Title of Proposal: Contraceptive Development: A Method to Prevent Pregnancy By Direct or Indirect Anti-Progestational Activity

Proposing Organization: The Population Council
245 Park Avenue
New York, New York 10017

Type of Organization: Non-Profit Research Foundation

Principal Investigator: Sheldon J. Segal, Director
The Bio-Medical Division
c/o The Rockefeller University
New York, New York 10021

Duration: Five years

Estimated Cost: Initial year - $2,000,000
Funding requirements for subsequent years to be determined

Action Officer: R. T. Ravenholt, WOH/PS

1. Background

There is a growing concern that the presently available methods of contraception are inadequate for the full success of family planning programs. Oral contraceptives (combination or sequential estrogen-progestin therapy) have made virtually no impact in the developing world. Data available for the first time from meaningful studies of continuation-of-use in a rural setting (Korea) suggest that even when provided these products have limited usefulness for the typical program in developing countries. The one-time-only methods, sterilization and IUD insertion, have accounted for roughly 90 percent of the effective contraception initiated through the services of national programs. Each method has well-known disadvantages. Considering that long-term hazards of IUDs remain an open question, it must be acknowledged as a possibility that even this method may not be available indefinitely. If this were to happen and if the long-term safety of combination hormonal therapy were to be questioned also, birth control efforts would be back to the traditional dependency on sterilization, abortion, vaginal methods, or abstinence. Overall planning for the future cannot overlook this bleak possibility.
There are three current developments that may lead to new contraceptive methods. The injection of large doses of progestin intramuscularly can inhibit ovulation and provide antifertility protection for three to six month periods and possibly longer. As compared to present hormonal contraception, some questions of safety are satisfied by the absence of an estrogenic component, but several questions of medical concern remain. Unpredictable and sometimes profuse bleeding occurs to an extent that raises doubt about general use without closely available medical supervision. Long periods of post-treatment amenorrhea may make it not possible to describe the method as reversible. Long-term metabolic effects have not been adequately investigated.

Another new development is the use of micro-doses of progestin on a daily oral basis to prevent pregnancy without inhibiting ovulation. This is a major breakthrough in reducing medical anxieties. The method eliminates the estrogen and reduces the progestational element to fractions of the dose currently employed. Contraceptive effectiveness is good but not perfect (not a serious disadvantage) and there is no reason to suspect any problems with reversibility. A commercial product of this type is already available. This is chlormadinone acetate, at a daily tablet dose of 500 microgram. It is being marketed by Syntex in France and North Africa. It will probably be introduced in several additional countries within the next six months and may be submitted to the United States Food and Drug Administration for approval within a year. Whether or not it will be approved is not certain. In any event, there are problems which present a limitation in usefulness. Irregular bleeding has been reported by three out of four women in the controlled clinical trials. Faithful adherence to the schedule of daily pill-taking is necessary to achieve good contraception. A slight modification of this method has been developed in the Population Council's study of megestrol acetate for continuous progestin therapy. Instead of tablets, oil-filled gelatin capsules have been developed. This modification in the dosage form appears to reduce the incidence of irregular bleeding, possibly by regularizing the daily absorption rate. This work has been in progress for over a year and will require at least an additional year before a possible recommendation for general use could be made. The accumulation of adequate data for submission to the FDA will require at least two years. Favorable clinical studies with this, or other, progestins notwithstanding, the practical significance of this development for national family planning programs must be viewed realistically. One of the early clinical trials, for example, has been in Pakistan under conditions far more favorable than the country at large. Yet, within three months many of the women failed to continue the method. In general, the logistical, motivational, and educational problems of a continuous-use method would restrict considerably the impact of the method in national programs. It may be worth mentioning that there is no example of a successful public health program of any
type in a less developed country, in which daily pill ingestion has been required.

A third development, the one that holds real promise, is the subdermal implant of Silastic capsules containing megestrol acetate. This is the thin thread that holds our hopes for the future. This work has now reached the stage of clinical trials. Although all indications so far are favorable, most of the key questions of effectiveness, acceptance, logistics of wide-scale use, side effects, etc. are still before us. Before large scale trials abroad can be initiated, FDA approval for testing in the United States must be obtained. This will probably be forthcoming within 90 days. Within one year from then, we can have answers to the basic questions, but at least two years will be required before recommending general use, even if all goes well.

Viewed from the perspective of this brief review, it is evident that contraceptive development requires urgent attention. Research on the contraceptive implant is only part of the needed effort. We believe, therefore, that we must identify at once the most reasonable leads to yet other contraceptive techniques and pursue their development without delay.

An approach to doing this is to give priority to leads on the basis of the type of contraceptive method that may emerge. In other words, working backwards from a prediction of the kind of methods that would be most successful, how could we use knowledge now available to make these methods reality? It is our judgment that the following potential methods would have a major role in national programs and are feasible to explore:

1) A pill or injection that could be taken by women on a regular monthly basis to assure menstruation or within ten days of a missed period to bring on a menstruation.

2) A long-term implant for men (two types).

3) A pill taken after coitus that would prevent implantation.

In each case there are particular compounds available for which we would seek licensing arrangements and could do so immediately. The steps needed to reach a "yes or no" answer are straightforward but they are not likely to be approached systematically in the normal course of independent research. The decision as to whether they will be undertaken in the context of industrial research depends on marketing potential, prospects for exclusivity, and the priority given such an endeavor by a multi-purposed commercial organization.
2. Objectives

The first item in the list above is the subject of this proposal. The objective is to develop a method of contraception that would involve regular once-a-month medication to bring on the menses whether or not a cycle has been fertile. Some women might prefer to use the medication only on the occasion of a suspected fertile cycle; this would be possible.

We propose to carry out a complete method-development program beginning with the identification of feasible leads, arranging for the cooperation of industry in making available potential compounds for use by the public sector, undertaking the appropriate intra-mural research, providing support for extra-mural research, organizing international cooperative evaluation projects so that the family planning programs in LDCs can participate in the development program, training of personnel from LDCs to participate in the research, monitoring of medical side effects in accordance with the requirements of drug regulatory agencies in the United States and abroad, assurance of high ethical standards in studies involving human experimentation, organizing scientific meetings and conferences to assure complete and rapid dissemination of information. Finally, we hope to make available within five years a finished packaged product that has been fully tested for effectiveness and safety.

3. Rationale

In all species studied including the human female a successful intra-uterine pregnancy requires adequate progestational preparation and maintenance of the endometrium. Interference with progestational stimulation of the endometrium before or at the time of a nascent implantation is the fundamental basis on which the proposed new mode of contraception will be developed. Three approaches to achieve this result will be pursued concurrently:

1) Synthetic compounds, active orally, that have anti-progestational activity. Several pharmaceutical companies and independent organic chemists have sought steroid inhibitors of implantation by examining a variety of compounds for their anti-progestational activity. A few compounds have emerged that appear to inhibit implantation while being virtually devoid of estrogenic activity. The toxicology and pharmacology of one of these compounds, 2,16-bis-ethyl-A-norandrostan-2-16-diol has been studied so that it is ready for immediate clinical trial. The compound has been offered to us for this purpose by the license-holding company with the understanding that a non-profit, public sector license will be provided to the Council, along with the right to sub-license governments and other non-profit agencies. In addition the French chemist (Collège de France) who initially synthesized the compound has expressed the intent to provide the Council with subsequent analogues that he synthesizes.
2) Synthetic or natural compounds, active orally or parenterally, that interfere with the function of the corpus luteum. Several non-steroidal derivatives of tri-phenyl ethylene have antifertility activity in laboratory rodents. The first of these, MER-25, was described by us in 1958 (Segal, S. J. and Nelson, W. O.: An orally active compound with antifertility effects in rats. Proc. Soc. Exp. Biol. & Med. 98: 431). Subsequently confirmatory reports have appeared involving the use of various analogues. In recent work, it has been suggested that these compounds act by a specific luteolytic activity, but this postulate requires confirmation and validation. One of these compounds, ORF-3558 has recently been placed in limited clinical study by the Ortho Company. The research design is such, however, that it will be several years before evidence of potential usefulness for human contraception will emerge. Three other companies have related compounds protected by licenses, but they are unwilling to invest in the required evaluation because patent protection is within a few years of expiring. Two of these companies are willing to sub-license the Council to investigate their compound under the conditions stated above.

In addition, several amine oxidase inhibitors with phenylhydrazine structure, when studied in the rat, appear to interfere with the function of the corpus luteum. It is not clear whether the general pharmacologic activity (amine oxidase inhibitor) or the structural moiety (phenylhydrazine) is associated with the luteolytic activity but the lines of research that need to be pursued are clear. The Department of Pharmacology at Hebrew University, Jerusalem, has proposed to us a program that would lead to the identification of specific antifertility compounds for clinical testing, based on this mechanism. At least two other groups, one in India and one in London could collaborate effectively in this work.

There is mounting evidence for the existence in many species of a humoral luteolytic substance produced by the uterus and transmitted by tissue diffusion and common blood supply to the ovary. Partial purification of the luteolytic factor from sheep uterus has revealed the material to be a polypeptide that has adequate stability for further purification and testing.

3) Immunologically induced cessation of corpus luteum activity through the use of specific enzyme antibodies or chorionic gonadotropin antibodies. Recent work in our laboratory and other has established that passive transfer of LH antibodies, or active immunization with 3-Beta-01-steroid dehydrogenase prevents progesterone production by the rat corpus luteum and, thereby, terminates pregnancy. With the emergence of dramatic new techniques for high molecular weight protein synthesis, the possibility now exists for specific antigen synthesis.
eliminating the problem of contaminating antigens when tissue extraction is used as the source of antigen. In recent years, purification of human chorionic gonadotropin has reached a high state of refinement, so that anti-HGG globulins may now provide a realistic means to inhibit corpus luteum function while minimizing the risk of tissue cross reactions. Several Japanese colleagues are prepared to initiate trials of this concept using cases scheduled for legal interruption of gestation.

4. Program Design

Our past experience in the development of intra-uterine devices, oral micro-dose contraceptives and subdermal contraceptive implants has established a pattern of organization, which we propose to follow for the purpose of this proposal. A team of clinical and laboratory investigators will be assembled to work full time toward development of the proposed new contraceptive method.

We propose to acquire two specific compounds, to begin with, and to complete whatever toxicologic work is required to permit investigative use in humans. Dosage estimates will be made by studying the effect of the compounds on serum progesterone levels in rhesus monkeys. Our present primate colony of 120 rhesus monkeys and 24 baboons is devoted entirely to our contraceptive implant studies. Space is available, however, to add an additional 150 monkeys for the purpose of the new program. The procedure for serum progesterone determinations (Neill, Johansson and Knobil, Endocrinology, 82:1161, 1967) has been adopted by our laboratory and is used on a routine basis. Dr. Johansson who participated in the development of this procedure while holding a Population Council Fellowship, will participate in this work as a grantee or a guest investigator in our laboratory.

Immunological leads mentioned above, will be advanced initially by directed grants to investigators now working in this field but not specifically with the objective of fertility control. We would enlist the cooperation of protein chemists to achieve high purification of antigens and would encourage work on total synthesis of antigenic haptenes, a procedure made possible only recently by advances in methodology for protein synthesis.

In general, we would enhance our grant program activity in the field of corpus luteum function and anti-progestational activity in a directed fashion. We would, of course, coordinate this program with that of the corresponding Review Panel of the NICHD’s Center for Population Research. Our grants would be used chiefly for essential foreign investigations and for specific domestic studies that we believe to be essential to our objectives that might not otherwise have a source of support.
Similarly, strategically selected fellowships for work in this field would be a part of the overall design. We have learned from past experience that early clinical investigations abroad can be made much more meaningful by delaying the onset of the program until key individuals have been adequately trained for the responsibility.

Our goal will be complete clinical evaluation of at least two compounds as soon as possible. We know that, one compound available to us can be placed into preliminary clinical trial at once. Pilot projects will be established at various locales where the opportunity for excellent patient surveillance exists. Physicians of the Council's Technical Assistance Division are associated with clinical services in many countries, where this type of research activity is welcomed. In addition, our broad network of Council Fellows and Grantees provides for collaborative research in virtually all countries. Clinical studies would be centrally evaluated by our biostatistical unit, supervised by Dr. C. Tietze. Examples of data schedules for other studies, prepared for computer tabulation, are appended.

5. **Budget**

The budget that follows is based on the experience of current parallel programs. It provides for the necessary expansion of laboratory, clinical, statistical and clerical staff to assure that all essential aspects of the coordinated program can proceed without delay.
ANNUAL BUDGET

Salaries:

- Associate Director - project coordinator (M.D.) $27,500
- Staff Associate (M.D.) $25,000
- Staff Associate (M.D.) $25,000
- Lab. Research Associate (Ph.D.) $25,000
- Lab. Research Associate (Ph.D.) $22,500
- Lab. Research Associate (Ph.D.) $19,000
- Lab. Research Associate (Ph.D.) $18,500
- 4 Lab. Assistants @ 7,500 $30,000
- 2 Animal care assistants @ 7,500 $15,000
- 1 Biostatistician $12,000
- 1 Coder $8,000
- 3 Secretaries @ 7,500 $22,500
- Fringes @ 20% $50,000

Subtotal: $300,000

Other Intramural Costs:

- Space requirements (rental or refurbishing) $100,000
- Lab. equipment $50,000
- Lab. supplies $100,000
- Animal costs and maintenance $20,000
- Computer costs $15,000
- Supply and packaging of test compounds $20,000
- Staff travel $15,000
- Legal fees $15,000
- University overhead on appropriate items @ 20% $35,000

Subtotal: $370,000
Research Contracts: *

- Primate colony maintenance: 130,000
- Activity studies (Madison Endocrine Labs.): 50,000
- Monkey and rabbit toxicity studies: 150,000
- Dosage form studies (various investigators): 50,000
- Blood level determination: 100,000
- Screening program: 150,000

Subtotal: 630,000

Research Grants: *

1) Role of corpus luteum in early human pregnancy: 50,000
2) Human pharmacology of anti-progestational steroid (a): 60,000
3) Human pharmacology of anti-progestational steroid (b): 60,000
4) Immunologic studies on anti-HCG: 80,000
5) Five pilot projects (international) on clinical effectiveness of anti-progestational steroid (a): 150,000
6) Five pilot projects (international) on clinical effectiveness of anti-progestational steroid (b): 150,000

Subtotal: 550,000

Research Fellowships, Travel and Study Awards:

- Five one-year fellowships for foreign M.D.s or Ph.D.s to prepare for work in this field: 50,000
- Short-term travel and study awards for collaborating scientists: 75,000
- Research planning discussions, etc.: 25,000

Subtotal: 150,000

Annual Total: $2,000,000

*The items listed are examples, but some flexibility is required
Personnel:

The present staff of the Bio-Medical Division will participate in this program in accordance with special skills and interest. This staff includes:

<table>
<thead>
<tr>
<th>Name</th>
<th>Interest</th>
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<tbody>
<tr>
<td>1) A. Brinson, D.V.M.</td>
<td>primatology</td>
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<tr>
<td>2) A. Cuadros, M.D.</td>
<td>obstetrics and gynecology</td>
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<tr>
<td>3) F. Kincl, Ph.D., D.Sc.</td>
<td>steroid biochemistry</td>
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<tr>
<td>4) S. Koide, M.D., Ph.D.</td>
<td>internal medicine, biochemistry</td>
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<td>5) K. Laurence, Ph.D.</td>
<td>immunology</td>
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<td>6) H. Rudel, M.D.</td>
<td>clinical endocrinology</td>
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<td>7) S. Segal, Ph.D.</td>
<td>experimental endocrinology</td>
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<td>8) S. Sundaram, Ph.D.</td>
<td>steroid determinations</td>
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<tr>
<td>9) H. Tatum, M.D., Ph.D.</td>
<td>obstetrics and gynecology</td>
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<tr>
<td>10) C. Tietze, M.D.</td>
<td>biostatistics</td>
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<td>11) E. Witschi, Ph.D., M.D. (h.c.)</td>
<td>embryology</td>
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We have an ample list of interested candidates from which the additional staff members for full time assignments to this project can be recruited without delay, as soon as funds and space are available. Representative biographic sketches for present staff members are appended.

Facilities:

The Bio-Medical Division now occupies a total of 7,500 sq. ft. of laboratory, office and animal room space and a primate facility that occupies 5,000 sq. ft. in several buildings on the campus of the Rockefeller University. Although administratively separate from the University, this laboratory functions in every respect as an integral part of the scientific community on the campus and has available all of the facilities of the University. In addition, the Biometrics Group is housed off-campus in rented space.

During early 1970, the Division will move into new quarters in a University building now under construction. This will triple the space available for laboratories and offices and permit the expansion of the primate facility from the present capacity of 140 rhesus or baboons to 500. Temporary, immediate expansion of the primate facility is possible at the present site. It will be possible, also, to expand office space by refurbishing or renting in a nearby commercial building until the new quarters are ready for occupancy. In all likelihood, the space required for this program which may exceed the capacity now acquired by us in the new building, can be provided by the University, but funds supplementary to our present contribution to the new building will then be necessary.
Our research laboratories are equipped for the needs of eighteen research scientists and supporting personnel, representing a variety of fields. Since the inception of the laboratory in 1954, instruments and equipment valued at over $500,000 have been acquired. The primate center is a unique research facility, made possible by a $1.5 million grant from the Ford Foundation. We believe it to be one of the finest reproducing monkey colonies in the world. The laboratory's finest asset, however, is a staff of devoted and talented technicians, animal attendants and helpers. The total number of personnel now in the Division is 54. The program envisaged in this proposal would increase by one third the numerical strength of the Division.