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FINAL EVALUATION OF THE POPULATION COUNCIL ACTIVITIES

CONDUCTED UNDER COOPERATIVE AGREEMENT

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EVALUATION REPORT

by

Michael J.K. Harper, Ph.D., Sc.D. (Team Leader)  
Terrence W. Jezowski, M.S.  
Michael E McClure, Ph.D.  
J. Joseph Speidel, M.D., M.P.H.

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Edited and Produced by:

Population Technical Assistance Project  
International Science and Technology Institute, Inc.  
1601 North Kent Street, Suite 1101  
Arlington, VA 22209

## EXECUTIVE SUMMARY

The Population Council's contraceptive development and contraceptive introduction programs have been extremely successful. The Population Council has been one of the most successful public sector programs in the contraceptive field and have indeed got more new methods to the market place than any other program. The ET2 is extremely enthusiastic about the past performance and the proposed continuation activities. It is felt that AID support has been critical in ensuring continued progress by the program and has been a most successful investment as judged by both actual and potential returns. The quality of the research performed, both basic and applied, has been exceptional.

The ET2 did, however, have some concerns that require attention. These involve the sufficiency of staffing in certain key areas of the development process, e.g., dosage formulation, toxicology, regulatory affairs, clinical trial coordination and monitoring and field staff for introduction activities. Some of the delays in registration of NORPLANT® in the USA can be attributed to this lack of manpower.

The ET2 therefore recommends that additional funding be provided to enable additional staff to be recruited, and that this funding be kept stable over a period of years. It is recommended that sources of funding for introduction activities other than from AID be explored, but that AID funding should also be increased. A portion of this funding (approx 10% of that devoted to contraceptive research and development activities) should be allocated broadly to basic probing studies and not allocated on a line-by-line basis. It is also recommended that the Population Council consider whether the needs for increased space to house the additional staff can be met in their present location. It would be useful to develop a long-range plan which would consider the optimal size for the organization (funding considerations aside) and how it should be optimally housed. Development of such a plan would be a useful tool for solicitation of the required funds from a variety of sources.

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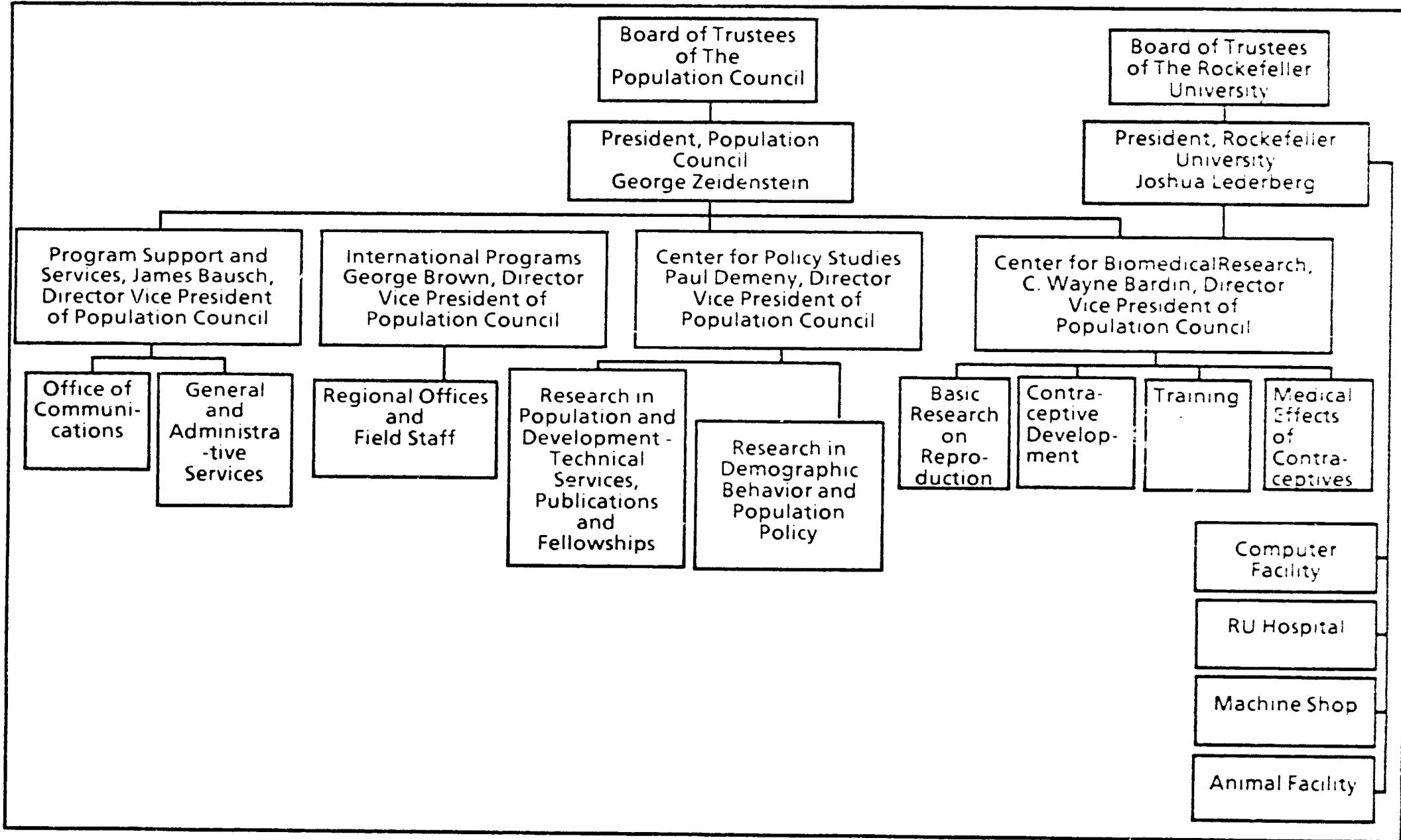
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## I. INTRODUCTION

The Population Council, an international, nonprofit organization, undertakes social science and biomedical research, advises and assists governments and international agencies, and disseminates information on population issues. Established in 1952, the Council is governed by a Board of Trustees whose members come from twelve countries. The Council is committed to the enhancement of human welfare and works in three areas: biomedical research in the field of human reproduction to develop and improve contraceptive methods; social science research into the causes of population change, their societal implications, and appropriate policy responses; and provision of technical assistance to family planning and other population-related programs at local, national, and regional levels. The Council produces publications for researchers, policymakers, and the concerned public and supports advanced training for population specialists.

To carry out its work, the Council is organized into the Center for Biomedical Research, the Center for Policy Studies, International Programs, and Program Support and Services, which includes the Office of Communications (Fig. 1.).

Fig. 1. Organization Chart of the Population Council



The Center for Biomedical Research endeavors to develop and improve contraceptive methods. Another important research objective is elucidation of the mechanisms of human reproductive physiology, especially in the male.

The Center for Policy Studies seeks to contribute to the understanding of population policy issues and to advance applications of that knowledge to the design of policies responsive to both individual and social needs. These goals are pursued through a program of social science research by Center staff.

International Programs brings the Council into working partnerships with policymakers and population professionals in developing countries. The Council maintains area offices in three regions: Latin America and the Caribbean, West Asia and North Africa, and South and East Asia. Council activities in sub-Saharan Africa are currently administered from New York. A multidisciplinary professional staff in New York provides interregional support and coordination. Areas of current work include contraceptive introduction, family planning programs, efforts to enhance women's roles and status, improvements in child health and survival, and population policy.

From the base of the work undertaken in the two Centers and International Programs, the Office of Communications publishes and disseminates scientific information to professionals and to a broader audience of policymakers and nonspecialists. The Office produces the Council's two journals, *Population and Development Review* and *Studies in Family Planning*, books, pamphlets, and brochures.

### *1.1. Cooperative Agreement*

The Cooperative Agreement between the United States Agency for International Development (AID) and the Population Council No. AID/DPE-3005-A-00-3003-00 provides support for a program in family planning services for the period 17 May 1983 through 16 July 1988. Programmatic areas supported under the

agreement are contraceptive development, contraceptive introduction, and family planning program design, implementation, evaluation, and dissemination.

#### I.1.1. Contraceptive Development

Support was provided for contraceptive development projects on levonorgestrel subdermal implants, contraceptive vaginal rings, levonorgestrel-releasing IUDs, LHRH analogs, inhibin, gonadotropin surge inhibiting factor and for a New Drug Application on NORPLANT® 2 subdermal implants. This work was carried out "in house" and under sub-awards and sub-contracts to other institutions.

#### I.1.2. Contraceptive Introduction

Support was provided for the Pre-Introduction Evaluation of NORPLANT® contraceptive subdermal implants. The planning phase of a major conference on NORPLANT® Subdermal Implants was initiated. Pre-introduction evaluation of NORPLANT® contraceptive subdermal implants studies continued in Brazil, Chile, Colombia, Dominican Republic, Kenya, and the United States; and a pre-introduction study was initiated in Mexico.

#### I.1.3. Family Planning Program Design, Implementation, Evaluation, and Dissemination

Support was given to build on the Council's ongoing family planning research and evaluation activities in Asia, Latin America, the Middle East and sub-Saharan Africa. The activities included program development, subawards to local institutions, monitoring and technical assistance publications, as well as synthesis and dissemination of the broader policy implications of these and related activities. Special emphasis was given to program development, technical assistance and implementation of field-based projects in sub-Saharan Africa. In addition, support was given under this component for the continued operation of the Council's Bogotá, Colombia office.

## ***1.2. Evaluation Scope of Work***

This evaluation was conducted at the Population Council, New York City on Jan 12-14, 1988 by Drs. Michael J.K. Harper, Terrence Jezowski, Michael E. McClure and J. Joseph Speidel. Dr. Laneta Dorflinger, AID was also present. The purpose of this evaluation (ET2) is to assess AID's support to the Population Council under the Programmatic Cooperative Agreement DPE-3005-A-00-3003 for activities conducted during the period from March, 1983 through December, 1987. For the contraceptive development portion of the portfolio, this evaluation will essentially update the previous interim evaluation (ET1) conducted in October, 1983. The evaluation team was to look both broadly and on a project-specific basis at activities funded over the five-year period of the agreement, and analyze the general portfolio and accomplishments of the program overall, the development and implementation of specific activities, project management, reporting and monitoring or evaluation of sub-activities, and collaboration and relationships with other organizations in the field. In addition, since AID is interested in determining any ways in which a follow-on program might be changed or improved, the team was to focus on the directions proposed for research over the coming five years, and discuss, when possible, how these proposed activities will complement those of other programs.

A list of issues to be discussed by the team, is set out below.

### **1.2.1. Interim Evaluation**

The evaluation team (ET2) should review the report of the interim evaluation (ET1) conducted in October, 1983 and the Population Council's response to the recommendations made following that evaluation.

### **1.2.2. The Contraceptive Development Portfolio**

The evaluation team should take a general look at projects being supported under the contraceptive development portfolio. They should examine plans for the

future, particularly the next five years, and discuss any hurdles they perceive for the methods under development addressing what these hurdles might mean in terms of funding needs.

Some specific questions to be explored by the team include, but are not limited to, the following:

- A. The way in which leads are chosen and projects are developed.
- B. The status of current leads including the level and duration of funding of those leads.
- C. The efficiency of reaching goals in the shortest amount of time and at the lowest cost.
- D. Any overlap or duplication of other R & D efforts, if applicable.
- E. Basic leads such as inhibin and GnSIF
  - i. how leads are chosen
  - ii. how activities are reviewed "in house" and "out of house"
  - iii. how leads are coordinated with other contraceptive development programs working on similar areas of research
  - iv. the process for reaching a decision point regarding the contraceptive potential of these compounds
  - v. the appropriateness of AID support to these basic areas
- F. Overall research staff strengths and weaknesses either in numbers or skills
- G. Capacity for regulatory filings
  - i. management plan for preparing INDs and NDAs — in the U.S. and abroad
  - ii. use of "in house" staff versus consultants
  - iii. could these areas be strengthened

H. The potential relevance of various contraceptive development projects to AID's overall program

I. The way decisions are made for allocation of AID funds by project

J. Are important areas being missed, perhaps for reasons of funding

I.2.3. Contraceptive Introduction Activities

A. Overall strategy for product introduction, addressing NORPLANT® implants and the Copper T 380A separately.

- i. effectiveness of the overall strategy
- ii. speed in implementation of strategy
- iii. staffing utilization and any constraints — currently and looking toward the future
- iv. coordination with other organizations
- v. user perspective studies
- vi. development of country-specific informational materials

B. The interaction and coordination between the contraceptive development and contraceptive introduction staff

I.2.4. Family Planning Program Research Activities

A. Project development and implementation

B. Project priority setting

C. Staff utilization and project management and oversight

D. Interactions with family planning programs and other AID cooperating agencies

E. Value of AID support to this area

I.2.5. Overall Staffing Pattern Funded by A.I.D.

A. Is expertise available in all required areas?

B. Is staffing level sufficient to meet needs in various areas?

C. Is subproject oversight effective and efficient?

- D. Use of consultants — not enough or too much?

#### I.2.6. Relationship of the Program with A.I.D.

- A. Washington staff
- B. AID missions

#### I.2.7. Funding

- A. Is the funding level of the current Cooperative Agreement sufficient?
- B. Can new leads be adequately pursued?
- C. To what extent do non-A.I.D. funds fill gaps in program or vice versa?
- D. How are decisions made as to when and how AID's funds are utilized?

#### I.2.8. Procedure of Evaluation

The Evaluation Team (ET2) met for a briefing at the offices of International Science and Technology Institute Inc., Population Technical Assistance Project, Arlington, VA on Jan 11 and then travelled to New York for the actual site visit on Jan 12-14. All members attended all presentations by the Population Council staff, but the leadership for the different areas of evaluation was divided as follows:

Drs. Harper and McClure — Contraceptive Development Program

Dr. Speidel — Contraceptive Introduction Program

Mr. Jezowski — Family Planning Program

All drafts were sent to Dr. Harper for collation into a final draft which was then sent to ISTI/Pop Tech. A debriefing session was subsequently held at ISTI/Pop Tech on Feb 1, 1988 to agree on the final version of the report.

## II. RESPONSE TO INTERIM EVALUATION

A previous evaluation had been done by Dr. Michael J.K. Harper (Chairman of the Present Evaluation Team) and Dr. Robert H. Williams in October, 1983 (ETI). At that time while, in general, the Contraceptive Development Program of the Population Council was felt to be successful and soundly based, certain specific

matters were felt to give rise to some concern. On these points specific recommendations were developed. A restatement of these recommendations is shown below.

### **II.1. General Conclusions of ET1**

The evaluation team were very enthusiastic about the quality and relevance of the projects at the Population Council being supported by AID. This is one of the most successful programs in the contraceptive R & D field. The leadership of Dr. Bardin is excellent and the quality and dedication of the staff commendable. The fact that two products are very near successful introduction speaks for itself, and the team has very few substantive recommendations or suggestions. These are listed below under specific recommendations. Despite these, the team feels that this is a highly successful program and that due credit should be given to all involved in it.

#### **II.1.1. General Recommendations**

A. Expansion of the membership of the ICCR and/or more frequent rotation of existing members should be considered.

B. Making efforts, in advance of need, to identify companies that can provide the expertise, commitment and financial resources necessary to complement the Population Council activities would be helpful.

C. Nominating one individual to be responsible for all toxicological studies while another (Dr. Moo Young) is monitor for good laboratory and manufacturing practice could improve efficiency. The individual in charge of toxicology could be the focal person for interaction with the FDA for reporting all severe adverse reactions occurring during clinical trials.

D. Some of the burden shouldered by Dr. Nash should be lightened, either by greater delegation of more routine matters and/or provision of extra staff assistance.

E. The use of a part-time consultant to assist with FDA filings is commended.

F. The addition of a staff member to act as clinical coordinator and monitor is felt to be useful.

G. The evaluation team were, in general, highly enthusiastic about the Contraceptive Development Program (CDP) of the Population Council, and the quality of its leadership and staff.

#### II.1.2. Recommendations on Specific Lines of Research

It should be noted that the points made below reflect, very largely, thinking already done by the Population Council, and therefore do not represent criticism, only a restatement of existing major priorities.

A. Continued major interaction with Leiras to ensure the speedy and effective introduction of the NORPLANT® and the levonorgestrel IUD is essential.

B. Completion and interpretation of the various toxicological studies with the CVR must be a major priority. Alternate strategies should be devised to circumvent adverse toxicological findings.

C. Mechanization of the closure process for the CVR needs to be speedily resolved.

D. There needs to be resolution of the toxicological problems with the LHRH antagonist (LHRH-22) and an alternate compound selected before too much is invested in the present one.

E. Major investment in the LHRH analog field should await the development or acquisition of a suitable delivery device, or convincing clinical evidence of their efficacy as male contraceptive agents.

F. A delivery system suitable for long-term administration of androgens needs to be developed or long-acting androgens acquired, as they will be required for successful use of LHRH analogs as male contraceptives.

G. The potential consequences of long-term anovulation and/or reduced luteal activity needs to be considered prospectively when clinical trials of agents with such properties are being designed.

H. Major investment in the inhibin area should await isolation and characterization of a pure protein/peptide with the desired biological activity. Funding at the present level seems likely to provide this information in the next 12-18 months.

### **III. FINDINGS AND CONCLUSIONS**

One of the first requests from the present evaluation team (ET2) was for the document prepared in response to these recommendations of ET1 outlining the corrective measures to be undertaken by the Population Council. No such document had been prepared at that time. It is understood by ET2 that verbal communications with AID staff provided satisfactory assurances that corrective measures would be applied or that the recommendations were not felt to be practical or relevant.

With the benefit of hindsight, the ET2 believe that some of these concerns were indeed warranted and that history has proved this. In response to the request of the ET2 a document was prepared dated Jan 6, 1988 which provides an indication of the views of the Director of CDP of the Population Council at the present. [This document is attached as Appendix I].

#### ***III.1 ICCR Membership***

The present membership is shown in Appendix 2. Expansion is contemplated in 1988, but this is largely due to certain members or consultants retiring for a number of different reasons. New members are presently under evaluation as replacements -- one of these is a clinician from Shanghai, People's Republic of China and the other a clinician from France. In addition, more use has been made of

outside consultants at ICCR meetings. Thus, the recommendation of the ET1 has been implemented, even if somewhat more slowly than envisaged in 1983.

Since many of the ICCR members are involved with those clinical centers in which initial clinical trials of new methods are conducted, the ET2 accepts the rationale for maintaining the central permanent nucleus. However, it is felt that addition of new members representing clinical centers in other regions that could also be involved at an early stage in new and ongoing clinical trials would be an advantage for the subsequent work of the Contraceptive Introduction group.

### *III.2. Relations with Industry*

The Population Council had been urged by ET1 to make greater efforts to identify companies with relevant expertise and commitment to the contraceptive development field in advance of need.

It was pointed out that the choice of companies available when patents are concerned was limited, and that many companies with relevant expertise did not wish to be involved with contraceptive products. Despite the concerns of the ET1 concerning the size of Leiras Pharmaceuticals and its ability to provide the support needed, it now appears that Leiras has been able to do most that has been required in a timely manner. Indeed the principal delays in the NORPLANT<sup>®</sup>/NORPLANT<sup>®</sup> 2 development programme have been due to factors not related to Leiras.

It is now apparent that more companies are willing to be involved in assisting the Population Council. Large companies are still not interested in products with total sales of less than \$30 million, and for many of the products being developed by the Population Council, e.g. levonorgestrel IUD (LNG IUD), annual sales to the private sector would be less than \$10 million. However, such companies now appear more willing to release interesting compounds, and information on their own studies with such products, to organizations like the Population Council than previously --- perhaps because of a sense of corporate responsibility to LDCs. Thus,

the Population Council has under evaluation, in probing studies, several spermicidal agents for development of new barrier methods.

In contrast, for smaller companies and new start up companies in the health care field, there is a window of opportunity to become aggressively involved in contraceptive development. Their strength is in registration and product sales, but not in the R & D process. Consequently they are eager to cooperate with the Population Council, as is exemplified by the licensing agreement recently completed with GynoPharma Inc (a new start-up) to market the Cu T 380A IUD.

Indeed, the Population Council now has agreements with some 10 companies at various stages, these range from letters of agreement for probing studies to full legal contracts for production and marketing. Legal advice is obtained at all stages of the agreement process to ensure that Population Council policy regarding provision of contraceptives to LDCs at the lowest reasonable cost is adhered to.

The ET2 commends the contraceptive development program of the Population Council for the efforts that have been made in this direction and for the success that they have achieved in involving the cooperation of industry in the contraceptive development process

### ***III.3. Individuals Responsible for Toxicology and Quality Assurance Programs***

ET1 had recommended that Dr. Sundaram should be responsible for all toxicology and Dr. Moo Young for the Quality Assurance Program.

This recommendation has been implemented. The concern of ET1 was that these were critical areas for the program and though in 1983 only at the initial stages would become of necessity more important as the development process proceeded. In 1983 there had been a breakdown in monitoring some of the toxicological studies required by the FDA. This was felt to be due to the lack of a designated responsible individual.

ET2 is therefore pleased that this situation has been rectified and that Dr. Sundaram is now in charge of all toxicology studies and interacts with FDA staff concerning the design of the studies required. The question was raised as to the cost-effectiveness of conducting short-term toxicology studies at the Population Council rather than through contracts to specialized contractors. Dr. Bardin noted that in 1983 toxicology studies were not done at the Population Council, but now all short term studies were. Long term studies were still, and would continue to be, contracted to others. He felt that there were significant advantages in having a trained physiologist, such as Dr. Sundaram, a member of the Population Council staff, supervising such activities because more information might be gained. As an example, the histamine-releasing effect of some LHRH analogs was noted during Population Council studies but had been missed in all other toxicological studies. In addition, many of these studies are funded by NICHD and can be done more cheaply by the Population Council than by a for-profit contractor. Dr. Bardin is convinced that one must understand the physiological processes affected by a compound before one can be convinced that it is safe. Lack of observable pathological changes in specified organs may not be adequate for such a conclusion.

Dr. Sundaram is not engaged full time in these activities, and is assisted by a research associate, an animal technologist and an animal care technician. About 5 toxicity studies have been done in the last 5 years. When pressed Dr. Sundaram admitted that if the requirement for such studies increased more staff would be required. For the foreseeable future adequate space in the Rockefeller University animal facility would be available. This is a well maintained facility with AAALAC accreditation, excellent veterinary care and an adequate disease control program. Per diems for animals while average for New York are high by comparison with institutions elsewhere.

Dr. Moo Young is responsible for quality assurance inspections and record keeping, except when his own projects are involved, in which case another professional staff member serves. Dr. Moo Young interacts with FDA personnel on all aspects of the GLP procedures.

The ET2 is convinced that the present allocation of responsibilities is appropriate and that these key areas are well controlled and conducted. They are also persuaded that the conduct of the short term toxicology studies "in-house" has proved to be cost-effective and also informative.

#### *III.4. Responsibilities of Dr. Nash*

The recommendation of ET1 that the responsibilities of Dr. Nash should be lightened by more delegation of routine matters was not implemented. ET1 was concerned that slippage in projects which was occurring could be avoided by reducing Dr. Nash's work load. The designation of Drs. Sundaram and Moo Young to be in charge of toxicology and quality assurance respectively was considered likely to be helpful in this regard, but of itself might not be sufficient.

Hindsight has proven the failure to implement this recommendation to be of key importance in the delays encountered in the filing of the NORPLANT<sup>®</sup> NDA (see below). It is recognized that Dr. Nash's management style is not to delegate, and given his breadth of experience and expertise, his value to many facets of the Population Council program is incalculable. Nonetheless, somewhat belatedly, a management reorganization has taken place, partly due to Dr. Nash's wish to scale down his activities, which may reflect his own realization of delays occurring due to work overload.

Dr. Nash will now concentrate on the NDA filing for NORPLANT<sup>®</sup>, and dosage formulation studies in the laboratory. Day to day management of the program has been assumed by Dr. Rosemary Thau. She was found to be the best candidate out of 30 applicants and has enthusiastically embraced this new challenge. To permit her

full time devotion to this position, she has ceased to be director of the NIH-funded radioimmunoassay core facility (assumed by Dr. G. Gunsalus) and has turned her laboratory work on vaccine development over to her associate (thus acting only in a supervisory role). One of her first responsibilities will be to reorganize the record keeping and management system to make it more effective and responsive to the requirements of FDA.

It is clear that her background has been more in biomedical research than in management, and that a learning process is required. However, Dr. Bardin is confident that she will prove to be effective in her new responsibilities and the ET2 wish her well. If after a year's evaluation of her performance problems are apparent, it would be necessary for the Director of Population Council to move quickly to reorganize the managerial responsibilities since this is a key position.

### *III.5. FDA filings*

ET1 had recommended that the use of a part time consultant for FDA filings would be helpful.

Apparently, such consultants have been used as needed. Filings of INDs have been successful, some 5-6 have been filed and approved in the last 4 years. In addition, there are requirements for a certain amount of upkeep on ones filed in the 1970's, especially with regard to reporting of Phase III trial results. Annual reporting has on occasions been dilatory.

Only one IND filing has not been approved. This was for ST-1435, for which more toxicological studies were requested. This request was predicated on changed FDA regulations

The Population Council has had prior successful experience with an NDA filing, for the CuT 220C, and for the CuT 380A. In the case of NORPLANT® 2, in 1983 it was anticipated that the NDA filing would have been completed by early 1985. However, the complexity of the task was underestimated, and in the interim period,

FDA regulations changed. Previous filings had been much less laborious because of the lesser standards required, e.g. use of published clinical papers. Now such studies all have to be re-analyzed according to a standard format and more information on adverse reactions has to be supplied. The need to file an NDA for NORPLANT® necessitated by the delays in NORPLANT® 2 has also been complicated, since, all the NORPLANT® and NORPLANT® 2 studies were not finalized in FDA format at the time of completion, and the necessity to go back and perform these tasks retrospectively has proved very time consuming. The revised date for this filing is June 1988. [Parenthetically it should be noted that this delay has impacted the Contraceptive Introduction program quite severely.]

For the future it is anticipated that the next two projected NDAs — for NORPLANT® 2 and the LNG IUD — will be simpler and more expeditious. NORPLANT® is the first example of a device releasing steroids over a long time and hence more careful FDA scrutiny and documentation is required. The next generation implant will be essentially a "follow-on," and if the same release rates and blood levels of LNG can be demonstrated then less documentation will be needed. For the LNG IUD additional toxicology may, however, be required because of the local action on the uterine endometrium.

Individuals involved in FDA filings are Drs. Nash, Spitz, Schmidt and Sivin. Dr. Spitz is concerned with clinical trial reports and adverse reactions, Mr. Sivin with statistical evaluation of the data and tabulations, Dr. Nash for the major writing of the body of the document, and Dr. Schmidt who has recently been involved full time in this process is the central figure in maintaining, updating and filing FDA required records. Through Dr. Schmidt's activities it is anticipated that formulation of FDA required reports on clinical and toxicological studies will be done in a more timely manner. All pivotal Phase III studies are done in ICCR Clinics (site visited by Dr. Spitz or Dr. Gill at least once per year), with a known good performance in such trials.

This also eases the burden of preparing reports of such multicenter trials for the FDA.

The cost-effectiveness of preparing NDAs "in-house" was questioned. Dr. Nash indicated that exploratory inquiries with groups skilled in this art indicated that a cost of \$2.5-3 million would be incurred which was not felt to be justified. The trade-off in time to filing was not, however, included in this calculation.

One of the greatest concerns of ET2 is the delayed filing of the NDA for NORPLANT®. Whether in fact the revised deadline of June 1988 can be achieved remains to be determined. Similar delays in the filings for NORPLANT® 2 and the LNG IUD would be unacceptable. Close monitoring of this situation is required by management, and provision of adequate help to overcome developing bottlenecks will be essential. Some assistance will be forthcoming from Wyeth Laboratories, who have become more enthusiastic about the potential of NORPLANT® 2, but additional "in house" help will still be required. This will have budgetary implications (see below).

### *III.6. Clinical Co-ordination*

ET1 recommended the addition of a staff member to act as a clinical coordinator and monitor.

In response to this Dr. Spitz was added to the staff. He conducts all site visits to clinical centers and has conducted random sampling of patient records for FDA purposes.

More frequent visits will be required by FDA in future and more intensive audits of patient charts/records (sometimes even 100% audit) will be mandated. This will increase the work load tremendously.

Clinical trials are discussed and designed at ICCR meetings, and the actual protocols developed by Dr. Spitz in conjunction with a small group of ICCR investigators. At this time admission criteria, exclusion criteria and cut-off points

for each study are established. Consultation with Mr. Sivin is done to ensure statistically sound designs and enrollment of appropriate numbers of patients to demonstrate the significance of differences to be assessed. All protocols are approved by the Rockefeller University Institutional Review Board and by the equivalent local committee at each participating institution prior to commencement of any study involving human subjects.

Once the trial is underway, each center sends batches of forms monthly to the Population Council where Dr. Spitz and Mr. Sivin review them for errors or omissions. Mr. Sivin then enters the data in the data base on the mainframe computer via local terminals. Up to date analyses are prepared for each four-monthly ICCR meeting. Mr. Sivin felt that he has adequate staff to handle all projected clinical trials, unless FDA audits increase greatly.

ET2 commends the clinical trial coordination and monitoring which seems to be in excellent shape. However, it is clear that additional manpower will be needed to assist Dr. Spitz. This individual need not be medically qualified but should be at least competent to conduct audits of patient records and knowledgeable concerning those medical events considered to be of importance. Dr. Bardin indicated that recruitment of such a person was under consideration. ET2 considers this addition to be of high priority but recognizes that it has budgetary implications (see below).

In addition, to these general recommendations the ET1 had made some specific recommendations related to individual program areas, i.e. NORPLANT<sup>®</sup> and NORPLANT<sup>®</sup> 2, vaginal rings, levonorgestrel IUD, LHRH analogs, androgen delivery systems and inhibin. The response to these recommendations is discussed in the section dealing with each of these individual program areas

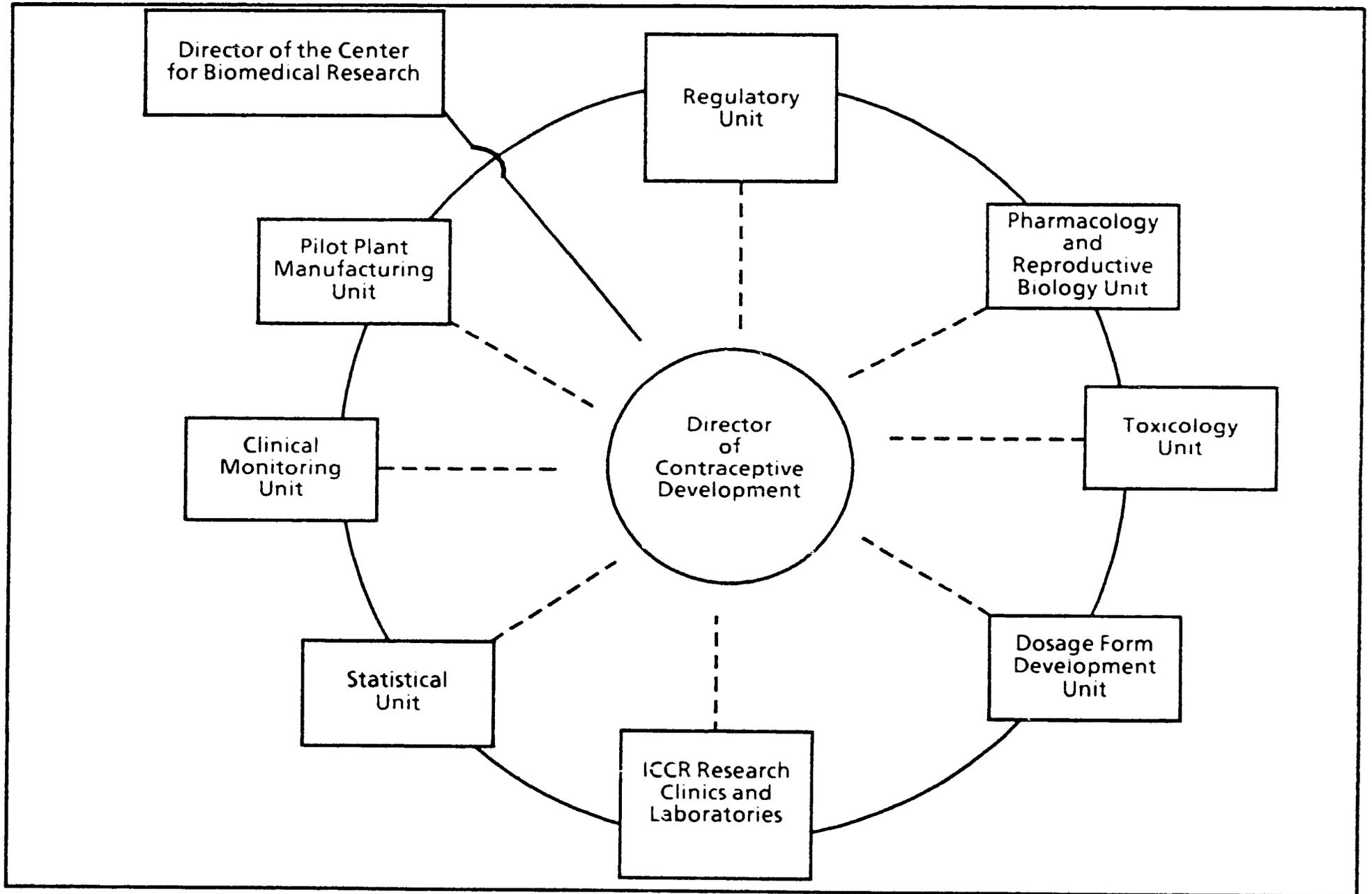
## IV. CONTRACEPTIVE DEVELOPMENT PORTFOLIO

### *IV.1. Introduction to the Contraceptive Development Program*

Dr. Bardin opened the evaluation by a brief statement of how the program operated. Since contraceptive development is a long term process, with limited patent protection, and a difficult registration process, the number of pharmaceutical companies working in this area has declined. To be successful the Population Council has had to adopt a modus operandi more related to a pharmaceutical company than a University. This includes a team approach, filing of patents, INDs and NDAs, and defined objectives.

Public sector research has been severely impacted in recent years by a changing mix of donors, the short term nature of funding, and often the absence of a clear path to development. In 1975, 75% of the Population Council staff time was devoted to exploration of new leads and this had been reduced to 20% in 1985. In contrast, the percentages devoted to clinical trials and management function have increased dramatically. The organization of the contraceptive development team is drawn in Fig. 2. The ET2 commends this focussed approach to the development process. The discussion of specific leads then commenced.

Fig. 2. Organization of the Contraceptive Development Team of the Population Council



#### IV.1.1. Development of leads

Most of the leads under development as new contraceptives were already under development at the time of the visit of ET1 in 1983, and their inclusion in the portfolio does not need to be discussed further here. The new areas that have been added since then include probing studies with GnSIF, vaccine development, nonsurgical sterilization procedures for men and development of new barrier methods/spermicides. Support from U.S.A.I.D. has only been in the established areas of subdermal implants, contraceptive rings, progestin IUDs, LHRH analogs, barrier methods and probing studies on GnSIF and inhibin. Each of these areas is discussed separately.

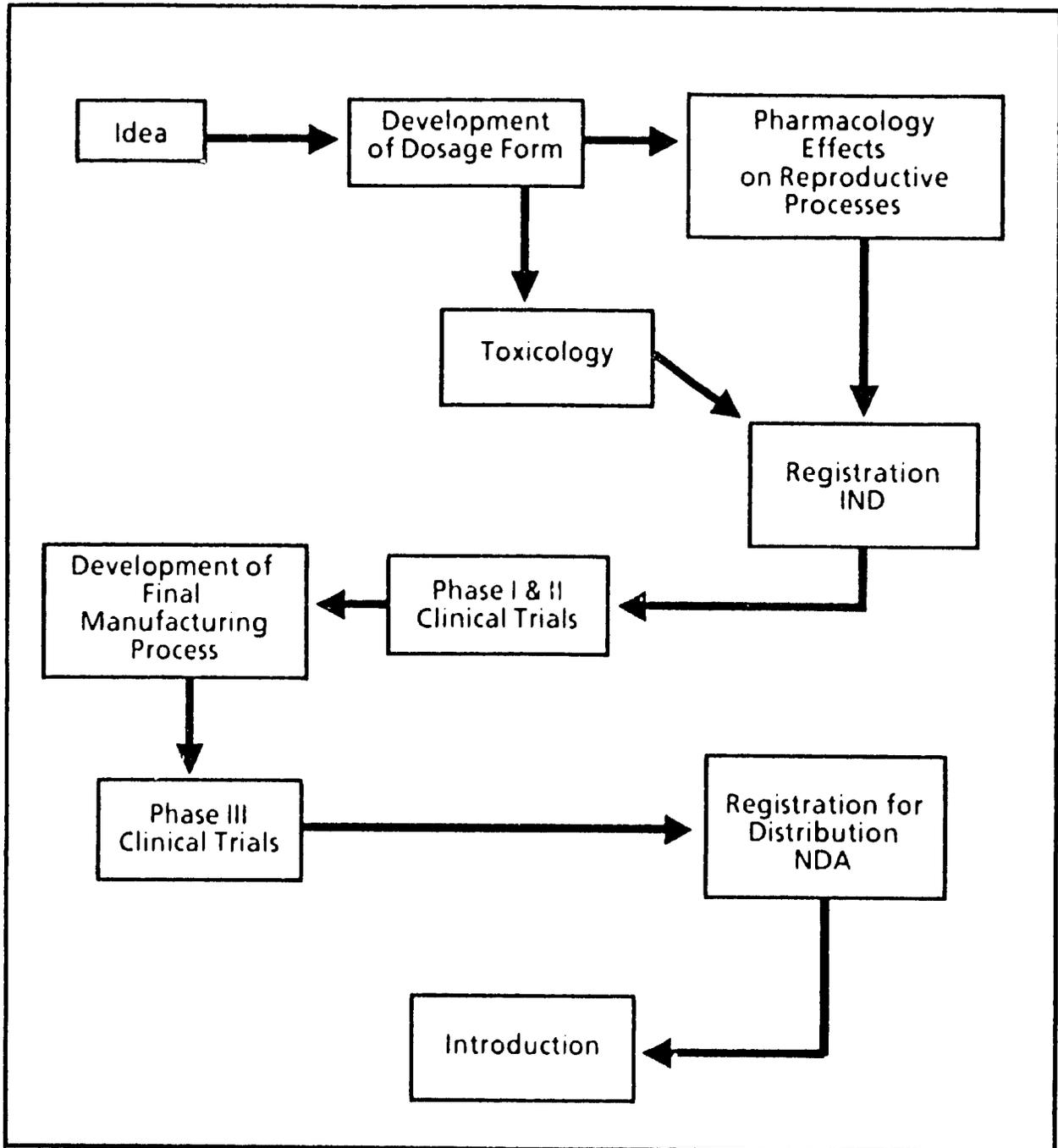
ET2 requested information on how new leads were developed. The process seems to be somewhat empirical in that at least once per year a portion of an ICCR meeting is devoted to a brainstorming session. A running list of all the ideas — both rational and irrational — is maintained, and members of the ICCR are assigned to provide small presentations describing the present status of work in a particular area and an outline of how it might be developed into a novel contraceptive. From the current list of 20 or so ideas, most fall by the wayside, but some are taken up for further study and thus enter the area of probing studies. Probing studies to gather pilot data are not very expensive and thus do not impact the major thrust on established leads. In many cases new leads are developed through the efforts and interests of individual ICCR members, e.g. the progesterone-releasing vaginal ring and the LNG IUD. Others arise from basic research studies, e.g. inhibin, and yet others from renewed interest of and/or approaches from industry, e.g. incidence of sexually transmitted diseases (STDs) and barrier methods.

Thus, there are many ways in which leads can be generated, and this catholic approach probably ensures that good novel ideas are not overlooked. Nevertheless,

certain criteria are applied before a decision is made to embark on a major expansion of work on a new lead. The proposed method must have a role in lesser developed countries (LDCs), (i.e. must meet an unfilled need), it must be not too technologically advanced, have no obvious competition (i.e. no duplication of R & D effort), have a reasonable unit cost, be doable by the Population Council and most importantly have an open path to completion (i.e. no patent problems, unfavorable toxicology, etc.). Final decisions on inclusion of new leads into the Population Council work plan are taken by Dr. Bardin after he has obtained advice from ICCR members, staff members and outside consultants.

Despite this relatively unstructured approach to new lead identification and development, the success achieved by the Population Council up to the present in development of new contraceptives testifies to the success of this approach. Once an idea has been identified the further stages in the development process are relatively standard, as outlined in Fig. 3.

Fig. 3. Drug Development Diagram



ET2 considered this process to be successful and makes no recommendations for any changes. Indeed, the success and minimal cost of the probing studies indicates that more flexibility of budget allocations in such areas would be cost-effective for A.I.D. ET2 recommends that a certain percentage of A.I.D. funds be allocated generally to probing studies without a line-by-line allocation. In this way the Population Council could allocate funds to whichever new leads seemed most promising. Owing to their past success in identifying and development new leads, A.I.D. could accelerate this process by a global allocation of funds to Probing Studies rather than the line-by-line approach used to date. Line-by-line funding allocations for major leads already in the development process continues to be appropriate. A specific recommendation to implement this change is made in the discussion of the Budget.

#### ***IV.2. Status of Current Leads***

##### ***IV.2.1. Subdermal implants***

The subdermal implant method entails introduction of a progestin in small tubes beneath the skin. The progestin diffuses out slowly to provide contraceptive effectiveness for as long as five years. The method provides long-term contraceptive action without requiring attention, except for the initial placement and eventual removal. The use of only a progestin in the implant is believed to avoid many of the more serious side effects associated with estrogens as they are used in the combination pill.

##### ***IV.2.1.1. NORPLANT™***

##### ***IV.2.1.1.1. Status***

NORPLANT™ is the first product resulting from the Council's implant development project and is a levonorgestrel-releasing system consisting of six implants, with the trademark NORPLANT™. Its introduction into family planning

programs has advanced during the past four years with the approval of this method by regulatory authorities in many countries. The implants are now approved for commercial distribution in China, Colombia, the Dominican Republic, Ecuador, Finland, Indonesia, Sweden, Thailand, Venezuela, Peru, and Sri Lanka. The Council intends to file an NDA with the US Food and Drug Administration (FDA) by June of 1988. Huhtamaki Oy/Leiras Pharmaceuticals, the Finnish company that manufactures the implants under a license from the Council, has filed for registration with regulatory agencies in more than a dozen additional countries. More filings are planned for the future. The method has received much publicity in both the lay and scientific press, and Council staff have participated in several international and US symposia at which discussion of the NORPLANT® method was prominent. A particular boost to its acceptance was a position paper issued by the World Health Organization (WHO) that states: "In summary, ... NORPLANT® provides an effective and reversible long-term method of fertility regulation. It is considered suitable for use in family planning programmes, along with other currently available contraceptive preparations and devices, since it provides an important option for women desiring long term contraception." The staff of the Population Council's contraceptive development program continue to play a primary role in publicizing clinical findings regarding the method and in familiarizing key persons in the developing world and in other organizations with it. The low pregnancy and high continuation rates found in the Council's earlier studies are being replicated in the ongoing preintroduction studies (see section on Contraceptive Introduction)

In 1986-87 safety issues have continued to receive attention in ongoing studies conducted by the ICCR and by investigators participating in the preintroduction trials. New studies of the effects of implant use on serum chemistry in Chile and Egypt have been published with no evidence of adverse effects. The consensus of all

the studies is that a slight decrease in HDL cholesterol occurs without significantly changing total cholesterol HDL ratios. Additional safety information was derived from a study conducted in Chile on the effects of NORPLANT<sup>®</sup> use on adrenocortical functions, which showed no adverse effects. These observations were confirmed by studies in Sweden. Additional detailed analysis of implant users indicated that the method does not cause endometrial cancer. Studies in five clinics of the effects of implant use on the duration of lactation and on the growth of nursing infants have been generally reassuring. The restriction on use of the implants in lactating women during the first six weeks postpartum will be able to be modified. Another study to assure the long-term safety of the NORPLANT<sup>®</sup> method has been organized in collaboration with WHO and Family Health International (FHI) to monitor prospectively the health effects caused by the implants. WHO will coordinate this study, which is expected to take eight years to complete.

One problem became apparent in the NORPLANT<sup>®</sup> trials. Examination of a large number of case records revealed that the occurrence of pregnancies is related to weight. Gross cumulative pregnancy rates for 3 and 5 years as a function of weight are as follows:

Weight Class (kg)	Pregnancies/100 Women-Years	
	3 yr	5 yr
<50	0.2 ± 0.2	0.2 ± 0.2
50-59	1.1 ± 0.4	3.0 ± 0.9
60-69	2.3 ± 0.8	3.5 ± 1.4
>70	6.3 ± 2.0	7.6 ± 2.3
All weights	1.9 ± 0.4	3.2 ± 0.6

It is anticipated that this trend will be exacerbated in subsequent years of use. However, for most women the method has proven to be effective for 5 years and for those under 60 kg will probably be effective for 7 years.

Studies have been done with two types of tubing used for manufacture of NORPLANT<sup>®</sup> – types A and B. Type A has a less dense matrix and therefore a higher diffusion rate. Although most of the studies have been done with Type B devices, the final version will be with Type A tubing. Indeed, available data which compare pregnancy rates using the two different types of tubing demonstrate the superiority of the A tubing. Consequently, there is some hope that lower pregnancy rates even for heavier women in later years of use may now be achieved. Continuation rates in Population Council Phase III studies have been around 76-90 percent after 1 year, and at the end of 5 years have fallen to 25-55 percent. The level of use depends greatly on the culture of a particular country.

#### IV 2.1.1.2. Conclusions

As discussed in Section III 5 on FDA filings, it is clear that the NDA filing for NORPLANT<sup>®</sup> has been greatly delayed. Despite the cogency of the various reasons which have caused this delay, the conclusion must be that the introduction of NORPLANT<sup>®</sup> in many countries has been greatly hindered by the lack of FDA approval. In many countries drug regulatory authorities are non-existent or understaffed and therefore feel reluctant, more for political reasons than scientific ones, to approve use of a US developed contraceptive in the absence of FDA approval despite registration in Finland, the country of manufacture. In addition, NORPLANT<sup>®</sup> is relatively expensive (public sector price of at least \$12.00 or more) owing to the necessity for hand manufacture. Amortized over the life of the implant, the annual cost becomes a more reasonable \$2.240. However, this cost has to be disbursed "up front," and hence AID support for purchase of initial supplies of the implant is critical. AID policy is not to purchase for widespread

distribution non-USFDA approved drugs or devices. Unless alternate donor agencies can be identified who will be willing to bridge the minimal 2-year gap before anticipated FDA approval, the contraceptive introduction program for NORPLANT<sup>®</sup> will be mainly "on hold." ET2 is concerned for closer oversight of the introduction process to ensure that this situation be resolved as quickly as possible and not occur in the future with the new methods in the development process.

#### IV.2.1.1.3 Recommendations

ET2 therefore recommends that:

(a) All avenues be explored for interim funding to purchase large numbers of NORPLANT<sup>®</sup> sets for the Contraceptive Introduction program. Private foundations, UNFPA and the World Bank are possible sources that should be actively explored. This proposition could be made more palatable by the fact that it is essentially a "stop-gap" measure intended only to bridge the gap until FDA approval and will not be an ongoing request. Parenthetically, ongoing support for this important program from other donors would be of enormous benefit to this important program of the Population Council and would be enthusiastically endorsed by ET2

(b) More managerial control should be exercised to ensure that FDA filings are rapid and timely. The lessons learned from the NORPLANT<sup>®</sup> NDA experience should be applied to future submissions, and additional staff may be needed to carry out such activities expeditiously.

(c) AID may wish to reconsider their policy with regard to purchase and supply of only USFDA approved drugs and devices. An alternate strategy is to have a broader distribution on a current research basis

#### IV.2.1.2 NORPLANT<sup>®</sup> 2

##### IV.2.1.2.1 Status

A major research activity during the past four years has been a clinical trial of the NORPLANT<sup>®</sup> 2 contraceptive implant system. This method consists of two rather

than six levonorgestrel-releasing implants that appear to be as effective as NORPLANT<sup>®</sup> for up to three years. These trials, which have been carried out in Chile, the Dominican Republic, Finland, and Sweden, were terminated in the fourth year because of high pregnancy rates, but are continuing in the United States, with different lots of rod implants. The massive job of organizing data for NDA presentation was well advanced, but delay in this effort occurred during the summer of 1987. The Council was informed by Dow Corning Inc. that they were discontinuing distribution of the particular Medical Grade Elastomer (#382) that formed the core of NORPLANT<sup>®</sup> 2 implants (as well as the levonorgestrel-releasing IUD and contraceptive vaginal rings). The decision by Dow Corning was associated with the proposed listing by the US Environmental Protection Agency of a possible component of Elastomer 382 as a suspected teratogen and carcinogen. After extensive scientific review, consultation with toxicologists, consultation with individuals interested in women's health, and review by clinical investigators, the staff at the Council concluded that Elastomer 382 posed no risk to humans as it is used in NORPLANT<sup>®</sup> 2 and other contraceptives. WHO and the FDA have subsequently concurred with this assessment. However, because Elastomer 382 will no longer be available, it is important to reformulate NORPLANT<sup>®</sup> 2. Another Medical Grade Elastomer that is used in the manufacture of NORPLANT<sup>®</sup> implants was found suitable for this purpose. A detailed comparison of the discontinued and the newly selected Elastomer will be completed within 6 weeks. These considerations have no effect on the availability or the introduction of NORPLANT<sup>®</sup>, which does not use Elastomer 382.

One problem that became apparent in the NORPLANT<sup>®</sup> 2 trials was the drop off in plasma levels of levonorgestrel after 30 months. Pregnancy rates were low up to 3 years (about 1/100 woman years) and then rose rapidly in the fourth year in some countries. NORPLANT<sup>®</sup> 2 cannot be expected to be effective for more than

3 years, in contrast to NORPLANT<sup>®</sup> which has a recommended life span of 5 years (and can even be effective up to 7 years). As for NORPLANT<sup>®</sup> both weight and time are implicated in the decrease in levonorgestrel plasma levels. It is hoped, but not certain, that the reformulation of NORPLANT<sup>®</sup> 2 will enable a long life span to be achieved. Whether an implant with a life span of only 3 years will be as acceptable in LDCs remains to be determined. ET2 recommends that all efforts be made to develop a reformulated NORPLANT<sup>®</sup> 2 that lasts for at least 5 years.

#### IV.2.1.2.2. Future Plans

The Council will replace Elastomer 382 in NORPLANT<sup>®</sup> 2 with another elastomer early in 1988. Laboratory tests are being conducted to confirm the equivalency of the present NORPLANT<sup>®</sup> 2 and the newly formulated product. It is possible that clinical trials may need to be conducted to show that the pregnancy rates of the new formulation are the same in the third and fourth years of use. The information necessary for an NDA can then be assembled and an NDA application then submitted. Council staff and ICCR investigators will review the comparative Phase III trials of NORPLANT<sup>®</sup> and NORPLANT<sup>®</sup> 2 to determine how the newly formulated NORPLANT<sup>®</sup> 2 can be integrated into this study.

The Elastomer that will be used to make the core of the newly formulated product has many desirable features which should facilitate manufacturing of implants and eliminate the hand work presently required to produce NORPLANT<sup>®</sup> 2 implants. Studies will, therefore, be conducted to determine whether the manufacture of NORPLANT<sup>®</sup> 2 implants can be completely mechanized. Success in this endeavor would considerably reduce the cost of implants, increasing their availability to family planning programs. Although the development of the NORPLANT<sup>®</sup> implant system is viewed as completed, the ICCR will continue to monitor lots to assure that the quality control procedures now in place are indeed appropriate.

#### IV.2.1.2.3. Dosage Formulation and Findings

The Population Council is examining several possibilities for the reformulation of the NORPLANT<sup>®</sup> 2 release system, including medical grade adhesive and uncured tubing. In vitro tests are underway and Dr. Robertson is confident that by the end of February 1988 a satisfactory system will have been established. It will then be important to show in vivo, as in vitro, that the release characteristics are similar to or better than the original NORPLANT<sup>®</sup> 2 so that all the data obtained in clinical trials conducted to date with NORPLANT<sup>®</sup> 2 can be used to support the NDA filing of the reformulated NORPLANT<sup>®</sup> 2. If the release characteristics are not identical or a resolution to the problem is not achieved by the present in vitro tests then significant delays are envisaged.

Dosage formulation is the key to the successful advancement of this project; consequently, all efforts must be devoted to this aspect of activities. It was noted that the dosage formulation group was composed of 5 professional and 4 technical individuals. However, the professionals were not devoting 100% of effort to these activities -- Dr. Jackanicz was mainly involved with vaginal rings, Dr. Robertson with implants, and Dr. Moo Young on peptide releasing systems. Priorities were set mainly on which system was nearest fruition, and for this reason all effort was being devoted to resolution of the Elastomer 382 problem since this would be of significance also for the vaginal rings and LNG IUD. However, work on the LNG IUD per se was on hold until the NORPLANT<sup>®</sup> 2 system was working satisfactorily. It may be argued that both devices should be pushed forward simultaneously, especially as the ET2 are particularly enthusiastic about the potential of the LNG IUD.

Development of new formulations/delivery systems arises out of discussions within the chemical group, and the limits of the possible options. Possibilities are evaluated, and the potential cost effectiveness assessed. A decision to proceed is then made in conjunction with the ICCR member or biologist concerned. Thus,

development of new and improved formulations/delivery systems is a continuum, and it is unlikely that this aspect of the work will be scaled down in future. With the heavy emphasis on delivery systems for delivery of all the leads in the pipeline, this could become a critical bottleneck within the foreseeable future.

Staff indicated that there was a need for additional junior staff, for an additional professional staff person and for provision of facilities for pilot scale preparation. With the present space availability it seems that it will be difficult to achieve this even if funding were to become available.

#### IV 2 1 2.4. Recommendations

ET2 recommends that:

- a) Reformulation studies for NORPLANT® 2 and LNG IUD take the highest priority and that all efforts be devoted to their resolution as soon as possible.
- b) Additional manpower and space be allocated to dosage delivery/formulation studies, with consideration of development of a more formal management structure for coordination of these activities and for setting priorities.

#### IV.2.1 3 Second generation implants

##### IV 2 1 3 1 Status

Over the past two years exploratory studies were conducted on implant systems that will eventually have some advantages over both NORPLANT® dosage forms and will fill special niches in contraceptive practice. One such implant contains the steroid ST 1435. Its attractiveness lies in its lack of effect on lipoprotein patterns, its poor absorption when administered orally, and the possibility that it can be incorporated in a single implant effective for two years. Its poor oral absorption suggests that it may be appropriate for lactating women since little active steroid will be absorbed by nursing infants even if it is secreted in milk. In the past, progress has been impeded by lack of a sustained release system adapted to the properties of the steroid and lack of sufficient toxicology to permit advanced

clinical trials. During 1986-87 these problems have been finally solved, and development can now continue.

The implant with ST-1435 will be comprised of a single unit and therefore easier to insert and remove. It is not intended to replace NORPLANT® or NORPLANT® 2, since it will only last 1-2 years. ST-1435 is a unique steroid in that it has a 3-fold higher affinity for the progesterone receptor than LNG. It circulates in blood bound to albumin, but not to CBG or SHBG. Thus, 13% of that present in plasma is not bound to protein. The amount required to suppress ovulation is therefore ten-fold less than that of LNG. ST-1435 is inactive taken orally (bioavailability about 15%) and is taken up and metabolized by the liver with a half life of about 6 h. The ratio of ST-1435 in plasma and milk is about 2:1 so little is taken up by the baby, and that ingested will have minimal effects due to the poor oral bioavailability.

In pilot studies, a 40 mg s.c. capsule suppressed progesterone and estradiol levels for 1 year. A specific RIA for ST-1435 has been developed. In the pilot clinical studies, bleeding problems were a problem for only the first 2 months in a small percentage of women with the 40 mg (30 mm) capsule. At present only a 90 day toxicity study in rats has been done. Further toxicology has been required by the FDA due to changed regulations. It is anticipated that these costs will be underwritten by CDB of NICHD.

#### IV.2.1.3.2. Future Plans

The progestin ST-1435 will be subjected to 90-day toxicology studies in monkeys and two-year toxicology studies in rats and monkeys. These will be performed in sufficient numbers of animals to support developmental activities not only on ST-1435-containing implants, but also on contraceptive rings and transdermal preparations. After dosage formulation, a two-year expanded Phase II study will be conducted, and Phase III studies planned. Experiments on the

manufacture of this implant system will be continued. Experience gained in the manufacture of NORPLANT<sup>®</sup> 2 will facilitate progress on the second generation implants. It is anticipated that the core of this implant will be manufactured by extrusion and then covered with Silastic tubing.

Another single implant method contains 3-ketodesogestrel, a progestin that also has minimal effects on lipoprotein metabolism. This implant has the potential to deliver contraceptive protection for two to four years. A plan for developing implants containing 3-ketodesogestrel has been concluded with the Dutch pharmaceutical company, Organon N.V. Phase I clinical trials on this implant to select the proper dose began in 1987 and will be completed by 1988. Phase II trials will begin by the end of 1989. Studies on 3-ketodesogestrel to date have not been supported by A.I.D. So far, the Council has not received permission to study this implant in the USA. This may change in the future.

#### IV.2.1.3.3. Recommendations

ET2 was particularly enthusiastic about the ST-1435 developments and felt that this steroid had unique characteristics which could be explored by a variety of different delivery vehicles, e.g. vaginal rings, implants and transdermal patches.

However, concern was expressed that development was proceeding without an adequate toxicological background, and it therefore recommended that:

- a) The requirements of the other implants under development have the highest priority,
- b) Work on ST-1435 should not be allowed to delay those key studies required for NORPLANT<sup>™</sup>-2 and the LNG IUD, and
- c) A first order of priority for ST-1435 is to start the toxicity studies required by FDA.

#### IV.2.1.4. Funding (see Appendix 3)

Over the past 4 years 1984-87 inclusive \$2.245 million were requested from U.S.A.I.D. for the total implant contraceptive development program. A total funding of \$2.234 million was in fact provided, almost 100% of that requested. Shortage of funds would therefore not appear to have been a major constraint on the development process. However, it could be argued that if additional funding had been requested to support salaries of additional staff or consultants to assist with the NDA filing and the reformulation problems with NORPLANT<sup>®</sup> 2 that further progress could have been achieved. Funding from other sources for the implant program totalled \$0.388 million for 1986 and 1987 combined, which is only 23% of the total funds expended on that activity for the same two years.

ET2 recognizes that addition of staff involves an ongoing commitment and without an ongoing stable funding base can necessitate termination of employment or constraints on other parts of the program in the event of a budgetary shortfall. Nevertheless, serious consideration should be given to addition of staff in those areas critical to the development process.

ET2 recommends that:

(a) A.I.D. provide additional funds to be used for Core support of key personnel essential to the drug registration process, and that this commitment should be recognized to be a multiyear one.

(b) The Population Council should explore all avenues to obtain funding from other sources to support the acceleration of the development and introduction of NORPLANT<sup>®</sup> and NORPLANT<sup>®</sup> 2.

#### IV.2.2 Levonorgestrel IUD (LNG IUD)

##### IV. 2.2.1. Current status

The levonorgestrel-releasing IUD involves the addition of levonorgestrel to the stem of a T-shaped IUD to enhance effectiveness. The development of this device is

considered fairly far advanced. Trials of limited scope have progressed through seven years in Scandinavia. More extensive trials conducted by the Population Council in Brazil, Chile, the Dominican Republic, Singapore, Sweden, and the United States will form the basis for regulatory approval. Additional studies are being conducted in Europe by Huhtamaki Oy/Leiras, co-developer with the Council of the device. The Council trials are beginning their fifth year. All of the trials indicate that this is one of the most effective IUDs ever developed, with pregnancy rates of less than 0.5 per 100 women-years. In addition to its high effectiveness, the device has the advantage of reducing two of the adverse effects of other IUDs: increased menstrual blood loss and menstrual pain. Studies of menstrual blood flow indicate that the volume of blood loss is markedly less than with other types of IUDs. These observations, coupled with results from blood counts, suggest that this IUD offers a particular advantage in societies where anemia is common. Furthermore, women using the levonorgestrel-releasing IUD have less dysmenorrhea than they experienced before using the device. This IUD may be suitable for women who experience cramps during menses; the levonorgestrel device would be expected to reduce such cramps, while other IUDs would increase them.

Additional safety information has recently been gathered. The lack of change in serum chemistry suggests that the IUD does not produce significant metabolic effects. To determine whether the device has any adverse local action, pathologists examined a large number of endometrial biopsies; no significant abnormalities were noted. A two-year study in rabbits to determine the potential carcinogenic effects of devices releasing levonorgestrel directly into the uterus has been completed. To ensure that the test would be meaningful, the investigator used older rabbits, which spontaneously develop a significant incidence of endometrial cancer. At the end of the two-year treatment period, more endometrial cancer

occurred in the control group than in those treated with levonorgestrel-releasing IUDs. These observations give further reassurance regarding the safety of this IUD.

#### IV.2.2.2. Future Plans

This is a relatively mature project, as clinical studies are in the sixth year. Regulatory approval was being sought in Finland, the country where the IUD will be manufactured, and is currently on "hold." The drug-containing core of this IUD will be reformulated following the withdrawal of Elastomer 382. A suitable replacement for Medical Grade Elastomer 382 is being tested and studies to be completed in early 1988 will indicate whether additional clinical studies will be required before final approval can be obtained from regulatory authorities.

#### IV.2.2.3. Findings

ET1 had found this development of the LNG IUD to be an appropriate initiative by the Population Council and ET2 were pleased to see that the development process had proceeded very satisfactorily. Obviously, this process had been delayed due to the unavailability of the Elastomer 382 which could not have been expected. In view of the very significant advantages that the LNG IUD is likely to have over even the CuT 380A, ET2 feel that highest priority be given to its further development. At present as noted above highest priority for resolution of the elastomer problem has been given to NORPLANT<sup>®</sup> 2. Since the same formulation should be satisfactory for both devices, ET2 recommend that on successful conclusion of the current in vitro tests, work should recommence on the LNG IUD.

ET2 was impressed by some of the attributes that distinguish the LNG IUD from other existing IUDs, in particular endometrial suppression and reduced bleeding with immediate recovery after removal, very low pregnancy rates for all age groups even young patients, absence of any hCG activity in any subjects (true contraceptive activity) and reduction of dysmenorrhea (suitable for most patients). It should be noted that the LNG IUD will be more than \$5 per device, which is expensive

compared to the Cu T 380A. However, ET2 feels that the advantages of the LNG IUD will overcome this higher cost.

#### IV.2.2.4. Recommendations

ET2 felt that this device provided significant advantages over currently available IUDs and were therefore enthusiastic about its continued development.

ET2 recommends that.

- a) Development of the LNG IUD proceed as rapidly as possible,
- b) Development should be in parallel with NORPLANT<sup>®</sup> 2 rather than sequential, and
- c) Additional funds be provided to enable this rapid development to occur.

#### IV.2.3. Contraceptive Vaginal Rings

##### IV.2.3.1. Current status

The contraceptive ring is a doughnut-shaped drug delivery system containing either a progestin or a progestin plus an estrogen. It is placed in the vagina, where these steroids are slowly released by diffusion. The method's attractiveness for public sector programs lies in the fact that the ring can be placed and removed by the woman herself, so that minimal attention by medical personnel is required. For rings containing progestin plus estrogen, the schedule of use is to leave the ring in the vagina for three weeks and to remove it for one week to permit withdrawal bleeding; rings containing progestin only are left in the vagina continuously except that they may be removed for a few hours for hygienic reasons.

An earlier, extensive investigation of a contraceptive ring delivering levonorgestrel and estradiol showed that the ring method is acceptable to women. Development of this particular formulation was discontinued in 1984 because the total doses of steroid as well as the ratio of progestin-estrogen were judged to be too high. This decision was based, in part, on a two year study showing that this ring slightly increased the rate of atherogenesis in female monkeys on a high fat

diet. An unexpected finding in this study was that the same dose of levonorgestrel plus ethinyl estradiol given orally was protective against atherogenesis. This suggested that the dose of estradiol in the original ring formulation had been too low to counteract the unfavorable effects of levonorgestrel on plasma lipids. Formulations with a reduced levonorgestrel dose and the same dose of estradiol were tested clinically on a small scale during the last two years. The rings containing the reduced doses were also discontinued, as they led to unsatisfactory bleeding patterns and had a greater than desired effect on lipoprotein patterns. The new ring formulations described below were then developed

All of the work on contraceptive rings conducted at the Population Council is affected by the summer 1987 decision of Dow Corning to discontinue manufacture of Elastomer 382. As with NORPLANT<sup>®</sup> 2, the contraceptive rings are being reformulated with an alternative Medical Grade Elastomer. Rapid progress has been made in the last half of 1987. As a result, reformulated rings are expected to be ready for clinical trials in early 1988. In view of this rapid progress, it is anticipated that the reformulation necessitated by the withdrawal of Elastomer 382 will not delay ring development

#### IV 2 3 2 Contraceptive Ring for Lactating Women

Preliminary trials conducted during the past two years suggest a special role for vaginal rings in delivering progesterone as a means of extending the period of anovulation associated with lactation. Progesterone is not a useful contraceptive in normal cycling women, but is highly effective when given to women who are nursing. Progesterone, a natural product of the ovaries, is a good candidate for this type of contraception because it is poorly absorbed orally, so that the amount of biologically active compound absorbed by the nursing infant is very small. Use of a ring for progesterone administration appears to be the method of choice because

the implant route is not suited to delivery of the doses required and oral administration has low effectiveness.

In preliminary studies with rings delivering 10 mg of progesterone/day only 1 pregnancy out of 1148 women months of exposure occurred; and this was due to a patient failure. Breast feeding was unaffected by the use of the ring, and the growth of the babies was normal. A program to explore and develop this means of contraception for use during lactation is being undertaken jointly with WHO. Clinical studies to determine the effective dose of this steroid have begun. ET2 welcomed this initiative but thought that rings releasing ST-1435 might be better because of the greater activity of ST 1435, combined with its known low oral bioavailability. Also it is a candidate drug for use in a ring for cycling women (see below), and development of fewer ring formulations may be more cost effective.

Priority for this lead was felt to be lower than for NORPLANT® 2, LNG IUD and rings for cycling women, since the target population is smaller and likely use of limited duration.

#### IV 2 3 3 Contraceptive Ring for Cycling Women

Continued examination of alternative formulations after cessation of work on the original formulations was based on the conviction that there is a definite place in the contraceptive catalog for rings that inhibit ovulation and give good bleeding control. One promising alternative ring candidate contains ST 1435, which is extraordinarily effective in inhibiting ovulation and has no effect on lipoprotein patterns. A method of ring manufacture was developed in 1986-87 that is considered adaptable to mechanization and that allows ready adjustment of the dose of drug(s) delivered. ST 1435 will be explored in a ring, both alone and in combination with low doses of ethinyl estradiol. Two other drug combinations are also being tested as ring components: norethindrone acetate plus ethinyl estradiol, and levonorgestrel acetate plus ethinyl estradiol. Both of these combinations have

only minor effects on lipoprotein patterns, and are adapted to inclusion in rings manufactured by the newer techniques. Of the three formulations, the one combining norethindrone acetate with ethinyl estradiol has a particular advantage since these steroids are widely used in contraceptives and will therefore require minimal animal toxicity before inclusion in the ring dosage form. Results from Phase I studies of combinations of norethindrone acetate plus ethinyl estradiol indicate excellent control of bleeding patterns and no decrease in HDL levels.

It is anticipated that these rings will be utilized over the same time period as oral contraceptive pills, that is inserted into the vagina on the fifth day after the start of menstrual bleeding and continued for 21 days. Ovulation is consistently inhibited over the period of use. Side effects are minimal -- usually related to expulsion, odor and coital problems. [N.B. The rings unlike the diaphragm can be removed during actual coitus, but must be replaced within a few hr.]

The formulation for the new ring will permit the release of norethindrone acetate (560 µg/day) and ethinyl estradiol (65 µg/day). This combination gives good bleeding control and shows no adverse effect on plasma lipids unlike the original ring formulations. Plasma levels of norethindrone were found to be 5 ng/ml and of estradiol 50-100 pg/ml. However, because of the relatively high release rates of ethinyl estradiol, angiotensin levels were unacceptably elevated. Pilot studies suggest that the release of ethinyl estradiol can be reduced to 30 µg/day without increased bleeding problems, and coincident with this, angiotensin levels are not so greatly increased.

#### IV 2 3 4 Future Plans

In the coming period increased effort will be focused on developing a contraceptive ring. As there is currently not a vaginal ring ready for use in family planning programs, the ICCR will conduct clinical trials on the most promising ring

formulations in an effort to select the one(s) with the most desirable features for rapid development.

At present, the ring containing norethindrone acetate plus ethinyl estradiol would appear to be the best candidate for blocking ovulation, as it will require additional toxicology studies only to show the local effects in the vagina. Phase I studies will be completed to determine the optimal doses of the two steroids. It is anticipated that two-year Phase II studies can be planned in late 1989. Once a final manufacturing plan has been established, the rings for the Phase III trials can be produced by 1991.

An alternative ring containing ST-1435 alone or in combination with an estrogen will also be tested as a back-up device for the norethindrone acetate ring. The alternative ring has the desirable features of high effectiveness and minimal effects on lipoproteins. However, as noted above, ST-1435 will require long term animal toxicology before it can be used in Phase III clinical trials. Plans are currently being made to share the cost of these studies with the National Institutes of Health (NIH) and the Contraceptive Research and Development Program (CONRAD). These toxicology studies should make ST 1435 available for a variety of contraceptive products in addition to the ring.

The progesterone releasing vaginal ring will also receive very high priority in the coming grant period. There are few contraceptives that are recommended for lactating women. A method that prevents pregnancy when lactating women begin to supplement infant feeding with solid food and that poses no potential risk to the baby would serve to prolong lactation and its health promoting effect on the infant. After Phase II studies are completed, studies in clinics of the ICCR and WHO will be conducted in an effort to determine whether 5 or 10 mg of progesterone per day is the optimal dose for lactating mothers. Once this is known, Phase III clinical trials will be planned.

#### IV.2.3.5. Findings and Recommendations

ET2 found these developments to be logical, but were concerned that development of too many rings might dilute effort on other higher priority areas of development. While ET2 felt that the ST-1435 might have the greatest promise, it recognized that the norethindrone acetate-ethinyl estradiol releasing ring would likely have a much shorter time to registration and market. Given that acceptability studies have shown that there is a segment of women who like this method of contraception, its development seems appropriate. However, ET2 feels that if this newest version fails then rather than further dose finding exercises, effort should be concentrated on ST-1435. If that fails then the whole approach should be reevaluated and probably abandoned.

ET2 recommends that work on contraceptive vaginal rings should be considered of lesser priority than NORPLANT<sup>®</sup> 2 and the LNG IUD. Among the rings, development of the norethindrone acetate-ethinyl estradiol ring should have highest priority purely for programmatic reasons, but the best long term hopes may be with a ring containing ST-1435. ET2 had less enthusiasm for the progesterone releasing ring *per se* but agrees that a ring for lactating women would be useful.

It does not appear that lack of funding is directly constraining these developments, rather this is due to a lack of manpower in the dosage formulation group. This may necessitate provision of additional funds for hiring of appropriate personnel.

#### IV 2 4 Barrier Methods

##### IV 2 4 1. Current Status

**[Note: the work described here has not so far been supported to any great extent by A.I.D.]**

A review in early 1986 by the ICCR noted that infertility continued to increase in many parts of the world, primarily because of sexually transmitted diseases

(STDs). It was decided that research should be initiated to develop contraceptives that would offer the option of delaying as well as preserving fertility. Since barrier methods offer this potential, it was decided that this line of research should receive top priority; by the ICCR. Even though condoms provide excellent protection against STDs, it was concluded that ICCR studies should focus on methods that could be used by women. While plans for research on new barrier contraception were being formulated, the Population Council staff decided that this project should be expanded to include agents and methods that offered protection against viral agents, such as herpes and HIV, particularly in view of the increasing evidence that the latter is transmitted heterosexually in many countries. Research has begun in three major areas: selection of new agents that protect against pregnancy; selection of agents that protect against STDs when administered vaginally; and development of new systems for the vaginal delivery of agents that protect against pregnancy and STDs.

New agents that could be used as barrier contraceptives were identified, and negotiations were begun with companies and individuals for rights to use such products. Negotiations with one company were completed in early 1987 for access to an acrosin inhibitor that blocks the fertilizing activity of sperm. A confidentiality agreement was signed in August, 1987 with another company which allowed access to a series of membrane active compounds which render sperm incapable of fertilization. If one or a series of these agents proves effective in animal tests, an agreement for development by the Council will be signed. Discussion has begun with a third company to gain access to additional compounds.

New agents that could be used to protect against STDs were also identified. Negotiations with a university based research group began in May, 1986. After some suggestions by Council staff, the group has continued studies to provide additional evidence for effectiveness. If results are promising, the Council will sign

an agreement for joint development. Discussions have also begun with a company that manufactures antiviral agents to identify those agents that would not be absorbed vaginally and therefore could be used in high concentrations.

Two new delivery systems are currently under development by the Council. Several years ago an ICCR member developed a vaginal ring covered with a membrane envelope that would hold a disposable drug delivery system. Studies are currently under way to complete the development of a diaphragm for delivery of the acrosin inhibitor described above.

#### IV.2.4.2. Future Plans

To increase the health-promoting effects of barrier contraception in women, the Population Council will conduct studies directed at improving the delivery of spermicides that are already in use. Fibers that slowly release these agents will be developed and incorporated into diaphragms or into covers for vaginal rings. Such fibers are designed to deliver spermicide for up to 24 hours. Studies will also be conducted to identify new agents that render sperm inactive. Agreements with pharmaceutical companies have been concluded, which will allow access to a series of such products. Studies on the mechanism of action, pharmacology, and toxicology of acrosin inhibitors and membrane-acting agents will be conducted in animals. Products that are promising will be formulated into dosage forms that can be used in humans. These products will be tested for their effects on HIV and other STDs in the Department of Microbiology at the University of Helsinki.

#### IV.2.4.3. Recommendations

ET2, while recognizing that HIV and other STDs are a major problem, feel that for the time being the Population Council should concentrate all efforts on rapid advancement of those methods already in the development process. ET2 is concerned that a new initiative such as this will dilute the concentrated effort that

will be required for NORPLANT<sup>®</sup> and NORPLANT<sup>®</sup> 2, LNG IUD and even one vaginal ring.

ET2 does not recommend that A.I.D. fund this initiative at present.

#### IV.2.5. Luteinizing Hormone Releasing Hormone (LHRH) Analogs

In mammals, female ovulation and male spermatogenesis are exquisitely dependent on the action of gonadotropins. LHRH, a peptide hormone secreted from a discrete region of the brain, controls the release of the pituitary gonadotropins-LH (luteinizing Hormone) and FSH (follicle stimulating Hormone) — and, thereby, the influence of these peptide hormones on gonadal function. Synthetic peptides with structures similar to LHRH, i.e., analogs, have been prepared which evidence potent agonist or antagonist effects. Agonist effects include desensitization of the pituitary leading to suppressed gonadotropin secretion, inhibition of ovarian or testicular steroidogenesis and sex steroid action antagonism in reproductive tissues. The physiological effects of LHRH analogs on reproductive organ functions suggested that these compounds might be useful in appropriately designed protocols as contraceptives. Over the past years, ICCR members have conducted a number of animal and clinical studies designed to elucidate the effectiveness and safety of LHRH analogs as inhibitors of ovarian or testicular functions and, respectively, a potential for the development of female or male contraceptive modalities.

##### IV.2.5.1. Contraceptive Potential in the Female

###### IV.2.5.1.1 Findings

The results of a number of studies using LHRH agonists or antagonists in attempts to induce infertile cycles in women have not been encouraging. In one approach, not supported by A.I.D. investigators, have shown that the daily administration of agonist commencing in the early luteal phase did not result in adequate luteal insufficiency. The induction of significant luteolysis was only

observed when the agonist was administered for one or two days at the day 5 to 8 post-ovulatory point in the cycle. Since the time window for administration is brief, narrow, and difficult to identify, an effective routine dosage schedule would be difficult, if not impossible, to devise. Additionally, hCG activity was found to maintain high serum progesterone levels and lengthen the luteal phase in agonist treated women. These outcomes make it unlikely that this approach will ever be suitable for contraceptive purposes.

In distinction to the above, studies in rats, monkeys and humans have shown an antifertility effect of agonists in which ovulation is significantly inhibited. For example, investigations designed to test the contraceptive suitability of this approach have been reported for the buserelin LHRH agonist [D-Ser (TBU)<sup>6</sup>-Pro<sup>9</sup>-EA]-LHRH (HOE 766) formulated as a nasal spray. Clinical trials were undertaken subsequent to evaluations for animal toxicology, effective dose range, and delivery device reliability in order to evaluate tolerance and effectiveness. The overall results were disappointing in that daily 200-400 µg agonist doses had no effect in some women, inhibited ovulation in others and produced estrogen deficiency secondary to ovarian inhibition in still others. A more recent report described the results of a clinical trial of the efficacy of the agonist nafarelin acetate or (6-D-[2-naphthyl]-alanyl)-LHRH in inhibiting ovulation. The consequences of a once-a-day intranasal administration of the agonist (125 µg or 250 µg) for six months was followed in 24 women. The results indicated significantly fewer presumed ovulatory cycles at the higher (2 of 60 cycles) than the lower (10 of 54 cycles) doses with re-establishment of average menstrual cycles within 33.7 and 28.5 days, respectively, after discontinuance. The side effects observed included galactorrhea (2 subjects) and vasomotor symptoms (7 subjects). Although reliable ovulation inhibition was found in this study, the continuous administration of nafarelin

acetate was not considered to be a practical approach to female contraception due to unacceptable side-effects.

#### IV.2.5.1.2. Conclusions

The results achieved to date clearly indicate a significantly diminished potential for this contraceptive lead since the last evaluation period. The clinical application of LHRH agonists as a single therapeutic agent requires a serious consideration of the risks and benefits in view of the availability of alternative therapies. The continuous administration of agonist alone would not appear to be practical as a female contraceptive. Although no toxic manifestations occurred in women treated with the agonists, physiological consequences related to the long term administration of the agonist remain unresolved. These concerns include intervals of chronic anovulation with normal estrogen levels unopposed by progesterone leading to endometrial hyperplasia, intervals of hypoestrogenism leading to menopausal-like vasomotor symptoms and the possibility of enhanced bone loss through osteoporosis. Any resolution of the above concerns would most likely involve administration of more than one therapeutic agent by more than one route of administration and this could lessen patient compliance. Extended long-term and costly endometrium and bone studies would be required to evaluate the risk of hyperplasia or osteoporosis.

Although development of a contraceptive modality did not prove practical in this case, the reliable inhibition of ovulation induced by intranasally administered agonists may prove useful in the treatment of serious medical problems such as precocious puberty and some cases of endometriosis.

#### IV.2.5.2. Contraceptive Potential in the Male

##### IV.2.5.2.2. Findings

Despite more than a decade of intense research efforts by numerous research groups throughout the world, an acceptable approach to reversible male

contraception based on the administration of one or more drugs has so far proved to be very elusive. LHRH analogs, which cause the inhibition of testicular function in animals and man, represent one of the few promising leads for the development of a reversible, non-steroidal contraceptive for men.

Although the mechanism is not entirely clear, the agonists inhibit spermatogenesis by depressing pituitary gonadotropin secretion and testicular testosterone synthesis. Early observations of the effect of chronic agonist administration on men showed, in one case, that small subcutaneous doses (5  $\mu\text{g}$  daily) decreased serum testosterone and gonadotropin levels without affecting spermatogenesis or potency. In another study, larger subcutaneous doses (50  $\mu\text{g}$  daily) showed more pronounced endocrine effects with a loss of libido and significantly decreased sperm counts and motility scores. In a follow-up study, another agonist-treated group receiving testosterone enanthate (100  $\mu\text{g}$  every two weeks) supplementation evidenced no loss in libido with sustained, reversible oligospermia. In all of these studies, the effects of the treatment were deemed fully reversible. These observations demonstrated that androgen replacement therapy was a necessary adjunct if LHRH agonists are to be used as a male contraceptive.

Men seem, in this regard, to be relatively sensitive to the effect of chronic agonist treatments. Significant species differences have been observed, however. Chronic LHRH agonist treatments in the rat and dog lead to markedly decreased serum testosterone levels, decreased libido and loss of mating behavior. In contrast, mice are insensitive to such treatments and the rhesus monkey appears much less sensitive to the agonist effect than the rat, dog, or man. It is of interest in the latter regard that the mode of administration was found to be an important factor. In earlier studies by ICCR members, the daily (noncontinuous) administration to male monkeys of relatively large doses (25-100  $\mu\text{g}$ ) of agonists ([D-Ser-His<sup>6</sup>-Pro<sup>9</sup>-NEt]-LHRH or [(imBzl)-D-His<sup>6</sup>-Pro<sup>9</sup>-NEt]-LHRH) resulted in pronounced pituitary responses

without a significant impairment of testicular steroidogenesis or spermatogenesis. In a subsequently reported monkey study from another laboratory, the continuous subcutaneous administration of agonist ([D-Ser-TBU<sup>6</sup>-Pro<sup>9</sup>-NEt]-LHRH) via osmotic minipumps (48 µg daily) resulted in dramatically suppressed levels of serum gonadotropin and testosterone within four weeks and a loss of the ejaculatory response by the thirteenth week. Restoration of the ejaculatory response was effected by the subcutaneous implantation of slow delivery, testosterone-filled silastic capsules. The restored ejaculates were, however, devoid of spermatozoa. This exciting new development suggested the possibility of using LHRH agonists in combination with androgen supplementation for contraception in men.

In a very recently reported study conducted by ICCR members, three of four male rhesus monkeys were rendered azoospermic by the chronic administration (100 µg daily) of a potent agonist ([*imBzl*] D His<sup>6</sup>-Pro<sup>9</sup>-NEt]-LHRH) via subcutaneous osmotic minipumps. However, the LHRH agonist failed to suppress testicular function uniformly in all the monkeys. In one monkey, some decrease in the sperm count occurred, but the ejaculatory response continued. In the three responsive monkeys, serum testosterone levels fell by 90% and the response to electroejaculation was lost. Androgen replacement using subcutaneous silastic implants releasing 7 α-methyl 19-nor-testosterone acetate restored the ejaculation response, but the ejaculates were devoid of spermatozoa. Under this schedule of treatment, azoospermia was maintained for about eight months. After more than one year of agonist suppression, withdrawal led to a complete restoration of testicular function.

The Population Council studies have also investigated the potential of LHRH antagonists for contraceptive development. Unlike agonists, which act by a desensitization mechanism, LHRH antagonists competitively achieve their effects by directly blocking pituitary LHRH receptors. The expectation has been, therefore,

that they might be more successful candidates for contraceptive applications. Studies have been reported in the literature showing that the in vivo administration of an antagonist leads to a rapid decline in serum gonadotropin levels and the subsequent impairment of gonadal function. Only in recent years, however, have LHRH antagonists been synthesized that are potent enough to have practical applications. Studies in cynomolgus monkeys by other workers, for example, have shown such antagonists to cause an immediate and precipitous decline in serum LH and testosterone levels, decreased testis volumes, and, in most monkeys, azoospermia. As in the case of the LHRH agonists, species differences in sensitivity (resistance) to the antigonadal effects of LHRH antagonists have been reported.

The ICCR plans to test one such antagonist were terminated by the unexpected finding that its binding by rat mast cells caused histamine release leading to transient edema of the face and extremities. This effect was not seen in mice, rabbits or rhesus monkeys, which are species more resistant (or insensitive) to the agent's effects. ICCR studies alerted the biomedical community to the toxicological problems with LHRH-22 and subsequently determined a correlation of the effect with the presence of a basic amino acid in position 6 of the peptide. At the Population Council, LHRH 22 studies have been discontinued and replaced by studies based on an equally potent antagonist (LHRH 34) which causes minimal histamine release. Animal studies preparatory to clinical trials with LHRH 34 have been conducted and an Investigational New Drug application has been submitted to the FDA. Phase I clinical trials were begun in the summer of 1987 and are in progress.

#### IV.2.5.2.3 Conclusions

Consideration of the available experience using LHRH analogs to interfere with gonadal function suggested that it may be possible to devise a protocol for achieving azoospermia in men. It is hoped that this could occur without a

significant decrease in libido by selecting the right dose, timing, and mode of LHRH analog administration coordinated with the subsequent rescue of libido by the appropriately timed administration of a supplemental androgen.

Studies recently conducted by the Population Council in monkeys have confirmed that the continuous administration of an LHRH agonist with the subsequent provision of an appropriate androgen did achieve a controlled, reversible state of azoospermia in some monkeys with a simultaneous maintenance of the ejaculatory response. These studies, however, showed the LHRH agonist did not uniformly suppress testicular function in all the monkeys. One monkey undergoing the treatment schedule showed some decrease in sperm count with a sustained ejaculatory response indicative of resistance to the agonist effect. A second monkey showed variability in spermatogenic suppression and maintenance of the ejaculatory response.

Findings from clinical trials reported elsewhere have shown agonist efficacies in suppressing spermatogenesis in men to be somewhat equivocal, and particularly so when exogenous androgen was provided to maintain libido and secondary sexual tissue functions. In one such report, stepwise increases in analog administration in successive trials failed to achieve azoospermia at even the highest dose (440 µg/day). Evidence has been noted in such studies that the administration of testosterone (intermittently) orally or by injection may counterproductively stimulate sustained spermatogenesis.

The sequential administration schedule designed by the Population Council has adequately considered these aspects and sought to incorporate an optimized schedule of sequential drug administration first to suppress spermatogenesis to azoospermic levels and then to rescue libido. Current results show that the design is highly effective in some individuals for a period of up to one year. These results also show, however, that some individuals are more sensitive than others in this regard.

Given the inter- and intra-species variations in sensitivity noted for such an approach, it would seem that genetic factors might determine responders and non-responders within study populations. The genetic control of gonadotropin induced ovulation rates in sheep suggests that such controls may also be a factor in males. In contrast to the highly inbred nature of many of the animal models being used, the human is an outbred species and genetic variation in sensitivity to gonadotropin suppression may determine responder and non-responder subsets complicating the global application of this approach.

It seems reasonable to expect, however, that the approach may yield a long-term contraceptive method acceptable to a subset of men, requiring a minimum of two episodes of physician contact per year. While the requirement for multiple contacts with health care professionals would somewhat limit the method's widespread applicability, it does seem likely that the method could be acceptable to a significantly large population of potential users to warrant further development as a contraceptive lead.

The Population Council is currently pursuing this further development with studies on two implant systems designed to deliver, respectively, a constant amount of a highly potent agonist and a constant amount of androgen. Prototype implant systems are now being tested (separately) in animals, (rats, monkeys, dogs). If promising results are achieved, toxicology studies are planned in support of future clinical trials. The hydrogel implant system that has been devised for the LHRH analog is a joint project of the Population Council and a pharmaceutical company. It is constructed of a material that permits the slow diffusion of small peptides, such as LHRH, into the blood over a prolonged period. The successful development of this implant system would indeed represent a breakthrough for the delivery of various contraceptive peptides. Separately, a long term delivery implant is being tested for administering the androgen, 7 $\alpha$ -methyl 19 nor testosterone acetate, at

effective levels for a one year period. Even if these implants are not subsequently incorporated into contraceptive applications, other medical applications could find them of immense value. Although this latter aspect may not reflect the priority interests of A I D , its importance per se should not be overlooked

The developmental potential of LHRH analog approaches to male contraception appears to be at a critical stage in time with respect to programmatic management interests. The ongoing animal and clinical trials will soon determine whether sufficient promise exists to continue. If induction of azoospermia with libido rescue cannot be demonstrated in sensitive species, including man, then there is no reason to continue the program

In comparisons of the agonist and antagonist studies currently available for evaluation, it would seem that the agonist approach is the only possibility for rapid development at present. Despite the advantage of the antagonist mechanism of action, a candidate antagonist would have to show a major advantage over the available high potency agonists to warrant consideration of its further development. In addition, while minimal histamine release has been accorded to antagonist LHRH 34, its potential toxicological problems do not appear to have been completely resolved at the present time. Extended toxicological studies will be required to establish that another antagonist, CDB2876, which is purported to have no histamine releasing activity, is safe and does indeed fail to elicit histamine release under the dose and administration made necessary for long term effectiveness in suppressing spermatogenesis. The present experience with use of analogs as male contraceptives does not encourage the creation of a program to synthesize new antagonists of sufficiently high potency to override the advantages of the current agonist approaches

In regard to the use of LHRH analogs as agents of male fertility regulation, it is instructive to consider whether the experience so far has met the requirements

envisioned for such an approach. The drug regimen employed must achieve complete azoospermia over a long period of time. Evidence indicates this can be achieved in some, but not all individuals, in the study population. Relaxation of this requirement is only reasonable if the spermatozoa of oligospermic individuals can be shown to be completely nonfunctional with respect to egg fertilizing ability. On this point, there is at best a paucity of information. Libido diminishment or loss must be avoided. The agonist induction of suppressed spermatogenesis also results in the suppressed production of androgens having important roles in erythropoiesis, protein metabolism, bone metabolism, secondary sexual tissue functions, libido, and potency. Any use of an exogenous steroid replacement regimen to rescue libido must lead to the recovery of these systemic androgen dependent functions without restimulating spermatogenesis. In this regard, the two-phase regimen developed by the Population Council does show promise. Lastly, the withdrawal of the agents inducing the sustained azoospermia must result in an adequate restoration of spermatogenesis and seminal vesicle/prostate secretory functions. The steroid therapy involved will require careful monitoring for side-effects, particularly with regard to the long term consequences to the seminal vesicles and prostate.

#### IV 2 6 Inhibin

##### IV 2 6 1 Findings

Evidence from numerous studies has established that peptide hormone-based endocrine suppression methods which inhibit spermatogenesis usually suppress androgen production as well. The unacceptable side effects of the latter thus require androgen replacement therapy as a component of any protocol for this mode of male contraception. This requirement poses additional complexities and problems that could be avoided, if an endocrine suppression mechanism was available which selectively eliminated FSH activity alone and, thereby, suppressed spermatogenesis without interfering with LH mediated Leydig cell steroidogenesis.

FSH immunoneutralization studies in monkeys have demonstrated the feasibility of such an approach.

More than fifty years ago, a non-steroidal testicular factor was postulated to exist that inhibited pituitary functions. Subsequently, a proteinaceous factor termed inhibin was described that appeared to suppress FSH secretion selectively. Recent evidence has shown that ovarian follicular fluid from a number of species contains an inhibin like factor which suppresses pituitary FSH secretion in a dose dependent manner without altering LH secretion (*in vitro* or *in vivo*) under basal endocrine conditions. The differential suppression of FSH and LH secretion has been attributed to an ovarian hormone termed folliculostatin or ovarian inhibin. Other experiments showing inhibin-like activity in the media of cultured rat Sertoli cells suggested a site of inhibin synthesis in the testes. Over the last decade, intense efforts have been undertaken by numerous laboratories to isolate inhibin. Until recently, these efforts produced equivocal results and inconsistent products. Of all the reproductive hormones, none have had a more equivocal reputation than inhibin.

In January 1983, the Contraceptive Development program of the Population Council initiated probing level efforts to purify, characterize, and test male inhibin as a candidate for male contraceptive development. In December 1985, the full sequences of two 32 K Dalton (molecular weight) forms of porcine ovarian (follicular fluid) inhibin (inhibin A and inhibin B) were reported by other workers and this was subsequently confirmed for bovine inhibin as well. Each form was found to be composed of two cross linked subunits consisting of a larger (18 K Mr) alpha chain common to both forms and a distinctly smaller (14 K Mr) beta chain. Two forms of the latter chain were identified (beta A or beta B) having amino terminal differences. During 1985-1986, a U.S.A.I.D. funded Population Council project collaborating with investigators at the Florida Institute of Technology and

the Salk Institute succeeded in isolating sufficient amounts of inhibin from ovine rete testis fluid to permit its characterization. This was the first reported purification and partial characterization of male inhibin. Based on in vitro bioassay monitoring, a 3000-5000 fold increase in specific activity was accomplished during purification. Two forms of ovine testicular inhibin were isolated and the N-terminal sequences of the alpha and beta subunits determined. Both forms were found to be heterodimers of one 18.0 K Dalton and one 16.5 K Dalton subunit. The two isoforms differed at the N terminus of the alpha subunit by one having 15 fewer amino acid residues. The testicular hormone was found to be homologous with ovarian inhibins in other species. It is notable that porcine and human beta-A chains are identical to each other. The amino acid sequences of human alpha-inhibin deduced from the reported cDNA isolated from testicular libraries is also the same as that reported for the ovarian and placental peptides. Characterization studies of the male inhibin isolated by the Population Council project has shown that immunostainable male inhibin is present in rat testes in the same sites as other Sertoli cell proteins known to be secreted into tubular fluid.

With the availability of highly purified ovine testicular inhibin, porcine activin, antisera to the alpha- or beta subunits, and an RIA for the alpha-chain, it was possible to conduct a variety of anatomic and physiologic experiments. In addition to effects on FSH secretion, inhibin and activin (a heterodimer of inhibin beta-subunits) are known to stimulate and inhibit, respectively, testosterone secretion by testicular Leydig cells. Other physiological studies at the Population Council have shown that FSH is a major positive regulator of inhibin accumulation in Sertoli-enriched (immature rat) cell cultures with steroids having a variable suppressive effect on inhibin accumulation. In the latter regard, testosterone had a minor influence and androstenedione a significant one. The current results taken collectively suggest that inhibin is a Sertoli cell protein product which exerts a

negative feedback control on pituitary FSH secretion. The latter, upon stimulating inhibin secretion, closes the circuit of a long feedback loop system. Since inhibin appears from current evidence to also facilitate testosterone secretion by testicular cells, an intra-gonadal short loop regulatory system may also be operant within the testis which represents an intra-testicular communication system.

#### IV 2.6.2. Conclusions

The Population Council project on inhibin has achieved remarkable advances in the last one to two years. Rising from the nebulous uncertainties apparent at the last evaluation, the project has generated significant and truly exciting progress. Although the mechanism of action of inhibin is more complex than first envisioned, inhibin continues to offer a clear potential with respect to new approaches to a mode of male contraception. The paucity of contraceptive leads for the male further heightens the current interest in inhibin as an agent that may provide the first acceptable male contraceptive based on an endocrine suppression mechanism which selectively suppresses FSH secretion and does not suppress LH mediated androgen production.

The purified male inhibin has been characterized as a 32 K Dalton heterodimer consisting of one alpha- and one beta subunit. Testicular inhibin made available by the Population Council project permitted physiological studies that have documented the need for further studies in several areas. The calculated EC<sub>50</sub> values obtained for the suppression of GnRH stimulated gonadotropin release by inhibin in a cultured rat pituitary cell system demonstrated significantly lower values for inhibin in the presence of androgen than for inhibin alone. These results suggest that the pathways taken by the two agents in influencing gonadotropin secretion may overlap. Do they? In *in vivo* studies, the purified inhibin strongly reduced GnRH induced FSH secretion in the immature rat model with no observed effect on LH release. The discrepancy between the in vitro and in vivo effects

requires further work to provide an explanation. These in vivo results remain most encouraging.

Recent studies have shown that ovine inhibin and activin modulate the induction of hemoglobin accumulation in a human erythroleukemic cell line (K 562) and the proliferation of erythroid progenitor cells in human bone marrow cultures. Activin was a potent agonist and ovine inhibin an antagonist of the induced effect. These results suggest these proteins may be involved in a humoral regulatory mechanism controlling erythropoiesis. If this is the case, would side-effect influences on erythropoiesis represent a significant negative concern for the use of inhibin as a mode of contraception? It would be most instructive to have further consideration directed to this aspect.

Major issues regarding the chemistry and physiology of inhibin and activin remain to be resolved. Most of the studies needed, indeed required, to be pursued will only be able to be pursued when adequate amounts of purified inhibin are made available for this purpose. While the use of native inhibin and activin isolated from biological sources has sufficed to prepare antibodies and reagents for the limited key biological studies already conducted, it is clear that if inhibin is to be considered as a potential male contraceptive, a means of producing large amounts of pure inhibin must be devised. The amounts that can be isolated from natural sources are very small, require a highly labor intensive (costly) effort, and face non-trivial losses due to surface adsorption and biochemical alterations. Moreover, it has been estimated that a further development of another 3 to 10-fold in purification (above 3000 fold) would be required in order to obtain a protein preparation sufficiently pure to be called pure. The 500 fold level achieved in some isolations and the realization that genetic engineering approaches represent the most likely avenue of producing inhibin in the amount and purity required have led to a major concentration on the latter aspect by the ICCR members.

The collaborative arrangements previously established for the effort to isolate male inhibin from biological fluids have been discontinued. The Population Council project has assumed a lead role for the completion of the cloning of the inhibin genes and devising a mammalian cell expression system. In the latter respect, the biological studies completed to date suggest, as a first step, that Sertoli cells might be used to produce an inhibin expression system. It is possible that useful transgenic animal models might be constructed in the future as a megasecretory source.

Work conducted by the Population Council investigators resulted in the construction of human testicular cDNA libraries which were screened with probings representative of selected sequence segments of the porcine or human inhibin alpha-subunit. Two human testicular alpha-inhibin cDNAs were obtained and subcloned into a plasmid (pGEM<sup>TM</sup>-13 blue) vector. The resultant cDNA clones were then sequenced. In a similar fashion, the two beta-subunits (beta-A and beta-B) were cloned. One clone specific for the human beta-A inhibin subunit and seven clones for the human beta-B subunit were isolated, subcloned, and characterized by restriction mapping. The two beta-B clones with the longest cDNA inserts were sequenced and provided the first information available for the signal peptide sequence for the beta-B inhibin protein. Signal peptide sequences are diagnostic of proteins that move through membranes. The analysis of the beta-A subunit specific cDNA is under investigation at present. Given the importance of the beta A subunit in the heterodimer form (activin, FRP) in stimulating pituitary FSH secretion, it is hoped that rapid progress on this aspect will be quickly forthcoming. These studies, begun at the end of 1987, are scheduled for continued efforts through 1988.

## IV.2.7. Other Basic Lead Approaches

### IV.2.7.1. Gonadotropin Surge Inhibiting Factor (GnSIF)

#### IV.2.7.1.1. Findings

A number of biological studies in monkeys and humans performed by Dr. Gary Hodger and his associates over the past eight years suggest that there is a peptide in porcine and human follicular fluid that will inhibit the surge of LH secreted by the pituitary in response to LHRH. This substance was designated gonadotropin surge inhibiting factor (GnSIF). Dr. Hodger proposed to A.I.D. that it would be worthwhile to isolate GnSIF as a potential contraceptive. A collaborative study was therefore initiated between Eastern Virginia Medical School, which collects ovarian follicular fluid and performs the bioassays of GnSIF, and the Population Council, which develops procedures required for GnSIF purification. The isolation of GnSIF is a probing study.

Present evidence suggests that GnSIF is a small peptide that could be used as a nonsteroidal form of contraception inhibiting ovulation. Since the project was initiated, a method of bioassay for GnSIF has been established that relies on cultured pituitary cells. Since inhibin in high doses inhibits the action of LHRH on pituitary LH secretion in vitro but not in vivo, it was important to distinguish GnSIF from inhibin. A technique for separating these peptides from one another has been developed, and the biological identity of GnSIF established. Preliminary studies established an approach to purifying this protein on analytical high-pressure liquid chromatographic columns. Studies conducted in 1987 designed a scale-up of this method using preparative high pressure columns. It is claimed, but unlikely, that highly purified GnSIF will be available for animal studies in 1988. Should these animal experiments prove interesting, toxicology and pharmacology will be performed in anticipation of human studies.

#### IV.2.7.1.2 Conclusions

During the past twelve month period efforts have been made to isolate GnSIF from porcine follicular fluid. These efforts have demonstrated that the purification of GnSIF is a more formidable task than had been expected due to its presence in extremely low concentration in follicular fluid, its heterogeneity, and the difficulty in discriminating it from inhibin. Progress has been achieved most recently with the demonstration that the major GnSIF activity of enriched preparations can be fractionated on a Vydac C4 reverse-phase HPLC column into three distinct peaks. The reason for the multiple peaks is unknown, but may relate to molecular aggregation or contaminant co-aggregation effects. The first clear evidence that GnSIF was not related to inhibin and is a separate entity has been obtained with the demonstration that inhibin is retained on a heparin-sepharose affinity column while GnSIF was eluted from it. A protocol for scaling-up the purification scheme to a preparative level has been devised and is proposed to be tested. The Population Council's role is to develop the separation and purification procedures, while the EVMS role is to provide the follicular fluid used as the biological source of GnSIF and to perform the bioassays of its activity. The overall usefulness of this project and its approach can only be considered from its strictly theoretical potential at present, since it has not yet been purified, characterized, or used as a contraceptive prototype in experimental trials. ET2 does not recommend significant funding of this initiative at this time.

#### IV.2.7.2. Anti-LHRH Vaccine

[Note that this work has not been supported under the present agreement.]

##### IV.2.7.2.1. Findings

LHRH is a 10 amino acid peptide made by the brain that regulates the secretion of LH and FSH. Neutralization of this peptide by antibodies is known to reduce the secretion of pituitary hormones and produce infertility in animals. Since both LH

and FSH are suppressed, both androgen production from the Leydig cells and spermatogenesis are blocked. Council scientists working with special funding from a US-Indo collaborative program have conducted studies in animals to determine the extent to which an LHRH vaccine would produce infertility in animals. Studies have now been completed using LHRH coupled to a carrier protein in different positions. In both rabbits and rats effective antibody titers produced infertility. Supplementation with low doses of androgens maintained sexual behavior so that it was possible to demonstrate that the animals were indeed infertile. If continued animal studies in monkeys suggest that this might be an appropriate vaccine for humans, then a long-term androgen replacement system would be needed in immunized individuals. The androgen implant currently being developed for use with the LHRH analog implant system for men might serve this need.

#### IV.2.7.2.2 Conclusions

As reported, probing studies on this lead have largely been completed. Studies in animals conducted at the Population Council and in the National Institute of Immunology in India have shown that vaccines using LHRH coupled to tetanus toxoid (TT) might provide a useful approach to developing a contraceptive for men. One advantage of LHRH is that this decapeptide can be supplied by synthesis rather than by isolation from biological sources. A disadvantage of the approach is the complexity arising from the necessities of marrying active immunizations, immunological neutralization, endocrine suppression, and hormonal replacement protocol components into one design for an azoospermic outcome of prolonged duration. The potential for variations in individual responsiveness to the regimen at each level could lead to non-trivial problems of efficacy, acceptability, side-effect monitoring and ease of delivery with respect to LDC applications. The Population Council investigations have shown that animals receiving an anti-LHRH vaccine will require androgen replacement therapy since the anti-LHRH antibodies will also

cause a decrease in testosterone secretion. However, this problem appears resolvable since androgen substitution, either by injection of a long-acting testosterone ester or by testosterone-releasing implants, is effective in maintaining normal sexual behavior in rats and rabbits which had become infertile following immunization against LHRH. The androgen implant being developed at the Population Council for use with LHRH analogs could provide an elegant mode of androgen administration for up to one year if the vaccine were proven suitable for human use.

The status of the current studies suggests that considerable work remains to be done before a vaccine formulation could be available which is suitable for further primate trials. Research in lower animal models is still needed to determine the optimal amount of antigen required to induce azoospermia. Additional studies should explore whether multiple antigens can be formulated which may optimize the immune response. Several carriers and adjuvants approved for human use need to be tested as alternate delivery systems in order to minimize the number of injections. Animals need to be tested with and without androgen replacement to ascertain whether infertility can be maintained for long periods of time and to determine whether the antifertility effect is reversible.

#### IV.2.7.3. Antisperm Vaccine

##### IV.2.7.3.1. Findings

In collaboration with the National Institute of Immunology of India, the Population Council proposes to develop polyvalent antibodies that can be used to identify sperm antigens that are suitable components of an immunocontraceptive. One antiserum has been prepared which agglutinates spermatozoa, blocks in vitro fertilization, and identifies only a few protein bands in extracts of human sperm on immunoblots. This antiserum will now be used to purify the proteins from human sperm in preparation for cloning its gene(s). Partial funding for this collaborative

probing study with the National Institute of Immunology has been sought through a grant to the Indo-US Subcommission on Science and Technology. If promising results are obtained, additional support will be needed to scale-up the process once the cloning and expression have begun.

#### IV.2.7.3.2 Conclusions

An application to the Indo-US Subcommission on Science and Technology has been made to develop an antisperm vaccine in collaboration with the National Institute of Immunology of India. To develop this product, the investigators will produce additional polyvalent antibodies against human sperm membrane antigens and use them to purify antigens from sperm extracts. These antigens will be used to produce monospecific antisera in rabbits. Functional tests will be used to select antisera that modify the fertilizing ability of sperm. These antisera will then be used to complete the purification of sperm antigens, so that the amino acid sequences can be determined and cDNAs selected from testicular libraries. The cDNAs identified in this way will be sequenced to determine the structure of sperm antigens. It is believed that antigens selected in this way will be one of the components of an antisperm vaccine. It is not possible to evaluate the current status of the approach at the Population Council, since the research is only a proposal. Documented progress suggests such studies are just beginning. As evidenced by twenty years of literature reports, the approach is fraught with conceptual and technical difficulties. It is unlikely that progress will be achieved as easily or directly as outlined. The probing status of this approach appears to be poised at the beginning of what may prove to be a long term, costly, and high-risk commitment.

#### IV.2.7.4 Probing Study Recommendations

##### IV.2.7.4.1 Conclusions on Basic Leads

New contraceptive leads are chosen by the ICCR based on members' recommendations from research findings reported in the world's scientific

literature. The proposed activities are evaluated by the ICCR prior to implementation. Initial (basic) probing studies appear to be largely supported by funding sources other than A.I.D. These approaches are coordinated with other contraceptive development programs on an international scale. There clearly does appear to be an effective decision point process regarding the evaluation of progress in the probing study areas and the upgrading of a "probing study" to a "contraceptive lead" status. The decision point process involves the commitment or non-commitment of U.S.A.I.D. funding support to underwrite applied research activities. There appears to be an effective dialogue with and involvement of the U.S.A.I.D. program management system in this decision point process. Additionally, a continuous Population Council-U.S.A.I.D. interchange in monitoring progress and evaluating continuation of probing studies and contraceptive leads is apparent. Such activities have in fact been amplified or discontinued, as a matter of record, by the process noted.

#### IV.2.7.4.2 Research Line Item Recommendations

a) Discontinuation of the LHRH agonist studies as a lead for a contraceptive modality in the female appears warranted from the progress reported. The ICCR studies completed in this area represent a careful, thorough, and very deliberate series of investigations providing important documentation and guidance to the field. The termination illustrates the functioning of the decision point process of the ICCR mechanism for allocating U.S.A.I.D. funds.

b) The LHRH analog studies in the male clearly represent an appropriate area of U.S.A.I.D. support at the level of a contraceptive lead. Experience in this area is well beyond the probing level of basic research and offers clinical applications of utility. The current experience, however, suggests that the lead is not one for imminent development. Accordingly, a major investment of funding and a highest-priority status would appear to be a premature response at this time.

A number of technical and conceptual aspects require resolution before a major funding investment would be reasonable.

- Although significant progress has been achieved in designing a mode and schedule for drug administration to induce and maintain spermatogenic suppression and provide libido rescue therapy, acquiring convincing clinical evidence of the regimen's efficacy should be pursued with the highest priority. In this regard, collaboration with the French group (P. Bouchart) and the ICCR may be very expeditious and should be encouraged.

- The new implant delivery systems should be tested for efficacy of delivery for a minimum of one year, with a view to development of one or both implant units with longer periods of use. Longer periods would minimize intervention intervals that may be a hindrance to patient acceptability and continuation of use.

- Monitoring for side-effects of the steroid replacement regimen should give careful consideration to the degree, quality and duration of restoring seminal vesicle and prostate functioning after withdrawal of the inducing agents. Reassurance that the functional recovery of the testis is adequate and normal after long periods of suppression will be a necessary component of this mode of contraception

c) The inhibin lead is an exciting one and, although yet a probing study, is of sufficient potential and importance to warrant U.S.A.I.D. support as a probable contraceptive lead. In view of the outstanding progress accomplished during the past two to three years, the inhibin work can now be entirely conducted solely at the Population Council. Sufficient support should be provided to permit a significant effort aimed at the production of inhibin by recombinant DNA technology. In particular, a priority effort should now be made to complete the cloning and characterization of the cDNAs for the human beta-A inhibin subunit

and to develop mammalian cell expression systems. Studies on the optimal conditions for the biological expression of inhibin in gonadal cells and physiological studies of inhibin-activin effects should follow as the next level of priority. At such time as sufficient material is available, the problem of a long term mode of administering inhibin-derived contraceptive peptide(s) must be addressed. Although the implant system presently being devised for the delivery of LHRH agonists may be of promise, there is, at present, no assurance that this will be so and no other long-term delivery method is available.

d) The GnSIF probing study is a straightforward basic research project. As noted, by the progress reported, it is still in the most initial stages of achievement. The purification strategy and outcome is still developing. The product so far is insufficient in purity, character, and amount to provide a true sense of identity to GnSIF. Clearly the expertise is on hand to pursue this project to a successful outcome given enough time and funding. However, a significant investment of U.S.A.I.D. funding for GnSIF studies should await the isolation, characterization, and production of a pure protein/peptide product having the desired biological activity.

e) The anti-LHRH vaccine appears to require a considerable amount of further study at the basic probing level before a significant investment of U.S.A.I.D. funding would be warranted. While it may produce a useful contraceptive lead appropriate to U.S.A.I.D. developmental interests, this consideration would appear premature at present in view of the unresolved complexities of the approach. The Population Council investigators will not request U.S.A.I.D. funding unless the androgen implant system being developed for use in conjunction with the LHRH-agonist implant becomes available and can be used as a component of the design protocol.

f) The anti-sperm vaccine studies at the Population Council are preliminary in nature, basic probing in level, and insufficiently developed to be considered of

appropriate potential for U.S.A.I.D. contraceptive development funding. These studies are not currently funded by U.S.A.I.D. Before a significant U.S.A.I.D. investment would be warranted, this approach must document the proven identity of one or more sperm antigens directly and causally associated with a critical fertility mechanism, demonstrate that an immunological method exists for inducing effective antibody levels at the relevant reproductive tissue site, and provide reassurance that immunopathological sequelae are not a problem with the desired long term use of this method.

## **V. CONTRACEPTIVE INTRODUCTION ACTIVITIES**

### ***V.1. Overview***

In 1983 the Population Council formally initiated a program to support systematic introduction of new contraceptives being developed by the Contraceptive Development Program. NORPLANT® was considered to need especially careful introduction.

The Population Council concluded that in the past, family planning programs had paid insufficient attention to this complex process which required activities which relate to: manufacture, supply, regulatory approvals, marketing, training of service providers, delivery system management and operations research, clinical trials, method information and educational efforts, consideration of country and program-specific parameters, and user needs and desires.

In short the Population Council believed a carefully planned and systematically executed effort for introduction of new technologies would optimize the chances of their success. With partial support of an A.I.D. Cooperative Agreement, the Population Council has carried out a program of contraceptive introduction since 1983.

## ***V.2. Purposes of A.I.D. Support***

In the Population Council Cooperative Agreement dated 05/17/83 and its amendment on 08/08/86 A.I.D. agreed to support contraceptive introduction activities.

The principal activities relating to Contraceptive Introduction to be undertaken during the 1983-1987 period were:

1. Production of information materials to make donor agencies and opinion makers in target countries more aware of the advantages of new technologies.
2. Training of local clinicians and program managers in appropriate use of new approaches.
3. Pre-introductory clinical studies designed to give local health care providers first-hand experience with new products.
4. Development of field worker- and user-informational materials to enhance acceptance.
5. Securing agreements with private sector organizations to provide the products at reasonable cost to nonprofit agencies, and with selected governments planning to establish local manufacture, thus assuring the wide availability of new technologies.

It was planned that during 1983 contraceptive introduction activities would be primarily directed to the introduction of the Copper T 380A IUD. Several countries were targeted for seminars, workshops, and introductory clinical studies. An integrated project, budgeted separately in 1983, was the development of course materials on contraception in clinical practice in Brazil.

Beginning later in 1983, strategy for the introduction of NORPLANT<sup>®</sup> was to be finalized and pre introduction training and informational activities initiated, expanded in 1984 and continued for another two years. Similar work for

contraceptives developed later such as the levonorgestrel releasing vaginal ring and IUD and LHRH analogs was expected to be initiated in 1985. However, it was recognized that the timing of initiating introductory efforts was dependent on the progress of development and the regulatory status of each new product.

### *V.3. Accomplishments*

Throughout most of this Cooperative Agreement A.I.D. funds have been used for partial support of successful Contraceptive introduction activities for NORPLANT<sup>™</sup> and the Copper T 380A. For these two methods of birth control the activities described in section V 2. above have been carried out. These have been the only contraceptive methods for which product registrations (drug regulatory agency approvals for use) have been obtained in various countries. Details of policies and programs are provided below:

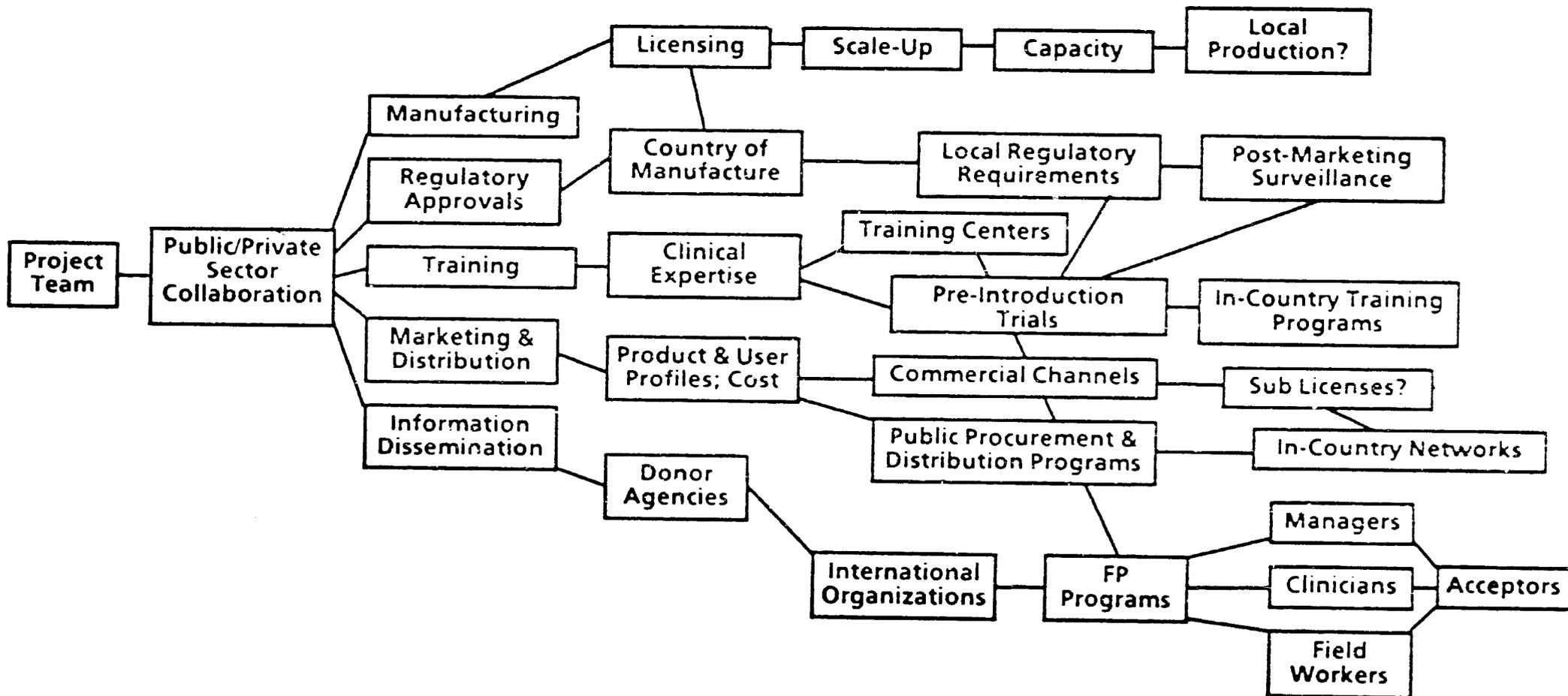
#### *V 3.1.1. Policy*

In 1983 an explicit decision was made that the Population Council would assume responsibility for those activities needed to introduce ICCR-developed contraceptives and to ensure high quality of care for the users, rather than hand them off to an uncertain fate in the custody of public and private sector service providers. Population Council policy recognizes four levels of responsibility: 1) to potential and actual users — fostering their informed choice of a broad array of competently provided methods, 2) to service providers — who should have good information and training, 3) to family planning program managers who need good technical and program information and 4) to policy level decision makers who need accurate information about the benefits and draw backs of each method of birth control

#### *V 3 1 2 Strategy*

A general strategy has evolved (see Fig 4) which features attention to a complex array of tasks including manufacturing, registration, information

Figure 4.  
Strategic Plan: Contraceptive Introduction



materials, development, training, and pre-introduction trials. The specific strategy for NORPLANT® is shown in Fig. 5.

### V 3.1.3 Organization

The Population Council's organization for contraceptive introduction activities has evolved over the past five years and now comprises a management infrastructure which has contributed to the success of the Contraceptive Introduction program.

The infrastructure is coordinated by a central management team in the Population Council's International Programs Division and draws on the expertise of staff from this division (both in the New York Inter regional Office and regionally-based offices), as well as the Center for Biomedical Research, the Center for Policy Studies, and linkages with other collaborating institutions to draw upon additional resources and expertise available outside the Council.

The central management team operates under the direction of the Vice-President and Director of the International Programs Division. Overall management for worldwide activities is provided by the Staff Associate for Contraceptive Introduction and management of administrative areas is handled by a newly appointed Project Coordinator. Originally technical support for Contraceptive Introduction management, with particular emphasis on regulatory affairs and licensing issues was provided by Population Council staff. For the past three years this input has been provided by the INTERCARE consulting firm. The Council also currently employs two full time regional staff.

The Contraceptive Introduction management team is responsible for the planning and oversight of contraceptive introduction activities which include:



Interactions with pharmaceutical manufacturers collaborating agencies and donors; development and conduct of pre-introduction trials, training and informational activities, preparation of prototype information materials for various audiences, facilitating communications with the public through a public information program, and the development of an integrated research effort to examine, from the user's perspective, those areas that will contribute to improvements in service delivery.

Strategy and management of contraceptive introduction activities is facilitated by two in-house advisory groups: the NORPLANT® Working Group and the NORPLANT® User Perspective Committee. The Working Group draws upon the expertise of the management team in International Programs (involved in policy-setting and implementation activities) and four scientists at the Center for Biomedical Research. It reviews issues as required e.g., the conduct of pre-introduction trials, data collection, interaction with the pharmaceutical company (Leiras), scientific and medical questions, and technology transfer. The User Perspective Committee includes staff of International Programs and the Center for Policy Studies. Disciplines represented on this committee include the social sciences, women's roles and development, and program management. This Committee has provided the guidance that shaped the direction of the introduction program's user oriented research.

The Council's Office of Communications has played a considerable role in information dissemination and public relations. The preparation of prototype information materials is coordinated by this office, as is the Council's newsletter, Norplant® Worldwide. All activities related to interactions with media and the press are managed through this office, including recent media events announcing the

return of the Copper IUD to the US market through the introduction of the Copper T 380A IUD.

The Population Council considers the field staff essential to establishing and maintaining relationships with institutions and Ministries in the developing world, and to the implementation and monitoring of pre introduction trials and training projects. Regional staff for the Contraceptive Introduction program include full time medical personnel in Campinas, Brazil and Bangkok, Thailand. They provide medical expertise and serve as liaison, in assisting with the initiation of users research and contraceptive introduction activities.

The Population Council has worked extensively with collaborating institutions in conduct of clinical trials, establishment of a worldwide database, development of informational materials and training curriculum development and evaluation. Principal collaborators are: Leiras-Medica, FHI, PIACT/PATH, AVSC and to a lesser extent JHPIEGO and the Population Information Program.

#### V.3.1.4. Budget

The overall budget for A.I.D. support to Contraceptive introduction activities excluding indirect support is \$3.9 million or 18.5% of the total program. Total expenditures for NORPLANT<sup>®</sup> introduction have been \$1.2 to \$1.3 million per year between 1985 and 1987 with A.I.D. providing 50% to 60% of the total (see Table 1). Expenditures for Copper T 380A introduction in 1986 were \$217,490 and in 1987 \$169,000 with over 95% provided by A.I.D. (see Table 2).

Table 1. Norplant® Introduction Expenditures

YEAR	TOTAL \$	% AID
1983	\$146,775	15%
1984	\$690,375	38%
1985	\$1,297,135	50%
1986	\$1,325,340	67%
1987	\$1,189,000	65%

Table 2. Copper T 380A Introduction Expenditures

YEAR	TOTAL \$	% AID
1983	\$290,225	69%
1984	\$96,870	56%
1985	\$21,897	30%
1986	\$217,490	97%
1987	\$169,000	95%

### V.3.2. Norplant® Introduction Activities

The NORPLANT® implant is an effective, long acting, reversible contraceptive developed by the Population Council. It provides continuous long-term protection from pregnancy by means of low dose, progestin only implants that are inserted beneath the skin of a woman's arm. NORPLANT® is a six capsule system that is effective for five years, a second generation system effective for three years, called NORPLANT® 2 uses only two implants.

The pregnancy rate for the method is less than 1 per 100 per year, lower than for oral contraceptives or most intrauterine devices and comparable to surgical sterilization during the first three years of use. The NORPLANT® method is reversible at any time during the period of use; there is prompt return to fertility following removal of the implants. The most common side effect associated with the method is change in menstrual bleeding patterns. These irregularities include more frequent bleeding episodes, spotting between periods, or amenorrhea.

The Population Council's NORPLANT® research and development effort began in 1966 with exploration of release of steroids from silicone rubber. Since then, an extensive program of clinical research conducted by the Council's International Committee for Contraception Research (ICCR) has evaluated the effectiveness and safety of NORPLANT® in a variety of clinical settings, culminating in the critical regulatory approval granted in Finland, the country of manufacture, in 1983. The Council's goal, now that the R & D phase is essentially complete, is to ensure that this new contraceptive technology is made available to women in both developed and developing countries in a manner consistent with safety and high quality of care.

In 1983 the Council, in collaboration with Leiras-Medica, and with other collaborating institutions, initiated a program to introduce the NORPLANT® method into family planning programs around the world. The first step, was the development of training facilities geographically placed in selected developing countries. These centers were selected on the basis of many years of clinical experience with the method, and a population of NORPLANT® users sufficient to provide trainees with experience with implant removal as well as insertion. Training centers are operational in Jakarta (Indonesia), and Santo Domingo (the Dominican Republic). Centers are being developed in Assiut (Egypt) and Campinas (Brazil). At these centers, leading physicians from countries wishing to introduce

the method receive initial training. The training sessions last three days and consist of didactic instruction about the method, "hands-on" experience in the insertion and removal techniques, and instruction in proper counseling of acceptors and potential acceptors. The physicians then return to conduct the pre-introduction trials in their own country setting. Family Health International is collaborating in the sponsorship of many of these pre-introduction trials and FHI serves as a central repository for trials data.

Simultaneously with the development of training centers and the initiation of pre-introduction clinical trials, the Council is working with several organizations including PIACT/PATH to develop prototypic training, counseling and informational materials. These will be adapted to local needs when the NORPLANT<sup>®</sup> method receives local governmental approvals for distribution and use in the various countries.

The information gained in the pre-introduction clinical trials, and subsequent user acceptability and programmatic needs assessment projects guides the Council and collaborating organizations giving technical assistance to country family planning programs

#### V 3.2.1. Current Status

The current status of NORPLANT<sup>®</sup> introduction efforts is as follows:

NORPLANT<sup>®</sup> has now received regulatory approval for commercial or programmatic distribution in eleven countries - Finland, Sweden, Thailand, Indonesia, China, Colombia, Ecuador, the Dominican Republic, Peru, Sri Lanka and Venezuela. In several additional countries, submissions to regulatory authorities are in preparation or under review. Teiras Medica takes responsibility for all registration efforts. The New Drug Application to the USFDA is nearly complete and will be submitted in 1988.

NORPLANT® 2 is approved in Finland. Unfortunately, one of the ingredients used in its manufacture recently became unavailable and the product will have to be reformulated. This will delay the timetable for introduction work of NORPLANT® 2 significantly.

Pre-introduction clinical evaluations of the NORPLANT® method are complete or ongoing in 26 developing countries (Table 3)

With the clinical aspects of the pre-introduction evaluation well under way, emphasis has shifted to research into the determinants of user satisfaction with the NORPLANT® method. Based on a model developed in Brazil, a user survey has been conducted in the Dominican Republic. Another user study has been undertaken in conjunction with a clinical study in San Francisco and one is soon to begin in Mexico. FHI has begun user satisfaction surveys in the nine countries in which it monitors trials. PIACT has completed focus-group interview-studies in Egypt, the Dominican Republic, Indonesia and Thailand, working with clinical investigators from Population Council-sponsored studies. The Population Council has now received non-A.I.D. funds to initiate a comprehensive program of use research designed to provide guidance to family planning managers in preparation for wider programmatic use of the method.

A draft training curriculum has been developed in collaboration with PIACT, FHI and the Association for Voluntary Surgical Contraception (AVSC). The curriculum will be tested in selected sites in 1988. Informational materials for clinicians and counselors are nearly completed. The Council is also assisting the World Health Organization in preparing a comprehensive publication to guide countries seeking to incorporate the NORPLANT® method into national family planning programs.

Table 3 Pre-Introduction Evaluations of NORPLANT® (NORPLANT® 2) Implants

COUNTRY	SITES	MONITOR	INITIATED	TRIAL STATUS	PROGRAMMATIC RESEARCH
Bangladesh*	3	FHI	Feb 1985	Follow-up	FHI user survey
Brazil*	21	PC	July 1984	Follow-up	PC user survey
Chile*	6	PC	Sept 1985	Enrolling	
China (PRC)	23	PC	Oct 1984	Enrolling	Training project
Colombia*	7	PC	July 1982	Enrolling	PC user survey
Dom. Republic*	4	PC	Dec 1984	Follow-up	PC user survey PIACT focus group study Training project
Ecuador*		PC	Mar 1985	Follow-up	
Egypt*	5	PC/FHI	Sept 1980	Follow-up	PIACT focus group study Training project
El Salvador*	4	FHI	June 1987	Initial training	
Ghana*	1	FHI	June 1987	Enrolling	FHI user survey
Haiti*	3	FHI	Nov 1985	Enrolling	FHI user survey
India	10	PC	Aug 1983	Enrolling	Training project
Indonesia	40	PC	May 1981	Follow-up	PIACT focus group study Training program
Kenya*	1	PC	Apr 1986	Follow-up	
Korea	1	PC	July 1986	Enrolling	
Mexico*	7	PC	Jan 1987	Enrolling	PC user survey
Nepal*	5	FHI	Feb 1985	Enrolling	FHI user survey
Nigeria*	5	FHI	Oct 1985	Enrolling	FHI user survey
Philippines*	2	FHI	Feb 1985	Enrolling	FHI user survey
Senegal*	1	FHI	Dec 1986	Enrolling	FHI user survey
Singapore*	1	FHI	Feb 1985	Follow up	FHI user survey
Sri Lanka*	3	FHI	May 1985	Enrolling	FHI user survey
Taiwan	1	PC	July 1986	Enrolling	FHI user survey
Thailand*	5	PC	May 1980	Complete	PIACT focus group study Training project
Tunisia	3	WHO	June 1987	Initial training	
Zambia	1	PC	Mar 1986	Enrolling	

\* Countries in which USAID funding supported NORPLANT® (NORPLANT® 2) implants.

### V 3.3. Copper T 380A Intrauterine Device

The Population Council has played a leading role in the research and development of intrauterine contraceptive devices since the early 1960s. Research on the intrauterine contraceptive action of copper led to a new design, the Copper T, which combined metallic copper and polyethylene in a "T"-shaped IUD, providing a high level of contraceptive effectiveness. This "T"-shaped IUD was a smaller device than previously "inert" IUDs such as the Lippes loop. The first Copper T IUD, the TCu 200, was introduced in 1973, and has now reached a worldwide distribution of over 30 million units. Continuous development efforts resulted in an advanced IUD, the Copper T 380A. By adding more copper in the form of sleeves on the horizontal arms of the "T", the contraceptive effectiveness was increased over that of the TCu 200, while maintaining the basic comfort and safety of the original Copper T. The Copper T 380A is among the most effective reversible contraceptives yet developed, and an important contraceptive option. This device received USFDA approval in 1984, and is now being introduced into family planning programs throughout the world. It will be marketed in the United States early in 1988.

Considerable controversy has surrounded IUDs over the past several years. In the early 1970s the Dalkon Shield was introduced into the US and other markets. This device had a faulty design, causing serious medical problems for many women who used it. Thus, the Dalkon Shield was removed from the US market in 1974. The negative publicity over the Dalkon Shield has placed all IUDs in a negative light among both providers and potential users of contraceptive products and services. This negative climate was a contributing factor in the 1986 decision by G.D. Searle and Company and Ortho Pharmaceutical to discontinue marketing IUDs in the USA.

Intrauterine contraception has undergone a considerable amount of scrutiny in the last year or so. Family planning experts, however, have concluded that

copper IUDs when used according to labeled instructions, are an effective and safe means of contraception. The Copper T 380A has been identified as an important method that should be available to women in all countries. Recently the Population Council negotiated a licensing agreement with a new company, GynoPharma, to introduce the Copper T 380A in the USA. Previous agreements had provided licenses for manufacturing and distribution through both public and private channels around the world.

In 1983 the Council and PIACT began development of a package of prototype training and informational materials, designed to support the introduction of the Copper T 380A IUD. These packages were distributed to family planning leaders around the world, and played a significant role in the incorporation of this advanced device into ongoing programs. Approximately 5 million Copper T 380A IUDs have now been distributed in 30 countries. Building on these materials, and the insight gained in the introduction of NORPLANT<sup>®</sup>, the Council, PIACT and other agencies have begun model country-specific needs assessment and training projects. (A case study of their first project undertaken in Bangladesh is included as Appendix 4) Projects in three additional countries are in the planning stages.

#### V 3.4 Future Plans

##### V 3.4.1 NORPLANT<sup>®</sup>

The Council and collaborating institutions have begun to utilize the prototype training and informational materials, and the network of trained individuals to provide technical assistance to "in-country" training programs. For example, over 700 Thai physicians have been trained in insertion and removal techniques. Training projects are being explored with leaders in Ecuador and Colombia.

The Council is working with government officials in selected countries to assist in incorporation of NORPLANT<sup>®</sup> into ongoing services. For example, looking ahead to Kenya's probable desire to provide NORPLANT<sup>®</sup> to its public through government

clinics, non-governmental organization (NGO) facilities and other outlets, the Council began a dialogue with government program leaders and policy makers. This will culminate in a country introduction strategy and the organizational upgrading needed to improve the abilities of concerned program managers and directors to manage this new method. Since this is likely to be the first undertaking of its kind in the region, it is expected that Kenya's experience will provide a "case study" for other African countries as they develop an interest in introducing NORPLANT®.

Three elements of the ongoing comprehensive NORPLANT® introduction program will be used to assist new countries wishing to begin using the method: the international training centers, the network of personnel in developed and developing countries experienced with the method, and a variety of prototypic informational and training materials.

The Population Council will draw upon the experience that it and collaborating organizations have gained in the program that has been successfully accomplished to date. This will allow the Population Council to assist new countries in initiating a clinical experience with NORPLANT® and in organizing for its introduction into family planning programs. Experienced personnel from collaborating agencies, along with Council inter regional and field staff, will form the core of expertise. Selected individuals from many of the institutions in developing countries that have participated in the pre introduction clinical trials and in the user-oriented research projects will also be called on to serve as consultants for needs assessment, medical backstopping and technical assistance assignments.

While it is important to provide technical assistance to institutions in each country planning introduction of a service intensive contraceptive such as NORPLANT®, it is especially so in sub-Saharan African countries in which clinical and

service provision infrastructure is less well developed. Accordingly, special attention will be given to the backstopping needs of African countries requesting assistance introducing NORPLANT<sup>®</sup>.

In order to prepare for the selection of participating countries, the Population Council plans to give the following planning and infrastructural considerations top priority as criteria:

- commitment of the Ministry of Health to the objectives of the project
- confirmation from the local government or a specific donor agency(ies) of commitment of financial support for local institutional costs during the course of the project and for subsequent support to the introduction effort after the initial enrollment period
- documentation for the Population Council and the manufacturer, Leiras Pharmaceutical, of local government approval for either commercial distribution and use of NORPLANT<sup>®</sup>, or for conducting a study
- adequate resources to assure appropriate staffing in clinics to perform insertions, removals and counsel potential users adequately, and to assure that the clinic facilities meet the criteria for proper aseptic conditions
- commitment from the Ministry and participating clinics to collect clinical data through one year of follow up on 100 cases, using Population Council approved protocol and record forms

Along with the human resources available from the Population Council's ongoing introduction program, a variety of informational and training materials will continue to be available for use and adaptation in new country settings. The Council, in collaboration with a number of other public sector organizations and Leiras Medica, has developed or is developing a variety of counseling, training,

management and other informational materials which directed to a specific audience important to the introduction process:

- A product monograph is nearly complete; this summarizes the available information on NORPLANT®: product profile, indications, pharmacology, mechanism of action, effectiveness, return to fertility and side effects.
- Leiras, PIACT and the Population Council have prepared, and are now updating, a clinicians' Manual which provides detailed instructions for insertion, removal, clinical follow-up, and other issues critical to appropriate clinical management. Similarly, a manual for counseling in the selection and use of the NORPLANT® method is near completion, and is currently being field tested in several countries
- Prototypic informational materials for users, which describe the method and provide important messages about its selection and use, understandable even by non literate women, are being developed by PIACT in collaboration with the Population Council and Leiras
- An interagency task group representing the Population Council, FHI, PIACT and AVSC is preparing a standardized training curriculum. The curriculum covers counseling, training of medical personnel, and other areas of importance in establishing an "in-country" training program
- The Population Council will continue a program of research on the determinants of user satisfaction with the NORPLANT® method and its service delivery system. PIACT has completed a series of group discussions with NORPLANT® users in four countries to guide informational materials development
- This array of training and informational materials and the clinical research aids that have been developed during the many years of pre-

introduction evaluations will be organized into a "starter package" to provide a strong base for management, clinical and service provision personnel in new countries preparing for their own introduction programs

- The Population Council's strategy in this inter-regional project will be to assist new countries in gaining initial experience with the NORPLANT® method, in devising country specific plans for introduction and in acquiring the local or regional resources needed to implement those plans.

**Other Future Activities with respect to NORPLANT®:**

U.S.A.I.D. Cairo has processed a (waiver) allowing purchase of 30,000 - 40,000 sets of NORPLANT® and a major training center may be established at Assiut

A full time medical representative may be sited in Africa to complement those in Asia and Latin America

An international conference, timed to coincide with the FDA approval of NORPLANT® is being considered. This is some two years in the future

The following additional countries have expressed interest in the NORPLANT® system: Panama, Jamaica, Bolivia, Burkina Faso, Uganda, Mauritius and Syria

The contraceptive introduction program has been successful in establishing an infrastructure for the management of the NORPLANT® and Copper T-380A IUD worldwide introduction. The Population Council feels that introduction strategy should go beyond the initial steps of familiarizing a family planning program with a new method. New methods, particularly provider dependent methods, place a special demand on the existing health care infrastructure. During the initial phase of introduction it is therefore important to assess the service delivery requirements of the method and assist programs in developing management systems with special

attention to maintaining quality standards of care and incorporating the user perspective.

The Population Council proposes to continue evaluation of the programmatic areas that will impact on the successful utilization of NORPLANT<sup>®</sup> and the Copper T 380A IUD worldwide. In addition, these strategies will be adapted to the introduction of other new methods during the ten year period 1988-1998. The Population Council's approach will be not only to introduce new methods into the health care system, but to aid in modifying the system to meet the needs of the new method. The Population Council proposes to build on their current management organization to ensure that Population Council inter-regional and regional programs have sufficient staffing to coordinate, develop, implement and monitor a multifaceted international effort. The introduction program will include continuation and expansion of activities with NORPLANT<sup>®</sup>, the reformulated NORPLANT<sup>®</sup> 2, and the Copper T 380A IUD. As these phase down, the Population Council will move toward the introduction of new methods, including the levonorgestrel releasing IUD, the progesterone vaginal ring and advanced barrier methods. The Population Council will focus on strengthening capacity to respond to a wide range of programmatic considerations such as

- the ability to oversee a broad based user oriented research program that will assist in the development of improved counseling, information, and training strategies, promote positive interaction with clinicians through mechanisms to provide feedback to family planning programs, and provide insights on unmet needs and user preferences that should be incorporated into the contraceptive development process,
- the development, testing and evaluation of a training strategy, curriculum, and informational materials that focus on providing adequate hands on training to physicians and paramedical personnel in

the insertion and removal and clinical management of clinic-based, provider dependent methods; allowing physicians and counseling staff to develop the appropriate communication skills and information base to ensure that potential acceptors make an informed decision about the contraceptive most suited to their needs and preferences; and overseeing the transfer and adaptation of a prototypic curriculum to different country settings;

- the continuation and expansion of the existing inter-agency collaborative network in order to maximize resources and institutional strengths as the programmatic phase of introduction begins; the development of a consultant resource database of international expertise in the medical, programmatic and communications areas, capitalizing on the existing international expertise developed through the NORPLANT® experience;
- collaboration with other Research & Development organizations to share Population Council management strengths in contraceptive introduction with other public sector institutions preparing to introduce new methods.

In addition to the above programmatic areas, the Population Council will plan to build upon its experience base in the areas of licensing, regulatory issues, and technology transfer. This will include interactions with the Population Council's Center for Biomedical Research and licensing organizations to fulfill regulatory requirements for availability and use of new methods, and working with licensees and appropriate "in-country" institutions to establish manufacture in those countries where demand is sufficient and technological expertise is appropriate.

### V.3.4.2. Issues

#### V.3.4.2.1. Effectiveness of Strategy

Both NORPLANT® and Cu T380A face political challenges and the potential of bad experience discrediting these methods. The avoidance of problems is a credit to the strategy and execution of the program. In the case of NORPLANT® opponents have charged that an "unsafe" method is being foisted on developing country women (unsafe because it contains long acting steroids similar to Depo Provera®). IUDs are under attack as causing infertility and "proven" unsafe because they were removed from the US market.

The development of well thought out training and introductory materials and their use by skilled trained clinicians in research settings has allowed relatively trouble-free introductions. However, one drawback to this strategy in the case of NORPLANT® is that there are only a small number of users — about 50,000 studied, with a total use of about 150,000 — and at a relatively high cost.

The Cu T380A has FDA approval and therefore can be purchased by A.I.D. In addition it is not a new method requiring difficult and slow registration and training activities. Therefore, introduction has gone very rapidly with about 5 million distributed so far.

#### V.3.4.2.2. Speed in Implementing Strategy

NORPLANT® introduction has been slow because of: 1) the complexity of the task, 2) the Population Council's careful approach to introduction 3) the need to work with other organizations, 4) the use of a non-FDA approved contraceptive, 5) the need to evolve a new and unique public sector program and to build an "in-house" and international staff and network for contraceptive introduction.

It is a matter of judgement whether faster work would have been possible. It is the view of the ET2 that although the Population Council may have erred on the

side of caution, the penalties of undue haste would have been severe and their course of action and pace while deliberate was prudent.

In the case of Cu T 380A commendably rapid progress has characterized the introductory activities. The imminent reintroduction of copper IUDs into the USA is a major achievement which will be very important to stimulating use of the same device in developing countries.

#### V.3.4.2.3. Staffing Pattern

As described above the Population Council has a small full time Contraceptive Introduction staff in New York and overseas. Over the past 5 years the Population Council has developed substantial institutional strength and steadily improved its intrinsic skills and its capability to recruit and use other "in-house" staff (e.g., user surveys and communications expertise, CBR staff) and the skills of outside organizations. New contraceptives will undoubtedly be introduced more rapidly and more efficiently now that the pioneering work has been done. While additional staff may be needed there appears to be little rationale for significant staff enhancements at this time.

This recommendation is, however, only relative to other programmatic needs under the cooperative agreement. Considering the magnitude of the task the Population Council is operating with a very small staff. For example, a drug company might have 100 to 300 sales representatives for the USA alone.

#### V.3.4.2.4. Coordination with Other Organizations

Ultimately NORPLANT<sup>®</sup> must be integrated into private and public family planning programs to developing countries. Therefore early involvement of major organizations supporting family planning service delivery is very important and at some point Population Council must decrease its role as custodian of the method.

Through an interagency task force the Population Council has systematically developed ties with and involved important organizations, e.g., PIACT/PATH, FHI,

AVSC, and to a lesser extent WHO and JHPIEGO. However greater effort is needed in the future to increase involvement of potential donors, e.g., World Bank (IBRD), UNFPA, trainers e.g., JHPIEGO and delivery organizations e.g., IPPF, IPPF/WHR, Pathfinder and FPIA. An important limiting factor in many countries is the product registration now handled by Lieras. Since Lieras is a small company it often works through other organizations to achieve product registration. Consideration should be given to speeding up this effort, and because the USFDA'S approval is highly influential on overseas registrations, completion of the NDA to the FDA should have high priority.

#### V.3.4.2.5. User Perspective Studies

Although these studies have been employed as a management tool, they are not predictive of ultimate acceptability of the method because the trials are in high quality clinics, i.e. those which are of a quality which is amenable to introductory trials.

What can be determined from such studies is what introductory methods are or are not working well. A principal finding from both focus groups and survey research is that problems of dealing with the authority figures in clinics' personnel are critical.

It has been found that: 1) provision of detailed risk-benefit information is very important — not just for NORPLANT<sup>®</sup> but for all methods. 2) counseling about anticipated side effects helps clients make informed choices and prevents drop outs — the original fears of "scaring away women" have proved unfounded. 3) psychological support is critical to acceptability — one aspect of this is access to needed medical instruction to care for any side effect. 4) experience both on the part of the clinics and users improves the acceptability and continuation. 5) spouses need to be involved.

The Population Council acknowledges that user studies cannot be carried out everywhere, but they believe that NORPLANT™ is so different from existing methods that failure to consider user needs would handicap the introductory effort.

The Population Council believes both studies of user needs and insertion techniques are essential. Experience in Brazil bears this out. The Ministry of Health (MOH) in Brazil became concerned about lack of informed consent and misinformation. However, the availability of the user survey which looked at three sites and the overwhelmingly positive responses on the part of users, allowed local NORPLANT® study personnel to confront the Sao Paulo state government and MOH personnel with the facts throughout 1986. They were able to demonstrate the value of the method and convince the authorities of the safety of the clinical trials.

The studies are also useful to improve the dialogue with feminist groups whose active opposition were it to occur, might hamper or even stop availability of a method. This too was important in Brazil.

The International Womens Health Coalition (IWHC) and the Population Council will hold a meeting for feminist leaders on what is new in contraception. A follow-up meeting to encourage continuing dialogue has involved US and overseas groups in discussing their concerns.

#### V.3.4.2.6. Country-Specific Informational Material

The Population Council strategy is to develop prototypic materials which can then be used by specific countries and regions. There are too many countries for them to take responsibility for development of all country specific material. PIACT has prepared a Spanish language version and India has already developed its own country specific materials.

The ET2 considers the printed informational materials developed by the Population Council and collaborating institutions to be of high quality, complete and readable. The strategy of preparing prototype materials seems appropriate.

The Population Council has noted a failure on the part of some countries to make wide enough distribution of informational materials.

#### V.3.4.2.7. Interaction and Coordination

Because the contraceptive development and introduction staff are close together physically and because initial contraceptive introductions have often been carried out at the ICCR clinicians' own institutions, there has been a high degree of communication between CBR and Contraceptive Introduction staff, including a formal committee, the NORPLANT<sup>®</sup> Working Group. The high quality of Contraceptive introduction activities and materials doubtless owes much to close ties with the contraceptive development expertise available in the CBR.

#### V.3.4.2.8. Staffing

The Population Council has developed a unique vertically integrated public sector program to develop and introduce contraceptives into developing countries. Analogous institutions in the private sector, i.e., drug companies typically spend tens of millions of dollars each year on R & D and marketing and overall employment levels may be in the thousands. By the standards of an ideal program, the Population Council effort is understaffed. However given total funds available and the uncertainty of funding levels year to year, the ET2 considers staffing — with a few exceptions — to be appropriate. These exceptions are discussed in Section VII. Overall Staffing Pattern.

#### V.3.4.3. Conclusions and Recommendations

a) The Evaluation Team was impressed by the overall high quality of contraceptive introduction activities. The very careful approach included an almost unique activity by taking into consideration the perspective of potential users. Information materials required for all levels of users for example, professionals, policy makers and clients were of the highest quality.

b) Speed of progress with respect to NORPLANT® introduction was slower than desirable for the following reasons:

- They need to build institutional capability
- The requirement that most introductions be carried out on a research basis
- Cost has limited availability of NORPLANT®
- The lack of a USFDA approval together with the relatively small size of the Lieras Company has hampered product registration in many countries
- Field staff has been of limited size
- The Population Council has chosen a very careful, deliberate and high quality introduction strategy. The ET2 recognizes that some of the reasons for a deliberate pace were beyond the control of the Contraceptive Introduction program staff.

c) The introductory activities relating to the Copper T 380A have proceeded quite rapidly and the anticipated re-introduction of Copper IUDs into the United States is a major achievement which will facilitate the widespread use of this device overseas.

d) The Population Council should seek the support of major donors for NORPLANT® introductory activities. It may be particularly valuable to have the support of donors which do not require a USFDA approval prior to purchase and distribution of contraceptives, i.e., the UNFPA and World Bank.

e) A.I.D. should consider enhanced distribution of NORPLANT® on a research basis if it is unable to waive the current policy relating to distribution of non-FDA approved drugs and devices

f) The Population Council should increase involvement of major service delivery programs, donors who support such programs, and technical

assistance agencies in their contraceptive introduction activities. Good collaborative arrangements exist with FHI, PIACT/PATH, PIP and AVSC. Principal agencies with whom greater involvement should be sought include the World Bank, UNFPA, IPPF, IPPF/WHR, JHPIEGO, Pathfinder and FPIA.

g) The Population Council should work closely with Leiras to ensure that each country's product registration activities go forward with as little delay as possible.

h) The Population Council should consider increasing the field staff by one or two persons particularly in Africa.

i) The Population Council should ensure that in depth documentation of contraceptive introduction activities including user perspective studies are carried out and are broadly disseminated to the population and family planning field.

j) Funding should be increased to accommodate more staff.

## **VI. FAMILY PLANNING PROGRAM COMPONENT**

### **VI.1 Overview**

The purpose of this component is to allow the Council to improve the implementation of family planning program efforts in developing countries through the conduct of field based projects, technical assistance and other activities. This program is intended to build on the Council's prior family planning research, evaluation and policy development activities in Asia, Latin America and the Middle East, and to extend expertise in this area to Africa.

#### **VI.1.1 Supported Projects and Activities**

A list of programmatic activities approved and funded by A.I.D. since 1983 under this cooperative agreement is given in Appendix 5. These activities generally fall into four broad categories: exploratory program development, in-country

technical assistance, operations research projects, and production of information and education materials. These are briefly described directly below.

Exploratory program development has been limited largely to Africa. From 1983 onwards, Council staff have traveled to various African countries, notably, Nigeria, Kenya, Zaire, Zimbabwe, Rwanda, Zambia and Mali, and have identified needs and worthwhile opportunities. These probings have led over time to several technical assistance activities and projects that either are completed or currently underway, and to several project ideas in various stages of proposal development. (See Appendix 6.)

Exploratory program development is now an intrinsic and active aspect of ongoing technical assistance and program monitoring travel by Council staff and consultants in Africa.

Several short- and long-term technical assistance activities have been conducted under the agreement. Examples in Africa include assistance to Rwanda and Mali in the development of family planning services statistics systems, assistance to Imo and Plateau States in Nigeria to develop five-year family planning strategies and plans, and on-going technical assistance to operations research projects in Zimbabwe and Zaire. As an indirect benefit of AID funding, the Council has established with non AID funding long-term technical assistance relationships with sub-Saharan African national programs, notably, Zambia and nine countries in the Sahel region (through the Sahel Institute in Mali)

A most significant long-term technical assistance effort supported under this agreement is the Council's work with the Bangladesh Ministry of Health and Population Control and International Centre for Diarrheal Disease Research, Bangladesh (ICDDR, B). The Council has supported family planning, MCH and demographic research in Bangladesh since 1972. Funding under the cooperative agreement since 1984 has allowed continued field research and extraction of

lessons learned to assist Bangladesh program managers to shape program policy and management decisions. Council staff are now engaged in documenting the operational research paradigm that has evolved in Bangladesh and are exploring potential applications in other countries with similarly weak bureaucratic infrastructures, particularly in Africa. A synopsis of the Bangladesh field research model is given in Appendix 7.

Other significant technical assistance efforts supported under this cooperative agreement include a 1987 review of Indian population program policies and guidance to the Mexican Social Security Institute (IMSS) in conducting a cost-benefit analysis of the IMSS family planning program. The results of both of these efforts are affecting national policy and program management practices in the respective countries.

The third major category of program activity supported under this cooperative agreement are in-country operations research projects. These have been developed following exploratory needs identification and program development trips and they are normally coupled with short- and long-term technical assistance commitments. There have been seven such projects funded under this cooperative agreement. These are

- Zimbabwe, The Kubatsirana Project — the purpose is to test the viability and effectiveness of an integrated approach to promoting family planning and expanding family planning services through women's income generating groups. Status: Current, in third and final year
- Zaire, The Kanaga Research Project — the purposes are to determine the demand for modern contraception in rural areas, to measure how much the demand for modern contraception can increase under optimal supply conditions, and to incorporate HIV information and prevention activities

as part of general family planning activities. Status: Current, in first of three years.

- Colombia, The Fundación Santa Fe de Bogotá Project. — The purpose was to test the cost and use effectiveness of integrating natural family planning methods into comprehensive health care systems. Status: Completed.
- Mexico, IMSS Cost Benefit Analysis Project — the purpose was to evaluate the benefits resulting from the IMSS family planning program in relation to the cost of carrying out this program. Status: Completed.
- Bangladesh, Support for Operations Research in Bangladesh — the purpose is to improve the efficiency and acceptability of family planning programs in Bangladesh through the support of various operations research activities in the Matlab and Expansion Project areas. Status: Current.
- Peru, The San Marcos HIV Project — the purpose is to learn if a special family planning service in a health center serving high risk women can increase contraceptive prevalence and appropriate HIV prevention behavior among the high risk women. Status: Current.
- Peru, The Prisma HIV Project — the purpose is to assess the impact and effectiveness of various HIV information and prevention activities. Status: Current.

The fourth major type of activity supported under the cooperative agreement is production of reports and information and education materials. Materials produced to date under the subagreement include the following.

- A videotape documenting the operations research project on household distribution of contraceptives in Boyaca, Colombia

- A camera-ready copy of the manuscript, Egypt: Demographic Responses to Modernization, edited by Awad M. Hallouda et al.
- Reprint of Handbook for Family Planning Operations Research Design, by Andrew Fisher et al.
- A report, Analysis of Population Policies and Programs in India, by George Brown et al.

In addition to the above, a number of research reports, particularly of the Bangladesh project, have been published in professional journals or presented at professional meetings, and there are plans to publish and present the results of other operations research projects and investigations funded under the cooperative agreement once they are completed.

A final type of cooperative agreement supported activity has been funding of the Council's Bogotá office. The office, established since the 1970s, has provided technical assistance, program monitoring and research services to several projects in Colombia. In recent years, staff of the office have become involved mainly with the development and monitoring of INOPAL projects in Colombia, Costa Rica and Panama. See Appendix 8.

#### VI.1.2 Funding

Of the three main components of the cooperative agreement, family planning programs receives the smallest share of funds. A total of \$3.4 million has been approved by A.I.D. from 1983 to date for the family planning program activities component of the cooperative agreement. This represents 16.2 per cent of total amount of \$21 million awarded by A.I.D. to date (22.3 percent if indirect costs are excluded from the base)

U.S.A.I.D./Mission "buy-ins" and A.I.D./Washington "add-ons" constitute a significant share of funds obligated for this component. Most of central A.I.D. funds have been used in Africa as a result of Population Council exploratory and

program development initiatives. "Buy-in" and "add-on" funding has been used mainly in Asia and Latin America. Projects and activities supported with "buy-in" funding are so indicated in Appendix 5.

### VI.1.3 Management and Staffing

The family planning programs component is managed from the International Programs Division which has primary responsibility for overseeing all of the Council's work in developing countries. International Programs (IP) work encompasses a broad range of activities. The principal program emphases for IP are operations research and evaluation in family planning; the world-wide introduction of Council-developed contraceptives; determinants of child health and mortality; enhancement of women's participation in development programs; and developing human resources and institutions. Publications, workshops, and seminars are integral to disseminating the results of these activities. Given the broad mandate of IP, there is a mutual interdependence with the policy development activities, biomedical research and publications work of other divisions of the Population Council and, indeed, linkages and communications between IP and the other operating divisions of the Council appear strong.

The work of IP is managed from an interregional New York office, which currently administers the Council's expanding activities in Africa, and by regional offices in Bangkok, Cairo and Mexico City. In addition there is an extensive network of sub-regional offices and country representatives located in Bangladesh, India, Indonesia, Zambia, Mali, Colombia, Brazil and Peru.

Professional staff at the end of 1987 included the Director, three Senior Representatives, 25 Associates, and seven Consultants. This includes 21 professionals based in 11 developing countries who maintain regular contacts with many other countries in each region.

In recent years the Council has devoted considerable attention to developing its management resources for sub-Saharan Africa. The Africa program is currently managed from New York under the supervision of the Director of IP who is the Acting Senior Representative for sub-Saharan Africa. Three additional New York-based professionals are dedicated full- or part-time to program development, monitoring and technical assistance in sub-Saharan Africa. A staff assistant is being recruited to manage the expanding administrative requirements for this program. This new position, according to Council staff, will allow for better monitoring and coordination of the sub-Saharan Africa program, including liaison with donors.

It is the Council's intention to place and delegate management responsibility for the sub-Saharan program to the field. The Council has placed two resident advisors in Zambia and in Mali. The Council is presently negotiating with the Government of Kenya to establish a regional office, and expects to place a senior representative in Nairobi by the end of 1988. It is envisaged that the senior associate will be responsible for Council work in East and Southern Africa. In Senegal, the Council is negotiating with the government to establish a sub-regional office in Dakar, which will be responsible for work in francophone Africa. The appointment of the senior associate to be based in Dakar is well advanced, and it is anticipated that the recruited individual will be in place by April 1988.

With the expansion of management capacity, both in New York and increasingly in Africa, the Council will be in a stronger position to expand its work and to engage in the long-term technical collaboration that is necessary to build strong population policies and programs in sub-Saharan Africa.

The A.I.D. cooperative agreement directly supports only a relatively small part of the IP's staffing and field structure. New York positions currently funded by the cooperative agreement include one Senior Associate (part-time), one Associate (part-time) and one Staff Associate (full-time). In addition, the cooperative

agreement currently supports an Associate (full-time) in Bangladesh with U.S.A.I.D./Dhaka "buy-in" funding. Part of the costs of the Bogotá office are also supported.

The following conclusions can be made about the Council's management structure and staffing, especially as they relate to the family planning programs component of the A.I.D. cooperative agreement. First, the Council has an extensively developed field network to which substantial authority has been delegated for developing, monitoring and assisting field-based programs and activities. Second, the professional staff in New York and the field have a well-deserved reputation for their high quality, commitment and productivity. Furthermore, whether in New York or the regions, they are pre-eminently field staff who are in close tune with developing country needs and realities. Third, the family planning program activities supported under the cooperative agreement have been well-informed by and benefitted from the Council's extensive field structure, only a small portion of which is directly supported by the cooperative agreement. Finally, the Council's largely successful effort to develop an effective management structure for sub-Saharan Africa, primarily with non-A.I.D. funds, is in alignment with A.I.D.'s own priority on Africa.

## ***VI.2 Review of Program Development***

This section reviews the effectiveness and appropriateness of the Council's identification, selection, development of program activities and projects.

The family planning programs projects and activities developed by the Council under the cooperative agreement that are discussed in Section VI.1.1 are rather diverse and wide-ranging. Considered in isolation their selection appears fairly ad hoc. However, program development activities must be viewed in the total context of the Council's overall international program and its extensive developing country field structure which is supported only in small part by the A.I.D. cooperative

agreement. In fact, the Council has a comprehensive international program and strategy with program emphasis in operations research and family planning program evaluation to expand low-cost contraceptive availability and use; investigations into the determinants of child health and mortality; enhancement of women's participation in development programs; and incorporation of population factors in the development process. To this set of program priorities, the Council recently added field research in the relationship between family planning programs and HIV information and prevention activities. All of the cooperative agreement funded activities fit into this framework which itself is largely consistent with A.I.D.'s own priorities and emphases.

From the review of project documentation and discussions with Council staff, it appears that projects and activities are carefully selected for their strategic value and impact potential. The Zimbabwe Kubatsirana project, for example, will allow testing of potentially lower cost alternatives to the national community-based contraceptive distribution program as the Zimbabwe national program looks to future sustainability. The technical assistance in 1986 to two Nigerian states in developing their statewide five-year plans for expanding family planning services produced prototypes for the development of plans in other Nigerian states. The new operations research project in Kanagu, Zaire will be critical in measuring demand for contraception in rural areas and testing pilot approaches in meeting and increasing demand.

The two HIV operations research projects in Peru are on the cutting edge of field research in whether and how family planning services can be successfully linked with HIV information and prevention activities. In response to concerns about the rapid spread of HIV in central Africa, the Council is undertaking a project to develop a computerized model that projects future trends in the annual number of HIV deaths, the number of HIV cases, and the prevalence and incidence of HIV

infection in populations with the African pattern of HIV transmission. The model will be made available on diskette for use in micro-computers and is of enormous potential value to health program planners and managers in Africa.

Of special importance not only to the Bangladesh national family planning programs but to national family planning programs in other countries with poor infrastructures, is the Council's work with the Matlab and MCH/FP Extension Projects in Bangladesh. This work, funded by a U.S.A.I.D. Mission "buy-in", has directly influenced national family planning program policy structure and management in Bangladesh's particular bureaucratic setting where the ability to utilize effectively research findings to affect structural and policy change has been very limited. The Bangladesh research decision-making model is of obvious potential value in other national family planning program settings with similarly weak infrastructures and rigid bureaucracies. The Council plans to assess the relevance of this model in Africa.

Another critical area with long-term potential impact where the Council has effectively worked has been with the provision of on-going technical assistance to fledgling national family planning programs in institution building and development of service statistics and management information systems. In the past the Council established successful technical advisory relations through resident advisors and other mechanisms in a number of countries including Tunisia, Bangladesh, Colombia, the Dominican Republic and El Salvador. Long-term technical assistance relationships are now being developed in African countries. The Council has undertaken a long-term technical assistance and research program in Zambia. This entails the placing of a resident medical advisor in Lusaka who works closely with the Ministry of Health and the Planned Parenthood Association of Zambia to develop a broad range of programs including improved management information systems, operations research, activities to design outreach family

planning programs, and ways to more closely integrate various agencies involved in family planning. Work has also been undertaken in helping to design HIV public information programs, and in broader population policy assistance.

In the Sahel region, the Council has initiated a major new project with the Sahel Institute based in Bamako, Mali. This project will provide evaluation and research technical assistance to the nine member countries of the Sahel Institute. A resident advisor on evaluation was stationed in Bamako in October 1987. This project builds upon close collaboration with the Sahel Institute in demographic and social research activities over the past seven years.

The Council has for many years worked with institutions in a number of African countries to build up their capacity to undertake training and to perform research. Most recently, this work has focused on the Universities of Zimbabwe and Nairobi. In Zimbabwe, the Council has worked with the Department of Sociology to develop a Masters level training program in population. This program has now been approved by the University, and is about to be initiated. The Council has provided technical assistance, and has assisted in identifying funding sources. It is expected that this long-term project will require continued Council participation. In addition to the training program, a number of Zimbabwean social scientists will receive training overseas, and funds will be provided for resident academic support until such time as the Zimbabwean professional capacity is expanded. Training will be provided not only for Zimbabwean students, but also those in neighboring countries.

In Kenya, the Council has worked with the University of Nairobi for the past ten years, in developing a Population Studies and Research Institute (PSRI). A new director of the Institute is interested in expanding collaboration with the Council, and in undertaking family planning program relevant research. It is anticipated

that the Council will have continuing close professional relationships with the University of Nairobi.

It should be mentioned that, with the exception of Bangladesh, virtually all of the Council's long-term technical assistance and institution-building activities are relying on non-A.I.D. funding for their support. They nevertheless are of direct relevance to A.I.D.'s support for international population assistance.

In summary, as the foregoing examples should amply illustrate, the Population Council's selection and development of family planning projects and activities have been appropriate, are undertaken within a consistent framework of program priorities, are in accord with A.I.D.'s own interests and priorities, are generally done with an eye on their strategic value and potential impact, and have a long-term underlying aim of developing local capacities and infrastructures.

### **VI.3        *Review of Regional Programs***

#### **VI.3.1      Sub-Saharan Africa**

Specific sub-Saharan African programs have already been discussed. Also previously discussed was the Council's largely successful and continuing effort to develop a strong, decentralized field office structure in the region staffed by well-qualified professionals. Thus this section will briefly comment on significant issues of the Council's sub-Saharan Africa program that have not already been discussed, and to summarize recommendations of specific relevance to Africa.

Council staff repeatedly affirmed that monies provided under the cooperative agreement were a crucial input enabling the expansion, development and maturation of the Council's overall sub-Saharan Africa program. Although the Council relies on several donors and funding sources for sub-Saharan Africa activities, A.I.D. cooperative agreement funding for headquarters staff time, travel, in-house projects and selected sub awards to local African institutions provided the wherewithal and flexibility needed to forge a comprehensive strategy and

management structure. In particular, the exploratory program development afforded by A.I.D. funding, especially in the first years of the cooperative agreement, allowed for a balanced assessment of needs, identification of priorities, and the development of a cohesive strategy for the region.

The Council's program in sub-Saharan Africa has now reached a critical take-off stage. Needs have been, and continue to be, assessed. Projects and project leads are being developed (see Appendix 6). Field staffing and management structures, while still being evolved, are well-positioned to develop and support programs. And, an extensive network of institutional and professional relationships has been cultivated and is ready to be tapped. These are major accomplishments for a difficult region and the momentum of this effort should be sustained.

Another important conclusion with future relevance is that the Council has demonstrated with its Zimbabwe and Zaire projects its ability to develop and undertake operations research in sub-Saharan Africa. In addition, it has undertaken extensive technical assistance activities in several countries to develop investigatory, operations research, service statistics and management information systems and skills. (In addition, the Council has extensive operations research capacity and experience in Latin America (with its INOPAL project) and in Asia (with the Matlab and MCH/FP Extension Projects in Bangladesh), and these can inform and benefit new operations research initiatives in sub-Saharan Africa. While it is understood that an A.I.D. operations research contract will be competed in 1988, and the possibility exists that the Council may not win the contract, we believe that it would be a considerable loss to family planning programs in Africa not to have access to the Council's capacity and expertise. Continued A.I.D. funding of selected operations research activities of the Council in Africa should be permitted (perhaps through "buy ins") even if the operations research contract is awarded to another institution.

In sub-Saharan Africa, the infrastructures are weak and there is limited capacity not only to undertake program-oriented research but to translate research findings into useful decisions and activities on program policy, structure, and management.

We were also impressed with the extent to which the Council has carved out an apparently unique role in establishing long-term technical assistance and institution-building relationships with numerous national family planning programs, particularly in the areas of developing service statistics, management information systems and program research and social science investigatory capacities. As previously mentioned long-term assistance is now underway in Kenya, Mali, Zambia, Zaire and to nine Sahel countries through the Sahel Institute in Bamako.

#### VI 3 1.1. Recommendations

ET2 recommends therefore that:

- a) Under a new cooperative agreement, A.I.D. continue to provide flexible funding to the Population Council for its sub-Saharan Africa family planning program activities so that the Council can maintain and accelerate its forward momentum in the region
- b) A.I.D. continue to fund and utilize the Council's extensive capacity to undertake in sub-Saharan Africa family planning program evaluation and operations research
- c) In the sub-Saharan context, the Council's work in Bangladesh may provide a useful model and we support the Council's intention to adapt it to several sub-Saharan countries
- d) In the next cooperative agreement the Population Council's long term technical assistance and institution building role in sub-Saharan Africa be explicitly recognized and supported through the allocation of funds for these activities

### VI.3.2. Asia

Virtually all the Council's activities in Asia under this cooperative agreement are supported through the "buy-in" mechanism and these have been limited to "buy-ins" from the U.S.A.I.D. Missions in Bangladesh and India. Both "buy-ins" have been for significant and fruitful projects in areas where the Council's interest are in accord with those of the respective U.S.A.I.D. Mission's.

It was beyond the scope of this evaluation to review comprehensively the Council's important Bangladesh program funded through a Mission "buy-in." Presumably this will be assessed separately at some point by the Mission itself. Nevertheless, it seems clear that the Council's work with the Matlab and MCH/FP Extension Projects has had a great impact in Bangladesh and the operational framework model for this work deserves adaptation and testing in similar settings of other countries, particularly Africa.

#### VI.3.2.1. Recommendations

a) Although it seems unlikely that scarcer central A.I.D. funds will be allocated for the Council's family planning program activities in Asia, it is recommended that the Council retain the capacity to use central A.I.D. funding in Asia for mutually agreed, high leverage projects and activities

b) We support the Council's intention to adapt the Bangladesh model to other settings and to document the system and publish results so others can also benefit from the experience

### VI.3.3. Latin America

The Council's extensive program in Latin America is managed by its Mexico City regional office and through country and sub regional representatives in Colombia, Peru and Brazil. With respect to family planning program activities, the bulk of these are done as operations research through the INOPAI project under a separate A.I.D. contract. Family planning program activities funded under the

cooperative agreement have been relatively few, especially when compared to Africa. These have included a natural family planning operations research project in Colombia; a cost benefit study of family planning programs in Mexico; the videotaped documentation of a community based distribution operations research program in Colombia, two HIV and family planning operations research projects in Peru; and partial support for the operational costs of the Council's country office in Bogota

The funding of the operational costs of the Bogota office under the cooperative agreement is somewhat anomalous. This was justified for historical reasons. The Council has had an office in Bogota since the early 1970s and there were several important program activities and relationships that were worthy of continued support at the time the cooperative agreement proposal was developed in 1983. However, since 1983 it is clear that the Bogota office is increasingly engaged in operations research and works under the aegis of the INOPAL program. (See Appendix 8.) While it seems apparent that projects and activities developed and managed by the Bogota office are appropriate and worthwhile, it is not clear why these should not be totally subsumed under the INOPAL program. However, the INOPAL contract with A I D. will soon expire and A I D. will again issue a RFP for the Latin America operations research contract, for which the Council intends to compete

Regardless of whether the Council wins the next Latin America operations research contract, the Council's long standing presence in Latin America, its operations research experience and track record, and the presence of a field structure to manage its regional programs is a considerable resource for A I D. and the international family planning community

### VI.3.3.1. Recommendations

It is recommended therefore that:

a) A.I.D. consider providing short term bridging support for the Council's Bogotá office until a decision on the Latin America operations research contract is reached. The Council should carefully consider whether to fold support for the Bogota office in their next proposal for the operations research contract

b) Under the next cooperative agreement the Council continue to be allowed to respond to worthy targets of opportunity in Latin America that cannot be supported by A.I.D. through other mechanisms, or where the Council clearly has the expertise and capacity to delivery quality results in timely and cost-effective ways.

### *VI.4 Management of Cooperative Agreement*

The scope of work did not permit a careful review of the Council's management of family planning projects and of the cooperative agreement itself. In particular, there were no visits to field projects or discussions with developing country counterparts of the Council and with U.S.A.I.D. Missions. Impressions are derived from discussions with A.I.D./Washington personnel who did not express any serious concerns or complaints, and from discussion with Council staff and review of documentation supplied by the Council

It does nevertheless appear that the Council is doing a good job in managing the workload, supporting field activities, complying with A.I.D.'s requirements, and responding to A.I.D.'s queries. With few exceptions, projects appear completed in a timely manner. On site monitoring (site visits) and project reporting was not identified as a problem. Staff resources have expanded and structures have been adapted to meet the growing challenge in Africa

The one area where some minor improvements can be made is that of reporting to and liaison with A.I.D. Both Council and A.I.D. staff, for example,

expressed dissatisfaction with the format and content of the Council's annual report to A.I.D. on the cooperative agreement.

A.I.D. staff reported occasional difficulties in getting timely information from Council staff due to their frequent absences for field travel and late submission of trip reports. The situation should improve considerably once the Council completes recruitment for a New York based staff assistant to help manage the expanding administrative and liaison requirements of the African program.

#### VI.4.1 Recommendations

a) The Council and A.I.D. should work together to develop an annual reporting format that is responsive to the needs of both agencies.

b) As regards trip reports, A.I.D. and the Council should discuss trip reporting requirements and incorporate agreements concerning deadlines, format and content in the next cooperative agreement.

#### VI.5 Value of Cooperative Agreement to A.I.D.

The overall conclusion is that A.I.D.'s support to the Council for the family planning programs component of the cooperative agreement has been extremely productive and worthwhile.

The ET2 believe there are several interrelated reasons that justify this broad endorsement of the Council's family planning programs work. First, there is the track record. The Council's approach, as this evaluation report documents, produces results that have made a difference to field programs. Second, the Council is a unique resource in the world with its extensive field structure, its multi-disciplinary approach to program development and research, and its highly professional and qualified staff. The family planning programs component of the cooperative agreement gives both A.I.D./Washington and U.S.A.I.D. Missions the ability to tap into this formidable and unparalleled resource. Third, insofar as the family planning programs component is essentially a field based operation, it helps to

keep the Council's work in the other vital areas of contraceptive development and introduction well-informed and directed by programmatic needs, constraints and imperatives. Fourth, the Council's family planning programs work has been responsive to A.I.D.'s own changing priorities over the years (e.g., sub-Saharan Africa, natural family planning, HIV). Finally, the Population Council is one of the very few international population agencies that has the capacity, with its field structure and multi-disciplinary focus to provide long-term, hand-holding technical assistance to national family planning programs in the areas of institution building, research, service statistics and management information systems. It did this successfully in the past in Asia and Latin America, and it has laid solid groundwork for doing the same in several sub-Saharan African countries where national family planning programs are in their earliest stages of development and in need of careful, professional nurturing.

#### VI.5.1 Recommendations

a) The ET2, therefore, recommend that the next cooperative agreement between A.I.D. and the Population Council continue explicitly to include and fund the Council's important, highly leveraged work in family planning programs.

#### VI.6 *New Directions*

Time did not permit a thorough review of new types of family planning program activities that might be supported under a new cooperative agreement. The ET2 understand the Council and A.I.D. have already exchanged preliminary ideas about future priorities. Below is a very brief discussion of a few ideas for new directions that emerged from discussions with Council staff during the evaluation. These new directions certainly seem reasonable, appropriate and consistent with A.I.D.'s own priorities.

#### VI.6.1 Emphasis on sub-Saharan Africa: Institution Building and Strengthening Family Planning Service

The Council's shifting focus to sub-Saharan Africa has already been extensively discussed in this report. The areas where the Council can make considerable contributions are in the areas of strengthening family planning services delivery, especially through operations research, and institutional development.

#### VI.6.2 Sexually-Transmitted Diseases, Including HIV, and Family Planning

The Council has already begun to investigate the important area of sexually-transmitted diseases and the special relationship with family planning programs. The emergence of HIV as a serious and unparalleled public health threat lends urgency to these investigations. The Council has the capacity to conduct operations research on the development of HIV information and prevention activities within family planning service programs.

#### VI.6.3 Quality of Care in Family Planning

In 1987 the Council began a program to investigate the relationships of the quality of family planning care with increased contraceptive usage. Several avenues for improving quality are being pursued: improving contraceptive choices, providing understandable information to users, improving provider competence, designing better follow-up mechanisms, and maintaining strong user perspectives in the design of services. This program, it seems, builds on the Council's experiences with its new contraceptive introduction program where concern for quality has been an organizing principle.

#### VI.6.4 Postpartum Family Planning and Health

The Council intends to develop and investigate new ways of delivering and expanding use of family planning and health services during the postpartum period.

#### VI.6.5 Policy Research

The Council hopes, as mentioned elsewhere in this report, to adapt and test the Bangladesh field research/policy development model to other countries where major structural and policy change is needed but where administrative capacity is limited.

### VII. OVERALL STAFFING PATTERN

#### *VII.1. Overall Expertise*

While it appears that overall expertise is available in all important areas, in many cases key activities depend on one or two individuals. The loss of a key person could seriously impact the progress of the program. For example, absence of Dr. Nash during the next few months would seriously affect the expected NDA filing for NORPLANT™ by June, 1988. Consideration might be given to the provision of key man insurance for selected individuals if the cost was not prohibitive. Clinical assistance is provided by Dr. Spitz and the members of the ICCR. Addition of an extra full-time clinician is likely to prove prohibitively expensive.

#### *VII.2. Staffing Level Sufficient*

In general staffing is appropriate, however the many delays experienced in NDA development for NORPLANT™ and the lack of capacity to prepare an NDA simultaneously for NORPLANT™ and the levonorgestrel IUD suggests that staff augmentation for the NDA process is desirable either through direct hiring or outside assistance. The staffing pattern for contraceptive introduction activities is also a constraint on the most rapid possible progress. With regard to overseas field staff it was not possible to make a firm judgment. However, at least one full time staff person — and preferably two for Africa — would appear to be desirable.

Thus, it is the general impression of the E12 that additional staff are required in several crucial areas — toxicology, clinical trial monitoring, dosage formulation,

preparation of FDA filings and field staff. It is recognized that these are ongoing activities and that recruitment of additional permanent staff will require an increased budget for funding these core activities on a multiyear basis. ET2 recommends that provision of such funding and recruitment of staff become a high priority for the next agreement.

### ***VII.3. Subproject Oversight***

To the extent it was possible for the ET2 to discern, oversight of all subprojects was appropriate. In the biomedical area, subproject investigators have been highly qualified and well established and their work needs little supervision. It was not possible to investigate developing country subprojects but documentation suggests close interaction has been possible on all subprojects.

Most of the subprojects in the future will consist of clinical trials and operations research projects. There is evidence that these have been conducted and monitored in an exemplary fashion. If expansion of such subprojects occurs additional staff will be required to ensure continued high quality monitoring.

### ***VII.4. Use of Consultants***

The ET2 were not given a list of consultants used in the last 4 years and so it is difficult to judge their use. In the response to ET1 it is claimed that consultants are used as necessary, but it is the impression of ET2 that greater use of outside experts may have been cost-effective in some areas.

As already noted, increased use of experienced outside consultants might have enhanced NDA preparation efforts. Another area where outside involvement should be improved relates to major service delivery organizations which eventually will incorporate new contraceptive modalities into their service and training programs i.e., AVSC, FHI, PIP, PIACT/PATH, IPPF, WHO, UNFPA, JHPIEGO, FPIA and Pathfinder.

## **VIII. RELATIONSHIP OF THE PROGRAM WITH A.I.D.**

### ***VIII.1. Washington Staff***

The program functions more as a grant to Population Council selected activities to a larger extent than for many A.I.D. agreements, where 90% or more of support comes from A.I.D. In the case of the Population Council many other donors provide a substantial share of overall support. Accordingly, A.I.D.'s level of control over the project is not as great as for many other programs. Even so A.I.D. only supports activities which are mutually agreed on. This process appears to be characterized by a high degree of collegiality between the Population Council and A.I.D., with a full exchange of information and mutual respect. A.I.D. project managers are provided a shopping list of possible projects to support each year from which they select those which have A.I.D. approval. In addition, from time to time unforeseen needs arise which receive A.I.D. approval on an ad hoc basis. This is particularly true for the family planning technical assistance aspects of the programs. It appears that there is a good working relationship between the Population Council and A.I.D. project staff. No obvious problems were described to the ET2.

### ***VIII.2. Missions***

The evaluation team was not in a position to assess directly Population Council relationships with mission staff. However, the fact that missions have made numerous "buy-ins" and requests for assistance suggests a strong and harmonious relationship exists. In addition A.I.D./W staff believe relations between the Population Council and A.I.D. missions are good. The missions themselves will have to be consulted as to their satisfaction with the Population Council performance on mission "buy-ins" and "add-ons."

## **IX. Funding**

### ***IX.1. Current Status***

The development and introduction of contraceptives is a very expensive and long term endeavor. In industry this process is estimated to require \$25-50 million and 10-15 years for each new contraceptive. New and improved contraceptives are one of the few proven ways family planning programs can make major advances in effectiveness and efficiency. The program therefore is both very important and very expensive.

The overall pattern of funding provided by A.I.D. in the years 1985-1987 inclusive is shown in Appendix 3. Total direct costs were \$2.374, 3.558, 3.665 and 3.186 million respectively. These amounts represented the following percentages of the amounts requested — 86, 85, 73 and 64% respectively. In percentage terms it is clear that there has been a steady decline in current dollar funding provided. In contrast, the actual dollar amounts provided showed an increasing trend up to 1986 and then a sharp fall. These figures are, of course, greatly influenced by the amount and number of "buy-ins" or "add-ons" and these cannot be predicted in advance.

For the contraceptive development program the current dollar amounts provided have remained relatively constant over the last 3 years but this is not true in constant dollar value when adjusted for inflation. Not including the "buy-ins", the percentage of the total support provided by A.I.D. for contraceptive development was 50% in 1986 and 60% in 1987 (63% if NIH funds are included). The level of the NIH contribution is not expected to increase significantly.

Support from other sources for the contraceptive development program for 1986 and 1987 totalled \$1.535 and 1.956 million respectively or 47% and 51% respectively of total program support. This indicates the large extent to which the contraceptive development program is dependent on A.I.D. support. In the past, support was provided by the Rockefeller, Ford and other Foundations. These

sources do not now provide continued funding except on a very minimal level. Owing to the desire of the Population Council to provide new contraceptives at the lowest price to the public sector, past licensing agreements have provided for very little return to the Population Council from sales of, for example, the copper T IUDs. In addition, the long lasting nature of most of the Population Council discoveries mitigates against streams of income from resales. This may change somewhat for new products in the pipeline, but is still unlikely to be a major source of income for operations support.

An endowment has been raised by the efforts of the President and Board of Trustees of the Population Council which generates sufficient income to cover approximately 5% of the annual budget of each of the component programs of the Population Council. This provides for flexibility, especially when delays in funding ongoing projects are encountered. Obviously, it would be very valuable to increase this percentage, perhaps up to 10% but that is a matter for internal Population Council decision and action. The Population Council maintains a unique public sector contraceptive development effort which works in partnership with private industry as needed. With the continuing withdrawal of the pharmaceutical industry from the contraceptive R & D field, the maintenance and even expansion of this program is of high priority for population program resources. Progress under this program is hampered by inadequate financial support of the Population Council's program. Overall funding should be increased in a stepwise fashion over the next few years by about 50% over the current level of funding. Stability of funding is particularly important to the Population Council since contraceptive development is a long term commitment and the maintenance of a highly qualified multi-disciplinary team is essential to the process.

The ET2 has recommended that increased funding be made available to the Population Council as indicated above. However, should A.I.D. budgeting

constraints result in the same or decreased funding levels in forthcoming years, ET2 recommends that the following order of priorities be followed.

(1) Actions needed to complete development and regulatory approval of those contraceptive methods close to clinical use — NORPLANT<sup>®</sup>, NORPLANT<sup>®</sup> 2 AND LNG IUD.

(2) Actions needed to complete development and regulatory approval of at least one vaginal ring — in order of priority and feasibility, norethindrone acetate-ethinyl estradiol ring, progesterone ring, ST-1435 ring.

(3) Support of contraceptive introduction activities.

(4) Biomedical probing studies (not more than 10% of total budget).

(5) Family planning program technical assistance and operations research.

### *IX.2. Findings*

At present all interesting new leads cannot be pursued, however, the most important leads can be investigated. There is not adequate staff or space for new staff at the Population Council to allow much expansion. Most of the important contraceptive development leads — the more applied aspect of the program — can be followed. However, if a number of contraceptive development tasks had to be carried out simultaneously both funds and staff would become a serious constraint. For example, if a transdermal contraceptive delivery system, a progestin vaginal ring, an estrogen + progestin vaginal ring and the levonorgestrel IUD needed NDA preparation simultaneously, serious delays would result.

The more basic probing studies are often carried out with or at other institutions. Since the odds for eventual "pay-off" of these studies is lower and since almost any level of support could be absorbed by the field, A.I.D. should be selective in supporting these studies.

Mention was made of the importance to the Population Council Contraceptive Development Program to the facilities at the Rockefeller University, e.g. machine

## APPENDIX 1

Actions taken by the Population Council in response to the recommendations made at the U.S.A.I.D. Review of the Contraceptive Development Program in 1983

### Response to the General Recommendations

1. Expansion of the membership of the ICCR and/or more frequent rotation of existing members should be considered.

ICCR members carry out most of the clinical trials for the Council and perform development work in their own laboratories. In that they spend one-third (or more) of their professional efforts on Council projects, they are viewed as "extended" Council employees. Therefore, when we identify an ICCR member who is valuable to the Council, we feel that it would not be to our advantage to rotate them on a regular basis just as a company or a university would not rotate staff.

We do rotate ICCR members when they change their professional activities in such a way as to have a conflict of interest with Council work or when they are no longer effective investigators. Four ICCR members have been rotated for these reasons, and we anticipate that another will be rotated in 1988.

In order to expand the consulting staff of the ICCR, in 1985 the Council established a new position termed "Consulting Scientist." This permits appointment of both senior and junior consultants of exceptional merit to work with ICCR members and Council staff for several consecutive years. There are currently four Consulting Scientists serving the Council's Contraceptive Development Program. One additional Scientist will be recommended for such a position in early 1988. These consultants provide our program expanded expertises in both laboratory and clinical sciences.

2. Making efforts, in advance of need, to identify companies that can provide the expertise, commitment and financial resources necessary to complement the Population Council activities would be helpful.

There is a limited choice of companies available when patented compounds are considered for contraceptive studies. Development work carried out at the Population Council on new delivery methods and with unpatented compounds has to be taken to fairly advanced stages before negotiations with companies are initiated in order to strengthen the Council's bargaining position. Therefore, advantages and disadvantages of early negotiations must be weighed very carefully. Our usual process is to sign a confidentiality agreement to allow for exchange of information. We then sign a letter of agreement that outlines the principles under which we will work together. If the work proceeds, we then negotiate a contract. In the case of Leiras, it is clear that our choice of a company and our method of negotiation led to successful production and introduction of NORPLANT<sup>®</sup> and NORPLANT<sup>®</sup> 2 into the public and private sectors. The collaboration between Leiras and the Population Council was also effective for training and promotional activities required for the introduction of these contraceptives. This and similar relationships may prove effective for the introduction of other methods in the future.

3. Nominating one individual to be responsible for all toxicological studies and as monitor for good laboratory and manufacturing practice could improve efficiency. The same person could be the focal person for interaction with the FDA for reporting all severe adverse reactions occurring during clinical trials.

Dr. Sundaram is now responsible for all toxicology studies. Dr. Moo Young is the Quality Assurance Officer. The regulations of the Food and Drug Administration require that different persons be responsible for these two areas of responsibility. All adverse reactions reported to the Council are now reviewed by I.

Spitz in consultation with D. Robertson and i. Sivin. If a reaction is judged to be "severe," it is reported immediately by Spitz in accordance with FDA regulations. If the reaction is judged not severe, it is reported in the annual report on the drug or the device associated with the reaction. All communications with the FDA are now filed with F. Schmidt who is in charge of the regulatory unit at the Council.

4. Some of the burden shouldered by Dr. Nash should be lightened, either by greater delegation of more routine matters and/or provision of extra staff assistance.

Recent changes in the management of the ICCR will make it possible for Dr. Nash to concentrate on the NDA for NORPLANT<sup>®</sup> and on the development of new dosage forms and delivery systems. Dr. Thau will assume responsibility for the day-to-day coordination of the contraceptive development program.

5. The use of a part-time consultant to assist with FDA filings is commended.

Part-time consultants have been used when needed to assist with FDA filings during the past granting periods.

6. The addition of a staff member to act as clinical coordinator and monitor is felt to be useful.

Dr. Spitz was added to the staff to function as Clinical Coordinator. He site visits all projects on a regular basis to assure compliance with protocols. In addition, Dr. Gunsalus is now monitoring the quality control of hormone assays in laboratories of collaborating clinics.

#### Response to Specific Recommendations

1. Continued major interaction with Leiras to ensure the speedy and effective introduction of the NORPLANT<sup>®</sup> and the levonorgestrel IUD is essential.

As has been mentioned above, our continued interaction with Leiras has been successful. The interactions not only with the Center for Biomedical Research,

but also the International Programs Division have led to the rapid introduction of NORPLANT<sup>®</sup> and NORPLANT<sup>®</sup> 2. The collaboration with other organizations such as WHO, FHI, and AVSC has also been very important in this effort. As noted in the progress report, the introduction of NORPLANT<sup>®</sup> 2 and the levonorgestrel IUD will be delayed due to the withdrawal of a Medical Grade Elastomer.

2. Completion and interpretation of the various toxicological studies with the CVR must be a major priority. Alternate strategies should be devised to circumvent adverse toxicological findings.

When toxicology studies are subcontracted, the laboratories are chosen based on merit and have their own quality control units. A liaison person at the Population Council is assigned to each study. However, incidences such as the unforeseen weight gain of monkeys and death of rabbits caused by hair balls could not have been prevented even by much more frequent surveys by Population Council personnel.

3. Mechanization of the closure process for the CVR needs to be speedily resolved.

With the use of alternate steroids with different diffusion properties, the problems of the closure process are no longer relevant.

4. There needs to be resolution of the toxicological problems with the LHRH antagonist (LHRH 22) and an alternate compound selected before too much is invested in the present one.

The toxicological problems with LHRH 22 and all other antagonists were due to the basic amino acid in position 6. Council findings alerted the worldwide research community to this problem and led to the development of alternate antagonists. At the Population Council LHRH 22 has been replaced by LHRH 34. The latter antagonist is as potent as LHRH 22, but causes minimal histamine release.

5. Major investment in the LHRH analog field should await further clinical evidence of their efficacy as male contraceptive agents and the development or acquisition of a suitable delivery device.

Clinical trials have now shown that long-term continuous administration of LHRH agonists can effectively suppress spermatogenesis in men. As noted in the progress report, we are now developing a delivery device which should deliver such agonists for one year

6. A delivery system suitable for long-term administration of androgens needs to be developed or long acting androgens acquired as they will be required for successful use of LHRH analogs as male contraceptives.

A device for long-term administration of a high potency androgen is being developed at the Population Council; we believe it will also be useful for one year.

7. The potential consequences of long-term anovulation and/or reduced luteal activity needs to be considered prospectively when clinical trials of agents with such properties are being designed

Potential consequences of long-term anovulation and associated hypoestrogenicity as observed in some women who received LHRH-13 daily coupled with the lack of any effect on ovulation in others who received the same dose of LHRH-13 led us to discontinue this contraceptive lead

8. Major investment in the inhibin area should await isolation and characterization of a pure protein/peptide with the desired biological activity.

The structure of inhibin is now established and many of its biological activities have been defined

January 6, 1988

**APPENDIX 2****International Committee for Contraception Research**

C. Wayne Bardin, Chairperson  
The Population Council

Horacio B. Croxatto  
Chilean Institute of Reproductive Medicine  
Santiago

Anibal Faundes  
University of Campinas  
Brazil

Elof D. B. Johansson  
University of Uppsala  
Sweden

Tapani Luukkainen  
University of Helsinki  
Finland

Daniel R. Mishell, Jr.  
University of Southern California

Regine Sitruk-Ware  
Ciba Geigy  
Basle, Switzerland

G. Pran Talwar  
National Institute of Immunology  
New Delhi, India

**Consultants**

Gary D. Hodgen  
CONRAD, East Virginia Medical School  
Norfolk, VA

Mamdouh M. Shaaban  
Dept. Ob Gyn, Assiut University  
Egypt

Badri N. Saxena  
Deputy Director General, ICMR, New Delhi  
India

Roy Hertz  
Hollywood, Maryland

## APPENDIX 3

	Council's FY 84 Request	Total	% of Request	Council's FY 85 Request	Total	% of Request
<b>Contraceptive Development</b>						
Implants	430	428		390	506	
Vaginal Rings	280	245		370	189	
LNG-IUD	220	225		200	166	
LH-RH Analogs	480	178		530	290	
Inhibin	150	287		350	336	
GnSiF	—	**		220	221	
Tolnidamine	60	66		30	—	
FDA	20	20		—	20	
NDA Contingency	—	—		—	100	
Subtotal	1640	1449	88	2090	1861	89
Indirect on subtotal	564.2	499		915.4	813	
<b>Contraceptive Introduction</b>						
NORPLANT <sup>®</sup>	350	299		1550	1300	
CuT 380A	—	—		—	10	
Subtotal	358	299	84	1550	1310	
Indirect on subtotal	119	99		594	498	84
<b>Family Planning Program</b>						
Latin America	295	—		—	—	
Africa	100	100		245	120	
Mexico, Nortman	40	40		—	—	
Begota	30	30		30	30	
Bangladesh	162	259		—	148	
Determinants	24	—		—	—	
Factbook	88	52		—	—	
Evaluation, Training, Service Delivery in Brazil	—	—		120	40	
Fellowship Program	—	—		—	—	
Other	—	115		—	19	
Subtotal	739	596	81	395	357	
Indirect on subtotal	246	185	143	90		
<b>Population and Development</b>						
Pop and Development Review				100	—	
Subtotal				100	—	0
Indirect on subtotal				36	—	
Other Direct (Audit)				30	30	
Indirect on audit	4	4		3.4	4	
Total Direct Costs	2767	1727		4165	3558	
Indirect Costs	933	697		1691	1444	
Total (Direct + Indirect)	3700	2424		5857	5002	

\*\* \$270,000 should be redistributed from other category suggestions to cover GnSiF costs.

	Council's FY 86 Request	First Increment Amend. 10-12	% of Request	Council's FY 87 Request	First Increment Amend. 13	% of Request
<b>Contraceptive Development</b>						
Implants	645	600		1,157	700	
Vaginal Rings	307	252		678	326	
LNG-IUD	222	172		283	200	
LH RH Analogs	476	100		347	150	
Inhibin	150	287		442	132	
GnSIF	200	150		102	86	
Sperm Suppression	—	—		49	—	
Barrier Methods	—	—		378	—	
NIH Transfer	—	—		—	278	
NDA Contingency	—	100		111	300	
Other	—	—		51	0	
Subtotal	2462	1774	72	3598	2172	60
Indirect on subtotal	1079	778		1577	952	
<b>Contraceptive Introduction</b>						
NORPLANT Implants	950	900		450	450	
CuT 380A	150	281		550	300	
Subtotal	1100	1181	107	1000	750	75
Indirect on subtotal	421	452		383	287	
<b>Family Planning Program</b>						
Africa	447	245		125	200	
Zimbabwe Rural FP Project	117	—		125	—	
Health Benefits of IMSS	100	—		—	—	
Bogota	45	45		35	35	
SE Asia MCH/FP Support	85	—		—	—	
AIDS	—	—		75	—	
Subtotal	794	474	60	360	235	63
Indirect on subtotal	293	163		129	82	
<b>Population and Development</b>						
Women's Conference	—	216		—	—	
Pop and Development Review	100	—		110	—	
Factbook	47	—		113	—	
Subtotal	147	216	149	223	—	0
Indirect on subtotal	53	—		80	—	
Fellowships	475	—		525	—	
Indirect on Fellowships	161	—		177	—	
Other Direct (Audit)	20	20		20	20	
Indirect on audit	2	2		2	2	
Total Direct Costs	4998	3665		4978	3177	
Indirect Costs	2009	1395		2091	1323	
Total (Direct + Indirect)	7007	5060		7069	4500	

## APPENDIX 4

### A CASE STUDY: PRODUCT INTRODUCTION ACTIVITIES IN BANGLADESH

#### COPPER T 380A IUD INTRODUCTION ACTIVITIES: BANGLADESH

##### Introduction

Over the last few years, several important and almost simultaneous developments in the area of contraceptive availability have combined to produce an unusual and exciting opportunity: the challenge to assist in the introduction of a new contraceptive product, the Copper T 380A IUD. Every new product -- even a contraceptive method -- needs to be properly positioned in the marketplace and in national distribution programs. And when the product involves a medical intervention, as the Copper T 380A does, it is also important to make certain that service providers are knowledgeable about the product and how to manage its side effects and are properly trained to insert it routinely.

India provides an example of what can happen to the acceptance of an IUD, in this case the Lippes Loop, if introduction activities are not carefully planned. In the 1960s and early 1970s, the Lippes Loop was introduced without proper attention being given to the needs of either the user or the provider. The latter group was not cautioned to refrain from inserting Loops into women with pre-existing vaginal infections. Women were often not counselled, and were seldom told they might experience heavier-than-normal bleeding, a common IUD side effect and generally not a cause for alarm. The result was that women -- and entire families -- became alarmed and angry, and vocal in their diatribes against the IUD, so much so that the entire national family planning program came under attack and family planning acceptability in India fell precipitously.

The opportunity for PIACT to initiate Copper T 380A IUD activities in Bangladesh was precipitated by the Government's wish to strengthen its national IUD program. This commitment to IUDs coincided with an overall renewed interest in promoting temporary methods and birth spacing to balance the emphasis on permanent methods seen in the past. Furthermore, the Directorate of Family Planning had already requested that U.S.A.I.D. supply several hundred thousand Copper T 380A IUDs, since its stock of Copper T 200Bs would be exhausted during 1987. The Copper T 380A would then be the only IUD available in the country. Also, the government of Bangladesh wished to strengthen its national IUD program.

The following example of Copper T 380A IUD introduction activities in Bangladesh is meant to provide you with an example of an introduction "process":

#### I Determining initial site for Copper T 380A introduction activities

1. PIACT acquired information from A.I.D. on countries receiving Copper T 380A IUDs, the amount, and when shipments were due to arrive. Since Bangladesh had already received 486,400 Copper T 380A IUDs and was due to receive 500,000 more in 1987, PIACT decided, in consultation with The Population Council, that it would be a good country in which to help launch a well planned introduction effort.

## II. Needs Assessment and Project Initiation Activities

1. PIACT conducted a needs assessment of Copper T 380A IUD materials in consultation with the Ministry of Health and Family Planning, local NGOs, and donor agencies. Discussions indicated to PIACT a clear need for improved training, reference, and support materials on IUDs in general, and on the Copper T 380A specifically. During these discussions, several critical issues arose, including the need to plan carefully for distribution of the IUDs and educational materials, how the device would be presented to the public, and the need for improved IUD program record-keeping and client follow-up.

2. We arranged a roundtable meeting with government officials, NGOs, and donor agencies to discuss further needs related to Copper T 380A IUD introduction activities and to make recommendations for future action.

3. The general perception of the roundtable meeting was that a high-visibility, mass media approach to Copper T 380A introduction was inappropriate, since the Copper T 200 IUD was still in use (supplies to be exhausted in 1987).

4. The Director General of the Ministry of Health and Family Planning requested assistance of PIACT/Bangladesh to develop training and reference manuals for clinicians and motivators and a pictorial booklet for illiterate clients, as well as a flyer for distribution to decision makers and service providers, with basic information on the Copper T 380A. Also, a distribution strategy was agreed upon by which Copper T 200s would continue to be inserted until all warehouses and clinics had received the Copper T 380As, and service providers had received information about this new device.

5. Our staff worked with PIACT/Bangladesh, previously trained in the materials development methodology, to initiate project activities.

6. PIACT/Bangladesh adapted, translated, and began to field-test training and reference materials for clinicians based on prototype materials prepared in 1984 by The Population Council and PIACT.

## III. Project Activities

1. PIACT/Bangladesh recruited a project advisory board composed of the government and other NGO representatives to review all materials developed on the Copper T 380A.

2. PIACT/Bangladesh sent out 9,500 copies of the flyer under the signature of the Director General of Health and Family Planning, designed to catch the eye of Bangladesh's family planning workers and decision makers.

3. During routine monitoring visits, PIACT staff held meetings with the National Institute of Population and Research Training to discuss the importance of and need for improved training for family planning workers on IUD-related service delivery.

4. Staff distributed a draft prototype five day refresher curriculum prepared by PIACT that emphasized how to provide informed choice, setting standards for client selection, counseling, and practice in inserting Copper T 380As.

to local NGOs, government officials, field staff of one cooperating agency, and the donor agency supporting most government training activities in Bangladesh.

5. PIACT/Bangladesh thoroughly field-tested the clinician and client materials, making revisions as necessary. The materials were reviewed by the advisory board and submitted to A.I.D. for printing.

6. A I.D. Mission floated tender for printing.

7. PIACT/Bangladesh planned distribution of materials, which should be ready by the end of the year. The service provider manuals will be printed in sufficient quantity to supply government and NGO workers. Since there has been considerable concern about the effectiveness of supply channels for contraceptives and educational materials, it was decided that only 50,000 copies of the client booklet would be printed initially. Copies of this booklet, to be used when motivating, will be given to all government Family Welfare Visitors and Family Welfare Assistants.

#### IV. Next Steps

1. Ensure that all Family Welfare Visitors have access to the fieldworker's manual and that doctors and Family Welfare Assistants receive the manual for clinicians that includes information on insertion and removal, handling side effects, and the importance of an aseptic environment.

2. Help create an environment in which the materials will be used by stressing the importance of introducing the materials in training sessions both for new service providers and for those already working in the field.

3. Collect information on experiences with the prototype record-keeping card developed by PIACT. The card is designed to help the client know when she has to return to the clinic for IUD removal (and placement, if so desired).

4. Work with the roundtable committee to develop a mass media campaign for Copper T 380A to reinforce introduction activities once Copper T 200 supplies are exhausted.

#### V. The Future

1. PIACT/Bangladesh with which PIACT is collaborating is offering the services of its staff to train government family planning workers in improved interpersonal communications/counseling techniques.

2. The government plans to conduct a study that will look at the benefits of giving clients a booklet versus showing it to them when explaining the method but not letting them keep it. Results of this study will be very important in determining future printing needs.

3. TCu 380A IUD materials produced in Bangladesh, in Bangla, will be available from PIACT/Bangladesh early next year. For copies please write to:

Yusuf Choudhury  
PIACT/Bangladesh  
1/7 Block A  
G.P.O. Box 3544  
Dhaka-7  
BANGLADESH

Please note: The scenario was designed and developed specifically for Bangladesh. Product introduction strategies for other countries will vary depending upon particular country needs.

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832.02.07

## APPENDIX 5

Programmatic Activities Approved and Funded Under  
Cooperative Agreement A.I.D./DPE-3005-A-00-3003-00

A. AFRICA

- |    |   |           |
|----|---|-----------|
| 1. | DESIGN, IMPLEMENTATION, AND EVALUATION OF FAMILY<br>PLANNING PROJECTS IN SUB-SAHARAN AFRICA |           |
|    | 05/17/83 - 06/30/85   | \$127,548 |
|    | 07/01/85 - 06/30/86   | 110,612   |
| 2. | THE KUBATSIRANA PROJECT, ZIMBABWE NATIONAL FAMILY<br>PLANNING COUNCIL                       |           |
|    | 09/01/85 - 11/30/86   | 91,023    |
|    | 12/01/86 - 11/30/87   | 96,022    |
|    | 12/01/87 - 11/30/88 (proposed)  | 88,253    |
| 3. | THE KANANGA RESEARCH PROJECT, ZAIRE   |           |
|    | 11/01/87 - 10/31/88   | 64,229    |
| 4. | EGYPT: DEMOGRAPHIC RESPONSES TO MODERNIZATION   |           |
|    | 06/15/87 - 01/31/88   | 8,431     |

B. LATIN AMERICA

- |    |   |         |
|----|---|---------|
| 1. | NATURAL FAMILY PLANNING METHODS, FUNDACION SANTA FE<br>DE BOGOTA (U.S.A.I.D./Washington "add-on")   |         |
|    | 01/01/84 - 02/28/85   | 59,384  |
|    | 03/01/85 - 02/28/87   | 151,420 |
| 2. | LOCAL OFFICE EXPENSES, BOGOTA, COLOMBIA   |         |
|    | 05/17/83 - 04/30/84   | 23,188  |
|    | 05/01/84 - 04/30/85   | 36,588  |
|    | 05/01/85 - 04/30/86   | 29,866  |
|    | 05/01/86 - 04/30/87   | 33,360  |
|    | 05/01/87 - 04/30/88   | 41,650  |
| 3. | IN-HOUSE PROJECTS AND AWARDS TO THE ACADEMIA MEXICANA<br>DE INVESTIGACION EN DEMOGRAFIA MEDICA A.C. |         |
|    | 01/01/84 - 12/31/87   | 89,481  |
|    | 10/01/85 - 02/28/86   | 4,981   |
|    | 01/01/87 - 03/31/88   | 14,051  |

4.	PRODUCTION OF A VIDEO TAPE DOCUMENTATING THE "HOUSEHOLD DISTRIBUTION OF CONTRACEPTIVES," BOYACA, COLOMBIA	
		<b>\$ 58,646</b>
C.	<u>ASIA</u>	
1.	BANGLADESH (U.S.A.I.D. Mission buy-ins)	
a)	ICDDR, B - BANGLADESH	
	05/16/84 - 06/30/85	137,530
	07/01/85 - 06/30/86	77,375
	07/01/86 - 06/30/87	110,900
b)	SUPPORT TO MOHPC AND ICDDR, BANGLADESH (PHILLIPS IN BANGKOK)	
	07/01/85 - 06/30/86	88,755
	07/01/86 - 06/30/87	185,591
c)	PC SUPPORT FOR EXTENSION PROJECT - ICDDR, BANGLADESH	
	07/01/87 - 06/30/88	346,175
d)	LAING TECHNICAL ASSISTANCE TO U.S.A.I.D., DHAKA	
	07/01/86 - 06/30/87	20,765
	08/15/87 - 09/30/87	10,000
2.	INDIA (U.S.A.I.D. Mission "Buy-ins")	
a)	POPULATION PROGRAM REVIEW	
	03/01/87 - 12/31/87	37,074
b)	CONTRACEPTIVE - FERTILITY RELATIONSHIPS	
	10/01/87 - 08/31/89	409,777
3.	ASIAN FAMILY PLANNING PROGRAM PERFORMANCE (U.S.A.I.D./Washington "add-on")	
		99,745
4.	REPRINT OF OPERATIONS RESEARCH HANDBOOK	
		<b>3,300</b>

D. HIV

1. THE HIV EPIDEMIC IN AFRICA: DEVELOPMENT AND APPLICATION OF A PROJECTION MODEL

080/1/87 - 04/30/88

\$ 25,000

2. HIV SUBCONTRACTS (U.S.A.I.D./Washington "add-ons")

SAN MARCOS  
PRISMA99,258  
118,488

## APPENDIX 6

### Sub-Saharan Proposal Development, Technical Assistance and Sub-Award Activities Funded Under Cooperative Agreement A.I.D./DPE-3005

- I. Progress Reports submitted to U S A I D. reported the following major activities.
  - A. Africa Family Planning Programs
    1. July - November 1983.  
 McEvoy assisted ONAPO Rwanda to redesign and pretest new service statistics clinic cards. Cassanova conducted training in Rwanda on IEC in the area of designing and pre-testing audiovisual materials. Followup planned.
    2. March 1984 - February 1985  
 Coeytaux technical assistance mission to Rwanda to assist ONAPO to expand OR capacity and activities. McEvoy technical assistance mission to Rwanda to help improve service statistics system
    3. March 1984 - June 1985  
 McEvoy/Coeytaux Zimbabwe mission completed Kubatsirana OR research design. George Brown/McEvoy later mission finalized Kubatsirana OR Design and proposal, and began preliminary discussions on NORPLANT<sup>™</sup> introduction in Zimbabwe
    4. February 1984  
 McEvoy technical assistance mission to Mali to help AMPPF to revise service statistics system and conducted feasibility analysis of a rural outreach program.
    5. March 1984  
 Arranged U S training from two doctors from Mali MOH in FP program management
    6. February 1986  
 Moore program review and development mission to ZNFPC, Zimbabwe which determined need for PC long term advisor, review and restatement of Kubatsirana OR research design and allocation of responsibilities
    7. February - April 1986  
 Moore personally provided technical assistance and arranged for 2 additional consultant inputs into Imo and Plateau States

in Nigeria to develop 5-year FP plans/strategies. Moore was a resource person at Nigeria planners workshop, JHPIEGO

8. June - November 1986

McEvoy project development missions to Zaire, Congo and Kenya. Participated in Columbia University Conference, Zimbabwe, "Bringing FP to the People."

9. November 1985 - June 1986

Moore project development missions to Kenya and Zimbabwe. Project initiatives identified included: "Analysis of Contraceptive Prevalence Differentials in Kenya;" "Analysis of Rapid Change in Contraceptive Use and Its Implications for Fertility Decline in Zimbabwe;" "Strengthening the Management Capabilities of FP Programs in Selected Countries in East and Southern Africa."

B. Kubatsirana Operations Research Project - Zimbabwe

Other major developments insufficiently covered in the attachments.

- PC recruitment of qualified professional (Dr. Maxine Whittaker) to be long-term advisor to the project half time. This required arranging funding for the other half and finding alternate country base when Zimbabwe refused residency request.

- Completed major project review in September 1986, which resulted in a number of design improvements and written clarification of workplan and responsibilities

- Negotiated stronger commitment to FP component by ZNFPC, which encouraged U S A I D to continue

- Strengthened overall research management, kept the project on track with numerous "saves" (unforeseen fund raising and sources of data analysis support when ZNFPC reneged on commitment).

- Now expects successful outcome, despite present leadership problems inside ZNFPC

II. Other Project Ideas or Completed Project Proposals Which are Direct or Indirect Result of Programmatic Grant Support

Those which are already fully developed and written up in proposal form are marked with an asterisk. The following mark (#) indicates that the project/idea has been submitted to U S A I D /with partial or full support

1. The Analysis of Contraceptive Prevalence Differentials in Selected Kenyan Districts\* #

2. Analysis of Rapid Change in Contraceptive Use and Its Implications for Fertility Decline in Zimbabwe #
3. Strengthening the Management Capabilities of FP Programs in Selected Countries in East and Southern Africa #
4. Further Strengthening of the Population Studies and Research Institute at the University of Nairobi\* #
5. Assessment for Broader Application in Kenya and Regionally of Lessons Learned in Machakos District, Kenya\* #
6. The Kananga Research Project, Zaire\* #  
[This is now funded by U.S.A.I.D./W]
7. Acceptability of Contraceptive Methods and Services in Kenya and Zambia\*
8. Strengthening FP Programs in the Sahel Region Through Improved Evaluation, Management Information, and Program Research\*
9. Making the NORPLANT™ Subdermal Implant Publicly Available in Kenya\*
10. Increasing the Capacity of the Nigerian Public Sector to Provide Contraceptive Services (a response to an RFP)\* #
11. Assessing the Impact of an Optimal FP Program in Kenya

III. Other Services Provided Under the Programmatic Grant Completed and Pending

- A. Study tours of U.S.-based population-development technical assistance agencies, donors, and research centers for Mr. Johnson Hungu (Director, NCPD, Kenya) and Professor H.W.O. Okoth-Ogendo (Director PSRI, Kenya). Fall, 1986.
- B. Evaluation of the NCPD services of Dr. Jim Phillips to be provided as team leader. Early 1988.

## APPENDIX 7

### TECHNICAL SUPPORT TO THE INTERNATIONAL CENTRE FOR DIARRHOEAL DISEASE RESEARCH AND THE MINISTRY OF HEALTH AND FAMILY PLANNING IN BANGLADESH

The Population Council has assisted the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) in research designed to extract lessons from a series of controlled field experiments in rural Bangladesh. One such lesson lies in the research paradigm itself — a system for fostering the use of research findings in a setting where major structural and policy change is needed but where bureaucratic capabilities are limited. Forthcoming work will be addressed to documenting this paradigm as it was developed in Bangladesh and exploring its possible relevance to other settings where policies have aimed to reduce fertility through the provision of contraceptive services.

The approach that has been developed represents a successful application of research to policy development in Bangladesh. A component of this research system, located in Matlab, has demonstrated that services can reduce fertility despite social and economic constraints to widespread fertility regulation. Building on this success, a broader framework for research has been developed in an "Extension Project," wherein committees of Government officers seek to replicate the Matlab approach, diagnose problems encountered, and communicate progress and constraints to their superiors. While Matlab represents a scientifically credible field trial, it is the operationally credible test in the Extension Project that has fostered policy change. Taken together Matlab and Extension have contributed to changes in the national staffing pattern, personnel procedures, logistics, training, and other aspects of the national service system. While operations research is used throughout this process, studies are conducted in a framework for institutional development that is more general than any particular study, emphasizing the interconnectedness of problems and the systemic nature of their resolution.

The Bangladesh system differs from the operations research projects funded through the USAID office of population. The flexibility that the programmatic grant affords has facilitated the development of an approach explicitly addressed to the problems of nonfunctioning public sector programs. Such programs are typically constituted as large standing bureaucracies with no established research and evaluation unit, and limited capacities to commission operations research. The Bangladesh organization development approach recognizes the need to develop systems for research communication and decision making that guide and direct the operations research system.

An important by product of the Bangladesh projects is the research system that has been developed. Sample registration systems, a familiar source of detailed vital statistics, have been established in numerous third world settings to produce timely data for routine demographic assessments. The quality of such data are typically poor, however, and design limitations prevent their use in addressing practical policy questions. Bangladesh Sample Registration System represents an effort to resolve these problems through the application of microcomputer technology and database software to vital data collection and maintenance. Database methods facilitate the editing process and generate data suitable for longitudinal studies of demographic inter relationships, the effects of health or family planning interventions, or other issues where cohort studies are required for addressing practical policy questions. The Population Council is currently

documenting and disseminating the Bangladesh data system in order to inform the development of such systems elsewhere.

The Population Council will undertake a review of this experience in 1988, and an assessment of its relevance to Africa. A number of small scale pilot projects have been fielded in Africa that have had an impact on demographic dynamics. It is possible that some of these projects could be incorporated into an organization development framework that more fully utilizes their relevance to national policy. To pursue this work, the Council envisions a sustained program of field work, writing, and research in the area of organization theory and the determinants of institutional development. This theoretical work will be undertaken in collaboration with field practitioners of operations research in Africa and South Asia

## APPENDIX 8

### Report on Bogota Office Activities

For the period 1 May 1985 until 30 April 1988 the Population Council has submitted three proposals to request continued annual support for the Council's office in Bogota. The office has provided technical assistance, program monitoring and research services to several projects in Colombia, many of which have been funded by A.I.D. These include a project with PROFAMILIA, a project with Fundacion Santa Fe, the Demographic and Health Surveys project and the Council's partially A.I.D. funded program to introduce advanced copper-T IUDs and NORPLANT® contraceptive implants. In 1985, the office collaborated with Merrick Communications on the production of a videotape, in both English and Spanish versions, describing the experience of the Boyaca Operations Research project. In 1986, the Bogotá office became responsible for the development and implementation of INOPAL projects in Colombia, Costa Rica and Panama. In order to continue these services A.I.D. assistance has been necessary for staff salaries, rent, communications, purchase of office supplies, travel within the region and international travel between Mexico and Colombia.

The Bogotá office provided technical assistance to the PROFAMILIA "Private Sector Community Based Distribution and Commercial Social Marketing Strategies in Colombia" project, a project which was designed to test the cost-effectiveness of a commercial social marketing (CSM) contraceptive delivery strategy. Over the forty-six month period from September 4, 1984 to May 31, 1988, two phases of activity are being carried out.

The first phase of the project, which took place between September 4, 1984 and June 3, 1986, demonstrated the success of a commercial distribution program. But, because of difficulties in the acquisition of contraceptives for commercial distribution, the CSM program had to be dismantled. In order to benefit from the advantages of the CSM strategy and avoid its supply problems, the second phase of the project tests the cost-effectiveness of a mixed CBD-CSM strategy, and the impact that incentives may have upon such a scheme.

The Bogota office worked with the Fundacion Santa Fe to develop the Natural Family Planning (NFP) project which began in early 1984 and was completed in February, 1987. Under this project, the Community Health Division worked with the Ministry of Health to augment health service coverage in Colombia through the implementation of an innovative comprehensive health model in which the integration of a family planning component, offering both artificial and natural contraceptive methods, was tested. It was hypothesized that the population exposed to the project would benefit from the services provided and that the experimental results would permit policy decisions to be made regarding the incorporation of NFP into official and private sector integrated health programs.

The purpose of this project was to (a) increase contraceptive use among poor marginal families through the provision of family planning services in an urban area of Bogota, (b) identify a cost and use effectiveness delivery strategy for NFP within the context of an integrated health program, and (c) detect user satisfaction with NFP contraceptive methods and the service delivery systems needed.

The project results suggested that even if the delivery of NFP services is expensive and NFP is not as effective as other contraceptive methods, it is

worthwhile to have them available. Women who use this method are usually satisfied with it and it offers an alternative to women who have experienced side effects from other contraceptives.

A new INOPAL project was approved in August, 1987 and is scheduled to operate for 18 months. This project, entitled "An Experimental Study to Select a Cost-Effective Promotion Technique to Distribute Intra-Uterine Devices Among Private Physicians in Colombia" was developed in conjunction with the Asociación Sociedad Médica Farmacéutica (SOMEFA). The project tests two promotion strategies — a postal and detailman system — to determine which is more cost-effective and which creates a larger demand for IUDs, and to expand its services to a larger number of physicians in semi-urban and marginal areas.

The Bogotá office and PROFAMILIA have collaborated on two INOPAL projects which will begin in January, 1988. One proposal, entitled "Operations Research on Different Approaches for Vasectomy Services Provision in Colombia," tests two vasectomy service delivery systems in medium sized cities; one strategy provides services for men in the traditional female clinics where men and women share clinic facilities. The other approach offers services for men during clinic hours reserved for men only. The clinic offers vasectomies, urological examinations, treatment of sexually transmitted diseases and minor surgery.

The other PROFAMILIA project concerns HIV education and prevention; it includes IEC activities and the distribution of condoms for the prevention of HIV and other sexually transmitted diseases.

The Bogotá office maintains close relationships with U.S.A.I.D./Bogotá, the Ford Foundation, the International Development Research Center and other donor agencies. It has also provided guidance on policy to the U.S.A.I.D. Bogotá Mission Director for the Ministry of Health.