all aborted, 95% within 20-24 hours. 90% of the cases required an oxytocic drip, there were no deaths, low morbidity, and no reported infections. Nabriski et al. ensured retention of the extra-ovular solution within the uterus by mechanical apposition of the cervical lips with a vulselleum clamp, and required Trendelenburg position for four to six hours.

Lewis et al. from England investigated the oxytocic effect of another member of the same chemical group, aminacrine B.P.(9-aminoacribine hydrochloride) administered into the extra-ovular space. 23 patients received 50 ml. of 0.1% aminacrine. The mean induction-abortion interval was 59 hours. Most patients required a pitocin infusion to complete the abortion, side effects and infection were minimal. However, more than 50% of the patients required surgical evacuation of products of conception. Finally, Lewis et al. were not able to confirm the acceptable induction-abortion time reported by Manabe and Nabriski et al.

Although the use of rivanol or related compounds may offer an alternative to saline injection, their use would not appear to be advantageous. The incidence of infection is approximately equal to that of saline injection. The method of application is more complicated, many patients are incompletely aborted, and the added stimulation of oxytocin was required in 90% of the reported cases. The injection of solution into the extra-ovular space cannot be considered simple, as hemorrhage or rupture of membranes can complicate the technique.

2. Bougie and Metreurynter

The Bougie and Metreurynter are now commonly used for second trimester abortions in Japan [Manabe, 1969b, Nishimura and Manabe, Manabe, 1967]. They were developed as alternative to Aburel's method of intra-amniotic injection of hypertonic saline., primarily because of the maternal mortalities associated with the former technique [Wagatsuma].

The Bougie, made of elastic gum, has a diameter of 0.5-1.0 cm., and a length of 30-45 cm. One or two soft pliable bougies are inserted between the uterine mucosa and the fetal membranes, with their tips finally resting at the fundal region of the uterine cavity. The excess bougie is cut off at the cervical os, and the stump is wrapped in disinfectant gauze to decrease the incidence of infection and prevent expulsion. Oxytocin is usually administered after uterine contractions begin, and the bougie is not removed until regular propulsive contractions are established. The advantage of the method is reportedly in the simple operative technique, requiring cervical dilatation to only the size of an 8-10 Hegar dilator. Its ability to induce labor is inferior to either rivanol or the metreurynter, but the incidence of morbidity is less than with the latter method. Alternative approaches are considered if labor fails to begin in 50 to 70 hours. Manabe reports on 58 patients treated with the bougie method; 36 aborted completely, with an average time from placement to abortion of approximately 31 hours. Labor appeared to be physiological with all fetuses being delivered alive. Studies of the placenta and fetal tissue revealed no significant changes. The mechanism of action appears to be mechanical stimulation of the uterus and not associated with fetal or placental factors.

The metreurynter method is described by Manabe as follows: Following disinfection of the vagina and catheterization of the bladder, the cervix is grasped with a tenaculum and dilated to a 12-16 Hegar dilator. The metreurynter, a rubber balloon-end tube designed on the principle of a Foley catheter, is introduced, and the balloon filled with 100-300 ml. of saline. Weights of 300 to 800 gm. are then tied to the tubing of the balloon, and hung over the foot of the bed. Such a traction device strengthens the mechanical action of the metreurynter on the uterus, and shortens the time required for effective treatment.

Oxytocin is usually given at appropriate intervals until uterine contractions sufficient for delivery are obtained. Weights on the metreurynter may be reduced or increased, and the cervix holds the balloon in place until it is well dilated by the evolving labor. Delivery of the fetus usually follows expulsion of the balloon within one to two hours. The advantages of the method are that traction weights can be varied and the balloon may be removed at any time. The operative technique is simple, and the method can be employed in patients with ruptured membranes. The only significant complication noted was fever, particularly when the treatment period is lengthy, and routine antibiotic treatment is recommended. Little information on resulting cervical and lower uterine damage is available.

Nishimura and Manabe in 1967 reported on oxytocin sensitivity and the effects of estrogen and progesterone on such abortions. Of 51 patients who were treated, 13 received no hormone treatment, 17 were given progesterone, 16 were treated with estrogen, and all cases were given periodic injections of oxytocin intravenously. They concluded that intrinsic oxytocin, secreted by a reflex in response to mechanical uterine stimulation, was necessary for the initiation of regular uterine contractions. There is, at this time, no physicological information that supports this conclusion. Hormone administration did not influence initiation or course of labor.

The Japanese conclude that the mechanical methods of uterine stimulation offer significant advantages over Aburel's method of hypertonic saline injection. More physiologic labor resulted, evidenced by the live state of delivered fetuses. Complications of saline injection, such as intestinal and bladder injury are avoided.

An analysis of the review by Manabe reveals that of 1,550 cases treated with the metreurynter, 87.3% aborted. Fever was listed as a complication in 14 of 19 publications reviewed. Oxytocin stimulation was employed in most series. Using the bougie, only 62% of patients aborted, and complications were not reported.

One concludes that the safety and efficacy of these methods was not clearly demonstrated. No method can be considered simple that requires an operative technique such as cervical dilatation to Hegar 12-16, utilization of one or more oxytocin agents, and routine antibiotic administration. Little data is available on the future reproductive performance of such treated patients.

V. Conclusion

Survey of the abortion literature clearly demonstrates an attempt by a multitude of investigators and clinicians to discover and effectively utilize both the mechanical techniques of uterine evacuation and chemical abortifacients. It is equally obvious that a vast number of unwanted pregnancies have been "by and large" satisfactorily terminated with the attendant costs of utilization of medical professionals and hospital services. Yet, there still does not exist an agent that may be self-administered that will effectively terminate both first and second trimester pregnancies. Such an agent must be inexpensive, safe, and efficacious. Until such an agent is available the termination of the majority of unwanted pregnancies will be wed to surgical procedures with their accompanying morbidity and mortality.

The only successful attempt to improve uterine evacuation has been the vacuum curettage, the application of other physical approaches have not been fully explored. As an example, the major component of time required for a D & C is the cervical dilatation, yet no significant application of improved devices or local pharmacological methods have been vigorously studied.

The currently exciting prostaglandins appear to have a role in the termination of mid-trimester pregnancies and hopefully in the post-conceptive period. No mortalities have been reported to date and the untoward effects of these compounds are usually self-limiting. It is possible that an analog of prostaglandin will be the ideal abortifacient for both the first and second trimester pregnancies.

Other approaches that warrant clinical exploration in the post-conceptive period are endometial shedding agents locally applied by douches and the various evolving immunological agents.

The mid-trimester abortion problem will continue to exist for the foreseeable future. An agent is required that would allow all such patients to be independent of hospital admission. The possibilities for this include the feto-toxic substances much as monamine oxidase inhibitors or chemicals that are non-toxic and can be administered in hypertonic solutions.

Finally it is evident that the vast majority of the reported clinical services do not eminate from units that are primarily pregnancy termination services staffed by investigators whose major interest resides in this clinical area. We would not expect major advances in a basic science laboratory if structured in such a non-goal oriented manner.

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SCIENTIFIC PERSONNEL AND THEIR QUALIFICATIONS

THEODORE M. KING, M.D., Ph.D.

Dr. Theodore M. King is Professor and Chairman of the Department of Gynecology and Obstetrics at The Johns Hopkins University School of Medicine. He assumed the responsibilities of this position in November of 1971. Prior to his appointment, he was Professor and Chairman, Department of Obstetrics and Gynecology at the Albany Medical College, Albany, New York.

Dr. King received his Ph.D. in Physiology from Michigan State University in 1959. In the same Year, he received his M.D. degree from the University of Illinois, as well as 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, Würzburg, 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.

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. His duties will not only include those of an Administrator, but that of primary responsibility in Project III, Second Trimester Terminations. Dr. King and the Coordinator for Education, who is to be appointed, will be primarily responsible for the education program for the trainees from underdeveloped countries.

GEORGEANNA SEEGAR JONES, M.D.

Dr. Georgeanna Seegar Jones has enjoyed a long and prestigious career in Gynecology and Gynecologic Endocrinology. Following her graduation from the Johns Hopkins University School of Medicine, she trained in Gynecology at the Johns Hopkins Hospital, and in 1939, became Gynecologist-In-Charge of the Gynecological Endocrine Clinic. 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. She has served as Vice-President, President

Elect, and President of the American Fertility Society. She was awarded a Doctor of Science degree from Goucher College in 1970. She is a member of multiple medical societies, and Co-Editor-In-Chief for the Gynecological and Obstetrical Survey. She has held the position of Associate Professor of Gynecology and Obstetrics from 1957 to the present. Her publications include over eighty journal articles and three textbooks.

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 the areas of 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 immensely in the interpretation of the hormonal data to be obtained. She is currently a member of the Food and Drug Administration Obstetrics and Gynecology Advisory Committee.

ANNE COLSTON WENTZ, M.D.

Anne Colston Wentz, M.D., graduated from Western Reserve University School of Medicine in 1966, having received 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.

LONNIE S. BURNETT, M.D.

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 1953, 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.

H. LORRIN LAU, M.D.

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.

CLIFFORD R. WHEELESS, JR., M.D.

Dr. Wheeless will be involved in this project only through the teaching of surgical techniques for female sterilization to the trainees of underdeveloped countries. Following graduation 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. Wheeless 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. Wheeless 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.

HUGH JAMES DAVIS, M.D.

Dr. Hugh Davis was graduated from the Johns Hopkins University School of Medicine in 1952, 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.

CURRICULUM VITAE

Theodore M. King

Born: [redacted]

Family: Married with two children

Educational and Professional Record:

1947-1950	Quincy College, Quincy, Illinois B.S. in Biology and Chemistry, June 1950
1950-1953	University of Illinois, Urbana, Illinois M.S. in Zoology, 1952
1953-1955	Michigan State University, East Lansing, Michigan Ph.D. in Physiology, 1959
1955-1959	University of Illinois School of Medicine, Chicago M.D., 1959
1955-1959	Assistant in laboratory of Professor W. V. Whitehorn, Department of Physiology, University of Illinois
1959-1960	Intern in Surgery, Presbyterian Hospital, Columbia Medical Center, New York City, New York
1960-1964	Assistant Resident and Resident in Obstetrics and Gynecology, Sloane Hospital for Women, New York City, New York
Nov. 1964-July 1965	Chief Resident in Obstetrics and Gynecology, Sloane Hospital for Women
July 1965-June 1968	Assistant Professor, Department of Obstetrics and Gynecology and Department of Physiology, University of Missouri School of Medicine, Columbia, Missouri
July 1968-Aug. 1968	Associate Professor, Department of Obstetrics and Gynecology and Department of Physiology, University of Missouri School of Medicine

August 1968- November 1971	Professor and Chairman, Department of Obstetrics and Gynecology, Albany Medical College, Albany, New York
November 1971-	Professor and Director, Department of Gynecology and Obstetrics, The Johns Hopkins University School of Medicine, and Gynecologist-Obstetrician-in-Chief, The Johns Hopkins Hospital, Baltimore, Maryland

Awards and Honors:

1959	Alpha Omega Alpha
1959	Sigma Xi Research Award, University of Illinois School of Medicine
1959	Borden Foundation Award in Medicine for meritorious research completed while a medical student
1961	Independent Investigator in the Reproductive Physiology Laboratory, Rockefeller Institute, under Dr. A. Csapo
1960-1964	Josiah Macy Fellow in Obstetrics and Gynecology, Columbia Presbyterian Medical Center, New York
Feb. 1964- Nov. 1964	Visiting Fellow, University Women's Clinic and Biochemistry Institute, Wurzburg, Germany
Nov. 1964- July 1965	American Cancer Society Fellow, Francis Delafield Hospital, a unit of Columbia Presbyterian Medical Center, New York
July 1966- June 1967	Macy Faculty Fellow in Obstetrics, University of Missouri School of Medicine, Columbia, Missouri

July 1966	Travel Fellowship, American Society of Pharmacology and Experimental Therapeutics, to attend their Fall meeting in Mexico City, Mexico
July 1967	Markle Scholar in academic medicine

Medical Certification and Licensure:

July 1960	Diplomate of National Boards
Nov. 1967	Diplomate of American Board of Obstetrics and Gynecology
May 1968	Fellow, American College of Obstetricians and Gynecologists
July 1970	Fellow, American College of Surgery
State Licensure:	New York, Missouri, and Maryland

Grants:

Aug. 1965-July 1968	National Institute of Child Health and Human Development, Uterine Contractile Protein
Sept. 1965-Aug. 1966	American Cancer Society, The Study of Contractile Protein of Leiomyomata and Normal Myometrium
May 1968-June 1969	Pharmacology-Toxicology Program, National Institute of General Medical Sciences, Studies in Enzyme Induction
Sept. 1969-present	Ford Foundation, Studies in Reproductive Pharmacology

Societies and Professional Organizations:

Society for Gynecologic Investigation
American Physiological Society
Society for Experimental Biology and Medicine
American College of Obstetricians and Gynecologists
American College of Surgeons
Sigma Xi
New York Academy of Science
Society for the Study of Reproduction
American Association for the Advancement of Science
American Fertility Society
Association of Professors of Gynecology and Obstetrics
Association American Medical Colleges
Northeastern New York Association of Obstetricians and Gynecologists

Consultant:

Obstetrical Consultant, New York State Health Department, Bureau of Medical Review

United States Pharmacopeia Advisory Committee in Obstetrics and Gynecology

Medical Consultant to Kimberly-Clark Corporation, Neenah, Wisconsin

Lecturer for G. D. Searle and Company, Chicago, Illinois

Consultant to Sterling-Winthrop Research Institute, Rensselaer, New York

Member, Primary Care Study Committee, Association of American Medical Colleges

Member, Advisory Council, Family Planning Program, Baltimore City Health Department

Representative of American College of Obstetricians and Gynecologists, Division of Medical Sciences, National Research Council

Home Address: [redacted]

Office Address: The Johns Hopkins Hospital, Baltimore, Md. 21205

PUBLICATIONS

1. Myocardial properties in experimental cardiac enlargement and hypertrophy. W. V. Whitehorn, J. P. Henry, B. R. Anderson, A. Grimm and T. M. King. J. Lab. Clin. Med., 52: 957, 1958.

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4. Electrolytic changes following transabdominal intraovular injection of hypertonic saline. A preliminary report. T. M. King, J. Friedman and C. M. Steer. Symposium on the Mechanisms of Labor, Wurzburg, Germany, 1963.

5. Toxic effects of the tetracyclines. T. M. King, E. T. Bowe and D. A. D'Esopo. Bull. Sloane Hosp. for Women, 10: 35, 1964.

6. Hypofibrinogenemia and intrauterine fetal death. L. L. Phillips, T. M. King and V. Skrodelis. Amer. J. Obstet. Gynec., 19: 914, 1964.

7. Aplastic anemia in pregnancy. T. M. King and W. D. Todd. Bull. Sloane Hosp. for Women, 10: 42, 1964.

8. Brain tumors in pregnancy. T. M. King and D. A. D'Esopo. Bull. Sloane Hosp. for Women, 10: 73, 1964.

9. Uterine tonoactomyosin. T. M. King. Bibl. Gynaec. Fasc. 35, S. Karger, Basel, Switzerland, 1965.

10. Placental contractile protein. T. M. King and W. Groschel-Stewart. Amer. J. Obstet. Gynec., 93: 253, 1966.

11. Current status of the Schauta-Amreich operation. T. M. King. Amer. J. Obstet. Gynec., 94: 130, 1966.

12. Anencephaly. Survey of 44 cases. S. Erez and T. M. King. Obst. & Gynec., 27: 601, 1966.

13. Water intoxication in pregnancy. T. M. King and D. G. Hall. Missouri Medicine, 63: 359, 1966.

14. Intestinal fistulae following pelvic exenterations. T. M. King, J. A. O'Leary and H. C. Frick. Surg., Gynec. & Obst., 123: 991, 1966.

15. Urinary calculi in pregnancy. T. M. King and W. T. Griffin. Missouri Medicine, 64: 218, 1967.

16. Amniography in intrauterine transfusion. T. M. King and Gertraud Wollschlaeger. Southern Med. J., 60: 189, 1967.

17. Uterine myoglobin. T. M. King, T. Hsu and H. H. Dorian. Obst. & Gynec., 29: 441, 1967.

18. The role of epidemiology in practical obstetrics. H. M. Parrish, D. G. Hall and T. M. King. Obst. Gynec. Digest, 9: 21, 1967.

19. Relationship of pregnancy to coronary atherosclerosis. H. M. Parrish, C. A. Carr, S. L. Silb[illegible] and T. M. King. Amer. J. Obstet. Gynec., 97: 1987, 196[illegible]

20. Drug interaction. T. M. King and J. Keith Burgard. Amer. J. Obstet. Gynec., 98: 128, 1967.

21. Time interval from castration in premenopausal women to development of excessive coronary atherosclerosis. H. M. Parrish, C. A. Carr, D. G. Hall and T. M. King. Amer. J. Obstet. Gynec., 99: 115, 1967.

22. New aspects in the pharmacology of reproduction. T. M. King, M. S. Fahim and D. R. Blitz. Bull. Sloane Hosp. for Women, 13: 87, 1967.

23. Induced alterations in the biologic activity of estrogen. M. S. Fahim, T. M. King and D. G. Hall. Amer. J. Obstet. Gynec., 100: 171, 1968.

24. Gynecologic manifestations of reticulum cell sarcoma. F. A. Iliya, F. M. Muggia, J. A. O'Leary and T. M. King. Obst. & Gynec., 31: 266, 1968.

25. Influence of enzyme induction in lactation and neonatal development. M. S. Fahim and T. M. King. Amer. J. Obstet. Gynec. 101: 1103, 1968.

26. Androgen response in phenobarbital treated orchiectomized rats. T. M. King, M. S. Fahim and D. J. Bolt. Amer. J. Obstet. Gynec. 101: 850, 1968.

27. Uterotrophic action of estrogens in phenobarbital treated mice. M. S. Fahim, T. M. King, V. Venson, C. Norwich and D. J. Bolt. Fertil & Steril. 20: 344, 1969.

28. The influence of chronic distention on myometrial contractile protein. J. W. DeClue, G. D. Comfort and T. M. King. Amer. J. Obstet. Gynec. 105: 1082, 1969.

29. Observation on uterine growth effected by mechanical distention. J. W. DeClue and T. M. King. Amer. J. Obstet. Gynec. 105: 517, 1969.

30. Estrogen receptor in human endometrium during the menstrual cycle and early pregnancy. K. Limpaphayom, C. Lee, H. I. Jacobson and T. M. King. Amer. J. Obstet. Gynec. 111: 1064, 1971.

ABSTRACTS:

1. Fundamental properties of rat heart tissue in experimental hypertension. J. P. Henry, W. V. Whitehorn and T. M. King. Fed. Proc. 16: 57, 1957.

2. Effects of castration on properties of rat myocardium. T. M. King, R. Kubota and W. V. Whitehorn. Fed. Proc. 17: 86, 1958.

3. Regulation of function and actomyosin contest of cardiac muscle by estrogen. T. M. King, W. V. Whitehorn, B. Reeves and R. Kubota. Fed. Proc. 18: 81, 1959.

4. Significance of gonadal steroids in myocardiac composition and function. T. M. King. Proc. XXI Int'l. Congr. Physiol. Sci., p. 293, 1959.

5. Induced alteration in the biologic activity of estrogen. M. S. Fahim, T. M. King and D. G. Hall. Fed. Proc. 26: 425, 1967.

6. Influence of enzyme induction in lactation and neonatal development. M. S. Fahim and T. M. King. Fed. Proc. 27: 469, 1968.

7. Luteinization and maintenance of pregnancy by transplanted follicles exposed to luteinizing hormone *in vitro*. P. L. Keyes, G. D. Canaster and T. M. King. Fed. Am. Societies for Exptl. Biol., Atlantic City, April 12-17, 1970. Fed. Proc. 29: 2596, 1970.

8. Estrogen receptor in corpora lutea of pseudopregnant rabbits. C. Lee, P. L. Keyes, H. I. Jacobson and T. M. King. Fed. Am. Societies for Exptl. Biol., Chicago, April 12-17, 1971. Fed. Proc. 30: 953, 1971.

SUBMITTED FOR PUBLICATION:

Effects of phenobarbital treatment on the decidua cell response in rats.
D. J. Bolt and T. M. King
J. Reprod. & Fertil.

MANUSCRIPTS IN PREPARATION:

Puerperal and interval tubal ligation.

Drugs and abortions.

Ovarian enlargements in pregnancy.

Bile flow in pregnancy.

CURRICULUM VITAE

GEORGEANNA SEEGAR JONES, M.D.

Birth:	[redacted]
College:	A.B., 1932, Goucher College.
Medical School:	M.D., Johns Hopkins University School of Medicine, 1936.
Post Graduate Training:	House Officer, Gynecology, Johns Hopkins Hospital 1936-37. National Cancer Institute Trainee at Johns Hopkins Hospital, 1937-38. Laboratory Research in Endocrinology in the Department of Surgery, Johns Hopkins University, 1938-39.
Hospital Staff Appointments:	Gynecologist, Johns Hopkins Hospital Director of Laboratory of Reproductive Physiology and Gynecologist-in-Charge of the Gynecological Endocrine Clinic, Johns Hopkins Hospital, 1939-
University Appointments:	Associate Professor of Gynecology and Obstetrics, 1957-
Other Appointments:	Co-Editor-in-Chief for Gynecological & Obstetrical Survey, Williams and Wilkins Company, Baltimore, Md.
Medical Societies:	Baltimore City Medical Society Medical & Chirurgical Faculty of Maryland American Medical Association Southern Medical Society American Fertility Society Sociedad de Obstetricia Y Gynecologia die Cordoba Sociedad Chilena de Endocrinologia Sociedad Peruana de Obstetricia y Ginecologia La Sociedad Chilena de Obstetricia y Ginecologia American Gynecological Society American Association of Obstetricians & Gynecologists
Honors:	Rubin Award, 1966 Vice President, American Fertility Society, 1960 President Elect, American Fertility Society, 1969 President, American Fertility Society, 1970 Doctor of Science Degree, Goucher College, 1970 Barren Foundation Award, 1971
Marriage:	Howard W. Jones, Jr., M.D., 1940
Children:	Three

DR. GEORGEANNA E. SEEGAR JONES

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OVARIAN DYSGERMINOMA. Jones, Georgeanna E. S. Arch. Surg., 37: 697 (Nov., 1938)

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ARRHENOBLASTOMA OF THE OVARY. Jones, Georgeanna E. S. and Everett, H. S. Am. J. Obst. & Gynec., 52: 614 (Oct., 1940)

MESONEPHROMA OF THE OVARY. Jones, Georgeanna E. S., and Jones, Howard W., Jr. Am. J. Obst. & Gynec. 39: 322 (1940)

PREGNANDIOL EXCRETION FOLLOWING BILATERAL OOPHORECTOMY IN EARLY PREGNANCY. Jones, Georgeanna E. S. and Delfs, Eleanor. J. A. M. A., 115: 1267 (Oct. 1940)

A SIMPLE METHOD FOR THE QUANTITATIVE DETERMINATION OF PREGNANDIOL IN HUMAN URINE. Jones, Georgeanna E. S. and Astwood, E. B. J. Biol. Chem. 137: (Jan. 1941) p.397

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AN EVALUATION OF PROGESTERONE THERAPY IN THE TREATMENT OF ENDOMETRIAL HYPERPLASIA. Jones, Georgeanna E. S. and TeLinde, Richard W. Bull. Johns Hopkins Hosp. LXXI: (Nov. 1942)

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STUDY OF EXCRETION OF PITUITARY HORMONES IN HUMAN URINE, Jones, G.E. Seegar and Bucher, N.L.R. Endocr. 32:46-50, 1943.

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THE EFFECT OF THIOURACIL HYPOTHYROIDISM ON REPRODUCTION IN THE RAT, Jones, G.E. Seegar, Delfs, E. and Foote, E.C., Endocr. 38:337, 1946.

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ENDOCRINE PATTERNS IN ABORTION, Delfs, E. and Jones, G.E.S., Obstet. Gynec. Survey 3:680, 1948.

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TRACER STUDIES OF RADIOACTIVE SODIUM ESTRONE SULFATE (S^{35}) IN CASES OF ADVANCED BREAST CANCER, Lewison, E.F., Levi, J. Elliot, Jones, Georgeanna S., Jones Howard W., Jr. and Silberstein, Hannah E., Cancer 4:537, 1951.

ENDOCRINE PATTERNS IN TERM PREGNANCIES FOLLOWING ABORTION, Jones, G.E.S. and Delfs, Eleanor, J.A.M.A. 146:1212, 1951.

THE USE OF CORTISONE IN FOLLICULAR PHASE DISTURBANCES, Jones, G.E.S., Howard, J.E. and Langford, H., Fert. & Ster. 4:49, 1953.

DOUBLE UTERUS AS AN ETIOLOGICAL FACTOR IN REPEATED ABORTION: INDICATIONS FOR SURGICAL REPAIR, Jones, H.W., Jr. and Jones, G.E. Seegar, Am. J. Obstet. & Gynec. 65:325, 19

THE USE OF ACTH AND CORTISONE THERAPY IN OBSTETRICS AND GYNECOLOGY, Jones, G.S. and Howard, John Eager, N.Y. State J. Med. 53:2463, 1953.

MEDICAL ASPECTS, Jones, Georgeanna Seegar, Md. State Med. J. 2:574, 1953.

THE FILTER PAPER ELECTROPHORETIC IDENTIFICATION OF URINARY CHORIONIC GONADOTROPHIN Stran, H.J. and Jones, G.E. Seegar, Bull. Johns Hopkins Hospital 93:51, 1953.

TREATMENT OF THE DYSMENORRHEA SYMPTOM COMPLEX. A PRELIMINARY REPORT ON THE EFFICACY OF A UTERINE "RELAXING FACTOR", Jones, G.S. and Smith, Frank, Am. J. Obstet. & Gynec. 67:628, 1954.

SOME PROPERTIES OF HUMAN URINARY GONADOTROPHINS AS ELABORATED BY FILTER PAPER ELECTROPHORESIS, Stran, H.J. and Jones, G.E. Seegar, Bull. Johns Hopkins Hospital 95:162, 1954.

THE GYNECOLOGICAL ASPECTS OF ADRENAL HYPERPLASIA AND ALLIED DISORDERS. Jones, H. W., Jr. and Jones, G. E. S. Amer. Jour. Obstet. & Gynec. 68: 1330, 1954

AMENORRHEA DUE TO POLYCYSTIC (STEIN-LEVENTHAL SYNDROME). Klinefelter, Harry F., Jr. and Jones, G. E. S. Jour. of Clin. Endocrin. & Metab. XIV: 1247, 1954

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VAGINAL FUNGI AND THEIR RELATION TO SPERM SURVIVAL. Jones, G. E. S., Wood, John, Bishop, David and Donoho, Robert Amer. J. Obs. & Gyn. 70: 1271, 1955

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EFFECT OF PROGESTERONE ON ENZYMATIC SYSTEMS REPRINTED FROM THE "PROCEEDINGS OF THE SECOND WORLD CONGRESS ON FERTILITY AND STERILITY" Naples, 1956. Dept. of Gynecology, The Johns Hopkins Hospital and University) Jones, G. E. Seegar, Wade, Ruth and Jones, Howard W., Jr.

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NOVAK'S TEXTBOOK OF GYNECOLOGY - 8th Edition. Novak, Edmund R., Jones, Georgeanna Seegar and Jones, Howard W., Jr. Williams and Wilkins, Baltimore, Md. (1970).

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GRANT SUPPORT

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2. Investigation of Prostaglandin F_{2a} as an Abortifacient Agent. (with Cushner, Irvin M.) Funded 7/1/71, Agency for International Development, AID/csd 2956

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4. Participation in a panel discussion on "Menstrual Regulation and Post-Fertility Control" at Scientific Workshop on "The Prostaglandins: Clinical Applications in Human Reproduction", 6/12-6/14/72.

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1. Efficacy of Intravenous Prostaglandin as an Abortifacient in Early Pregnancy. with Cushner, Irvin M. Submitted for publication.

2. Intra-Amniotic Administration of Prostaglandin F_{2a} for Abortion. with Cushner, Irvin M., Austin, Karl and Shams, Mohammed. In Press. American Journal of Obstetrics & Gynecology.

3. Luteolytic Activity of Prostaglandin F_{2a}. with Jones, Georgeanna Seegar. In preparation.

4. Investigation of Serum Prostaglandin Levels in Dysmenorrheic Women. with Jones, Georgeanna Seegar, In preparation.

5. Myometrial Necrosis in Therapeutic Abortion. In preparation.

6. Serum Prostaglandin Levels in Normally Ovulating Women. with Wilks, John, In preparation.

7. Efficacy of Intravaginal Prostaglandin F_{2a} as an Abortifacient. with Shams, Mohammed. In preparation.

8. Stimulation of Cortisol Synthesis in Females Receiving Prostaglandin F_{2a}. Abstract for IV International Congress of Endocrinology. with Jones, Georgeanna Seegar, Rocco, Laura and Bledsoe, Turner).

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Curriculum Vitae

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1949-1950	Research Assistant, Department of Anatomy, University of Texas Medical Branch; Galveston, Texas
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1953-1954	Internship - Medicine, Henry Ford Hospital; Detroit, Michigan
1954-1955	Fellowship, Internal Medicine, Mayo Clinic and Foundation; Rochester, Minnesota
1955-1957	U.S. Air Force, Flight Surgeon, School of Aviation Medicine; Gunter Air Force Base, Alabama
1957-1958	Junior Assistant Resident, Department of Gynecology and Obstetrics, The Johns Hopkins Hospital; Baltimore, Maryland
1958-1959	Fellowship, Department of Pathology, The Johns Hopkins Hospital (on leave from Department of Gynecology and Obstetrics); Baltimore, Maryland
1959-1962	Assistant Resident and Resident, Department of Gynecology and Obstetrics, The Johns Hopkins Hospital; Baltimore, Maryland
1962-1964	Research Fellowship, Department of Microbiology (Division of Immunochemistry), The Johns Hopkins University School of Medicine; Baltimore, Maryland
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ACTIVITIES AND AWARDS

1953-	Alpha Omega Alpha Honorary Medical Society
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4. "Immune hemolysis: The steady state system in the reaction between EAC′ la 4 and C′2; application to measurement of C′4." Fed. Proc., Part I, 1963, 22: 613. (with Hoffmann, L. G. and Mayer, M. M.)

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6. Chapter on "The quality of the next generation." The Social Responsibilities of Gynecology and Obstetrics, edited by A. C. Barnes. Johns Hopkins Press; Baltimore, Maryland, 1965.

7. "A quantitative in vitro study of the chromatographic distribution and immunoglobulin characteristics of human blocking antibody." J. of Immunology, 1968, 101: 317. (with Lichtenstein, L M. and Holtzman, N. A.)

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10. "Skin disinfection." Johns Hopkins Med. J., 1970, 126: 169. (with White, John J. and Wallace, Craig, K.)

11. "Synthetic pelvic floor sling to decrease small bowel complications after total exenteration." Obstetrics and Bynecology, 1971, 38: 779. (with Clifford R. Wheeless, Jr., Conrad G. Julian and James H. Dorsey)

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Chronological List of Pertinent Publications

1. Value of Preparative Thin Layer Chromatography for the Routine Determination of Pregnanediol, Lau, H.L. and Jones, G.E.S., Amer. J. Obstet. Gynec. 90: 132, 1964.

2. Immunoassay of Serum Human Chorionic Gonadotrophin by Quantitative Complement Fixation and Its Comparison with the Delfs Bioassay and Two International Standard Preparations, Lau, H.L. and Jones, G.E.S., Amer. J. Obstet. Gynec. 92: 483, 1965.

3. Factors and Artifacts in the Formation of the Trimethylsilyl Ethers of Steroids, Lau, H.L., J. Gas Chromatography 1936, April 1966.

4. Lau, H.L.: Tests for Pregnancy, in Rawnsley, H. editor: Tice's Practice of Medicine, Hagerstown, Maryland, 1970, Medical Department Harper & Row, vol. II.

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1. A New, Simple Immunoassay for HCG, Lau, H.L, Amer. J. Obstet. Gynec. accepted August 1970 for publication.

2. A New Immunoassay for HCG Utilizing an Indicator Particle With a Covalent Bond, Lau, H.L., Butler, M., Ferraz, E.M., and G.E.S. Jones, The Johns Hopkins Medical Bulletin.

Projects Completed or Nearing Completion But Not Yet Reported

1. Differences Between LH and HCG on Cholesterol Esters In Rat Testes, Lau, H.L., Harrison, B.L., and G.E.S. Jones.

2. Immunoassay for PMSG Utilizing an Indicator Particle With Covalent Bond, Lau, H.L. and Butler, M. U.S. patent application submitted.

3. The Eye and Ovulation, Lau, H.L. and Butler, M.

4. Effect of External Environmental Factors in Reproduction, I. Light, Lau, H.L., Butler, M. and G.E.S. Jones.

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PUBLICATIONS

I. Papers

1. "Reproductive Potential of Anomalies of the Mullerian Duct." (with Jones, H.W.). American Journal of Obstetrics-Gynecology, 104: 348, 1969.

2. "A Rapid, Inexpensvie, and Effective Method of Surgical Sterilization by Laparoscopy." Reproductive Medicine, 5: 65, 1969.

3. "Out-Patient Tubal Sterilization." Obstetrics-Gynecology, 36: 2, 1970.

4. "Evaluation of Prognosis and Treatment in Adenoepidermoid Carcinoma of the Cervix." (with Graham, Ruth and Graham, J.B.). Obstetrics-Gynecology, 35: 6, 1970.

5. "The Use of A Synthetic Pelvic Floor Sling after Total Pelvic Exenteration to Decreast Small Bowel Complication." Obstetrics-Gynecology. (In press)

6. "Out-Patient Sterilization by Laparoscopy--A Report of 666 Cases." Obstetrics-Gynecology. (In press)

7. "Elimination of the Second Incision in Laparoscope Sterilization." Obstetrics-Gynecology. (To be published)

8. "Anesthesia for Diagnostic and Operative Laparoscopy." Fertility and Sterility. (to be published)

9. "Placental Imaging with ^{113m}In Transferrin and ^{99m}Tc Serum Albumin." Obstetrics-Gynecology, 37: 602-611, 1971.

10. "The Use of a Prophylactic Antibiotic in Elective Major Gynecological Surgery." Obstetrics-Gynecology, (In press.)

11. "Outpatient Laparoscope Sterilization Under Local Anesthesia." Obstetrics-Gynecology. (To be published).

PUBLICATIONS:

II. Books

Surgical Techniques of Family Planning and Population Control. Yearbook Medical Publishers, Chicago, 1972. (In Press).

CURRICULUM VITAE

HUGH JAMES DAVIS

BIRTH	:	[redacted]
COLLEGE	:	B.S., 1949, UNIVERSITY OF GEORGIA
MEDICAL SCHOOL	:	M.D., 1953, JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE
POST GRADUATE TRAINING	:	INTERN, GENERAL SURGERY, JOHNS HOPKINS HOSPITAL, 1953-54 ASST. RESIDENT, GYNECOLOGY, JOHNS HOPKINS HOSPITAL, 1954-58 RESIDENT GYNECOLOGIST, JOHNS HOPKINS HOSPITAL, 1958-59 RESEARCH FELLOWSHIP, RADIUMSTATIONEN, DENMARK, 1959-62 CYTOLOGIC EFFECTS OF RADIATION
HOSPITAL AND UNIVERSITY APPTS.	:	GYNECOLOGIST-OBSTETRICIAN, JOHNS HOPKINS HOSPITAL ASSO. PROFESSOR OF GYNECOLOGY AND OBSTETRICS JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE DIRECTOR OF OUT-PATIENT SERVICES DEPARTMENT OF OBSTETRICS AND GYNECOLOGY ASST. PROFESSOR OF POPULATION AND FAMILY HEALTH (POPULATION DYMANICS) JOHNS HOPKINS UNIVERSITY SCHOOL OF HYGIENE AND PUBLIC HEALTH ASST. PROFESSOR OF INTERNATION HEALTH JOHNS HOPKINS UNIVERSITY SCHOOL OF HYGIENE AND PUBLIC HEALTH
MARRIAGE	:	JYTTE A.M. PETERSEN, 1961
CHILDREN	:	TWO

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FACILITIES AND EQUIPMENT

The facilities and equipment of the Johns Hopkins Hospital, Johns Hopkins University School of Medicine Department of Gynecology and Obstetrics, Johns Hopkins University Applied Physics Laboratory, Johns Hopkins University School of Public Health, COPLAC Clinic, clinics of Planned Parenthood of Maryland, and the county clinics of the Maryland State Department of Health will be utilized for research and teaching in this proposal.

Research Projects. The Clinical Research Unit will occupy a patient area adjacent to other inpatient service of the Woman's Clinic. It will incorporate 1,848 square feet, and be a self-contained 12-bed clinical unit. It will include an operating room for the performance of procedures under local anesthesia, and a treatment room. A two to three bed room will be utilized for intensive care of patients undergoing monitoring, or equivalent procedures. One four-bed area will be utilized for patients in the process of abortion and as a recovery area for patients following surgical termination of pregnancy under local anesthesia. Patients undergoing laparoscopic sterilization will also use this area as a recovery room. The remaining beds will be employed for mid-trimester abortions. An office, data collection, and professional working area is provided within the Unit, and can also be used as a private interview area. Space will be provided for a nursing station and for a ward clerk. Also included in the Unit is a patient bathroom including a hopper area, bathroom and shower facilities. It is planned that this 12-bed unit will be fully acquired.

Needed remodeling of this area to be appropriate for use as a Clinical Research Unit is minimal, a coat of paint is needed. No partitions or walls will have to be constructed or removed, plumbing is already in place in all areas of the Unit, and only in the area designated to be the operating room will any plumbing renovation be required. A scrub sink will have to replace an already available sink. Adequate space is also provided for storage of linen, equipment, medications, and drugs. Room is also available for placement of refrigerator for storage and freezer for preservation of vital material obtained for analysis. A laboratory technician will be assigned to the Unit, for collection and preservation of materials. The refrigerated centrifuge will be maintained in the laboratory of one of the investigators. Specific laboratory procedures will be completed in individual investigators laboratories.

The investigators now occupy 1,000 square feet of laboratory space. The only additional laboratory equipment required would be a refrigerated centrifuge as previously mentioned, and an additional freezer.

The clinical laboratories of the Johns Hopkins Hospital will be utilized. A description of their capabilities follows.

Hematology. The Hematology Laboratories at The Johns Hopkins Hospital perform routine as well as sophisticated hematologic determinations. The routine measurement of complete blood counts on all patients will be essential. In patients undergoing evaluation with hyperosmolar drugs, the necessity of

performance of hematologic indices is obvious. In addition, since many drugs have been found to exert effects upon the clotting mechanisms, these parameters will also be tested. Finally, disseminated intravascular coagulation has been shown to be a problem in saline abortion patients, and may not be limited to hypertonic saline induction. Sophisticated determinations in the study of this entity are being performed at this Hospital.

Chemistry. The complete metabolic and chemical evaluation of every patient is essential. The laboratory at this Hospital performs the routine tests as a service, and will provide certain studies under research development at the present time. Osmolarity and osmolality determinatins can be obtained. The evaluation of lipids, lipid fractionation, cholesterol esters, renal and liver function tests, and lipid protein electrophoresis are also available.

Hormonal. Performance of hormonal assays will be essential. The primary concern, of course, will be the development of a serum immunologic HCG determination that can reliably indicate the presence of a very early conception. The study of radioimmunologic FSH and LH values will be essential in the testing of anti-LH and estrogen assays will also be essential. The performance of various studies on amniotic fluid are currently available, including estriol, electrolytes, and various hormonal determinations. The study of amniotic fluid after drug administration intra-amniotically will be essential, and such studies will include the disappearance curves of drugs, the electrolyte patterns, and the appearance of isotopically labelled materials in the peripheral blood. In addition, a prostaglandin assay is presently under development and should be available within one month.

Gynecological and Obstetrical Pathology. This department has a division of pathology responsible for the evaluation of all tissue, under the direction of Dr. J. Donald Woodruff. All tissue obtained from the patients of this program will be submitted for pathological diagnosis.

Other facilities of The Johns Hopkins Hospital will be utilized as described below.

Instrumentation. The recording of physiologic data, such as myometrial contractions and blood flow will be an integral part of labor evaluation. The purchase for the model experimental unit of a recording apparatus with Statham transducers is an essential in the management and evaluation of patients. The utilization of three more such monitoring units will be essential.

The Department of Biomedical Engineering has provided essential assistance in the past in the design of equipment for patient monitoring. Their Department provides such service throughout the Hospital, and their assistance would be necessary on a consultant basis from the onset of the project.

The Applied Physics Laboratory has been concerned with aspects of biomedical engineering for some time. Their Department would provide strong input into various physical and mechanical considerations of the project.

Animal Studies. The Department of Animal Medicine of The Johns Hopkins University has both a primate colony with pregnant and nonpregnant Rhesus monkeys, as well as extensive laboratory facilities housing lower animals for research purposes. Certain techniques and drugs will have to be tested in animals prior to their utilization in humans. A fund must be set aside for animal investigations, the performance of safety and toxicity experiments, and to provide other physiologic data before undertaking certain human studies.

PROJECT BUDGET

3 Year Period

Personnel	789,075
Fringe Benefits @ 13%	102,580
Indirect Costs @ 36.1%	159,201
Hospital Overhead	191,169
Operating Costs for Clinical Research Unit	492,000
Project Costs	219,000
Training Costs	660,000
Equipment	41,625
Travel	3,000
Publications Costs	4,000
Office Supplies	12,000
	2,673,650

BUDGET

PERSONNEL-PROFESSIONAL Position	% Effort	SALARY Year 1	Year 2	Year 3
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
Salary Subtotal		250,500	263,025	275,550
Fringe Benefits @ 13% Salaries		32,565	34,193	35,822
Indirect Costs @ 36.1% Salaries (excluding Clinical Research Unit Staff)		50,540	53,067	55,594
Hospital Overhead		63,723	63,723	63,723
Operational Costs of Clinical Research Unit (includes all hormone assays, blood chemistries, X-rays, pathology, and other hospital costs)		151,000	170,500	170,500
Additional costs for each project (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		250,841	196,657	212,502
Project Subtotal		346,841	274,657	257,502
Office Supplies		4,000	4,000	4,000

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

BUDGET JUSTIFICATION

Personnel

The principal investigator does not require support from this application. Other personnel, currently employed by the University and participating in this project are Drs. Georgeanna Seegar Jones, Anne Colston Wentz, and Lonnie S. Burnett. Their annual rate of pay, percent of effort devoted to the proposal and amount allocated to the proposal follows:

Principal Investigator	Theodore M. King	42,000	10%	------
Assistant Principal Investigator	Georgeanna S. Jones	31,000	17%	5,500
Director	Anne C. Wentz	23,000	50%	11,500
Assistant Director	Lonnie S. Burnett	22,250	45%	10,000
Clinical Research Unit Physician	To Be Appointed	20,000	50%	10,000

These individuals will be responsible for the completion of the clinical investigation projects of this program.

I - Evaluation and Development of IMproved Pregnancy Testing Technology: Georgeanna S. Jones and Lorrin Lau

II - Menses Regulation and Termination of Early Pregnancy: Lonnie S. Burnett and Anne C. Wentz

III - Development of Improved Means of Second Trimester Termination of Pregnancy: Theodore M. King and Anne C. Wentz

IV - Improved Pharmaceutical and Physical Means of Cervical Dilatation: Lonnie S. Burnett and personnel of Applied Physics Laboratory

V - Improved Clinical Equipment for Surgical Termination of Pregnancy: Anne C. Wentz and personnel of Applied Physics Laboratory

VI - Training of Personnel from Lesser Developed Countries: Theodore M. King and the Educational Coordinator who is to be appointed

In addition, they will be responsible for the recruitment of private and service patients, inpatient and followup care of the patients of the fertility control unit. In addition, this faculty will have didactic input into the educational program for trainees from lesser developed countries.

Clinical Research Unit Staff

Bioengineer	To Be Appointed	20,000	50%	10,000
Pharmacologist	To Be Appointed	20,000	50%	10,000
Physiologist	To Be Appointed	20,000	100%	20,000
Coordinator for Training	To Be Appointed	18,000	100%	18,000
Coordinator for Patients (2)	To Be Appointed	18,000	100%	18,000
Secretary (2)	To Be Appointed	14,000	100%	14,000
Lab Technician	To Be Appointed	8,000	100%	8,000
Statistician	To Be Appointed	20,000	25%	5,000

Clinical Research Unit Staff: To Be Appointed, Administered by The Johns Hopkins Hospital.

Bioengineer: 50% effort, $10,000 - To Be Appointed

Salary for a half-time individual from the Applied Physics Laboratory of The Johns Hopkins University is essential. This individual will be selected by Dr. Joseph T. Massey of the Applied Physics Laboratory. The input from this individual will be of great importance in providing the bioengineering talen necessary for research and development into improved means of cervical dilatation, and improved equipment for pregnancy termination and sterilization. It is visualized that this individual will maintain a research laboratory at the Applied Physics Laboratory and be provided laboratory space as needed within the Womans Clinic.

Pharmacologist: 50% effort, $10,000 - To Be Appointed

A pharmacologist will be required at least one-half time to evaluate and design animal experiments involving investigative drugs and serve as a consultant to the human studies. These studies of metabolic effects upon the human organism as well as upon animals are essential. This individual will be able to investigate and develop the utilization of abortifacient drugs, endometrial shedding agents, and to provide therapeutic regimens to decrease the observed side effects and untoward reactions. The pharmacologist is considered an integral and essential part of the Unit to evaluate mechanisms of drug action, drug tolerance, and any observed untoward patient responses.

Physiologist: 100% effort, $20,000 - To Be Appointed

A physiologist, with a primary interest in smooth muscle and cardiovascular physiology would be a member of the program, for coordination, and implementation of studie . These investigations would include myometrial and cervical response to abortifacients, as well as resulting local and systemic fluid and electrolyte patterns. It is expected that the physiologist will institute studies on the mechanisms of drug initiation of uterine contractility, and to provide necessary backup to the bioengineer for work on cervical dilatation. Ideally, he should be from a couotry that has had a long experience with abortion and should have, in the recent past, participated in goal-oriented clinically applied investigative programs.

Coordinator for Training: 100% effort, $18,000 - To Be Appointed

The Coordinator for Training will be a physician primarily interested in education in family planning, social implications of human reproduction and population control. He will be responsible for the ultimate scheduling of trainees, and integrally involved in screening the applicants for acceptance into the traineeship. He would also be concerned with the administrative details of these visitors, and would require the use of a secretary in this management. This individual will be required to relate directly to Dr. Theodore King, Director of the Educational Program. He would also be one of the individuals involved in trips to lesser developed countries for monitoring and feedback of the training program, and therefore insuring program relevance. Ideally, this individual should have had a recent past experience in the population problems of lesser developed countries.

Coordinator for Patients (2): 100% effort, $18,000 - To Be Appointed

The necessity for individuals familiar enough with the details of contraception, sterilization and abortion, but with some background in sociology or social work, and counseling will be essential. Experience with individuals involved in recruiting for experimental studies has shown that their input is crucial. Not only do they provide an interface between the patient and the doctor, but they provide for immediate followup as well as day-to-day scheduling. The coordinator would be visualized as located primarily in the central abortion referral area, and would have complete control of all scheduling for the Unit. Explanation of procedures and details, and counseling would be provided. Close work with social agencies throughout Maryland would be maintained.

Secretary (2): 100% effort, $14,000 - To Be Appointed

One secretary will be assigned full time to the Clinical Research Unit, to assist in preparation of detailed reports of all procedures, and maintaining an ongoing system for data collection and data filing., for each patient cared for. The necessity for record keeping is obvious, and only an individual assigned primarily' to the Unit will be able to keep abreast of the multitude of data emerging from it. A second secretary will be responsible for the clinical work of the physiologist, pharmacologist, and bioengineer. This individual will also assist in compilation of semi-annual reports, and to aid in literature research and library work.

Laboratory Technician: 100% effort, $3,000 - To Be Appointed

A laboratory technician is essential for the project because of the large volumes of vital material to be obtained. Specimens must be collected, cataloged, labelled, and at all times be accountable. Blood specimens will be sent to laboratories outside of the Hospital, and it will be the responsibility of the technician to know at all times what studies are in progress at other Institutions. The technician will work one-half time in the Clinical Research Unit, and one-half time in adjacent laboratory space providing for cataloging and details conced with vital specimens.

Statistician: 25% effort, $5,000 - To Be Appointed

A statistician is obviously essential, to be employed from the onset of the program to provide assistance with design of projected studies and critical evaluation of number of patients and experimental requirements for establishing statistical validity. The evaluation of the large quantities of data will benefit from such input.

The salary requests for all personnel reflect the dollar amount for the percentage of effort indicated.

Fringe benefits are calculated at the institutional rate, for both the University and the Hospital, of 13% of direct salary.

Indirect costs are calculated at 36.1% of direct salary. This rate is the current provisional on-campus rate in the NEGOTIATION AGREEMENT as determined by the HEW Audit of Fiscal Year 68-69 of the University. This rate is currently higher and under negotiation with H.E.W.

Hospital overhead has been determined, not as a percentage of a direct cost base, but as the sum of audited unit costs multiplied by a usage factor. This is the basic operational cost of the clinical research unit and includes depreciation, administrative costs, heat and utilities, linen, housekeeping, etc.

Operational (ancillary) costs of the Clinical Research Unit were determined by estimating as precisely as possible the actual usage of routine ancillary services, e.g., laboratories of the Johns Hopkins Hospital necessary for the care and treatment of the patients admitted to the Unit. Published charges for these services were reduced to cost, multiplied by usage, and compiled to produce the total shown.

Both Hospital overhead and the operational costs of the Unit have been determined by utilizing accounting procedures already existent for funding H.E.W. supported Clinical Research Units in hospitals; accounting procedures approved by the Social Security Administration for its reimbursement of hospitals in the Medicaid program.

Recovery of these costs is required to assure the Unit of the continuous flow of patient material mandatory to the success of the research and training components of this application. Without such recovery, the availability of patients willing to participate in clinical experimentation would be severely jeopardized.

Cost for Each Project

I. Improved Pregnancy Testing Technology. The costs illustrated include those of a separate laboratory, and include reagents, production, and packaging and supplies. Part of the expense will be involved in serial testing and comparative testing with known bio- and immunoassay reagents.

II. Menses Regulation and First Trimester Termination of Pregnancy. The project costs include a large outlay to the Department of Animal Medicine for purchase, housing and care of animals to be used in screening studies. The cost, for instance, of each Rhesus monkey is $600, while the costs for housing and care are quite minimal.

In addition, the institution of safety studies both in humans and in laboratory animals will require sophisticated hormonal, biochemical and metabolic assays. Facilities will not be covered by the contingency costs of the Clinical Research Unit, and will be provided fro from the Project costs. Also included are costs of pathologic examinations. Those done on patients for pathologic examination of the products of conception after termination of pregnancy are included in the operational costs of the Clinical Research Unit. Those pathologic examinations, including tissue fixation and preparation and making slides is a direct cost. Costs to develop forms of mini-curettage, as of polyethylene catheters and other devices for modification are included in the direct cost.

III. Second Trimester Termination. The primary costs to be included are those of assays and biochemical determinations not covered in the contingency fee, and monkey testing is required. It is expected that hyperosmolar agents, oxytocins, and other stimulants will be tested in the Rhesus monkey which provides an admirable model.

IV. Improved Pharmaceutical and Physical Means of Cervical Dilatation. The project budget for development of improved means of cervical dilatation includes costs for design, production and testing of the instrument to measure work and force, per the Applied Physics Laboratory; design conversion of metal dilators; production and testing of the Hopkins dilator already designed; hystero-cervicograms; conversion of self-contained units utilized in cardiovascular work for expansion purposes; investigation of hydrophilic laminaria and other expansion systems utilizing inducible chemical changes.

V. Improved Clinical Equipment for Surgical Termination. The budget for development of improved mechanical means of pregnancy termination includes the research design and development costs of the Applied Physics Laboratory; cost of animals essential for the testing of such instruments; formulation, development and printing costs of manuals of instruction for use of instruments.

VI. Training. The utilization of moneys provided for training is described in detail in the budget of that specific project.

Non-Expendable Equipment

The equipment requested is the minimum required to permit the conversion of the existing inpatient unit to the research unit described. No expenditures for equipment will be made if other equipment is available or suitable for the intended use.

Equipment and Supplies

These supplies include items required for the establishment of an office for the fertility control unit. The fertility control unit requires equipment for the intrauterine monitoring. Centrifuges, freezer, freezer-refrigerator are required for specimen preparation and storage.

Travel Expenses

Travel expenses shown in the principal budget are for domestic travel to scientific meetings for the purpose of presentation of results emanating from the research proposed. Foreign travel to less developed countries is envisioned and is discussed in the presentation of the educational program.

Publication Costs

It is expected that a minimum of 10 publications a year will emanate from this program. Publication costs include cost of reprinis, Xeroxing, Xeroxing for literature surveys, and secretarial supplies as needed for publication preparation. Also included are costs for graphic work, art supplies, and slide preparation.