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EVALUATION OF
THE PROGRAM FOR APPLIED RESEARCH
ON FERTILITY REGULATION
(PARFR)

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GLOSSARY

AGB	Aryl-4-guanidinobenzoates, a potential spermicide
AID	Agency for International Development; also USAID
AVS	Association for Voluntary Sterilization
CDB	Contraceptive Development Branch, Center for Population Research, National Institute of Child Health and Human Development
CTO	Cognizant Technical Officer
DHHS	Department of Health and Human Services
EE	Ethinyl estradiol, a synthetic estrogen used in contraception
FEMCEPT	A device used to instill sclerosing agents into the fallopian tubes via the uterus
FDA	United States Food and Drug Administration
FHI	Family Health International
FPIA	Family Planning International Assistance
GMP	Good Manufacturing Practices
HRP	Human Reproduction Programme, World Health Organization
ICCR	International Committee for Contraception Research of The Population Council
IDE	Investigational Device Exemption
IND	Investigational New Drug Exemption
IRB	Institutional Review Board; reviews protocols for human experimentation
ISTI	International Science and Technology Institute
LDH-C	Sperm isoenzyme of lactic dehydrogenase
LDC	Less Developed Country
LNG	Levonorgestrel, a synthetic progestin used in steroid contraceptives

MCA	Methylcyanoacrylate, a chemical used to occlude the fallopian tubes in nonsurgical sterilization procedures
NET	Norethindrone, a synthetic progestin used in steroid contraception
NICHD	National Institute of Health and Human Development
NIH	National Institutes of Health
NU	Northwestern University
PARFR	Program for Applied Research on Fertility Regulation
PI	Principal Investigator
PI/T	Program for the Introduction and Adaptation of Contraceptive Technology
Phase I	First time a device or drug is tested in humans, limited number of subjects, for purpose of finding dose and gross metabolic or toxicologic side effects
Phase II	Testing for approximately one year for efficacy and side effects in small number of volunteers
R&D	Research and Development
RFFR	Research Frontiers in Fertility Regulation
SAC	PARFR's Scientific Advisory Committee
SHUG	A device used to block the vas deferens, originally meaning the combination of sleeve and plug
SRI	Southern Research Institute, Birmingham, Alabama
UAB	University of Alabama, Birmingham

APPENDICES

- Appendix A: Names of Persons Interviewed by Telephone
- Appendix B: Workscope and Issues to be Addressed in PARFR Evaluation
- Appendix C: Recommendations from the 1983 Evaluation of PARFR
- Appendix D: List of PARFR Contraceptive Leads That Have Been Discontinued
- Appendix E: List of PARFR-Sponsored Workshops and Symposia
- Appendix F: Sample Issue of Research Frontiers in Fertility Regulation

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The Evaluation Team would like to thank the staff of PARFR who provided the timely and complete background materials for this evaluation and made many on-site arrangements. We also wish to thank the ISTI staff for their coordination of the evaluation and invaluable editorial assistance.

EXECUTIVE SUMMARY

PARFR is meeting the goals of AID to develop new and improved contraceptive products that will have application in less developed countries. The evaluation team is enthusiastic about several research areas in PARFR's portfolio including microencapsulated steroid injectables, reversible sterilization for men and women, new vaginal contraceptives, and ovulation indicators. Within these areas, the team gives high marks to the 90-day NET, progesterone, and testosterone injectables; the SHUG device for reversible vasocclusion, and the plug and clip device for tubal occlusion. The team is in favor of exploring the high risk area of immunocontraception but is uncertain if the projects in that area are focused and cohesive. The team is somewhat less enthusiastic about anordrin. Percutaneous vas occlusion needs careful preclinical studies but with the right technique could be expanded. The use of iodine with FEMCEPT for nonsurgical sterilization, though it is thought to be encouraging, should provide tubal blockage rates on one instillation of over 90% if it is to have widespread potential in LDCs. There is little project overlap with other agencies.

PARFR retains the advantages of its operating mechanism--flexibility and adaptability--that enable it to respond quickly to program needs as established both internally and externally. This advantage of initial speed and rapid course corrections can be muted and compromised by the insufficient time the PARFR staff can devote to focusing work by grantees and to adequate forward planning.

PARFR is now facing a time of greater challenge because of the large number of projects in its portfolio that require improved technical monitoring and the need to coordinate complex projects in the product development stages. It is the evaluation team's opinion that PARFR must modify its management style by considering the following elements:

1. Increase by two the number of senior technical professionals and increase the management oversight by the Principal Investigator;
2. Give a greater substantive role to the Scientific Advisory Committee by seeking its advice on overall program planning and by improving its technical input through increased time and depth devoted to project analysis.
3. Commit to paper meaningful priorities, forward planning, and budgets; and

4. Promote an open, collegial relationship with other contractive research organizations as it appears to have established with the private sector.

If carried out successfully, the above suggestions will no doubt help to improve relations with AID as it will gain confidence once again in PARFR's management capabilities. AID should also act to reduce PARFR's frustrations with the AID Contract Office, clearly communicate its own priorities and concerns on paper, and observe the line of communications PARFR has with its subgrantees. To this end, the evaluation team suggests that the relevant parties in AID and PARFR meet to discuss their differing points of view and to try to arrive at mutually beneficial solutions.

I. INTRODUCTION AND BACKGROUND

I.1 Purpose of the Assignment

This assignment served to provide both an interim and final evaluation of the Program for Applied Research for Fertility Regulation (PARFR) specifically relating to its activities during the current Cooperative Agreement, July 1, 1981 to June 30, 1986. The evaluation focused on the PARFR administration, management, project portfolio, collaboration and relationships with other organizations, and their technical approach and accomplishments.

I.2 Team Composition

The members of the evaluation team were:

1. Linda E. Atkinson, Ph.D. (Chairperson)

Consultant in reproductive biology and contraceptive research and development, Portola Valley, California

2. Richard Derman, M.D., M.P.H.

Department of Obstetrics and Gynecology, Cornell Medical School, New York, New York

3. Henry L. Gabelnick, Ph.D.

Contraceptive Development Branch, Center for Population Research, National Institute of Child Health and Human Development, Bethesda, Maryland

I.3 Methodology and Plan of Work

PARFR provided the evaluation team with a complete inventory of projects, expenditures, funding, consultants, prior evaluations, publications, workshops, a semi-annual report, etc. for a background information and preparation. The Chairperson interviewed staff of agencies involved in contraception research and development, and family planning assistance, and also the principal investigators of several PARFR subprojects (See Appendix A for list of persons interviewed). A briefing at the offices of the Agency for International Development (AID) in Russlyn, Va. with Duff Gillespie, Deputy Director, Office of Population, Jeffery M. Spieler, the PARFR Cognizant Technical Officer (CTO), and Dotty Wexler, the International Science and Technology Institute (ISTI) editor took place on November 18,

1985. The team then proceeded to the PARFR offices in Chicago, Illinois and held discussions on November 19, 21, and 22 with the following PARFR staff:

John J. Sciarra, M.D., Ph.D., Principal Investigator;
 Gerald I. Zatuchni, M.D., M.Sc., Director;
 Alfredo Goldsmith, M.D., M.P.H., Assistant Director; and
 Diane Krier-Morrow, M.B.A., Director of Administration.

In addition, David Mintzer, Ph.D., Vice President of Research and Dean of Science, Northwestern University (NU); and Donald Nutter, M.D. Senior Associate Dean, Northwestern University Medical School, were also present during the morning of November 19. Jeffrey M. Spieler represented AID's Office of Population during the first two days of the evaluation.

A site visit was held on November 20 at Stolle Research and Development Corporation, Cincinnati, Ohio, to assess its new facility and to discuss in detail the PARFR/Stolle injectable subagreements with Drs. Danny H. Lewis and Lee R. Beck.

On November 21, the evaluation team also met with four principal investigators (PIs) of PARFR subagreements to discuss their research in detail: Lourens J.D. Zaneveld, D.V.M., Ph.D. Rush-Presbyterian-St. Luke's Hospital, Chicago; Robert T. Chatterton, Ph.D., Northwestern University, Chicago; John C.M. Tsibris, Ph.D., University of Illinois, Chicago; and Erwin Goldberg, Ph.D., Northwestern University, Evanston.

The issues to be addressed by the evaluation team are presented in detail in Appendix B. The team was able to obtain enough information through background documents and discussion to make an assessment of every issue except that of PARFR's relationship with AID regional bureaus and USAID missions. In addition to the issues listed in the work scope, AID staff requested that the team pay special attention to certain projects, i.e., injectables, anordrin, immunocontraception, male and female sterilization, and vaginal contraception.

The following chapters of the evaluation generally follow the major issues raised in the work scope.

I.4 Project Background

PARFR is a division of the Department of Obstetrics and Gynecology of Northwestern University (NU) Medical School, a private university located in Chicago, Illinois (main campus in Evanston, Illinois). The PARFR project began in 1972 at the University of Minnesota and was transferred to NU when the principal investigator moved there in 1975. PARFR has received all its funds from AID during the period of the Cooperative

Agreement, 1981-1986. PARFR was established to serve as a flexible administrative mechanism to provide scientific, technical and financial assistance to U.S. and foreign investigators/institutions for applied research projects aimed at improving existing methods and developing new, safe, effective, and acceptable methods of fertility regulation.

In order to accomplish these purposes, PARFR develops projects and supports solicited and unsolicited subprojects at institutions in the U.S. and abroad. A specific interest of PARFR is to encourage and support applied research projects in the less developed countries (LDCs), either through LDC-based projects or as collaborative efforts between U.S. and foreign institutions.

Applied research has been defined in the broad sense to include laboratory studies, animal studies, preclinical research and early human trials (Phases I and II). However, PARFR does not support "basic" research. Previous and current areas of research supported by PARFR include: reversible and/or non-surgical sterilization techniques for men and women; intrauterine contraception; long-acting steroidal contraceptives and delivery systems (injectables and implants) for men and women; barrier methods including new chemical spermicides; vaccines (immunocontraceptives); and other pharmacological methods (e.g. neuropeptides, nonsteroidal male methods).

Both solicited and unsolicited research proposals can be submitted to PARFR either as pilot studies (approximate maximum of \$10,000 per year), informal proposals, or formal proposals (approximate maximum support of \$66,000, recently raised to \$100,000 per year). Pilot studies are intended to provide the investigator with initial funding to accumulate sufficient data for submission of a formal proposal to PARFR. Informal proposals are written with a brief statement of the objectives, protocol, expected end results, and budget. When informal proposals meet PARFR objectives, investigators are requested to submit formal proposals.

Proposals are reviewed by PARFR's Scientific Advisory Committee (SAC), a committee of about 12 experts in the field of reproductive science and clinical fertility regulation. When a proposal is approved, PARFR's funds are provided through a cost-reimbursable agreement. PARFR staff, consultants, and the SAC monitor the progress of all projects, including through site visits as indicated.

In addition to supporting research, PARFR organizes international and regional workshops, which bring together leading national and international scientists and clinicians from many disciplines to present their work and exchange ideas on research related to specific topics of fertility regulation.

The proceedings of each workshop are published and the background papers for regional workshops are made available for dissemination. PARFR also publishes and distributes internationally a tri-monthly research review entitled Research Frontiers in Fertility Regulation (RFFR). Each issue deals with a specific area of research in the field of fertility regulation.

II. PARFR'S RESPONSE TO THE 1983 EVALUATION

II.1 Approach

The team reviewed and discussed with PARFR staff each of the recommendations of the 1983 evaluation and its disposition. The complete list of recommendations is found in Appendix C. The parenthetical number(s) before each section refers to the specific recommendation(s) of the previous evaluation.

II.2 Staffing

(1) The present evaluation team does not concur with the previous assessment that additional expertise in clinical trials alone was needed. Instead a person with product development skills and experience should be added to the staff. This issue is discussed more fully in the section on management (Chapter IV). PARFR did not add additional staff subsequent to this recommendation, but decided to expand its use of consultants.

(25) PARFR has attempted to have the salary of the Director of Administration increased but was not successful in overcoming NU personnel classification and salary restrictions. Further, a physician's incentive bonus has not been applied by AID to PARFR staff.

II.3 Information Storage and Retrieval

(2,24) PARFR has obtained two Zenith microcomputers and letter quality printers. The staff also has appropriate programming and software at its disposal. The system is compatible with PARFR needs for information retrieval, mailing, and accounts management needs and could be used with the NU mainframe for data analysis. At this time the system is nearly in full operation.

II.4 Scientific Advisory Committee

(3-10) PARFR is following the guidelines suggested by the last evaluation for SAC membership term and rotation and eligibility for receiving support on major subagreements.

In regard to broadening the expertise represented on the SAC, PARFR has added an epidemiologist to the SAC in lieu of a biostatistician. PARFR has not adequately diversified SAC expertise to match the areas of research upon which it is concentrating, however, e.g. immunocontraception and product development (Chapter VI).

PARFR is following the suggestion that SAC members absent themselves from discussion of proposals from their own institutions and that PIs on SAC absent themselves from the discussion of their own proposals. Dr. Sciarra, as the chairperson of SAC, continues to vote on proposals. While the team does not believe this makes a substantial difference in outcome, the practice is not desirable.

Proposal summaries prepared by the PARFR staff for the benefit of SAC still contain recommendations for approval or disapproval in about half of the cases. Thus this practice, which may influence the ensuing SAC discussion, has not been entirely avoided.

There is little evidence that PARFR staff has utilized the SAC to discuss and evaluate priorities for ongoing research or to provide advice on program strategy. To some extent SAC members have suggested topics for research or workshops.

PARFR staff now accompanies all principal investigators to other agencies such as the Food and Drug Administration (FDA) when they are used as technical consultants.

II.5 Subagreement Funding and Institutional Review Board (IRB) Requirements

(11-13) The funding level for formal proposals was raised from \$66,000 to \$100,000 per year, although PARFR staff claims that it was one of the last AID contractors to receive permission to do so. PARFR has not chosen to advance contract funds for certain purchases or personnel hiring at this time but would like to keep this option open particularly in view of the need to have coordinated startups in clinical trials.

Northwestern University has agreed to accept any review by a United States Department of Health and Human Services (DHHS)-approved Institutional Review Board (IRB) thus eliminating the delay in obtaining a second IRB approval. NU continues, however, to review IRB equivalents from institutions outside the United States.

II.6 Portfolio and Setting of Priorities

(15-17) PARFR has finished its studies on quincrine and has transferred the technology to Family Health International (FHI).

For quite legitimate reasons, PARFR and AID were unable to establish a small Phase I clinical trial for anordrin in China or through the good offices of the Human Reproduction Programme

(HRP) of the World Health Organization.

While PARFR has obtained immunology consultations on one or two projects, the overall work in immunocontraception has not been critically assessed.

(14, 18-20) Until 1983, with or without the help of SAC, PARFR does not seem to have formally given attention to research priority setting, except for some annual meetings with AID. PARFR has now begun to develop tabulations of projected activities, but these are as yet superficial and priorities are not clear.

Recently, summary flow charts have been constructed for each of the major projects, but none of them has been expanded into critical path charts or other detailed operational pathways. Cost estimations are at a preliminary stage and do not go beyond Phase II.

PARFR has begun to develop tabulations of projected activities but these are as yet superficial and priorities are not clear.

II.7 Publications

(21-23) PARFR has followed the advice of the previous evaluation in the matter of RFFR manuscript solicitation and remuneration (now \$600). It has made an effort to identify young researchers, with particular success in Latin America and Asia, to add to its mailing list.

II.8 Funding and Semiannual Reports

(26) Difficulties remain with timely annual funding of PARFR by AID and with adequate warning of budgetary decreases to permit realignment of project funding.

(27) PARFR has clearly reduced the paperwork and eliminated redundancy in its semiannual progress reports.

III. ASSESSMENT OF PARFR'S CURRENT SUBPROJECT PORTFOLIO

III.1 Microencapsulated Steroid Injectables

III.1.1 Status and Funding of Lead

A major component of the PARFR program has been the development of microcapsule delivery systems for a variety of steroids. Both improved microencapsulation technology as well as potential products have been supported in part by PARFR or have evolved with private sector support based on information obtained from PARFR projects. The modern pilot plant facility recently built by Stolle Research and Development Corporation will allow a variety of steroids to be encapsulated using Good Manufacturing Practices (GMP) for proposed clinical trials. Systems either currently under clinical investigation or about to begin clinical trials include norethindrone (NET) in 30-, 90-, and 180-day preparations, and 90-day systems for progesterone, testosterone, and ethinyl estradiol (EE).

The vast majority of the encapsulation work supported by PARFR has centered on the processes developed by Southern Research Institute (SRI) using either poly(d,l-lactic acid) or copolymers thereof containing poly(glycolic acid) in addition. The encapsulating processes including the "two-stage" process developed with Stolle support led to microspheres with drug dispersed throughout, although higher concentrations of drug with nearly drug-free outer layers are more readily achieved with the two-stage process. This situation is in contrast to a true microcapsule, which controls release by an exterior membrane. As a result the release patterns obtained are not usually truly zero order. On the other hand, the higher loadings, i.e. about 40-50% drug, routinely obtained in recent years appear to give systems from which the release is sufficiently constant to make them quite suitable for clinical evaluation. It should be noted, however, that since the release mechanism is a mixture of diffusion, leaching and eventual erosion due to hydrolysis of the polymer, the reproducibility of batch-to-batch characteristics must be examined closely for purposes of quality control. Unfortunately, there are not enough data to assess quality control due to the paucity of replicate batches in the past. Future development of all of the microcapsule projects must place greater emphasis on establishing reproducibility of release rates in vivo. Demonstration of repeated drug loading, particle-size distributions, and accelerated release profiles in vitro are necessary but not sufficient to establish reliable estimates of reproducibility in vivo until we know more about these systems. In fairness, it is recognized that the limited funding of subprojects inherent in the PARFR mechanism has made it difficult

to justify these reproducibility studies in the past. The time has arrived, however, to do them.

About \$2.8 million has been expended or committed to the development of microencapsulated steroids of various types over the period of the current Cooperative Agreement. The first subcontract in this area was executed in 1976 with the University of Alabama, Birmingham (UAB), and during the five years preceding the Cooperative Agreement, about \$0.9 million was spent for a total of \$3.7 million over 10 years.

III.1.2 Likelihood of Progress to Advanced Clinical Testing.

Of all the microcapsule leads, the one most likely to reach Phase III trials is the three-month norethindrone system (Poly NET 0). However, a strong need exists for an androgen delivery system (testosterone microcapsules) and a post-partum system (progesterone); therefore, these leads should be pursued as well.

The current "30-day" NET system which AID requested PARFR to develop is probably too long-acting to work well in a monthly combination system that would emulate oral contraceptives and makes little sense in a progestin-only modality except as a trial system to check on possible adverse reactions in a potential user of a longer-term injection. This system, however, would not necessarily reflect the bleeding irregularities of extended systems. The 180-day NET preparation may also present problems in its formulation, total body load of steroid, and length of time to complete Phase II and Phase III clinical trials.

Finally, the combination of EE with NET is currently proposed for development. It is not completely clear whether the approach was merely to give estrogen continuously in the hope of improving bleeding patterns by the effect it would have on the endometrium or to administer NET and EE for 90 days and then have a withdrawal bleed, i.e., induce 90-day cycles. PARFR staff indicated the former while the investigator indicated the latter. The FDA is likely to have difficulty with either approach.

PARFR should give priority to determining the reproducibility of NET microcapsule batch manufacture as it effects in vivo performance, thereby validating current quality control procedures.

Microencapsulated injectables represent one of PARFR's most significant efforts. Therefore, major developments should continue on the encapsulation of the 90-day NET, progesterone, and testosterone with less emphasis on 30- and 180-day Poly NET and EE.

III.1.3 Regulatory Exemptions, Patents, and Protection of Public Sector Interests.

Investigational New Drug Exemptions (INDs) currently exist with UAB sponsorship for 90- and 180-day Poly NET and with NU sponsorship for 30-day NET and 90-day progesterone. INDs will be submitted in the near future with NU as the sponsor for microcapsules containing levonorgestrel (LNG), testosterone, EE and the combination of NET and EE.

It appears that only one U.S. patent exists for the microencapsulation process and it is the "two-stage" process owned by Stolle with an exclusive license to Ortho Pharmaceutical Corporation. A three-party agreement between AID, Stolle and Ortho apparently has been worked out and when signed it should provide adequate protection to provide cost-plus pricing to the public sector. Specific arrangements on pricing have not yet been established.

III.2 Anordrin

Anordrin, an antiestrogenic steroid with weak estrogenic activity, is undergoing toxicology testing as a potential candidate for ovulation inhibition. Anordrin or one of its isomers has been used in China as the once-a-month vacation pill (where its effectiveness may have been as a postcoital agent). Dr. Robert Chatterton, NU, has directed studies in monkeys and rodents. When given in the early follicular phase, Anordrin appears to prevent follicular development and ovulation is postponed until a new set of follicles is recruited. Luteal function may also be abnormal. The drug is active orally and has a half-life of about 7 or 8 days. Pre-phase I toxicology is nearly completed with teratology studies being done at Hazelton Labs.

While this steroid is interesting in its action, careful consideration must be given to its potential as a contraceptive versus the great expense of doing the requisite toxicology for advanced clinical trials. (The advantage of NET and LNG is that their FDA master file can be cross-referenced for toxicology data.) Advanced planning for route of administration--oral, transdermal, and injection have been mentioned--to determine appropriate toxicology tests is also crucial. It is the team's assessment that funds for this project should take second rank to completing the microencapsulated steroid injectables.

Over \$500,000 have been spent on this project since 1980, or about \$100,000 a year, which seems about right for preclinical work, although there are no studies in primates with long-term administration of the compound. Dr. Chatterton stated that the

budget of the last grant was cut by 50% and that the preclinical toxicology might have been completed earlier had funds not been cut. AID and SAC suggested that a small Phase I trial be conducted through HRP but this was not possible. Northwestern University holds a "use-patent" for anordrin. PARFR is exploring the interest of the private sector in the compound.

PARFR should carefully assess the cost implications of long-term toxicology requirements and clinical trials for anordrin and weigh these factors against its potential impact on family planning.

III.3 Immunocontraception

PARFR has been involved in immunocontraception since 1979 mainly through support of studies on the utilization of the sperm isoenzyme lactic dehydrogenase (LDH-C) as an antigen for a fertility vaccine (Goldberg, NU). The advantage of this system is the availability of a well-characterized protein and peptide subunits that can be chemically synthesized. The main problem is that there is only a 60-70% reduction in pregnancy observed in immunized baboons. So far, attempts to increase the immune response by stimulation of local secretory responses (in collaboration with Dr. Nancy Alexander, Oregon Regional Primate Research Center), or to increase the antigen-to-carrier ratio and try other types of conjugation (with Dr. Vernon Stevens, Ohio State University) have not yet made a noticeable difference in efficacy. Antisera to various murine LDH-C peptides are being assessed in in vitro fertilization tests (with Dr. Kenneth Tung, University of New Mexico). The PI hopes to begin preclinical toxicology in three to four years but before then he will need to decide what peptide, carrier, and adjuvant system will be used. This project has received over \$600,000 since its beginning. NU holds patents on all the peptides.

Other immunocontraceptive projects include the production and testing of zona pellucida purified glycoproteins in baboons and in monkeys, purification of a human sperm antigen whose monoclonal antibody blocks fertilization in vitro, and testing the utility of idiotypic antibodies against sperm as vaccines. It would appear that the zona pellucida project was suggested by AID and it is not clear how these fit into the overall immunocontraceptive strategy. It is paradoxical that immunocontraception was ranked 21st in importance to the program by PARFR staff but it is second only to female steroidal contraception in expenditures (\$938,646).

It came to the team's attention that AID had requested that PARFR use the occasion of Dr. Goldberg's grant renewal to hold an overall evaluation and planning consultation of the LDH-C project. Instead, PARFR held a consultation to develop

Dr. Goldberg's new proposal. The team thinks this was a lost opportunity and an inappropriate response to AID's concerns. Particularly as immunocontraception research is expanding into other antigen candidates, PARFR should hold such a consultation before too long.

It is premature to judge if these leads or variants of them will go to clinical trials. Immunocontraception presents a paradox for those agencies with projects in it. The vaccine concept is particularly attractive from an LDC point of view yet the kind of research and development that is required is very basic in its nature--that is why overall progress toward a vaccine has been slow. Given the amount of money PARFR has had at its disposal, it should be congratulated for keeping its hand in the arena: it is a high risk venture but one that could pay off handsomely if planned carefully.

III.4 Female and Male Sterilization

III.4.1 Transcervical Sterilization

In 1982 sterilization accounted for one third of overall contraceptive use. The possibility of avoiding significant dangers of anesthesia and moving sterilization services away from a hospital environment are important reasons for PARFR to support this line of research.

PARFR, in collaboration with Dr. Ralph Richart at Columbia University and BioNexus, Inc., has developed the FEMCEPT system, a balloon mechanism on a spring which rapidly forces nonviscous liquids through the utero-tubal junction of the uterus to permit the delivery of sclerosing agents to the fallopian tubes. Several agents, including phenol-based compounds, quinacrine and more recently methlycyanoacrylate (MCA) have been tested. During the time Dr. Richart was funded, the device was improved by BioNexus, Inc. to improve the probability that bilateral instillation of the material actually occurred. Subsequently, FEMCEPT was used to deliver MCA in extensive clinical testing. It was stated that BioNexus spent \$8 million developing the FEMCEPT device, which has been approved for use in Canada and is expected to be approved by the FDA shortly. PARFR is now exploring the use of an iodine-based sclerosing agent which is said to look "promising," as well as the instillation of Hypan gel. (The team has some concerns over this latter material, see III.4.2). PARFR has expended \$359,977 on transcervical female sterilization--about 50% of that during the current Agreement.

Previous work with quinacrine and the carefully done MCA studies raise some concerns about transcervical sterilization:

- (1) Possible intra-peritoneal damage and/or exacerbation of

infections of the tube; (2) Tubal closure rates of about 80% with a single instillation, the necessity of performing a second procedure to obtain closure rates approaching 90%, and the programmatic difficulties this presents in LDCs; (3) unsatisfactory correlation of closure with hysterosalpingogram findings; (4) possibility of ectopic pregnancies; (5) cost; (6) the unsolved problem of tubal spasm and (7) need for extensive follow-up.

While the idea of transcervical sterilization is attractive, its transformation into a highly effective method is difficult. PARFR has probably devoted an appropriate amount of funds to this area so far. PARFR should seek a critical outside review of the promise this general area offers before embarking on further major efforts with other sclerosing agents such as iodine.

III.4.2 Reversible Female Sterilization

All clinicians would agree that achieving reversibility in male and female sterilization would have an advantage over permanent procedures, and that the development of such methods would be met with overwhelming consumer acceptance. The evaluation team would concur that research on reversibility deserves attention and that PARFR scores reasonably well in this area. Research into the use of tubal hoods does not, in the opinion of this team, represent a realistic use of scarce resources because of the need for major surgery for application and removal and the attendant costs. For these reasons, PARFR has discontinued this lead. The two other areas of investigation--the clip and the plug and clip--appear to hold greater promise, however.

An intratubal device has shown initial promise in the hands of Dr. Jacques Hamou. The team was able to contact other clinicians who have visited Dr. Hamou's facility and observed the speed and agility with which he utilizes a specially adapted hysteroscope. Results of the first trials reveal two pregnancies among 150 women. Despite relative ease of removal of these plugs and minimal histopathologic changes in the tubes, however, it remains to be seen if fertility potential is subsequently diminished. On the negative side are the cost for each instrument, the technical training necessary to operate the instrument, and the overall hospital costs. A recently published article on the clip and plug device now being tested in animals by Dr. Meeker seems shows this to be a reasonable approach also. PARFR has spent about \$178,000 in this area of research.

Continued investment is warranted in the Hamou plug and in Dr. Meeker's clip and plug device.

III.4.3. Reversible Male Sterilization.

The refinement of a vas occlusive device, the "SHUG," has shown promise for reversible male sterilization. The completion of two primate studies with 100% azoospermia is encouraging. The team is pleased that an Investigational Device Exemption (IDE) was submitted and recognizes the need for additional toxicology studies to satisfy FDA requirements. Phase I and II clinical testing should commence as soon as approval is received. Issues such as leakage around the device, pain and infection during use, possibility of fistula formation, and degree of permanently impaired fertility must be addressed. Insertion using a trochar may be difficult for some clinicians. It is encouraging that a joint effort with a manufacturer is already underway. PARFR should continue its efforts in reversible male sterilization but seek additional consultations from urologists not involved in ongoing studies.

III.4.4 Percutaneous Vas Occlusion

Relatively small resources have been allocated to this potentially promising area of investigation, perhaps because prior trials utilizing the injection of ethanol and formaldehyde had an unacceptably high failure rate. The opportunity to reduce the risk of postoperative hemorrhage and infection without the use of special surgical equipment is appealing. While the team concurs with the appropriateness of this line of investigation, it is concerned about the polymer, Hypan, which is being used. Two members of the team have had experience with Hypan and recognize the possibility of a breakdown of the material with the possible release of the potential carcinogenic monomer, acrylonitrile. (PARFR staff seemed unaware of this potential problem.) All research efforts with Hypan, which contains acrylonitrile, should be placed on hold until PARFR can obtain a clear idea from qualified toxicologists about the possible release of the carcinogenic monomer acrylonitrile from Hypan and a reading from the FDA about the acceptability of this polymer for long-term human use.

III.4.5 Transcutaneous Bipolar Vas Occlusion

After some time trying to design a workable electrode, PARFR is going back to animal studies to determine if bipolar electrocoagulation can indeed close the vas effectively. There may be possibilities for this approach to sterilization however, as one of the team members heard a presentation of clinical data by Dr. Denniston at a recent medical meeting. The reported simplicity of the procedure and successful achievement of azoospermia is encouraging.

III.5 Vaginal Contraceptives: Sperm Enzyme Inhibitors

Researchers in both the private and public sectors have attempted repeatedly to develop new spermicides with an efficacy and therapeutic ratio more favorable than that of nonoxynol-9, but the FDA has been particularly cautious in approving new compounds. Even when the FDA advisory panel suggested approval of Menfegol based upon widespread use by millions of couples worldwide, the FDA declined to accept these recommendations. FDA's reluctance has suggested to pharmaceutical companies that their research priorities should be directed towards other areas. Thus the evaluation team was pleased to review Dr. Zaneveld's work of the past two years on aryl-4-guanidinobenzoates (AGB) as potential contraceptives.

Four phenol-containing compounds that inhibit the sperm enzyme acrosin have been studied in laboratory animals for acute and sub-acute toxicity as well as for spermicidal effectiveness. A single compound (AGB) containing the phenol acetaminophen appeared to show the greatest potential for safety and efficacy. This compound is presently being incorporated into the Today (R) Contraceptive Sponge as a delivery system. Preliminary studies apparently show no alteration in either the sponge or the spermicide. As bulk materials are now being produced and Phase I studies are beginning, the team commends the process by which selection of the final compound was determined. However, it would have seemed appropriate for PARFR to contract for the synthesis of the compound rather than having the PI do it. Stability, effect of vaginal pH, and irritation of the male and female mucosa are only a few of the issues which require examination. Nonetheless, this area of research has potential both domestically and internationally, particularly with innovative delivery systems.

III.6 Ovulation Prediction

The team heard a presentation by Dr. John Tsibris on his progress in evaluating cervical peroxidases as indicators of impending ovulation. From the data provided it appears that the specific activity of guaiacol peroxidase in cervical mucus and vaginal fluids drops sharply four to five days before ovulation and rises again one or two days after ovulation. The levels of guaiacol peroxidase are negatively correlated with estradiol concentrations and in cases of anovulation, do not change. Unlike most other markers examined in the past, the peroxidase level decline yields a clear signal several days in advance of impending ovulation. As important, the levels of guaiacol peroxidase can be monitored by a simple color determination. Current work will determine if women are able to obtain adequate samples of cervical mucus themselves to develop a kit for an

at-home procedure to be used for detecting their fertile period for family planning or for infertility treatment.

Continued support of this work should be provided as long as it remains promising.

III.7 Efficiency in Achieving Goals

The PARFR organization has many characteristics that lead to efficiency of operation: a small, competent administration, personally dedicated technical staff, rapid turnaround on proposals, quick access to investigators and CTOs, no undue delays in publications, and a fair degree of flexibility. As noted elsewhere, this efficiency could be increased by two additional technical staff. However, the larger issue is whether the emphasis on great efficiency has promoted or compromised effective programming. The team has seen evidence in both directions: projects are started quickly but may have to be redone because they were not thought through carefully. This issue is addressed in Chapters IV, VII, and VIII.

III.8 Duplication of Effort With Other Agencies

For the most part PARFR's effort on microcapsules has avoided duplication with others. In fact, in this area an effort has been made to collaborate with the Contraceptive Development Branch (CDB) of the Center for Population Research, National Institute of Child Health and Human Development (NICHD) both in the evaluation in baboons of LNG microcapsules made by Biotek, Inc. under a NICHD contract and in the support of further development work by Biotek. The only duplication is the simultaneous research on LNG microcapsules by Stolle. This effort can be justified, however, on the basis of the need to compare the two microencapsulation processes and to have microcapsules similar the NET for assessing comparative pharmacodynamics.

Moreover, there has not been a great deal of duplication in the research effort overall. Although many projects have been passed back and forth among public sector agencies--e.g., the NET pellet, LNG intracervical device, and anordrin--significant overlap in support has not occurred with the possible exception of MCA nonsurgical female sterilization, where the role of PARFR vis-a-vis HRP is not clear. On the other hand, multiple approaches by various agencies to one product type, e.g., injectables or vaccines, should not be equated with duplication, since several approaches must be tried to obtain the best product. We find further that increased communication among all public sector agencies in recent years has nearly eliminated the possibility of undesirable duplication.

III.9 Discontinued Leads

A list provided by PARFR of representative projects that are no longer being supported and the reasons for discontinuation is appended (see Appendix D). The reasons stated are self-explanatory and reasonable, however, the term "discontinued" should only be applied to those leads dropped because they did not work. Projects such as the Wing Sound II that were transferred to the private sector and MCA/FEMCEPT and the quinacrine pellets that were transferred to FHI should not be cited by PARFR as discontinued leads, but rather as successful projects passed on to others for further development.

IV. MANAGEMENT AND ADMINISTRATION ISSUES

IV.1 Staffing

Over two years ago, a prior evaluation recommended that staff with knowledge in disciplines not covered by the present two-man technical staff be hired. AID concurred with this suggestion. PARFR chose instead to continue the use of ad hoc consultants who had specific expertise related to proposed or ongoing projects, a move which was consonant with its management style. While this management style may have been appropriate in prior years when subcontracts were small and represented research in early experimental stages, the successful growth of key contraceptive leads, the increased complexity of such projects, PARFR's greater involvement in regulatory affairs, and its cumulative funding level of over of over \$10 million, indicates that PARFR should add to its staff a minimum of two full-time senior professionals with backgrounds in bio-medical engineering and/or pharmaceutical science, and product development experience.

The level of support staff appears adequate for the present demand. With the addition of technical staff, at one secretary/ clerical assistant will be required.

IV.2 Monitoring and Subprojects

With about 50 subagreements ongoing at any one time, it is obvious that the technical monitoring of subprojects could be better. Although PARFR has an energetic and knowledgeable staff, they are spread too thinly for the present research challenge. PARFR has chosen to work with some of its sub-grantees in a trusting and collegial manner often reflective of the private and academic sectors. There is much to be said for this approach, and it is no doubt responsible for the usual high marks that the various PIs have bestowed on PARFR. The approach, however, is not consistent with AID's management style, which encourages more technical/evaluation oversight to ensure that their scarce research dollars are being utilized most effectively. Further, AID has limited staff travel opportunities and must rely on its agents for rigorous technical oversight. There is reason to believe that AID, until recently, did not fully share the extent of its concern with PARFR, and in turn, PARFR has not paid as close attention to specific technical points and issues as AID would want.

Clearly, PARFR has done a commendable job in initiating and maintaining several projects that have promise to be completed and have a major impact on fertility regulation. This is

no mean task given the fact that the PI, Dr. Sciarra, allocates only 10 percent of his time to the effort and the time of the two senior scientists combined represents 1.8 man-years of work. Their output assumes that a great deal of efficiency has evolved within PARFR in reviewing and monitoring projects. What cannot be clearly determined is the incremental achievements that might have occurred with the addition of one or two scientists whose prime function would be to assist in the monitoring of ongoing clinical trials and technical monitoring of preclinical studies. It would appear that PARFR has given higher priority to efficient administration than to effective and competent management of projects. With the addition of new staff and more appropriate use of consultants PARFR could upgrade both the frequency and the quality of technical assessment function of its site visits.

IV.3 Administration

In the area of administration, the team echoes the sentiments of prior evaluations in noting the exemplary service of the PARFR Director of Administration. Despite repeated recommendations, no mechanism has yet been found within the University structure to provide adequate compensation for the outstanding quantity and quality of work she performs. The PI should find a mechanism to increase the compensation of the Director of Administration.

While program administration has been uniformly excellent, there has been occasional misuse of this position. Examples were found where technical site visits were performed either only by the Administrator or by the Administrator with one outside person. While site visits may occasionally require administrative inputs, for the most part it is the clear mandate of the scientific staff to be involved in each site visit. Ideally, this should occur (as suggested in the prior evaluation) even when another clinical trial specialist is participating in the peer review process. Another improper use of administrative personnel is the designation of the Director of Administration as the primary correspondent with the FDA; since communication is usually on technical matters, letters from the FDA should be sent to technical staff such as the Assistant Director.

The Director of Administration should not be the only PARFR staff member present at site visits. In addition, the Assistant Director should be named primary correspondent on FDA matters.

IV.4 Use of Consultants

The list of PARFR's non-SAC consultants is clearly an impressive one, though weighted too heavily towards female endocrinology and clinical medicine. In addition, many of the consultants used during the period of the Cooperative Agreement

were PIs on subagreements who would ordinarily be involved in project development and clinical trial protocol planning. Only four of the consultants utilized during the last five years were not currently PIs. In addition, no single consultant was retained for any significant length of time on any project or group of projects during the past few years, thus not providing the kind of in-depth assistance and analysis needed for the many tasks facing PARFR. Consultants, in addition to those who are PIs, should be included in project development and technical reviews and some consultants who do not have conflict of interest should be viewed as long-term advisors to the overall program.

IV.5 Facilities

The existing facilities, while adequate for the present complement of staff, would become confining should additional personnel be recruited. While PARFR headquarters are only two blocks away from the medical campus, the opportunity for interaction with NU faculty occurs primarily at the medical school rather than at PARFR headquarters. The team learned that additional space adjacent to the present offices is available should it be required.

The acquisition and utilization of microcomputers for mailing, budget review and other administrative chores has been an important administrative accomplishment. Project flow charts and budgets recently developed should be transferred to the computer to use it as a tool for project planning and monitoring.

IV.6 Relationships with Northwestern University

Relationships with the Department of Obstetrics and Gynecology at Northwestern appear uniformly good, and, of late, input on programs has been sought with selected faculty. Relationships need to be strengthened within the other science and social science disciplines, however, particularly as they relate to members of the Evanston campus, a considerable distance away. PARFR sponsorship of a one-day symposium for NU faculty should be considered to bridge the distance and increase dialogue.

Discussions with Deans Mintzer and Nutter clearly revealed the regard in which NU and its medical school hold the PARFR program. This is moral support, however, not direct financial payments, except as the University includes PARFR under its liability insurance and discounts certain indirect costs. The University has provided in-kind contributions of \$650,000 over the last 5 years.

IV.7 Reporting

PARFR's semiannual reports are comprehensive and submitted in a timely manner.

V. PARFR RELATIONSHIP WITH AID

V.1 Program Response to AID's Goals and Objectives

AID's general goal to develop new or improved means of fertility regulation suitable for use in LDCs and to strengthen and encourage applied contraceptive research is being met by the current PARFR program. PARFR's portfolio contains several projects that have potential as new or improved family planning methods in LDCs. Its continued support of research in LDCs, sponsorship of regional symposia and scientific workshops, and publications relating to new methods of fertility control provide the basis for encouraging expanded research in the field.

The fact remains, however, that after 13 years of AID funding, PARFR has not produced a new method that AID can use in LDC family planning programs. It would be unfair not to note that except for the Copper T380A and NORPLANT implant system developed by the International Committee for Contraceptive Research (ICCR) of The Population Council, no other contraceptive research and development (R&D) organization has completed such methods either. With the exception of microcapsule injectable development (see Chapter III), the team cannot say with any degree of certainty that PARFR has significantly shortened the development time of any method areas it is currently working on.

AID's specific objectives have for the most part been met within the context of the current Cooperative Agreement. These objectives have remained much the same since 1972, when they may have been quite appropriate. There is a sense, however, that what worked then may not be the best strategy for the present, particularly if PARFR's emphasis is to be on the cutting edge of identifying new contraceptive leads from basic research. Therefore, AID and PARFR should reconsider the specific operating constraints of the Agreement, e.g., restriction of activities to preclinical and early clinical trials. Annual meetings to discuss PARFR priorities should be re-established.

One component of the PARFR agreement, though perhaps beyond the workscope of this assignment, deserves special mention, notably the need to hand over projects to other AID-funded agencies as they progress through Phase II testing. It is not difficult to understand the frustrations that become evident when, after 5-10 years of nurturing, a project is removed prior to the logical culmination of the research initiative. In addition, there is a good chance that expertise developed in the PARFR system may not be transferred with the project, or that the recipient agency will not attend the project with the same priority. While the use of transitional product management teams

may partly compensate for this, many characteristics requiring both an entrepreneurial and advocacy approach to a given method may be lost. Further, limiting the planning responsibility of one agency to a certain time frame rather than thinking through to the ultimate development steps may not be very efficient or effective. Requiring PARFR to pass on leads after Phase II may not be in the best interests of either AID, its grantees, or the development process. This procedure needs re-evaluation by AID.

V.2 Professional Relationship Between AID and PARFR

A widening communication gap between AID and PARFR deserves special note. The gap appears to be due to differences in operating style that have emerged as AID's technical capacity has increased. Until the recent past, AID had relatively less technical interaction with PARFR, and PARFR developed a modus operandi of strong independence. As the contraceptive technology field in general, and PARFR's advanced leads in particular, have increased in complexity, AID appropriately has brought on additional technical staff. This provided an avenue for increased collaboration, but, perhaps because PARFR was not accustomed to closer monitoring, a delay in adapting to the new situation has become apparent.

As is the case in most areas of miscommunication, each side feels the other to be primarily at fault. From PARFR's viewpoint, it has been uncomfortable with the changing of AID contract officers and CTOs during the present Cooperative Agreement. For example, subagreements may be delayed because contract officers are switched in the middle of the approval process. On the technical side, it has sometimes been unclear as to which oversight suggestions to follow when they originate from more than one CTO, and PARFR feels that AID has often provided mixed messages on issues. Of greater concern, PARFR indicates that AID has frequently by-passed it and dealt directly with its subgrantees on issues that are of direct concern to PARFR.

From AID's perspective, PARFR has not been responsive to its concerns regarding increased technical monitoring and evaluation by the addition of staff or better use of consultants. Another area of irritation is PARFR's inattention to explicit project justification and priority setting that AID considers critical for assessing its own internal funding priorities. AID is also concerned that PARFR's technical staff is not totally well informed on each project. AID points out that PARFR does not respond to these concerns in a positive manner as do other AID grantees but rather with a defensive and resistant posture. These tensions can often translate into adversarial situations rather than those of negotiation and collaboration.

The team feels strongly that both parties need to share in the responsibility for rectifying this situation. It appears that AID sometimes has not clearly stated its wishes and committed them to paper and then has pointed to PARFR's inadequacies after the fact. Clearly AID has signaled a lack of confidence by going around PARFR to the subgrantees. On the other hand, PARFR on occasion has shown an unrealistic response to appropriate AID requests. This is reflected in its decisions regarding the hiring of additional staff and more directly in the style it uses in setting priorities, providing evaluation/technical assistance, and its failure to invite the CTO on site visits as required by the Cooperative Agreement.

It is to everybody's relief that despite these communication gaps and philosophical differences the program has functioned as well as it has. PARFR can proudly point to its administrative record, its ability to move rapidly in responding to AID and LDC needs, and most important to some of its leads which in the viewpoint of the team have much promise for additional development and perhaps for widespread consumer application.

As PARFR prides itself on the collegial relationships it has developed with its investigators, it should similarly be able without too much difficulty to re-establish such ties with AID. The bases of positive interactions are already in place: an excellent administration with good contract office relations and a portfolio of projects, many of which both AID and PARFR can proudly exhibit.

AID should communicate its needs for specific information and its preferences on management issues to PARFR in writing. To alleviate the evident communication problems that exist between AID and PARFR, a meeting between the relevant parties should be convened, perhaps with the aid of a mediator, to share the different points of view. It is hoped that out of such a meeting would come a written document reflecting ways of addressing the concerns of both parties.

V.3 Relationship of PARFR Administration and AID Contract Office

PARFR's administration is the paradigm of efficiency and has established a minimum response time for subagreements. AID's Office of Contract Management, however, has not always been able to respond with similar efficiency. The result is that PARFR's flexibility and quick responsiveness are sometimes compromised at AID headquarters and a great deal of frustration is introduced when contract officers are abruptly changed or when a response to a simple request is not obtained. The team realizes, however, that PARFR is not receiving different treat-

ment in this respect from other grantees. The CTO should do whatever is in his power to expedite paperwork through the contract office.

V.4 Relationship Between PARFR and AID Missions and Bureaus

PARFR appears to have been responsive to LDC requests and to have developed appropriate relationships in some of the countries where USAID missions are based. However, the team can not comment with authority on LDC-PARFR interaction, and points out that no time was allocated for interviewing AID staff in the field. It will be necessary for future evaluators to visit investigation sites in both the U.S. and LDCs to assess the issue of responsiveness and to determine if PARFR's revised management style is in keeping with AID's mandate.

AID and PARFR staff have recently spent a great deal of effort establishing a U.S.-Indo science project on immunology. PARFR is now the executing agency for this project.

VI. PARFR RELATIONSHIPS WITH INDUSTRY, OTHER AGENCIES, AND INVESTIGATORS

VI.1 PARFR Relationships With Other Agencies and Investigators

Because PARFR has not been involved in product introduction, the AID-supported family planning organizations--Family Planning Assistance International (FPIA), Association for Voluntary Sterilization (AVS), and the Pathfinder Fund--are not really cognizant of its activities and their interaction has therefore been minimal. AVS staff however expressed appreciation for PARFR's workshop on Female Transcervical Sterilization (June 1982) and its publications, which serve as invaluable sources of information about methods under development. AVS was particularly helped by the opportunity to meet and exchange information at the workshop with investigators from China and other developing countries.

The extent of interaction of PARFR with FHI and CDB has been greater than with other contraceptive research and development programs. PARFR has collaborated with CDB in arranging subgrants for projects that presented difficulties to CDB's funding mechanism. Recent examples are support for Dr. Dunbar's production of zonapellucida antigens; for Biotek, Inc., to whom a subagreement was provided for reformulation of LNG microcapsules; and for UAB for the biological assessment in baboons of various progestins.

PARFR and FHI have a special relationship as sister AID-sponsored organizations. PARFR is expected to hand off projects to FHI for advanced clinical testing and development. In the opinion of the evaluation team, this represents a difficult situation at best for both organizations. In spite of this, and with a few shaky starts, accommodations have been achieved and relationships on major product hand-offs are now fairly productive. Use of FHI's computer facility, data analysis capabilities, and expertise in clinical trials research have been ultimately good for PARFR's program.

While PARFR staff interact informally with staff of the Program for Introduction and Adaptation of Contraceptive Technology (PIACT), ICCR, and HRP at PARFR workshops and Interagency Meetings on Long-Acting Methods, there is no formal collaboration with these agencies on mutual projects at this time although PARFR states that it has shared documents with the other agencies. Some staff of these agencies have expressed a certain hesitation to collaborate with PARFR. This is because PARFR and its projects are not viewed as being open to scrutiny and some of the publicly expressed views of PARFR staff are considered less

than ingratiating. With the continuing expansion of interagency collaboration and the increasing complexity of tasks being undertaken by all agencies at this time in product development, PARFR would certainly benefit from extended collegial and open rather than competitive interactions with these organizations.

The staff of the Ford and Rockefeller Foundations have had only peripheral relationships with PARFR over the years. They are not closely aware of PARFR's current projects even though PARFR's staff are familiar to them. Consideration of future funding opportunities might indicate that PARFR should increase the foundations' awareness of its projects.

No specific information about PARFR's relationship with FDA was obtainable.

Principal investigators of PARFR subprojects give generally high marks to PARFR's program and staff. The Director of Administration was consistently praised for her help, expertise, and quick follow-through on many problems. These good relations are particularly obvious with those investigators who have had longstanding relationships with the organization. Most feel they have been given appropriate technical assistance.

VI.2 PARFR Relationship With Industry

To its great credit, PARFR has recognized early on the need to interact with private industry in order to hasten the manufacture of products suitable for clinical testing, i.e., made under GMP, and also to increase the likelihood of eventual marketing. Examples of this interaction include: (1) BioNexus, Inc.--work on the FEMCEPT device for the delivery of MCA and iodine for female sterilization; (2) Organon--provision of an LHRH (luteinizing hormone-releasing hormone) antagonist delivery system for evaluation; (3) Bivona, Inc.--collaboration on the development of the SHUG reversible vasectomy device; (4) Reznik, Inc.--a bipolar needle for percutaneous vas occlusion; and (5) Ortho Pharmaceutical Corporation and Stolle Research and Development Corporation--development of microcapsule delivery systems for steroids. In this connection, Ortho has the license to Stolle's "two-stage" microencapsulation process and also has an option on the Poly NET-90 system.

The relationship with Stolle deserves special consideration. A review of its history is in order because of the significant effect that the PARFR interaction has had on the creation of this organization. The original connection was between Dr. Lee Beck (UAB), who has received project support from PARFR almost from its inception, and Ralph Stolle, an industrialist and philanthropist who supported Dr. Beck's research. Mr. Stolle became interested in the work being done with PARFR

support on microcapsules at UAB and the SRI. This interest eventually evolved into the incorporation of a biotechnology research company with a mandate to pursue microencapsulation technology. Dr. Danny Lewis, another PARFR investigator, left SRI to become a Vice President Stolle Research and Development Corp. and Dr. Lee Beck has joined the management of Stolle. In addition to its laboratory facilities, Stolle has just built a pilot plant at a cost of several million dollars. This is a completely up-to-date GMP facility for the production of up to 50 kilograms of microcapsules. This valuable pilot plant, although built with private funds, most likely would not have come into being if it had not been for PARFR's support of research on microencapsulation.

PARFR's initiatives in establishing interaction with the private sector should be continued and expanded when possible.

VII. SCIENTIFIC ADVISORY COMMITTEE

VII.1 Purpose and Membership

The purpose of SAC as viewed by PARFR staff is to supplement and complement its own work. SAC is basically requested to review and comment on new and continuing proposals, vote for approval amendments, or disapproval, review technical progress reports and suggest topics for workshops in a thrice-yearly, one-day meeting. SAC members are occasionally asked to go on site visits. None of the SAC members who were interviewed believes his or her role extends beyond these functions.

The SAC comprises up to 12 members including the permanent Chairman. Members are appointed by Dr. Sciarra with the concurrence of the AID CTO for a period of three years. The expertise of the Committee has always been heavily weighted toward obstetrics and gynecology and reproductive endocrinology. Given the program emphases on, for example, immunocontraception and vas occlusion, it is surprising that no immunologists or urologists have been included. Of equal concern is the lack of expertise in product development and toxicology, given PARFR's increasing involvement in those areas. The recent addition of a consultant with skills in biostatistics is a major step forward. SAC membership should more completely reflect PARFR's areas of research and program activities.

VII.2 Modus Operandi

The SAC is sent proposals and progress reports to review prior to the meeting. The progress reports tend to be uneven in quality and detail. On occasion, there is not enough data presented to make an informed decision. Progress reports provided to SAC should include enough detailed information to allow members to make informed decisions.

Each SAC member is expected to read each proposal and make brief comments on it. Several SAC members thought that a better review of proposals might result if two or three reviewers were assigned to make detailed comments on each proposal. This and other ways to improve the quality of reviews should be instituted.

PARFR staff are still in the habit of preparing a synopsis of proposals that contains their recommendations for approval. Several SAC members believe this procedure prejudices the subsequent discussion and kept diverse opinions in check. PARFR staff should no longer provide their own reviews to the SAC but restrict their comments to introductory, factual remarks. Further, a secret ballot is taken to indicate support or lack of

support of applications. There is a feeling among some members that the vote, as well as advice, is disregarded in some important instances. The result of the vote should be tallied openly so that additional discussion might occur and the vote can go on record.

It may be that a one-day meeting is not sufficient to discuss all proposals fully, but PARFR staff indicate consultants have refused to extend meeting times because of other commitments. This is in contrast to HRP Steering Committee members who routinely participate for 10 days or more per year and to the service extended by National Institutes of Health (NIH) Study Section members. If SAC members are given additional responsibilities, the number of days for meeting will need to be extended. The time allocated to SAC meetings should be increased.

VII.3 SAC Role in Decisions and Planning.

Because PARFR staff is small, it would be logical to seek advice from the SAC on matters of policy, strategy, and overall program direction. This, according to SAC members interviewed, does not occur. While brain-storming sessions have been attempted, these are in the order of informal conversations which PARFR has not found useful. It is evident, however, that PARFR would greatly benefit from seeking and applying the advice of its SAC. Therefore, PARFR should increase the role and responsibilities of its Scientific Advisory Committee.

VIII. THE CURRENT PARFR MECHANISM

The major advantages of the operating mechanism of PARFR are its inherent flexibility and adaptability. These permit speedy response to program needs as established both externally and internally, a virtue at a time when bureaucratic undertakings and requirements often paralyze rational decisions. The team has the impression, however, that these advantages have been muted because PARFR has not been able to devote sufficient time and depth of attention to focusing the work of grantees and to forward planning. A lean staff must be complemented by other methods to assess priorities and plan strategy and tactics. These do not reside in the SAC or the ad hoc consultancies as presently constituted.

In the early years of the PARFR program, potential leads were abundant and a reasonably broad mix of investigators, institutions, and activities were supported. In more recent years, unsuccessful leads have been dropped but few new leads have replaced them. Therefore, the scope of the program has narrowed somewhat as it has in many organizations. Nevertheless, PARFR's mandate does emphasize identification of new leads, but this is no longer a major effort and the number of leads in the pipeline may not be optimal. In addition, there appears to be even more concentration of the effort among a select group of investigators above and beyond what might be expected from the normal maturation of certain leads such as the microencapsulation of steroids. This concentration might, hypothetically, cause problems if, for example, Stolle Research and Development decided to stop its involvement in contraception because of product liability problems.

With respect to the monitoring of various subagreements, working with investigators in the development of protocols for preclinical and clinical studies, and interacting with FDA on regulatory affairs and with industry in the pursuit of licensing agreements and production, PARFR is hampered by the lack of sufficient manpower and expertise. Therefore, many of these activities which might be considered the responsibility of PARFR are delegated to the subproject investigators. One area that cannot be delegated, and therefore often has not been done properly, is technical monitoring of various subprojects by the staff.

In spite of the above criticisms, the PARFR mechanism itself is valid and expansion of the staff could readily resolve most of the difficulties described. It should be noted that help is sorely needed in the nonclinical areas, e.g. bioengineering, toxicology, and pharmaceutical sciences. The mechanism could also be strengthened by the addition of in-house research

capability, which would enhance the capability to respond to technical problems by having a core of active researchers as well as scientific administrators available. This capability would enable PARFR to become more aggressive in its product development research and in the time-consuming search for new leads.

The final point to be addressed in this section is the degree of "openness" of the program. To realize a more open collaboration with other agencies, such as inviting representatives to their meetings, PARFR would need to create an appropriate forum for this to take place since the nature of the present SAC would hamper full and open discussion of projects of mutual interest. In the absence of an expanded staff, close technical monitoring and more thorough documentation of research reports, "openness" is only an academic issue.

IX. PARFR'S ACTIVITIES IN INFORMATION DISSEMINATION

IX.1 PARFR Workshops and Regional Symposia

Perhaps the least controversial components of PARFR's operations are its workshops, symposia, and publications. These activities have been praised by the SAC, AID, and the field in general. The selection of workshop topics was developed jointly with AID at the time the Cooperative Agreement was signed and jointly modified throughout the project. Similarly, PARFR and AID have jointly selected the sites as well as the workshop participants. In almost all cases, other public sector agencies have been encouraged to have representation, and, where appropriate private industry has also been invited. The selection of speakers has for the most part been excellent, and the relationship developed with Harper and Row publishers has been mutually beneficial, allowing the editing and publication of the workshop proceedings within nine months. Because the volumes are popular, PARFR should obtain from the publishers an accurate count of the total number of books sold and determine if an opportunity for receiving royalties exists from Harper and Row or another publisher.

PARFR selectively mails the workshop proceedings to 1,200 of its mailing list of 5,000. About 50% of the mailings are to LDCs, with another 150-300 copies distributed by AID to missions and bureaus. (Time limitations prevented the examination of the mailing lists.)

The workshops and subsequent proceedings serve at least two purposes--they bring both national and international recognition to PARFR and they collate the state-of-the-art information on a given contraceptive area to a significant audience of clinicians, researchers, and students in the U.S. and abroad.

The mix of topics was broad, ranging from the most practical to those of specific interest to researchers concerned with conducting toxicology and Phase I and II research. In general, the editors have done a superior job within a reasonable time frame.

The team is aware of two symposia which were already in the planning stage but were not convened. One workshop was concerned with bridging the gap between basic science and applied research, product liability, addressing FDA regulations, and the transfer of technology. These problems in contraception research and development are important and timely issues and should be considered for a workshop in the near future. Appendix E lists the workshops and symposia proceedings already completed and

includes dates of publication.

IX.2 Other Publications

PARFR also publishes a series entitled Research Frontiers in Fertility Regulation (RFFR), which has a distribution of 5,000 copies. Of these, approximately one-third are mailed to LDCs. The selection of topics by a single author for this format is focused and is printed to fit in a loose-leaf binder. The RFFR series appears to fill a void in the field by offering an overview towards one specific area of contraceptive research. These publications enhance the transfer of current knowledge and should be continued.

In order to further upgrade its mailing list, PARFR should also scan the lists of the Population Information Series and that of International Family Planning Perspectives to obtain additional addresses. Selection of appropriate individuals from these mailing lists should extend PARFR's reach into LDCs. PARFR also has an opportunity to utilize RFFR as a medium to solicit new research proposals. Appendix F provides a representative sample of the RFFR.

A number of international journals have asked permission to reprint all, or part, of their publications in the local language. The publication of papers in peer-reviewed journals is another important index of the quality of the research that is being reported. PARFR has been responsible for 425 publications which have appeared in a variety of domestic and international journals and books since 1976. These articles cannot help but have an impact on the field of contraceptive development. PARFR should continue to submit original papers for publication and suggests that PARFR develop a series of loose-leaf binders by research category. This material could then be made available as an additional resource to collaborators and might serve as a guide to LDC investigators who might wish to submit proposals to PARFR.

X. PARFR FUNDING SITUATION

Sufficient information was not available from either PARFR or AID to make a proper assessment of funding on a year by year basis prior to the current Agreement, which started in 1981.

Although several organizations provided material support to PARFR between 1981 and 1985, no direct financial contributions were made to the program. To achieve greater program flexibility and to cover AID shortfalls, PARFR should consider seeking funding from other sources.

The authorized funding level of \$12,363,280 for the current Cooperative Agreement was sufficient to accomplish the workscope; however, the actual funding provided was less than that negotiated by nearly \$2,000,000--or 15%--over the five year period. Because the fixed commitments for core staff, publications, etc. were met on the whole according to plan, the actual funds committed to research were only \$6,500,890 or 62% of the allocated funds. This compares with the projected fraction of the total budget to be allocated to subagreements of 69%. The shortfall of \$2,000,000 was taken from the research subagreements category, a decrease of 23%, which probably had a significant impact on program operations.

In addition to the shortfall described above, PARFR maintains that the actual incremental funding from AID was slow in arriving even after Congress had provided the Agency with a budget. According to PARFR, uncertainties in the amount of funding and the timing of payments led to difficulties in the funding of the subagreements and on at least one occasion even forced PARFR to borrow from other funds to pay the PARFR staff. Under these circumstances, PARFR has done a good job obligating funds.

Because this is the final year of the Cooperative Agreement, there have been problems in effectively obligating funds for projects (e.g., Poly NET 90 Phase II clinical trials) that will take more than one year to complete but which should and will be started during this last year. Signals from AID at first indicated that there should not be any new projects started, but it was recognized that this would cause unnecessary delays. It is clear that in the event that PARFR does not win the new competition, the most efficient means of completing the studies in progress would be to provide PARFR with an extension sufficient to phase out the ongoing studies. The time involved in getting other organizations ready to take over precludes that option. AID should indicate to PARFR how continuing studies will be supported if the Agreement is not continued. A careful plan for the continuing development of POLY NET 90 should be made.

The funding made available to LDCs amounted to about 15% of the total budget. However, it appears that the funds have gone mostly for the evaluation of methods invented in developed countries except for immunocontraception and Thai plant proteins. PARFR should strengthen its efforts to obtain original research proposals from LDCs.

The mix of funds allocated to developed country investigators is reasonable. The major funding has gone to U.S. investigators and it is not clear how concerted an effort was made to attract investigators from other developed countries or what AID policy is on this issue.

XI. SUMMARY OF RECOMMENDATIONS

XI.1 Portfolio

1. PARFR should give priority to determining the reproducibility of NET microcapsule batch manufacture as it affects in vivo performance thereby validating current quality control procedures.
2. Major development efforts should continue on the encapsulation of the 90-day NET, progesterone, and testosterone with somewhat less emphasis on 30- and 180-day Poly NET and ethinyl estradiol.
3. PARFR should carefully assess the long-term toxicology costs of bringing anordrin through clinical trials and weigh these factors against its potential impact on family planning programs.
4. A planning and strategy evaluation of PARFR's research program on immunocontraception should be held soon.
5. Before embarking on other major efforts for female chemical sterilization with sclerosing agents such as iodine, PARFR should seek a critical outside review of this general topic.
6. PARFR's interest in reversible sterilization seems appropriate. New possibilities that appear promising include the Hamou plug, the Meeker plug and clip, and the SHUG device. Additional consultations should be obtained from urologists on the SHUG device.
7. All research efforts with Hypan should be placed on hold until PARFR can obtain a clear idea from qualified toxicologists of the possible release of the carcinogenic acrylonitrile monomer and a reading from the FDA about the acceptability of this polymer for long-term human use.
8. Continued support of the guaiacol peroxidase work should be provided as long as it continues to look promising.
9. A separate category should be created for projects transferred to other agencies for additional development rather than including them among discontinued leads.

XI.2 Management and Administration

10. PARFR should add to its staff a minimum of two scientists, one of whom should have expertise in the biomedical engineering or product development area.
11. Additional secretarial help will be required when the technical staff is increased.
12. PARFR should upgrade both the frequency and the quality of technical assessment of site visits and other project monitoring functions.
13. A mechanism should be found to increase the compensation of the Director of Administration.
14. The Director of Administration should not be the only PARFR staff present at site visits.
15. The Assistant Director should be designated primary correspondent with the FDA, not the Administrator.
16. Consultants who are not PIs should be included in project development and technical evaluation. Further, some consultants who do not have a conflict of interests should be viewed as long-term advisors to the program.
17. Microcomputers should be used as a tool for planning and project development.

XI.3 PARFR Relationship With AID

18. AID and PARFR should reconsider the specific operating procedures of the Cooperative Agreement, e.g., restriction of activities to preclinical and early clinical trials, requirements to advertise broadly, review of unsolicited proposals.
19. Requiring PARFR to pass on leads after Phase II may not always be in the best interests of AID, its grantees, or the development process, and therefore this procedure should be re-evaluated.
20. AID should advise PARFR in writing of its needs for specific information and its preferences on management and technical issues.

21. To address the evident communication problems that exist between AID and PARFR, a meeting between the relevant parties should be convened, perhaps with the aid of a mediator, to share the different points of view. It is hoped that out of such a meeting would come a written document reflecting ways of addressing the concerns of both parties.
22. The CTO should do whatever is in his power to expedite paperwork through AID's Office of Acquisition Assistance Management (formerly Office of Contract Management).

XI.4 PARFR Relationships with Industry and Other Agencies

23. With the continuing expansion of interagency collaboration and the increasing complexity of tasks experienced by all agencies at this time in product development, PARFR would certainly benefit from extended collegial and open, rather than competitive, interactions with other organizations.
24. Consideration of future funding might indicate that PARFR should increase foundations' awareness of its program.
25. Efforts to establish interaction with the private sector should be continued and expanded when possible.

VII.5 Scientific Advisory Committee

26. SAC membership should more completely reflect PARFR's areas of research and program activities.
27. Progress reports provided to SAC should include enough information to allow members to make informed decisions.
28. A process to improve the quality of reviews of proposals and continuing projects should be instituted.
29. PARFR staff should no longer provide their own reviews to the SAC, and the result of the vote to approve or disapprove proposals should be tallied openly.
30. The time given to SAC meetings should be expanded.

31. PARFR should enlarge SAC's role and responsibilities.

XI.6 Information Dissemination

32. Because the workshop volumes are popular, PARFR should obtain from the publishers an accurate count of the total number of books sold and determine if an opportunity for receiving royalties exists.
33. A workshop on generic problems involved in contraceptive research and development, e.g., product liability, should be considered in the near future.
34. The series Research Frontiers in Fertility Regulation should be continued.
35. PARFR should obtain additional addresses in LDCs from the mailing lists of Population Information Series and International Family Planning Perspectives.
36. Submission of original papers for publication should continue and PARFR should develop a series of loose-leaf binders by research category to be shared with collaborators.

XI.7 PARFR Funding

37. To achieve greater program flexibility and to cover AID shortfalls, PARFR should consider seeking funding from other sources.
38. AID should indicate to PARFR how continuing studies will be supported if the Agreement is not continued. A careful plan for Poly NET 90 should be drawn up.
39. Greater effort should be made to obtain original research proposals from LDCs.

APPENDIX A

NAMES OF PERSONS INTERVIEWED BY TELEPHONE

I. PARFR Investigators

Dr. Nancy J. Alexander, Oregon Regional Primate Research Center, Beaverton, Oregon

Dr. Brig B. Saxena, Cornell University College of Medicine, New York, New York

Dr. Rochelle Shain, University of Texas, San Antonio

Dr. Roberto Rivera, University of Durango, Durango, Mexico

Dr. John P. Wiebe, The University of Western Ontario, Ontario, Canada

Dr. Bonnie S. Dunbar, Baylor College of Medicine, Houston, Texas

Questions: How did you find out about PARFR? Was funding adequate? Strengths, weaknesses of the program? Nature of technical assistance? Quality of site visits? Nature of interaction with staff?

II. Staff of Family Planning Agencies

Mr. Hugo Hogenboom, Association for Voluntary Sterilization, New York, New York

Dr. Douglas Huber, Association for Voluntary Sterilization, New York, New York

Mr. Dan Weintraub, Family Planning International Assistance, New York, New York

Questions: What do you know about PARFR? What interaction does your organization have with PARFR?

III. Staff of Contraceptive Research and Development Agencies

Dr. Wayne Bardin, International Committee for Contraception Research, Population Council, New York, New York

Dr. Harold Nash, International Committee for Contraception Research, Population Council, New York, New York

Dr. Jose Barzelatto, Human Reproduction Programme, World Health Organization, Geneva, Switzerland

Dr. Peter Hall, Human Reproduction Programme, World Health Organization, Geneva, Switzerland

Dr. Gordon Perkin, Program for the Introduction and Adaptation of Contraceptive Technology, Seattle, Washington

Mr. Michael Free, Program for the Introduction and Adaptation of Contraceptive Technology, Seattle, Washington

Dr. Gabriel Bialy, Contraceptive Development Branch, National Institute of Child Health and Human Development

Dr. Albert Siemens, Family Health International, Research Triangle Park, North Carolina

Dr. Malcolm Potts, Family Health International, Research Triangle Park, North Carolina

Questions: What is PARFR's mandate? How would you approach it? What is the relationship of your organization and PARFR? Most promising, least promising leads?

IV. Members of PARFR's Scientific Advisory Committee

Dr. William Droegemueller, University of North Carolina, Chapel Hill, North Carolina

Dr. Miriam Labbock, Johns Hopkins University, Baltimore, Maryland

Dr. Nancy J. Alexander (previous member)

Dr. Gary Hodgen, Eastern Virginia Medical School, Norfolk, Virginia

Dr. Antonio Scomegna, University of Chicago, Chicago, Illinois

Dr. Alvin Paulsen, University of Washington, Seattle, Washington

Dr. Anne Colson Wentz, Vanderbilt University, Nashville, Tennessee

Questions: What is PARFR's mandate and is PARFR fulfilling it? What is the purpose of SAC?, How does it operate? Is SAC

involved in overall planning for PARFR? Does the present review process work? Strengths and weaknesses of PARFR staffing? Most promising leads, least promising leads?

V. Staff of Foundations

Mr. Oscar Harkavy, The Ford Foundation, New York, New York

Mr. J. Kellum Smith, The Andrew W. Mellon Foundation, New York, New York

Dr. Sheldon J. Segal, The Rockefeller Foundation, New York, New York

Questions: What is PARFR's mandate? Mode of operation? Relationship with organization? Contraceptive leads under development by PARFR?

APPENDIX B

WORKSCOPE AND ISSUES TO BE ADDRESSED IN PARFR EVALUATION

VIII. Issues to be Assessed by the Evaluation Team

- A. Review report of last assessment (June 1983) and PARFR's response to recommendations.
- B. Assess current PARFR subproject portfolio.
 1. What is the status of current leads and duration of funding of those leads?
 2. Comment on which leads are likely to reach Phase III trials.
 3. What patents, INDs and IDEs is PARFR responsible for and what guarantees has PARFR obtained to protect public sector rights?
 4. How efficient is PARFR in reaching goals in shortest amount of time.
 5. Comment on duplication of other R&D efforts.
 6. Comment on anticipated usefulness of PARFR products to LDC programs.
 7. Are current PARFR priorities too restrictive or too wide, and are there any missed opportunities?
- C. Assess Discontinued Leads (since 1981)
 1. Which leads were discontinued?
 2. When?
 3. Why?
- D. Assess PARFR Management and Administration
 1. Staffing - comment on
 - a. Available expertise in all areas/disciplines.
 - b. Whether staffing level is sufficient to meet needs.
 - c. If subproject oversight is effective and efficient?
 - d. The level of support staff available.
 - e. Appropriate degree and role of consultants used to augment the staff.
 2. Facilities - Adequacy in terms of
 - a. space
 - b. equipment
 3. Relationship of PARFR with Department of Obstetrics and Gynecology and Northwestern University Administration

4. Reporting
 - a. Semi-annual reports complete and submitted on time.
 - b. University and PARFR submit financial reports and vouchers in timely manner.

- E. PARFR Relationship with AID (AID and PARFR staff will be interviewed by team)
 1. Are AID's goals and objectives being met?
 2. Professional relationship between AID and PARFR staff in terms of collaboration/cooperative spirit and AID "substantial involvement"
 3. Relationship between PARFR administration and AID Contract Management Office.
 4. Relationship between PARFR and AID Regional Bureaus and USAID Missions in LDCs.

- F. PARFR Relationship with Agencies and Investigators (scientific and administrative peers) working on contraceptive R&D and family planning. In addition to the Team meeting with PARFR, the chairperson will speak with staff of other agencies and collaborating investigators.
 1. World Health Organization (WHO)
 2. Family Health International (FHI)
 3. Population Council
 4. Program for the Introduction and Adaptation of Contraceptive Technology (PIACT)
 5. Ford Foundation
 6. Rockefeller Foundation
 7. Food and Drug Administration (FDA)
 8. FPLA/AVS/Pathfinder
 9. Principal Investigators of about six different PARFR projects
 10. Members of the PARFR Scientific Advisory Committee

- G. Review PARFR Relationship with Private Industry
- H. Assess Scientific Advisory Committee (SAC)
 - 1. Purpose of SAC
 - 2. Membership
 - a. How selected
 - b. Adequacy for covering all required disciplines
 - 3. Review procedures - proposals and technical reports
 - a. Modus Operandi
 - b. Adequacy of time
 - 4. Role in decision making, strategy formulation and day-to-day PARFR operation
- I. Assess the current PARFR Mechanism in terms of
 - 1. Establishing priorities.
 - 2. Engaging in a wide mix of subproject activities, investigators and institutions.
 - 3. Developing new, and improving existing, methods of contraception.
 - 4. Ensuring proper development of subprojects, protocols and conduct of studies to maximize output.
 - 5. Alternative mechanisms for accomplishing goals and purpose of PARFR and AID.
 - 6. Degree of "openness" of the program.
- J. Assess Information Dissemination - Review and comment on:
 - 1. PARFR Workshops - appropriateness of topics, locations, costs, and timely publication of proceedings. Also, discuss appropriateness of choice of speakers and participants.
 - a. PARFR to provide a table by year, since first workshop, detailing the above information.
 - 2. PARFR Regional Symposia - same information as 1 above is to be provided and assessed by Team.
 - 3. Research Frontiers in Fertility Regulation - topics per year.
 - 4. Distribution of PARFR publications.

5. Scientific publications of PARPR-supported investigators (PARPR to provide samples of ten most important publications)

- a. Bibliography of all published papers under current Cooperative Agreement.
- b. Comment on topics, quality of journals and quality of selected papers.

K. PARPR Funding - Review and comment on:

1. Total budget submitted to AID under each funding document prior to 1981 and budget per year under current Cooperative Agreement (FY 1981-1985).
2. Actual funds provided by AID, under each document prior to 1981 and, by year, under current Cooperative Agreement.
3. Non-AID financial resources available to PARPR, by year, for period 1981-1985
4. Is funding level of current Cooperative Agreement (FY 1981-1985) sufficient to accomplish workscope?
5. Efficiency of PARPR in obligating funds during current Cooperative Agreement.
6. Line item budget evaluation (PARPR to prepare line item budget for current Cooperative Agreement by year for FY 1981-1985 and total)
 - a) Is the mix (percent going to each category), appropriate?
 - b) Were sufficient funds provided for subprojects? workshops? publications?
7. Funds (and percent) provided to LDC investigators/institutions, by year, under current Cooperative Agreement.
8. Funds (and percent) to developed country investigators/institutions, by year, under current Cooperative Agreement. PARPR to show total funds provided to each principal investigator and institution.

APPENDIX C
RECOMMENDATIONS FROM THE 1983 EVALUATION OF PARFR

IV. SUMMARY OF RECOMMENDATIONS

1. The Team concurs with the recommendations of the previous site visit team that, when additional professional staff are hired, they should have expertise in the clinical trial area.
2. One of the major deficiencies that the program has at this time is the ability to store, collate and retrieve information with regard to ongoing projects, clinical trials, site visits, financial expenditures and program management. The Team recommends very strongly that monies be expended to purchase a mini-computer and to hire (on a part-time contract basis) a programmer to develop the appropriate software necessary for implementation of these recommendations.
3. The Team recommends that an individual should be appointed to the SAC for an initial probationary term of one year during which time his performance, interest and expertise can be evaluated. If this individual proves to be satisfactory, he can then be appointed for a further two years. At the end of the initial three-year term, his membership can be extended under special circumstances on a year-to-year basis for an additional two years, up to a maximum of five years.
4. The previous team had recommended that the new SAC members should not receive funds from PARFR at the time of appointment, nor be eligible for contracts while serving on the SAC. The present Team are in general agreement with this recommendation, but feels that under exceptional circumstances a SAC member should not necessarily be barred from undertaking a pilot project.
5. The previous Team had recommended that PARFR broaden the areas of expertise of the individuals on the SAC. It would appear that indeed the PARFR staff have moved in this direction, but the present Team still

- feels that certain disciplines are lacking — for example, a biostatistician, individual experts in clinical trial methodology and execution (other than the PARFR staff themselves), and a polymer chemist — and recommends that such individuals be added.
6. To avoid perceived conflict of interest, as a minimal requirement, the Team recommends that individuals from an institution absent themselves from discussions concerning projects originating from their own institution, even though they are not principal investigators.
 7. The Team recommends that Dr. Sciarra should not vote on the actual projects, although he can continue as Chairman of the SAC.
 8. The Team recommends that the administrative staff of PARFR present the individual projects, placing them in perspective with regard to their total program and possibly also pointing out the strengths and weaknesses in the protocols, but reserving any indication of their own recommendations as to funding until after the SAC members have had a full discussion on the individual project.
 9. It appears that it is not the usual practice for the SAC to be involved in discussions of strategy, and the Team recommends that, in the future, a portion of the SAC meeting be devoted to a brain-storming session at which the SAC members would be encouraged to discuss new lines of research, to re-evaluate priorities of ongoing lines of research and to suggest potential new areas and investigators that might be of interest to PARFR and AID.
 10. The Team recommends that, in general, the PARFR administrative staff should either go by themselves or accompany the principal investigator on site visits, but that principal investigators can continue to be used for purely technical visits.

these funds be made available at the budgeted level and in a timely manner for the program.

27. The Team recommends that submission of semi-annual progress reports of research activities by PARFR to AID should be continued. However, the Team recommends that AID and PARFR attempt to reduce the amount of paperwork and redundancy of the material that is submitted in the six-monthly reports, particularly in regard to expenditures, organizational charts, and publications.
28. The Team wishes to congratulate all PARFR staff on the excellent job which they are doing, and has no hesitation in recommending that the program be continued in its present shape and form.
29. In view of the excellent progress of the PARFR program, the Team concurs that an interval of 3 years before the next in-depth review seems perfectly appropriate.

16. The Team recommends that, since Anordrin is widely used in the People's Republic of China, and since PARFR has good relations with the World Health Organization and its clinical network, WHO and/or PARFR should be encouraged to approach Chinese or other non-US clinical centers to determine whether a small Phase I study could be done. Specifically, this study should evaluate whether a small dose of Anordrin given on the first day of menstruation does indeed suppress ovulation and, if so, for how long.
17. The Team discussed the viability of a new initiative in the area of immunoreproduction, especially in context of certain Indo-US interest. The Team strongly recommends that advice and consultation be provided by bona fide immunologists prior to the initiation of such a program.
18. The PARFR staff reported that Dr. Greenslade's flow chart was going to be improved and made into a proper PERT chart or critical path map, and that similar charts were going to be developed for each of the other major lines of research. This is felt to be a very commendable and useful exercise. The Team recommends that the PARFR staff accomplish this as soon as possible.
19. The Team strongly recommends that these charts show the estimated duration of each phase of the developmental process and an estimate of the anticipated target dates for start and completion of the actual activities. The estimated cost for each phase should also be identified, since this will be required for financial projections.
20. The Team recommends that, in the future, all tabulations of projected activities be given careful thought and consideration, and be laid out in much more extensive and informative fashion, being broken down by year and listed by order of priority.

APPENDIX D

LIST OF PARFR CONTRACEPTIVE LEADS THAT HAVE BEEN DISCONTINUED

DISCONTINUED LEADS AND TRANSFER OF TECHNOLOGY

(Since 1981)

<u>Title</u>	<u>Principal Investigator</u>	<u>Reason</u>
I. <u>VAGINAL CONTRACEPTION</u>		
Vaginal Spermicidal Barrier	Gerald S. Bernstein, M.D.	Unacceptable results in post-coital test studies.
Collagen Sponge	Milos Chvapil, M.D.	Unacceptable pregnancy rate.
Norgestimate Vaginal Ring	Richard L. Dunn, Ph.D.	Feasibility study discontinued because of lack of interest of private sector.
Vaginal Contraceptive (Orabase)	Arthur D. Little, Inc.	Preliminary data not encouraging.
Thai Plants - Vaginal Contraceptives		After completion of fertility study, data not very encouraging to pursue lead.
II. <u>INTRAUTERINE CONTRACEPTION</u>		
Levonorgestrel ICD	Tapani Luukkainen, M.D.	Contracted 5/1/83-4/30/86 Terminated 6/30/85 due to an unacceptable expulsion rate.
Wing Sound II	Harrith M. Hasson, M.D.	Transferred to private sector.
Estrogen-Progesterone Fibers	Richard L. Dunn, Ph.D. Antonio Scommegna, M.D.	After development and small animal studies completed, studies were discontinued and IND was not pursued because maximum steroidal release rate with the T-vector was only feasible for up to 2 years.

<u>Title.</u>	<u>Principal Investigator</u>	<u>Reason</u>
III. <u>STEROIDAL AND NEUROPEPTIDES</u>		
Phase II Poly NET 90 341 Series	Charles Flowers, Jr., M.D. Lee R. Beck, Ph.D.	Unacceptable release rate during first month of early exposure, 1 pregnancy out of 19 women. Reactivated December 1, 1985.
LHRH Antagonist	Andrew V. Schally, M.D.	Continuation studies proposed not needed for IND submission. Private sector completing own studies.
Dynatech Levonorgestrel Rods (PARFR-320)	Donald L. Wise, Ph.D.	IND and European studies were not pursued because of anticipated duration of release over 4 years and problems with removal of the rods.
NET Pellet Implant	Brij B. Saxena, Ph.D.	Phase I and II complete. Technology transferred to FHI.
IV. <u>FEMALE STERILIZATION</u>		
MCA/FEMCEPT Transcervical	Robert Neuwirth, M.D. Ralph M. Richart, M.D.	PARFR completed 2 year follow-up in the clinic studies. Technology transferred to FHI for long-term follow-up.
Tubal Hood	Leonard F. Laufe, M.D. Carlton A. Eddy, Ph.D.	After completion of animal study, patent acquired by private sector who decided not to pursue clinical trials because of extensive FDA toxicology requirements for an IDE.
Quinacrine Fiber Pellet	L.J.D. Zaneveld, D.V.M., Ph.D.	Animal studies completed. Technology transferred to FHI.

<u>Title.</u>	<u>Principal Investigator</u>	<u>Reason</u>
V. <u>MALE STERILIZATION</u>		
Transcrotal Bipolar Cautey (PARFR-328B)	Marcos P. de Castro, M.D. Sao Paulo, Brazil Technical Assistance: Michael J. Free, Ph.D. Bioengineering: Ben Reznik	Prototype I and II did not perform as expected. Prototype III is being designed and is soon to be tested.
Transcrotal Chemical Male Male Sterilization	Ralph M. Richart, M.D. (PARFR-344) Ronald W. Lewis, M.D. (PARFR-308)	Feasibility animal studies with several chemicals in 2 animal species show unencouraging data with the exception of one com- pound (iodine/iodide) which is being pursued by PARFR.

APPENDIX E

LIST OF PARFR-SPONSORED WORKSHOPS AND SYMPOSIA

PARFR WORKSHOPS

7/1/81-6/30/86

Male Contraception: Advances and Future Prospects May 28-31, 1985 Noga Hilton Geneva, Switzerland 62 participants, representing 13 countries	Total Cost:	\$ 72,695
Intrauterine Contraception: Advances and Future Prospects May 29 - June 1, 1984 Northwestern University Medical School Alumni Center for Continuing Education Accommodations: Sheraton Plaza Hotel Chicago, Illinois 90 participants, representing 22 countries	Total Cost:	82,979
Long-Acting Contraceptive Delivery Systems May 31 - June 3, 1983 Royal Orleans Hotel New Orleans, Louisiana 115 participants, representing 16 countries	Total Cost:	95,228
Female Transcervical Sterilization June 22-24, 1982 Ambassador East Hotel Chicago, Illinois 65 participants, representing 14 countries	Total Cost:	45,561
LHRH Peptides as Female and Male Contraceptives May 13-15, 1981 Ambassador East Hotel Chicago, Illinois 70 participants, representing 11 countries	Total Cost:	45,679
	TOTAL WORKSHOPS:	<u>\$342,142</u>

PARFR SYMPOSIA

7/1/81-6/30/86

Intrauterine Contraception May, 1981 Salvador, Bahia, Brazil 150 participants	TOTAL:	\$18,000
Clinical Aspects of Human Reproduction April 15-17, 1982 Santiago, Chile 450 participants	TOTAL:	51,000
Long-Acting Contraception November 3-4, 1983 Alexandria, Egypt	TOTAL:	47,500
Recent Advances in Human Reproduction April 13-14, 1984 Sanfo Domingo, Dominican Republic	TOTAL:	3,600
Latin America Congress of Obstetrics and Gynecology October 20-31, 1984 Caracas, Venezuela	TOTAL:	8,300

APPENDIX F

SAMPLE ISSUE OF RESEARCH FRONTIERS IN FERTILITY REGULATION

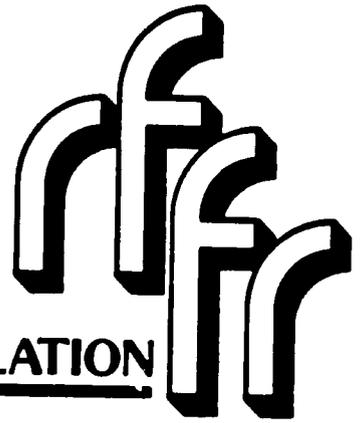
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RESEARCH FRONTIERS IN FERTILITY REGULATION

TRANSCUTANEOUS MALE STERILIZATION

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Vasectomy is one of the safest, simplest, and most effective methods of fertility regulation. Compared to female sterilization, it is safer and cheaper and has a similar rate of effectiveness. In spite of these advantages, in most countries the number of contraceptive female sterilizations performed each year continues to exceed the number of male sterilizations performed (30). In Latin America, the Caribbean, the Middle East, and Africa, fewer than one-half million couples rely on vasectomy for contraception, compared to about 5 million couples in the United States and about 12 million couples in both India and China (30). The reasons cited (30) for the low prevalence of vasectomy in some countries include:

1. Lack of vasectomy services
2. Emphasis on providing female and not male sterilization services
3. Negative attitudes of physicians toward vasectomy.

Even if there were a greater emphasis on the provision of male sterilization services there might not be a greatly increased demand for these services, especially in cultures where men have a fear of surgery in the scrotal area and where vasectomy is equated with castration. However, many experts argue that a simple nonsurgical method of male sterilization would have the potential to overcome the fears associated with the standard methods of vasectomy requiring a scrotal incision.

Advantages of Transcutaneous Procedures. For over 20 years, research has been conducted to develop a transcutaneous method of male sterilization in which the

scrotum is punctured by a needle or needle-like instrument. By means of this instrument, chemical agents or electro-coagulation can be used to block the vas lumen. The ideal has been to develop a procedure that is inexpensive, can be administered by trained paramedical personnel, and can be performed with simple instrumentation. The potential advantages of transcutaneous vas occlusion compared to standard surgical vasectomies include the following (12):

1. The risk of postsurgical hemorrhage is eliminated. At present, about 1.6% of surgical vasectomy patients develop postoperative hematomas (31).
2. The risk of postoperative infections should be greatly diminished. Presently, about 1.5% of men undergoing surgical vasectomy procedures develop infections (31).
3. The procedure should be more acceptable to men who have a fear of genital operations.
4. Surgery and surgical equipment are not required.
5. The procedure can be taught to paramedical personnel. Once learned, the procedure can be done rapidly at low cost.

Despite the many advantages of transcutaneous male sterilization, only a minimal amount of research has been conducted to develop this method for widespread use in sterilization programs.

In spite of the apparent simplicity and advantages of a transcutaneous sterilization procedure, outside of the People's Republic of China, very little work has been done to evaluate the safety and effectiveness of these

procedures in men. Most of the work has been limited to sporadic efforts to investigate the effects of various sclerosing agents using animal models. Some efforts have been made to improve the technical feasibility of the procedures through the development of improved equipment.

The purpose of this report is to review and summarize these research efforts and to provide an update on current research. In the following sections, current research and the results from animal and human studies are reviewed for each of the listed approaches to transcutaneous sterilization.

METHODS OF TRANSCUTANEOUS STERILIZATION

The following methods of transcutaneous sterilization have been evaluated in animals and/or man:

1. Intratesticular injection of chemical agents to affect spermatogenesis.
2. Intraepididymal injection of chemical agents to affect sperm transport.
3. Obstruction of the vas lumen by the intravasal injection of chemical (sclerosing) agents or by electrocoagulation of the vas lumen.

Intratesticular Methods. For over 25 years, research has been underway to develop a male contraceptive pill that would interfere with spermatogenesis, either by direct action on the pituitary by suppressing the production of gonadotropins or by direct interference with spermatogenesis in the testes. Numerous steroidal and non-steroidal agents have been evaluated, including luteinizing hormone releasing hormone (LHRH) agonists and antagonists, progestogens, and androgens, either in combination or alone, and other drugs such as gossypol, a phenolic compound isolated from the cotton plant (15, 22, 29). These drugs are usually administered orally or by systemic injection, and their use has been associated with undesirable side effects, including loss of libido and various effects on accessory sex glands. Although many of these compounds can produce oligospermia, they do not consistently produce azoospermia. Also, the effects of most of these compounds are temporary, and repeated administrations are required to maintain oligospermia/azoospermia. As an alternative to the interference of drugs, the direct injection of compounds into the testes has been investigated (32, 33).

Wiebe and Barr evaluated the effects of the direct injection of aqueous 1, 2, 3-trihydroxypropane (THP; glycerol), a normal component of living cells, into the testes of Sprague-Dawley rats (32, 33). Spermatogenesis was inhibited by a direct and local action of THP on the seminiferous tubules. The THP injections had no apparent effects on mature sperm stored in the epididymides. The

first mating of treated rats resulted in normal offspring. After the fourth postinjection week no matings resulted in pregnancy. The THP injections produced long-term infertility (up to 21 weeks) without producing any significant effects on Leydig cell steroidogenesis, on testosterone and LH and FSH serum levels, or on secondary sexual characteristics and mating behavior. No undesirable side effects were noted. The investigators found that by 14 days after injection of THP, there was a 50% reduction in the weight of the testes. Although this is not considered an undesirable side effect in animals, in man a reduction in testicular size might limit the acceptability of the procedure. Additional studies are currently being undertaken to determine the mechanism of action of THP on the testes.

The only other intratesticular method that has been investigated is the use of ultrasonic energy. In one study of the effects of different ultrasound intensities on the testes of mature rabbits, ultrasound at 1.5 W per sq cm for 15 minutes produced degeneration of the seminiferous tubules (23). Whether the use of ultrasound can be developed into a practical method of nonsurgical sterilization will require further evaluation. One obvious limitation of the method, especially in developing countries, is the cost of the equipment and the difficulty in obtaining routine maintenance.

Intraepididymal Injection. Although the injection of sclerosing agents directly into the epididymis is technically simpler than injection into the vas lumen, the intraepididymal approach to nonsurgical sterilization is known to have been evaluated in only three studies. The advantages of intraepididymal over intravasal injections are that the cauda epididymis is easily palpated and intraluminal placement of the needle in the epididymis is not necessary.

Bowman and coworkers evaluated the effects of injections of anhydrous calcium chloride dissolved in sterile saline directly into the cauda epididymis of mature rams on ejaculate volume, sperm concentration, and mounting time (4). Five rams received injections of calcium chloride and five received injections of saline. By 2 weeks after the injections, the calcium chloride-treated rams had a significant reduction in ejaculate volume and sperm concentration. None of the animals became azoospermic, but semen analysis was characterized by the absence of sperm motility and by head-tail fragmentation. Mounting times were not affected. The sterilizing effects of the calcium chloride most probably were due to its necrosing effects on the epididymis. No histopathology studies were performed.

Lewis and Garcia evaluated the effects of three sclerosing agents (formaldehyde, methylcyanoacrylate (MCA), and quinacrine hydrochloride) in mature *Macaca fascicularis*

monkeys (18). These agents were injected directly into the cauda epididymis either transcutaneously or after exposure of the epididymis through a scrotal incision. All animals were sedated with ketamine hydrochloride intramuscular injection (0.1 ml/kg of 100 mg/ml solution). The results of the study are summarized in Table 1 and show that none of the agents evaluated was effective. Histologic evaluations of testicular biopsies performed after 6 months showed normal testicles in all monkeys but one. That MCA-treated monkey had testicular atrophy. Other complications included abscess formation at the site of injection in two MCA-treated animals and two quinacrine-treated animals. In the formaldehyde-treated group, a moderate to marked inflammatory cell infiltrate and fibrosis were noted in most testicles evaluated. Four animals (1 MCA-treated; 3 quinacrine-treated) died after the intraepididymal injections. Three deaths occurred on the day of the procedure and one (in a quinacrine-treated animal) occurred 1 week after the procedure. Autopsies did not reveal the cause of death in any of the animals. In the quinacrine-treated group, death may have resulted from the quinacrine or from the combined toxicity of quinacrine and ketamine. Based on the unsatisfactory results obtained with all of the agents evaluated, no additional studies are being undertaken with intraepididymal injections of sclerosing agents.

Experimental Group	No Initially Azoospermic	Recanalization	No Azoospermic After 6 Months
Formaldehyde (4%) in glycerate (n=5)	4	2	2
MCA (0.5 cc) (n=5)	5	2	3
Quinacrine hydrochloride (100 mg) in water (n=5)	4	3	1

Source: Lewis and Garcia (18)

Table 1. Results of a study of intraepididymal injections of various agents.

Davis evaluated the intraepididymal injection of formaldehyde in alcohol and MCA in adult mongrel dogs (8). In the first two animals evaluated (one treated with formaldehyde in alcohol and one with MCA) severe toxicity and death occurred within 1 week of the injection. The cause of death of these animals was not stated, but may have resulted from the relatively large doses of the drugs administered. Gross examination indicated bilateral acute necrosis of the epididymides and testes in both animals. In other animals, in which lower doses of these chemicals were injected directly into the epididymis, extensive necrosis of the epididymides and testes was observed.

The appeal of the intraepididymal approach to transcutaneous sterilization is that it is easier to inject a chemical into the epididymis than into the vas lumen. To

date, the limited evaluations of the intraepididymal injection of chemical agents has shown this to be an unsatisfactory approach to male sterilization. Whether improved results can be obtained with other chemical agents remains to be evaluated.

Intravasal Methods. The concept of transcutaneous vas occlusion with either chemical agents or electrocoagulation is not a recent one. Over 20 years ago Lee, in a series of experimental studies in dogs, evaluated the effects of electrocoagulation of the vas through a transcutaneously inserted electrode, or the transcutaneous injection of different concentrations of phenol, glycerophenol, or a combination of quinine and urethane (17). He also investigated the effects of the transcutaneous injection of liquid Biowax, a wax used in cosmetic surgery (17). Shortly after injection, the liquid Biowax solidifies, causing obstruction of the vas. Lee noted that if a radiopaque material were mixed with the Biowax, its placement could be checked using x-rays. Although none of the transcutaneous methods tested by Lee resulted in vas occlusion in all animals injected, the studies did demonstrate that the transcutaneous approach was a feasible method of vas occlusion.

Chemical Agents. Numerous chemical agents have been injected into the vasa of rats, dogs, and rabbits to evaluate their effects in producing vas occlusion. The agents evaluated are listed in Table 2. Most of the studies have been experimental, in that they have evaluated relatively few animals and have been conducted to screen chemicals that might be worthy of either more extensive trials in animals or preliminary trials in man.

Of the many chemical agents that have been evaluated in animals, only two are known to have been tested in man: 3.6% formaldehyde in 90% ethanol (5, 11) and 4% formaldehyde in 90% ethanol (6, 7) and a carbolic acid, n-butyl alpha cyanoacrylate mixture (21). The mode of action of all of the sclerosing agents tested is thought to be similar; they produce local necrosis and fibrosis and vasal closure through scarring.

One of the principal objectives in choosing a chemical agent for use in human sterilization procedures is to select one that has minimal toxic effects and will produce a minimal amount of damage if injected into structures other than the vas. Ideally, damage caused by the chemical should be limited to the basal epithelium of the vas, without damage to the muscularis. Although it is not the intent of this review to summarize the effects of each of the chemical agents used for vasal occlusion in various animals, it is noteworthy that in most of these procedures the epididymides and testes were not affected by the intravasal injections. Also, toxicity appeared to be minimal. None of the investigators reported any animal deaths or severe adverse reactions that could be attributed to the intravasal injections.

Chemical Agent & Reference	Animals Evaluated
Sodium chloride (5, 12)	Rat
Ethanol (5, 12, 13)	Rat, dog
Formaldehyde (5, 12)	Rat, dog
Formaldehyde with ethanol (5, 12)	Rat, dog
Silver nitrate (5, 12)	Rat, dog
Acetic acid (5, 12)	Rat
Sodium tetradecyl sulfate (5, 12)	Rat
Potassium permanganate (5, 12)	Rat
Sodium morrhuate (5, 12)	Rat
Camphor (28)	Rat
Potash (28)	Rat
Quinacrine dihydrochloride (28)	Rat
Quinacrine, urethane (17)	Dog
Phenol (17)	Dog
Glycerophenol (17)	Dog
Biowax (17)	Dog
Phenol, cyanoacrylate (25)	Rabbit
Methyl cyanoacrylate (8, 25)	Rabbit, dog
Tincture of iodine, potassium iodide, sinograffin, carboxymethyl cellulose (25)	Rabbit, dog
Phenol, glycerine, sinograffin, gum tragacanth (25)	Rabbit
Silver acetate alginate (8)	Dog
Calcium chloride, gum tragacanth, glycerine (21)	ns
Sodium, cod liver oil acid, gum tragacanth, glycerine (21)	ns
Carbolic acid, gum tragacanth, glycenne (21)	ns
Carbolic acid, n-butyl alpha cyanoacrylate (21)	ns
Ethyl alpha-cyanoacrylate (21)	ns
n-Butyl alpha cyanoacrylate (21)	ns

ns = not stated

Table 2. Chemical agents evaluated to produce occlusion of the vas in animals.

Based on their studies of the intravascular injection of various sclerosing agents in rats and dogs (whose vasa are similar to those of man), Coffey and Freeman elected to evaluate a combination of 3.6% formaldehyde in 90% ethanol in human trials (5, 11). One advantage to the use of this combination is that both chemicals are easily metabolized and leave no residuals to produce adverse effects. The method used by these investigators was simple and did not require the use of any elaborate surgical equipment. One disadvantage of the procedure is that the investigators found it necessary to inject 1 ml of 1% lidocaine alongside each vas before injection of 0.25 ml of the formaldehyde and ethanol mixture. After each vas was located and stabilized between the thumb and forefinger, the mixture was injected through a 25 gauge needle. By the 24th post-procedure week, 7 of the 8 men injected were azoospermic. The other man had a sperm count of 67 million sperm per ml at the 14th post-procedure week. Once azoospermia was established, none of the men followed-up for the 14-40 weeks was found to again have sperm in his semen.

Additional trials of the intravascular injection of formaldehyde in ethanol have been conducted by Davis (6, 7). The procedure used by Davis was essentially the same as the

one used by Coffey and Freeman. Davis injected 0.5 ml 4% formaldehyde in 90% ethanol into each vas. In the first 27 procedures, an Allis clamp was used to stabilize the vas. In the next group of 27 men, a specially designed clamp was used to stabilize the vas. A 25-gauge needle was passed through holes in the jaws of the clamp to inject the formaldehyde in ethanol mixture into the vas. The results of the studies by Davis are summarized in Table 3.

Series	No. Subjects	Percent
First		
Azoospermic within 16 weeks	13	48.2
Failures	11	40.7
Decrease in sperm count, further follow-up required	3	11.1
Second		
Azoospermic within 10 weeks*	17	65.4
Failures	4	15.4
Decrease in sperm count, further follow-up required	5	19.2
Failed injection (retractile testes)	1**	—

* Includes two men who had repeat injections

**Not included in calculation of percentages

Source: Davis (6, 7)

Table 3. Results of studies of the transcutaneous injection of 4% formaldehyde in 90% ethanol.

In the second series of subjects there was a significant increase in the incidence of azoospermia. Whether this was due to the use of the specially designed clamp or was due to the increased experience of the operator cannot be determined from the study data. For six men, the duration of follow-up was insufficient to determine success of the procedure. Davis noted that once a man became azoospermic, he remained that way (7). Some of the men, for whom the procedures had been classified as a failure, had a transient drop in their sperm counts that later returned to near baseline levels. This drop was most likely due to an initial inflammatory reaction in the vas following the injection, causing temporary obstruction of the vas.

The combined data on the intravascular injection of formaldehyde in ethanol into men show that the time to achieve azoospermia is highly variable and may take up to several months. The differences in the failure rates reported in the series by Freeman (11) and Davis (6, 7) may be due to the different lengths of follow-up rather than to factors related to the way in which the procedures were performed.

Using dogs, Davis compared the effects of direct injections of MCA or silver acetate alginate into the vas lumen with effects of perivascular injections of these agents (7). In most cases, the injections produced vascular occlusion, whereas perivascular injections did not. These data indicate that for transcutaneous injections of

sclerosing agents to be effective in occluding the vas, they must be made directly into the vas lumen. Although this is a technically more difficult procedure, the requirement should not limit its widespread use.

In sharp contrast to the few studies on transcutaneous sterilization procedures with sclerosing agents in the United States, reports from the Peoples' Republic of China indicate that since 1972, this procedure has been used in over 500,000 men, with satisfactory results (2, 20, 21). The sclerosing agent used is carbolic acid and n-butyl alpha cyanoacrylate. In spite of the very extensive experience with intravasal injections of chemical agents, very little information is available on the procedure, either in Chinese or Western medical journals. Precise data are not available on the effectiveness of the procedure or on the incidence and types of complications occurring either at the time of or after the procedure. In the most recent report from the Peoples' Republic of China, long-term follow-up data were given for two series of men (21). The first series included 919 men who had been followed up for up to 10 years. The second series included 640 men who had been followed for up to 8 years. The only stated difference between the two series was that in the second series 0.02 ml compared to 0.01 ml of the sclerosing agent was used. Of the 1,345 men who were followed up and examined, small nodules could be palpated at the site of intravasal injection. In 99.4% of the vasa examined, the diameter of the nodules was estimated to be less than 0.5 cm. Only one man reported that the nodules were painful. Follow-up data relating to the effectiveness of the procedures are summarized in Table 4. For both series, azoospermia was achieved in 95.9% of the men. In the second series, the pregnancy rate among spouses was reduced from 11.5% to 2.6%. Of the 109 pregnancies recorded in both series, 56% occurred to the spouses of men who had been shown to be azoospermic. Since no information was given on the time between vas injection and the time the pregnancies occurred, it cannot be determined if the pregnancies occurred before azoospermia had been confirmed.

The transcutaneous intravasal sterilization procedure developed by the Chinese is simple and requires the use of minimal surgical equipment (19, 20, 21). The following briefly describes the principal aspects of this procedure, which has been widely and successfully used in China since 1972.

The vas is stabilized by use of a vas deferens fixing clamp. This is a straight hemostat with flattened tips that permits the vas to be grasped without injuring the scrotum. With the patient under local anesthesia, the operator clamps the vas and grasps it between the thumb and index finger. A sharp needle is inserted into the vas perpendicularly. The needle is withdrawn and a blunt needle is placed through the puncture hole. The operator can

First Series: 919 men followed up to 10 years

Semen analysis performed: 456 men
Azoospermic (%): 95.6

Couples evaluated: 829

Pregnancies (%): 11.5

Semen analysis for the 95 men whose spouses became pregnant:

Azoospermic — 54.7%

Sperm in semen — 42.1%

No semen analysis — 3.2%

Second Series: 640 men followed for up to 8 years

Semen analysis performed: 404 men

Azoospermic (%): 96.3

Couples evaluated: 577

Pregnancies (%): 2.6

Semen analysis for the 14 men whose spouses became pregnant:

Azoospermic — 64.3%

Sperm in semen — 21.4%

No semen analysis — 14.3%

Source: Li S, Zhu J (21)

Table 4. Summary of long-term follow-up data from The Peoples' Republic of China on the effectiveness of the transcutaneous injection of a sclerosing agent.

usually feel when the needle has entered the vas lumen. Two simple tests can be performed to determine whether the needle is in the vas lumen:

1. A syringe containing 4 ml of air is attached to the needle. With the vas firmly compressed by an assistant at the site of puncture and at the distal end, 2 ml of air is injected into the vas. The syringe plunger is released. If the needle has been placed in the vas lumen, the plunger should return to its original position within a few seconds.
2. A small amount of saline is injected through the blunt needle. If the needle is in the vas lumen, the injection should proceed easily and should be made without undue pressure. Examination of the scrotal skin and subcutaneous tissues should indicate no local edema.

If the second test is used, all of the saline is aspirated from the vas before injection of the sclerosing agent. The vas sclerosing agent (0.045 ml of carbolic acid, n-butyl alpha cyanoacrylate) is then injected through the blunt needle into the vas. The drug polymerizes after about 20 seconds. The needle is then withdrawn. Only about 0.02 ml of the drug is actually injected into the vas. The procedure is then repeated for the other vas and both puncture sites are covered with sterile gauze. The procedure takes about 10 minutes to perform.

Electrocoagulation. The use of transcutaneous sterilization with electrocoagulation was first reported by Lee in 1964 (17). In that study, bilateral closure of the vas was obtained in four dogs and unilateral closure on two others. In one dog, testicular atrophy was noted. This atrophy was attributed to extensive burns to spermatic vessels other than the vasa. In the Peoples' Republic of

China the use of transcutaneous electrocoagulation of the vas has been investigated in animals, but no information on the procedures was given (21).

In 1966, Schmidt first reported on a vasectomy procedure he had used in 144 men. A bilateral incision was made in the scrotum, the vasa were divided, and the vas ends were electrocoagulated with unipolar electrodes (27). Schmidt found that the incidence of sperm granulomas could be minimized if the vas ends were electrocoagulated rather than ligated. In a later series of 1,000 vasectomies in which electrocoagulation of the cut vas ends was used, Schmidt reported no failures, and fewer than 1% of the men had clinically significant sperm granulomas or other complications (26). In the procedure used by Schmidt, the vasa were electrocoagulated in such a way that the lesion was confined to the vasal epithelium, lamina propria, and part of the muscle wall.

To further advance the electrocoagulation procedure developed by Schmidt, bipolar electrodes have been developed. The use of these electrodes can eliminate the danger of damage to vessels other than the vas resulting from stray currents, and at the same time confine the lesion to the vasal epithelium and lamina propria. Preservation of most of the vasal muscles is thought to be important, because the muscle is the source of the fibrous tissue that ultimately results in occlusion of the vas.

Adair developed a transcutaneous electrocoagulation procedure that used bipolar electrodes (1). In an initial series performed by the investigator, there were no failures and no clinically significant complications attributable to the procedures. Subsequently, an independent, multiclinic evaluation of the procedure developed by Adair that included 33 men was curtailed due to the high failure rate of the procedure to attain azoospermia (24). In the second series, the only complication was a scrotal hematoma. It has been suggested that the failure rate of the procedure was high because placement of the tip of the bipolar needle into the vas lumen was extremely difficult, due to the relative diameters of the bipolar needle and vas lumen (10). The bipolar needle has a diameter of 1.6 mm; the average diameter of the human vas lumen is 0.55 mm, but it may be distended to 1.2 mm (16).

Black, at the Marie Stopes Clinic in the United Kingdom, is currently investigating a transcutaneous electrocoagulation procedure (3). The procedure gradually evolved through several steps designed to provide a simpler, quicker, and less traumatic method of sterilization. Initially, the vasa were electrocoagulated after they were pulled out through a small scrotal incision. Electrocoagulation was then performed through a small scrotal incision, but with the vas in the scrotum. The final step in

the development process was to perform the electrocoagulations transcutaneously. Black has performed about 80 of these procedures using prototype bipolar electrodes (3). Although the success rate of his transcutaneous procedure does not yet approach that of the standard vasectomy procedure used at the Marie Stopes Clinic, Black is of the opinion that improvement of the electrodes and some changes in the technique of performing the electrocoagulation will result in an effective procedure.

In the United States, Denniston will evaluate whether electrocoagulation of the vas by insertion of the electrode into the vas lumen under direct vision, and without division of the vas, will result in high rates of vasal closure (9). The effectiveness of this procedure will be compared to the standard electrocoagulation procedure. If electrocoagulation of the vas under direct vision, and without division of the vas, results in high rates of vasal closure, additional trials will be undertaken in which electrocoagulation will be performed transcutaneously.

COMMENT

Over the past 20 years, a transcutaneous method of male sterilization has been sought in a haphazard manner and the limited developmental efforts have been sporadic. In spite of the apparent simplicity of the procedure and its potential for widespread use and acceptance, no systematic efforts have been undertaken in the United States to develop a transcutaneous procedure, except for the research supported by the Program for Applied Research on Fertility Regulation (PARFR) over the past 7 years.

Compared to standard surgical vasectomy procedures, there are many advantages to the transcutaneous procedures that are applicable to both developed and developing countries, including a possible reduction in the incidence of certain complications commonly associated with vasectomy, such as scrotal hematomas and infections.

In the United States, fewer than 100 men have had transcutaneous sterilization procedures either by injection of formaldehyde in alcohol or electrocoagulation. In sharp contrast to this, reports from the Peoples' Republic of China refer to over 500,000 transcutaneous sterilization procedures using a cyanoacrylate mixture. Unfortunately, the reports from China provide few data on the effectiveness of the procedure or on its short-term or long-term complications. Also, information on the development of the procedures and any associated toxicology is not available in the literature.

In view of the many advantages of the transcutaneous sterilization procedure, the importance of an organized research program is obvious if such a procedure is to become widely available in the United States and elsewhere. Electrocoagulation of the vas and occlusion of the vas with sclerosing agents are the two best candidates for further development. Regardless of the methods of transcutaneous sterilization used, criteria should be developed for determining acceptable failure rates of the procedures. Failure can be defined in terms of either the pregnancy rates of the partners of the sterilized men or the proportion of men who achieve azoospermia within a specified time period. Consideration should also be given to defining an acceptable proportion of men who do not achieve azoospermia but who become severely oligospermic.

The scanty literature on transcutaneous male sterilization procedures indicates that the research efforts have been directed to developing a procedure that will result in azoospermia in a very high proportion of men after a single application of the agent. This may not be feasible. Therefore, research efforts might concentrate on a two application procedure. Such a procedure could be highly effective with minimal rates of complications or side effects. If, for example, a single application procedure produces bilateral vasal occlusion and azoospermia in only 90% of the men, then a two-application procedure can be expected to produce azoospermia in 99%.

In women, nonsurgical methods of sterilization have been evaluated extensively (14). Methods currently under investigation in the United States include one or

two applications of MCA and three applications of quinacrine. However, in the Peoples' Republic of China, nonsurgical methods of sterilization have been developed and used successfully since the late 1960s (34, 35). All of these methods are more difficult to perform than transcutaneous male sterilization and they have a higher risk of potentially serious complications, such as uterine perforation and intraperitoneal placement of the chemical agents.

Also, assessing the effectiveness of the procedure in the female is more difficult. If radiopaque MCA is used, flatplate x-rays can be taken to determine if MCA was present in the fallopian tubes. Alternatively, some time after the procedure, hysterosalpingograms may be performed to determine if there is bilateral tubal closure.

Neither of these two procedures is 100% accurate and neither is appropriate for areas where there are scarce medical resources. In countries that have the available medical resources, flatplate x-rays and hysterosalpingograms significantly add to the cost of the procedure. Evaluation of sterility in the male is a relatively easy matter. Semen analysis may be performed with simple laboratory equipment by laboratory technicians who have minimal training. If the two or three application nonsurgical sterilization procedure will be acceptable to women, there is no reason why a two application procedure should not also be acceptable to men.

Future research efforts on nonsurgical methods of male sterilization need to focus on the use of sclerosing or occluding agents or electrocoagulation of the vas when delivered as either a one or two application procedure.

REFERENCES

1. Adair EL: Transcutaneous closure of the vas deferens: a new procedure. Unpublished, 1980.
2. Anonymous: New method of male sterilization. *Chin Med J* 93:205, 1980.
3. Black T: Population Services. Personal communication, 1984.
4. Bowman TA, Senger PL, Koger LM, Gaskins CT, Hillers JK: Blockage of sperm transport using intraepididymal calcium chloride injections in rams. *J Anim Sci* 46:1063, 1978.
5. Coffey DS, Freeman C: Vas injection: a new nonsurgical procedure to induce sterility in human males. In Sciarra JJ, Markland C, Speidel JJ (eds): *Control of Male Fertility*. Hagerstown, Harper & Row Publishers, 1975.
6. Davis JE, Richart RM: A new method for obstructing the vas deferens by direct injection of chemical agents: a non-operative technique of male sterilization. Unpublished, 1980.
7. Davis JE: New methods of vas occlusion. In Zatuchni GI, Labbok MH, Sciarra JJ (eds): *Research Frontiers in Fertility Regulation*. Hagerstown, Harper & Row Publishers, 1980.
8. Davis JE: Study of the vas occlusion in animals using chemical agents. Unpublished, 1982.
9. Denniston G: Population Dynamics. Personal communication, 1984.
10. Free M: Program for the Introduction and Adaptation of Contraceptive Technology (PIACT). Personal communication, 1984.
11. Freeman C: Preliminary human trial of a new male sterilization procedure: vas sclerosing. *Fertil Steril* 26:162, 1975.
12. Freeman C, Coffey DS: Sterility in male animals induced by injection of chemical agents into the vas deferens. *Fertil Steril* 24:884, 1973.
13. Freeman C, Coffey DS: Male infertility induced by ethanol injection into the vas deferens. *Int J Fertil* 18:129, 1973.
14. Goldsmith A, Edelman DA: Nonsurgical methods of female sterilization. In Sciarra JJ (ed): *Obstetrics and Gynecology V. 6*. Philadelphia, Harper & Row Publishers (in press).
15. Heber D, Swerdloff RS: Brain peptides and fertility control in the male. In Zatuchni GI, Labbok MH, Sciarra JJ (eds): *Research Frontiers in Fertility Regulation*. Hagerstown, Harper & Row Publishers, 1980.
16. Hulka JF, Davis JE: Vasectomy and reversible vas occlusion. *Fertil Steril* 23:683, 1972.
17. Lee HY: Studies on vasectomy. I. Experimental studies on nonoperative blockages of vas deferens and permanent introduction of nonreactive foreign body in the vas. *New Med J* 7:117, 1964.
18. Lewis RW, Garcia RR: The results of epididymal ablation by sclerosing agents in the nonhuman primate. *Fertil Steril* 41:465, 1984.
19. Li S: Clinical application of the vas deferens puncture. *Chin Med J* 93:69, 1980.
20. Li S: Non operative sterility research with intravasal injecting drug: a clinical report. *Reprod Contracept* 1:24, 1981.
21. Li S, Zhu J: Non operative sterility research with intravasal injection drug (clinical report). Unpublished, 1984.
22. Lobl TJ, Bardin CW, Chang CC: Pharmacologic agents producing infertility by direct action on the male reproductive tract. In Zatuchni GI, Labbok MH, Sciarra JJ (eds): *Research Frontiers in Fertility Regulation*. Hagerstown, Harper & Row Publishers, 1980.
23. Mahmoud KZ, Abdou MS, Hemeida NA, Salour LS, Mahmoud S, Girgis SM, Fahim MS: Effect of ultrasound on mature rabbit testes. (Abstract) *Arch Androl* 9:87, 1982.
24. Program for Applied Research on Fertility Regulation (PARFR): A multisite evaluation in developed and developing countries of a technique and equipment for transcutaneous closure of the vas deferens by electrocoagulation. Unpublished, 1981.
25. Richart RM, Li XZ: A rapid and effective percutaneous intra vas injection for male sterilization. Unpublished, 1984.
26. Schmidt SS: Prevention of failure in vasectomy. *J Urol* 109:296, 1973.
27. Schmidt SS: Technics and complications of elective vasectomy. *Fertil Steril* 17:467, 1966.
28. Setty BS, Dasgupta PR, Kar AB: Chemical occlusion of vas in rats. *Contraception* 6:329, 1972.
29. Smith DK, Rodriguez Rigau LJ, Steinberger E: Hormonal methods for male contraception. In Zatuchni GI, Labbok MH, Sciarra JJ (eds): *Research Frontiers in Fertility Regulation*. Hagerstown, Harper & Row Publishers, 1980.
30. Vasectomy — safe and simple. *Population Reports Series D*, No. 4, November-December 1983, Population Information Program, The Johns Hopkins University.
31. Vasectomy. What are the problems? *Population Reports Series D*, No. 2, January, 1975. The George Washington University Medical Center.
32. Weibe JP, Barr KJ: Suppression of spermatogenesis without inhibition of steroidogenesis by a trihydroxypropane (glycerol) solution. (Abstract) *Biol Reprod* 28 (suppl. 1):256, 1981.
33. Weibe JP, Barr KJ: The control of male fertility by 1,2,3-trihydroxypropane (THP, glycerol): rapid arrest of spermatogenesis without altering libido, accessory organs, gonadal steroidogenesis, and serum testosterone, LH and FSH. *Contraception* 29:291, 1984.
34. Wu Y-H, Qian P-L, Tien S-P: Nonsurgical procedures for manual instillation of a phenol atabrine paste (PAP) for female tubal occlusion. In Zatuchni GI, Shelton JD, Goldsmith A, Sciarra JJ (eds): *Female Transcervical Sterilization*. Philadelphia, Harper & Row Publishers, 1983.
35. Zheng H-G, Chen X-H: A study of phenol mucilage induced tubal occlusion for sterilization. Analysis of the results in 4,784 cases. In Zatuchni GI, Shelton JD, Goldsmith A, Sciarra JJ (eds): *Female Transcervical Sterilization*. Philadelphia, Harper & Row Publishers, 1983.