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932-532-1

PROJECT STATEMENT

PD-AAF-172-B1

932-532

March 19, 1971

A. Project Summary

25p.

1. Statistical

Project Title: Research on Prostaglandins in Relation to Human Reproduction

New or Extension: New

Contractor and Address: Makerere University, Kampala  
P. O. Box 7062  
Kampala, Uganda

Principal Investigator: Sultan M.M. Karim, B.Pharm., M.Sc., Ph.D.(Lond.)  
Professor and Head, Department of Pharmacology and Therapeutics

Duration: Three Years

Total Estimated Cost: \$1,099,825

Funding by Fiscal Years: Current Year - FY 1971: \$1,099,825

Project Manager: J. J. Speidel  
Chief, Research Division, TA/POP

2. Narrative

AID/cad 3300

This project will carry out research essential to further develop and test the value of Prostaglandins as a means of fertility control. The program will involve synthesis, assay, testing of new analogs and training of fellows but will focus on clinical trials. New formulations and routes of administration will be developed and tested. Special studies on the safety of prostaglandins will examine the effects of prostaglandins on the human cardiovascular, respiratory, thyroid, gastrointestinal, hematological and ocular systems. The project will allow Dr. S. Karim to extend his pioneering clinical trials of prostaglandins as a means of pregnancy termination and as a once-a-month means of fertility control. It will also serve to strengthen Makerere University in Uganda as a center for fertility control research.

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## B. Expanded Narrative Statement

### 1. Project Description and Background

Dr. S. M. M. Karim of Makerere University in Kampala, Uganda has been working with prostaglandins for the past five years. In spite of handicaps, including principal reliance on materials he synthesized himself and a University base not nearly so strong as many found in the developed countries, Karim has been a leader in prostaglandin research, demonstrating the role of prostaglandins in human reproductive biology and in clinical trials of this substance as a means of fertility control.

He has carried out some of the best studied and the largest series of clinical trials demonstrating labor induction and pregnancy termination with prostaglandins. At Makerere University Medical School he first demonstrated the use of prostaglandin as a "menses inducer" when administered by the vaginal route (and therefore that self administration was possible).

The proposed research program will continue clinical trials of prostaglandin as a once-a-month means of fertility control and for the termination of pregnancy. It will also study side effects and possible hazards of prostaglandins in man and will train fellows and otherwise disseminate prostaglandin technology via collaborative arrangements with scientists in other countries. Development of capability to synthesize, test and analyze both the natural prostaglandins F<sub>2α</sub> and E<sub>2</sub> and new analogs will be included as part of the project.

### 2. Significance of Project to AID Objectives

A consistent goal of AID's population research program has been to develop a once-a-month means of fertility control which was not dependent upon clinical facilities for its use. This objective was chosen because the highly determinative influence of fertility control technology on the effectiveness and efficiency of family planning programs is readily apparent from studies of family planning practices and programs in many cultures. These studies have also made it apparent that two foremost determinants of the efficacy of a means of fertility control for implementation of family planning programs in developing countries are the time of use (relative to conception) and the requirements for administration (relative to clinical or self-application).

Effective use of preconceptive (contraceptive) means of fertility control requires the exercise of foresight. For many individuals, particularly in developed countries, these methods have been quite successful. But for many others in all societies and particularly in the less developed countries, use of foresight means of fertility control is difficult and reliance solely on these means is therewith less efficient and more expensive. For these

groups, access to postconceptive (hindsight) means of fertility control is imperative for adequate control of fertility.

Therefore, it is clear that the development of a substance or method which could be self-administered to control fertility after exposure to or recognition of pregnancy could produce a quantum increase in the speed and effectiveness with which family planning could be extended around the globe.

A year ago it seemed likely that at least several years would elapse before a technological breakthrough could be achieved, but developments during 1970 have been surprisingly favorable: Karim has shown that prostaglandins, administered by the vaginal route, are extremely effective for post-conceptive control of fertility and to date serious side effects are not evident.

This development has revolutionary implications for family planning strategy and programs, and the addition of this technology to current methods would greatly facilitate the extension of effective fertility control throughout the world.

One requirement to establish this technology is to carry out more extensive clinical trials and studies of safety which can be conducted in a controlled but flexible fashion at Makerere.

In addition to the importance of this topic for study, this project provides an opportunity to support a first rate research worker and strengthen an institution in a less developed country. Under Karim's leadership Makerere has pioneered the development of prostaglandins as a means of fertility control. This project will help maintain this leadership which should serve to increase acceptability of this new means of fertility control in Africa and other LDC's.

### 3. Relation to Existing Knowledge

Prostaglandins have been shown to be effective in the induction of labor, termination of pregnancy and for inducing menstruation. These studies of the use of prostaglandin on a once-a-month or missed menses basis are very promising but several years of research will be required to establish this new technology on a sound basis.

Particularly important in this effort will be to establish the practicality of this new method in terms of safety and acceptability and develop the best formulations for and routes of administration in carefully controlled field trials.

Experimental evidence from the rhesus monkey, rabbit and rat indicate that parenteral administration of prostaglandin F<sub>2α</sub> during early pregnancy or during pseudo-pregnancy may inhibit corpus luteum function. It is also known that some prostaglandins when administered intravenously are able to

stimulate the pregnant human uterus in vivo throughout gestation. This has led to the use of these prostaglandins as oxytocics and abortifacients and they might prove useful as a "morning after" or once-a-month type of contraceptive.

Recent studies in non-pregnant women show that intravenous administration of prostaglandins E<sub>2</sub> and F<sub>2α</sub> initiate vigorous uterine contractions and produce menstrual-like bleeding during the advanced secretory phase of the cycle. Similar results have been obtained with intravaginal administration of these two prostaglandins. Prostaglandins E<sub>2</sub> and F<sub>2α</sub> applied by this route are also effective for termination of pregnancy from six weeks onwards and for the induction of labour at or near term.

Intravaginal administration of prostaglandins E<sub>2</sub> or F<sub>2α</sub> in twelve women who had passed their expected day of menstruation by 2 to 7 days has been shown to induce menstruation in eleven out of twelve women. The menstrual bleeding was always preceded by an increase in uterine activity which was similar to that recorded during spontaneous menstruation. The mechanism of prostaglandin action in inducing menstruation is not certain. The strong and frequent uterine contractions could dislodge the endometrium or the fertilized implanted ovum and initiate uterine bleeding. It is of course possible that impairment of corpus luteum function is an additional causative factor for the induction of menses.

The first study on the use of prostaglandins for the termination of unwanted pregnancy was reported from Uganda (Karim, and Filshie). Prostaglandin F<sub>2α</sub> infused at the rate of 50 μg/min. and pregnancy was successfully terminated in fourteen out of fifteen women. With prostaglandin E<sub>2</sub> infusion rate of 5 μg/min. was sufficient to terminate pregnancy in twelve women. These findings have since been extended and confirmed by us and others.

In order to make the use of prostaglandin more practical Karim has recently attempted abortion with intra-vaginal administration of prostaglandins E<sub>2</sub> and F<sub>2α</sub>. With 20mg prostaglandin E<sub>2</sub> or 50mg prostaglandin F<sub>2α</sub> in the form of a pessary inserted into the vagina every 2½ hours in 45 women, abortion was successful in every case. The average abortion interval was less than 15 hours.

Another area where it is essential that careful studies be carried out is on possible side effects of prostaglandins. In doses higher than required for its abortifacient effect prostaglandins have been shown to produce an effect on the following systems in laboratory animals:

a. Cardiovascular: The blood pressure lowering effect of some prostaglandins in laboratory animals has been known since these substances were first discovered in human semen. Investigation of the cardiovascular

effects of prostaglandins in man is limited to four studies only. It has been shown that E prostaglandins produce a fall and the F<sub>2</sub>α prostaglandins a rise in arterial blood pressure. However, the doses required for producing changes in blood pressure are much higher than those required to produce an abortion or to induce menstruation.

b. Respiratory: Prostaglandin E<sub>1</sub> and isoprenaline have similar bronchodilator activity when injected intravenously in anaesthetised guinea-pig, but when given by an aerosol prostaglandin E<sub>1</sub> is 10-100 times more active than isoprenaline. A recent study has shown that in five out of six asthmatic volunteers inhalation of 55 μg of prostaglandin E<sub>1</sub> produced an increase in forced expiratory volume in one second, comparable in both degree and duration to that produced by an inhalation of 550 μg isoprenaline.

c. Thyroid: Observations on the detailed mechanisms by which thyroid stimulating hormone (T S H) stimulates thyroid function suggest that they include:

- (1) Increasing the intracellular concentration of cyclic 3': 5' A M P by activating adenyl cyclase;
- (2) Promoting glucose oxidation in the thyroid gland cells;
- (3) Increased synthesis of thyroglobulin;
- (4) Increased release of thyroxine.

These effects have also been produced in tissue slices by means of prostaglandins E<sub>1</sub>, E<sub>2</sub>, F<sub>1</sub>α and F<sub>1</sub>β. Of all the prostaglandins E<sub>1</sub> has been demonstrated to do this most consistently.

d. Gastrointestinal: Inhibition by prostaglandin E<sub>1</sub> of gastric acid secretion induced by histamine in rats and in dogs has been shown. Prostaglandins are also known to be released spontaneously into the lumen of the rat stomach. They are also found in the gastro-intestinal wall and many have a role in the control of gastro-intestinal motility and secretions.

So far very limited studies in man have been carried out. A decrease in mean volume and acidity in human volunteers with prostaglandin A<sub>1</sub> after inducing gastric secretion by histamine has been shown. Diarrhoea as a side effect, when prostaglandin E<sub>2</sub> and F<sub>2</sub>α are used as abortifacients has been reported.

e. Hematological: Thrombocytes play an essential role in intra-vascular thrombosis. Blood platelets carry a negative surface charge which would normally repel each other. During platelet aggregation this electrostatic force must be overcome. A suggested mechanism for this is that the ATP formed leads to release of ADP on the surface of blood platelets thus

increasing the negative charge as evidenced by increase in their electrophoretic motility. The increased negative charge leads to  $Ca^{++}$  - protein complex formation and removal of repulsive charge and permitting platelet aggregation.

Whatever the mechanism of platelet aggregation may be prostaglandin  $E_1$  is a powerful inhibitor of the process, and prostaglandin  $E_2$  on the other hand increases platelet aggregation.

f. Ocular: Prostaglandins are known to be present in the iris of sheep and rabbits. Chemical or mechanical irritation of the rabbit eye has long been known to cause prolonged miosis, vasodilation, increased capillary permeability and a sustained rise in intra-ocular pressure.

Prostaglandin  $E_1$  and  $E_2$  injected into the anterior chamber of the rabbit eye produced a marked and sustained rise in intraocular pressure frequently accompanied by miosis; prostaglandin  $F_2$  was very much less potent. Similar effects were demonstrated with prostaglandin  $F_2\alpha$  and  $A_1$  which also showed the descending order of ability of prostaglandins to elevate rabbit intraocular pressure to be  $E_1 > E_2 > F_2 \geq A_1 > F_1\alpha$ ; marked tachyphylaxis occurred with all of these compounds.

The means by which prostaglandins produce miosis remain to be elucidated. They may be distinct from cholinergic and adrenergic mechanisms. In the cat and monkey prostaglandin  $E_1$  produced sustained miosis without any rise in the intraocular pressure. Prostaglandin  $E_1$  - induced miosis is not prevented by atropine and atropine - induced mydriasis is abolished by prostaglandin  $E_1$  indicating a nonmuscarinic site of action. In the rabbit eye, prostaglandin  $E_1$  - induced miosis is prevented by norepinephrine and by propranolol, but the accompanying sustained rise in intraocular pressure is unaffected by either compound.

Work on assay techniques is needed because reliable, accurate, and sensitive methods for the estimation of prostaglandins and their metabolites are required to:

(1) Establish more precisely the role of prostaglandins in the natural process of menstruation and spontaneous abortion.

(2) Estimate blood levels of prostaglandins and analogues when these are used clinically in order to work out dose schedule.

(3) Determine the fate of prostaglandins by measuring the blood, urine and tissue levels of prostaglandins and analogues and their metabolites after administration of these substances.

#### 4. Relation to Other Research

There are numerous steps to developing and obtaining new contraceptives; the table below presents present activities in progress developing prostaglandins as means of fertility control.

<u>Research Activity</u>	<u>Conducted by</u>
✓ 1. Synthesis of Prostaglandin Analogs and Natural Compounds	Drug companies - A.I.D.: Worcester Foundation (Corey) Univ. of Wisconsin (Sih)
✓ 2. Screening of Compounds for reproductive biological activities and side effects	Drug companies A.I.D.: Worcester Foundation
✓ 3. Development of formulations for human use	Drug companies - A.I.D.: Makerere Univ. (Karim)
✓ 4. Development of Assay Techniques	Drug companies - University Workers - A.I.D.: Worcester (Samuelsson) Washington Univ. (Caspo)
✓ 5. Fundamental work on mechanism of action	University Workers - A.I.D.: Washington Univ. (Caspo)
✓ 6. Animal Toxicology	Drug companies Southwest (Goldzieher)
✓ 7. Limited human clinical trials including study of side effects and new routes of administration	Drug companies collaborating with University Workers - A.I.D.: Worcester (Yale) UNC (IFCR Program) Washington Univ. (Caspo) Makerere Univ. (Karim)
✓ 8. Controlled field trials	Drug companies UNC (IFCR Program)

It should be noted that each of these steps is essential. Studies carried out by drug companies frequently are kept secret and therefore are not readily available in the less developed countries whereas data and inventions from A.I.D.-sponsored projects are in the public sector without proprietary secrecy or patent protection restricting usage and availability. Where more than one A.I.D.-sponsored project is operative, they are usually pursuing differing approaches; for example:

Synthesis: Corey is working on total synthesis, Sih is working on microorganism catalyzed synthesis.

Assay Techniques: Worcester is developing radio immuno assay, Samuelsson is developing physical chemical assay, Caspo will work on bio-assay.

Limited Human Clinical Trials: The need for data, the importance of the data, the importance of verification of this data by several talented investigators, and the desirability of bringing several of the leading clinical centers into this research activity suggest that some overlap is desirable. However, each of the A.I.D. supported centers will have differing contributions, Karim can innovate the most freely; UNC will focus on somatic side effects and Caspo will study endocrine and uterine contraction effects.

Each of these groups have been chosen by A.I.D. for support because of the complimentary of their research activities.

In addition collaborative and mutually beneficial arrangements will be worked out between the Makerere project and other AID-sponsored projects as follows:

The Worcester Foundation:

- a. Developments in assay techniques can be provided to Makerere.
- b. Prostaglandin analogs which are being screened for antifertility activity can be provided Makerere for further testing and clinical trials; similarly any analogs synthesized at Makerere can be thoroughly tested at Worcester.
- c. Information from animal work on routes of administration will be of value to human studies at Makerere.
- d. Worcester will be able to analyze steroid hormones and gonadotrophins derived from clinical material at Makerere.

The Southwest Foundation:

- a. Testing of prostaglandins and analogs for possible teratogenic effect.
- b. Expert assistance to Makerere in the setting up of their small baboon colony.

The International Fertility Control Research Program (Univ. of N. Carolina:

- a. Data from all clinical trials at Makerere will be processed in the IFCR program and added to its international data base.
- b. Dr. Karim will serve as an expert consultant to the International Fertility Control Research training program in prostaglandins at the University of North Carolina.

## 5. Proposed Work Plan

- (1) To synthesize prostaglandins E<sub>2</sub>, F<sub>2α</sub> and other naturally occurring prostaglandins and their analogues.
- (2) To carry out clinical trials of prostaglandins E<sub>2</sub> and F<sub>2α</sub> as once-a-month antifertility agent.
- (3) To carry out clinical trials of prostaglandins E<sub>2</sub> and F<sub>2α</sub> for the termination of unwanted pregnancy.
- (4) To carry out studies on other actions of prostaglandins in man.
- (5) To develop methods for measuring prostaglandins in body fluids and tissues.
- (6) Screening of prostaglandin analogues in animals and in man.
- (7) To train Fellows from abroad in prostaglandin technology.
- (8) To make prostaglandins available to interested scientists in other countries and to collaborate with them in carrying out clinical trials of prostaglandins.

## 6. Research Methodology

### A. Synthesis of Prostaglandins E<sub>2</sub> and F<sub>2α</sub> and their Analogues

Most of the prostaglandins used in Uganda for clinical studies (including abortifacient and once-a-month menstruation inducing studies) have been biosynthesized in the Department of Pharmacology at Makerere. This method of producing prostaglandins is very expensive and time consuming. Also the amounts that can be biosynthesized are limited. Recently, naturally occurring prostaglandins have been totally synthesized by several groups in the U.S.A. Because of the F.D.A. regulations these prostaglandins produced in the U.S.A. cannot be made available overseas for clinical use on a large scale.

Therefore there is a need to synthesize in Uganda up to kilogram quantities of prostaglandins E<sub>2</sub> and F<sub>2α</sub>.

A team of Chemists (one senior Chemist with two assistants) will carry out this synthesis. In addition to synthesizing naturally occurring prostaglandins E<sub>2</sub> and F<sub>2α</sub> the chemists would be involved in a program of synthesizing analogues of prostaglandins with the hope of discovering compounds with more selective and longer duration of activity which could be self administered.

A great deal of progress has been made in recent years in prostaglandin synthesis technology and no doubt in this extremely fast-moving field newer and improved methods for prostaglandin synthesis will become available. For the present the methods reported by E. J. Corey for synthesis of naturally occurring prostaglandin will be followed.

B. Clinical Trials of Prostaglandins E<sub>2</sub> and F<sub>2α</sub> as a Once-a-Month Means of Fertility Control

Proposed clinical studies of antifertility effects include three groups:

Group I

Initially 100 women of proven fertility in the reproductive age group who are anxious to avoid pregnancy will be selected. They will not use any other form of contraceptives during the study period. The women will be under constant supervision and will be followed up for not less than one year.

If menstruation does not occur within 2-3 days of due date then prostaglandins E<sub>2</sub> or F<sub>2α</sub> will be used to induce menstruation. Prostaglandins will be administered intravaginally. Prostaglandin E<sub>2</sub> 40mg in two divided doses or prostaglandin F<sub>2α</sub> 100mg in two divided doses.

Group II

In this group prostaglandins E<sub>2</sub> or F<sub>2α</sub> will be administered to 100 women (selection criteria as in Group I) once-a-month two days before the date of due menstruation. As before the route of administration will be intravaginal.

Group III

In this group women who are on other form of contraceptives or who have had unprotected intercourse and in whom menstruation is delayed by up to a maximum of seven days will be included. Menstruation will be induced with intravaginal administration of prostaglandins E<sub>2</sub> or F<sub>2α</sub>.

In groups I and II it is hoped to increase the number to a total of 500 in the second year of study and to 1000 in the third year of study.

<sup>a</sup>  
At the initial visit/couple's history and physical examination will be performed on all women by the medical specialists.

The following data will be collected:

1. Identifying data

2. Obstetrics History
3. Menstrual History
4. Dysmenorrhoea
5. Intermenstrual Bleeding
6. Previous Medical History
7. Reason for selecting this method (Prostaglandins)
8. Physical Examination
9. Pelvic Examination

**Follow-up Studies:**

Patient to be seen one week after drug administration. The following details to be taken:-

- (1) Menstrual period after drug administration:
    - Amount of bleeding:
      - Scanty/Average/Severe
    - Duration of Bleeding ..... days.
    - Pain experienced (if any)
  - (2) Nausea/Vomiting/Diarrhoea
  - (3) Headache
  - (4) Whether the patient would like to continue in the present study.
  - (5) In patient with no bleeding or scanty bleeding:
    - Pregnancy test: Positive/Negative
  - (6) Complete physical and vaginal examination
- C. Use of Prostaglandins to Terminate Pregnancy

Further studies in the use of prostaglandins as abortifacients will include efforts to improve the formulation of these compounds to simplify the administration of these substances and to give longer duration of action.

Different formulation to achieve slow absorption after intra-muscular injections or intravaginal administration will be studied.

**D. Studies of Side Effects of Prostaglandin**

**(1) Cardiovascular Studies:**

It is proposed to carry out a detailed study of the effects of naturally occurring prostaglandins given by different routes on the cardiovascular system in male and non-pregnant female volunteers. Some pregnant women recommended for abortion will also be included in the study.

The parameters to be measured would include:-

- (a) Measurement of systolic and diastolic pressures.
- (b) Heart rate.
- (c) Electrocardiogram.
- (d) Cardiac output.
- (e) Peripheral resistance.

It is also hoped to study the mechanism of the cardiovascular effects of prostaglandins. Before any synthetic analog of prostaglandins could be used as an abortifacient or contraceptive, it would be essential to study its effect on the cardiovascular system in human subjects.

**(2) Respiratory Tract Studies:**

It is proposed to study the effect of prostaglandins and analogs given systemically and by aerosol on the following parameters:

- (a) One second Forced Expiratory Volume.
- (b) Vital capacity.
- (c) Blood pressures, heart rate and E.C.G.

**(3) Thyroid Function Studies**

Since prostaglandins are being used for therapeutic purposes e.g. inducing labour, procuring abortion, it is worth investigating their possible effect on the thyroid, both acute and long term. No report has been seen in relation to the protein binding of the thyroid hormones. The investigation will follow these lines:-

- (a) Preliminary work to be done on women volunteers.

(b) Then the work to be repeated on pregnant women having induced abortion.

(c) If these substances are used eventually as contraceptives then those who have used them would be studied at convenient intervals; at least a year is envisaged in this regard, i.e. at say 3 monthly intervals.

The study method is as follows:

After clinical evaluation of each patient:-

(a) Small doses of radioactive iodine to be given orally; 4-8 micro-curries of I -131.

The thyroid uptake to be measured by external detection from 6-48 hours or longer, perhaps up to 96 hours.

(b) Some patients are to be studied soon after administration of the prostaglandins and a week, a month, 2 months, etc.; later, to see when the effects disappear if at all.

(c) Measurements of thyroxine binding are to be done using the T<sub>3</sub> assay technique and the free thyroxine index estimation technique.

(4) Gastrointestinal Studies:

It is proposed to study the effects of natural prostaglandins and their analogs given by different routes on:-

(a) Gastrointestinal motility.

(b) Gastric acid secretion.

(5) Hematological Studies:

It is proposed to study the effect of various prostaglandins on platelet aggregation as well as on blood coagulation, as platelets also participate in the events which finally lead to the transformation of soluble fibrinogen into insoluble fibrinogen.

Though the effects of prostaglandins on platelet aggregation have been reported, their effects on blood coagulation and on fibrinolysis have not been reported.

Their effects following prolonged infusion, as required for therapeutic abortions have not been studied and the only study on post-infusional effects of prostaglandin E<sub>1</sub> has been following infusions of about 15 minutes duration.

The following studies will be carried out on specimens before and after incubation with various prostaglandins as well as on those obtained from subjects in whom prostaglandins have been infused for therapeutic abortions.

I. Platelet Function:

- (a) Platelet-to-glass adhesiveness.
- (b) Platelet aggregation and disaggregation.
- (c) Platelet electrophoretic motility.

II. Coagulation Function:

- (a) Whole blood coagulation time.
- (b) Prothrombin time.
- (c) Thromboplastin generation test.

III. Cell Counts:

- (a) Red blood cell count.
- (b) White blood cell count.
- (c) Platelet count.

IV. Cell Morphology

V. Fibrinolysis

- (6) Ocular Studies:

In view of the widespread therapeutic potential of prostaglandins and the ocular effects in animals referred to, in particular the marked and sustained elevation of rabbit intraocular pressure it is essential to investigate in man the ocular effects of systemically, vaginally and orally administered prostaglandins. Parameters would include alteration in pupillary size and reaction, alteration in the intraocular pressure, vascular changes in the iris and the presence or absence of ocular pain or headache. Alteration in pupillary size and reaction may provide further evidence for the possible mode of action/prostaglandins on iris smooth muscle.

Prostaglandins may be of physiological significance in the human eye and may be implicated in human ocular disease involving the region of the iris. Qualitative and quantitative assays would be carried out on samples of aqueous humour obtained during appropriate surgical procedures.

**E. Development of Improved Methods for the Measurement of Prostaglandins and their Metabolites**

The most promising method for this purpose is gas liquid chromatography with mass spectrometry developed by Professor Samuelsson at The Karolinska Institute.

A specialist chemist with expertise in prostaglandins work will be recruited to run the mass spectrometer unit and further develop the method for prostaglandin measurements.

**F. Screening of Prostaglandins-Analogues in Laboratory Animals and in Man**

The team of chemists recruited to synthesize naturally occurring prostaglandin for clinical use will also be involved in a program of synthesis of analogues of prostaglandins. These analogues will go through the following routine tests:-

(1) Screening of analogues on isolated tissue preparations and in laboratory animals (including rats, guinea-pigs, mice, rabbits, cats, dogs, monkeys and baboons) for pharmacological activities. Much of this work can be done at the Worcester Foundation.

(2) Human studies - pharmacological actions, toxicity and tolerance.

With analogues which show promise as abortifacients and anti-fertility agents, it is proposed to carry out some or all of the following studies in human volunteers:

(a) Cardiovascular effects: Blood pressure, heart rate, electrocardiogram, cardiac out-put, peripheral resistance. Drugs to be administered by different routes.

(b) Gastrointestinal system: Motility, gastric secretion, etc.

(c) Haematology: In vitro and in vivo studies influence on clotting mechanism, platelet, aggregation, adhesiveness, cell count, cell morphology.

(d) Effects on endocrine functions.

(e) Urinalysis.

(f) Effect on the eye and ocular functions.

(g) Blood biochemistry, effect on blood sugar level, etc.

(h) Effect on the uterus (pregnant and non-pregnant) and on corpus luteum.

G. Expected End Results by the End of Three Years:

- (1) To have available results from the antifertility study carried out in about 1000 women with naturally occurring prostaglandins E<sub>2</sub> and F<sub>2α</sub> or/and their analogues.
- (2) To have results from abortifacient study carried out in about 1000 women with naturally occurring prostaglandins E<sub>2</sub> and F<sub>2α</sub> or/and their analogues.
- (3) Information on best routes of administration and dose schedule.
- (4) Whether there are any serious side effects that would limit the use of prostaglandins as antifertility agents or abortifacient.
- (5) Whether any prostaglandin analogues show any improvements over naturally-occurring compounds.

7. Researcher Competence

Scientific Personnel, their Function and Qualifications

Programme Director and Principal Investigator:

1. Sultan M.M. Karim, B.Pharm., M.Sc., Ph.D., M.P.S.  
Professor and Head,  
Department of Pharmacology and Therapeutics,  
Makerere University, Medical School, Kampala.  
(25 - 30 hours per week).

Dr. Karim is 36 years old, trained at the University of London and has published about 50 articles on prostaglandin. He is an acknowledged expert in the prostaglandin field.

The following personnel employed by Makerere University are available to participate in the proposed study as collaborators or consultants/advisers without additional remuneration. (In alphabetical order).

2. F.M. Bulwa, M.B.Ch.B., M.R.C.O.G.  
Reader, Department of Obstetrics and Gynaecology,  
Function: Consultant/Adviser on abortifacient and  
antifertility studies.  
(5 hours per week).
3. S.K. Kajubi, M.B.Ch.B., M.R.C.P.  
Senior Lecturer in Applied Physiology,  
Department of Medicine,  
Function: Will participate in the study of the effects of  
prostaglandins on endocrine systems.  
(5 - 10 hours per week).

4. S.R. Landor, Ph.D., D.Sc.,  
Professor and Head,  
Department of Chemistry,  
Function: Consultant/Adviser on problems related to the  
Chemistry of prostaglandins.  
(5 hours per week).  
  
Dr. Landor is British trained, an experienced senior chemist  
with over 50 scientific articles published.
5. D.M. MacIntosh, M.B.Ch.B.  
Senior Lecturer,  
Department of Pharmacology and Therapeutics,  
Function: Will participate in the study of the ocular  
effects of prostaglandins.  
(10 hours per week).
6. N.J. Mody, M.B.Ch.B., Dip.Clin.Path.(Lond.),  
Senior Lecturer,  
Department of Biochemistry,  
Function: Will participate in haematological studies  
with prostaglandins.  
(10 - 15 hours per week).
7. E. Nzaro, M.B.Ch.B., M.R.C.P.E.,  
Consultant Haematologist,  
New Mulago Hospital, Kampala.  
Function: Consultant/Adviser on haematological studies  
with prostaglandins.  
(5 hours per week).
8. R. Owor, M.B.Ch.B., M.D., M.C.Path.,  
Senior Lecturer, Department of Pathology,  
Function: Consultant/Adviser on Pathology and Histopathology  
problems.  
(5 hours per week).
9. P.H. Sebuwufu, M.B.Ch.B., F.R.C.S., Ph.D.,  
Professor and Head,  
Department of Anatomy,  
Function: Consultant/Adviser on problems with  
Anatomy and Histology.  
(5 hours per week).
10. S.D. Sharma, M.B.Ch.B., M.R.C.O.G.,  
Senior Lecturer,  
Department of Obstetrics and Gynaecology,

Function: Will collaborate on antifertility and abortifacient studies with prostaglandins. (15 - 20 hours per week).

Miss Sharma is Indian and British trained, and now the recipient of a WHO research fellowship.

11. K. Somers, M.B.Ch.B., M.R.C.P., D.C.H.,  
Professor of Clinical Medicine,  
Department of Medicine,  
Function: Will collaborate and act as Consultant/Adviser on the Cardiovascular studies with prostaglandins. (5 - 10 hours per week).

Dr. Somers is an experienced research worker in the cardiovascular field with over 70 scientific publications.

12. R.R. Trussell, M.B.Ch.M., F.R.C.O.G.,  
Professor and Head,  
Department of Obstetrics and Gynaecology,  
Function: Will collaborate and act as Consultant/Adviser on the antifertility abortifacient effects of prostaglandins. (5 hours per week).

Dr. Trussell will serve as project director on the Maternal Health/Family Planning project supported by AID.

#### Facilities and Equipment:

The available facilities at Makerere University include well-equipped laboratories for pharmacological and physiological studies with prostaglandins. The animal house attached to the Department of Pharmacology has facilities for breeding mice, rats, rabbits and guinea-pigs. Cats, dogs and monkeys are readily available and are purchased as required. A site has been made available to extend the animal house facilities and to accommodate a small colony (20-30) of baboons for reproductive biology work.

Other research laboratory equipment include Balances, PYE gas Chromatography set up, equipment for radioisotope work, Spectrophotometer, Nuclear magnetic resonance machine, etc.

Facilities for clinical studies are available at the Hospital attached to the University and are excellent.

sq.

Laboratory space is very limited, 3000/ft. being available for research use in the Department of Pharmacology. It is proposed to extend this to obtain a further 3000 sq. ft. of laboratory and office space, (Including space for a Family Planning Clinic for antifertility studies with prostaglandins.)

## 8. Contribution to Institution Building

This project together with the recently concluded AID contract to strengthen the "Training in Maternal and Child Health and Family Planning Services" program at Makerere could serve as the initial phase of a long-term AID program to strengthen Makerere University as an African resource for solution of population problems and a center for family planning services and reproductive biomedical research and training.

This project will necessitate that Makerere recruit additional staff personnel to carry out the proposed studies. These personnel will of course strengthen the biomedical staff capability at Makerere.

The requirements for additional professional personnel number 18, including a junior and senior chemist, a junior and senior biochemist, a junior and senior physiologist/pharmacologist, a senior hematologist, obstetrician/gynecologist, an electronics engineer, an epidemiologist, technicians and nurses.

In addition, increased laboratory space and new acquisitions of scientific equipment are planned.

Training functions will include a fellowship program.

South of the Sahara and outside of South Africa, medical and family planning training facilities are very deficient. This project will serve to further strengthen one of the best of these institutions. It will also serve to attract to and retain scientific talent in a less developed country.

## 9. Utilization Plans

This program includes fellows and will collaborate with other AID research programs, and national family planning programs. Dr. Karim publishes promptly, has traveled widely and will continue to do so and to act as a consultant to ensure most efficacious and speedy dissemination of his techniques and the findings of his research work.

## 10. Budget Analysis

Extension of the department of pharmacology and departmental animal house are essential to carry out the project. Existing laboratory and animal space is already committed (this has been confirmed at the site visit in October 1970). The University reduces overhead from 15% to 2 1/2% when a project includes building funds. (AID may elect to pay the 15% overhead and delete the figure for construction--the total cost to AID is identical in each case).

Costs for personnel are quite low for two reasons; first, much of the staff will be supported by the University as full time University personnel; second, the prevailing salary scales are quite low. The remainder of the budget appears appropriate except as follows:

The estimated costs for fellows may be low; however it is expected that the majority of these will be African with low subsistence and travel expenses. Also, additional funds are set aside for this contingency.

For assay, synthesis and purchase of prostaglandins the budget requests \$193,000 for equipment and supplies and \$123,000 for personnel costs. It is not yet certain what analytic methods will prove most useful or what steps will be needed to obtain prostaglandins over the future three year period. The requested funds reflect a good estimate of what is required with the present state of the art and it is recommended that these amounts be obligated. However new advances in synthesis and assay techniques may result in a lower net cost for these activities over the life of the project. In the attached budget, a request of \$27,500 (in the original proposal) for hormonal assays has been reduced to \$8,500 on the assumption that the Worcester Foundation will carry out most of this work. Other changes in this budget reflect more up to date information than was contained in the original proposal.

Altogether the cost of this project is probably less than half the cost of similar work in the U.S.

#### 11. Internal and External Reviews

This proposal has been reviewed and approved by a joint Regional Bureau--TA/Office of Population internal review committee (8 February 1971) and by the Research and Institutional Grants Council (18 February 1971). RIGC reviewers suggested consideration of the appropriateness of the very low overhead--this will be considered as noted above.

External expert review on this proposal has been received from Dr. Michael J.K. Harper, Prostaglandin Project Director, The Worcester Foundation for Experimental Biology; Dr. Joseph W. Goldzieher, Director, Division of Clinical Sciences, The Southwest Foundation for Research and Education; and Dr. Edwin Gold, Professor in Residence, Maternal and Child Health, The School of Public Health, The University of California, Berkeley.

In general, these reviewers are highly favorable to this project. Dr. Gold who served as Visiting Professor of Obstetrics and Gynecology at Makerere in May 1969 observed that "an excellent ~~academic~~, clinical and research setting exists in which to proceed with the proposed study."

Drs. Harper and Goldzieher questioned the wisdom of a major entry into research on the synthesis of prostaglandins and analogs, assay techniques and compound screening. They suggest focusing efforts on clinical trials. The Office of Population agrees with these suggestions, and, as noted in the budget analysis section above, the technology is changing rapidly for synthesis and measurement of prostaglandins. The same amount of funds set aside for these activities may be better spent by a combination of purchase of prostaglandins and synthesis at Makerere. (Because of export-import restrictions, it is essential to allow

some local synthesis of prostaglandins). Purchase of expensive equipment for prostaglandin assay will be deferred until the technique of choice is more clear from other ongoing research. Development of a small primate colony is essential to allow experimentation with routes of administration, but it is agreed that a major drug screening program is inappropriate (Worcester for example can do this work better).

Dr. Goldzieher noted the value of a computer based record keeping system. This will be provided for through the recently approved International Fertility Control Research Program at the University of North Carolina.

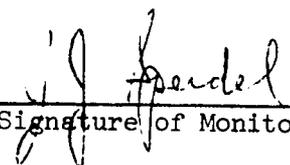
A site visit to Makerere University in October 1970 by TA/POP/Research Division confirms the interest of the University in this project and the high quality of leading investigators, i.e. Karim, Trussell, Sharma and MacIntosh. The presence of a U.S. full time advisory staff for the MCH/FP project from the University of California at Berkeley in the Department of Obstetrics and Gynecology will also be quite useful.

Physical facilities lack the polish normally found in comparable U.S. laboratories but they are adequate and will be strengthened by this project.

Discussion with Dr. Vernon Johnson, USAID Mission Director on this visit revealed a basic interest and approval of this project on the part of the mission and the recommendation that it be handled as a centrally funded project.

12. Proposing Office General Evaluation

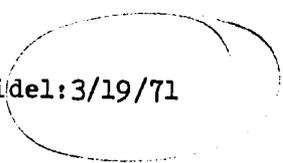
This project presents an unusual opportunity to support leading investigators in a high priority research activity in a less developed country and to advance clinical trials of prostaglandins at low cost. Support of this project is strongly recommended.

  
\_\_\_\_\_  
Signature of Monitor

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

*G.E.S.*

TA/POP/R:JJSpeidel:3/19/71



B U D G E T

<u>PERSONNEL:</u>		<u>YEAR I</u>	<u>YEAR II</u>	<u>YEAR III</u>	<u>TOTAL</u>
Senior Chemist	U.S.\$	14,000	15,000	16,000	45,000
Junior Chemist		5,000	5,500	6,000	16,500
Senior Biochemist		14,000	15,000	16,000	45,000
Junior Biochemist		5,000	5,500	6,000	16,500
Senior Physiologist/Pharmacologist		12,000	12,500	13,000	37,500
Junior Physiologist/Pharmacologist		5,000	5,500	6,000	16,500
Haematologist		14,000	15,000	16,000	45,000
Obstetrician/Gynaecologists (Junior)		8,000	16,000	16,000	40,000
Electronics Engineer		12,000	13,000	15,000	40,000
Technicians		13,000	16,000	16,000	45,000
Nurses		8,000	16,000	16,000	40,000
Epidemiologist		8,000	9,000	10,000	27,000
Record Keepers		4,000	8,000	8,000	20,000
Drivers (Motor Car)		1,000	2,000	2,000	5,000
Animal House Technician		10,000	15,000	16,000	41,000
Secretary		4,000	4,500	5,000	13,500
Copy Typist		2,000	2,000	2,500	6,500
		<u>          </u>	<u>          </u>	<u>          </u>	<u>          </u>
PERSONNEL TOTAL:		139,000	175,500	185,500	500,000
		<u>          </u>	<u>          </u>	<u>          </u>	<u>          </u>

**EQUIPMENT AND LABORATORIES:**

	<u>YEAR I</u>	<u>YEAR II</u>	<u>YEAR III</u>	<u>TOTAL</u>
Extension to the Department of Pharmacology to provide a further 3000 sq. ft. of laboratory space. U.S.\$	70,000	-	-	70,000
Extension to the departmental Animal House	10,000	-	-	10,000

**CHEMISTRY AND BIOCHEMISTRY LABORATORIES:**

Mass Spectrometer LKB 9000 Swedish make.	70,000	-	-	70,000
Spectrophotometer SP 800 PYE UNICAM for synthetic chemistry work.	10,000	-	-	10,000
Other permanent equipment.	12,000	3,000	3,000	18,000
Expendable supplies: Reagents, glassware for prostaglandin synthesis.	10,000	20,000	20,000	50,000
Purchase of finished prostaglandins and intermediates	15,000	15,000	15,000	45,000

**OCULAR STUDIES:**

Tonometer for measuring intra-ocular pressure.	3,000	-	-	3,000
Ophthalmoscopic and other instruments.	2,000	1,000	1,000	4,000

**HAEMATOLOGY LABORATORY:**

## Permanent equipment:

(1) EEL Titrator	1,000	-	-	1,000
(2) COULTER Counter with print out	7,000	-	-	7,000
(3) Other permanent equipment	1,700	-	-	1,700
(4) MSE High Speed 18 Centrifuge	5,000	-	-	5,000
(5) Microscopes (two)	2,300	-	-	2,300

<u>HAEMATOLOGY LABORATORY:</u>	<u>YEAR I</u>	<u>YEAR II</u>	<u>YEAR III</u>	<u>TOTAL</u>
(6) Refrigerator	1,000	-	-	1,000
(7) Deep Freeze	1,000	-	-	1,000
(8) Expendable supplies	1,500	2,000	2,000	5,500
 <u>CARDIOVASCULAR RESEARCH LABORATORY:</u>				
Complete equipment for measuring Cardiac output by dye-dilution methods. U.S. and U.K.	15,000	-	-	15,000
Four Channel recorder for E.K.G., Heart rate, Blood pressure.	8,000	-	-	8,000
Other equipment: Surgical Catheters, needles etc.	1,000	2,000	2,500	5,500
 <u>THYROID FUNCTION STUDIES:</u>				
Chemicals, Isotopes etc.	2,000	3,000	3,000	8,000
 <u>Physiology and Pharmacology Laboratories:</u>				
Pen recorders and transducers for Pharmacological studies with prostaglandins.	6,000	2,000	-	8,000
Animals, purchase, maintenance, feeding.	5,000	7,500	10,000	22,500
 <u>OTHER EXPENDITURES:</u>				
Consultants Fees: Short term visits by specialists from abroad.	5,000	7,500	10,000	22,500
Publication Costs: Reprints, postages, photocopying and stationery.	2,000	3,000	4,000	9,000
Traveling and subsistence to Conference or visiting other Institutions in connection with prostaglandin research.	5,000	10,000	10,000	25,000

<u>OTHER EXPENDITURES:</u>	<u>YEAR I</u>	<u>YEAR II</u>	<u>YEAR III</u>	<u>TOTAL</u>
Training of Fellows; Travel, subsistence etc. Average 4-6 Fellows per year.	10,000	20,000	20,000	50,000
Motor Car for field work in connection with antifertility clinical trial. Maintenance, road tax, fuel.	5,000	10,000	15,000	30,000
Typewriter and adding machine	1,000	-	-	1,000
Air freight to Worcester Foundation and other costs for measurement of steroids and gonadotrophins, progesterone, oestrogens, L.H., F.S.H., Prolactin.	2,500	3,000	3,000	8,500
Additional unexpected expenditures for fellows, subcontracts, supplies, etc.	14,500	25,000	25,000	64,500
	<u>          </u>	<u>          </u>	<u>          </u>	<u>          </u>
TOTAL:	304,500	134,000	134,500	573,000
 TOTAL PERSONNEL:	139,000	175,500	185,500	500,000
TOTAL OTHER:	304,500	134,000	134,500	573,000
TOTAL OVERHEAD 2 1/2%	<u>11,088</u>	<u>7,738</u>	<u>8,000</u>	<u>26,825</u>
TOTAL INCLUDING OVERHEAD	<u>454,588</u>	<u>317,238</u>	<u>328,000</u>	<u>1,099,825</u>