

BIBLIOGRAPHIC DATA SHEET1. CONTROL NUMBER
PN-AAJ-1262. SUBJECT CLASSIFICATION (698)
PC00-0000-0000

3. TITLE AND SUBTITLE (240)

Program for applied research on fertility regulation; progress report, Jan.-June 1980

4. PERSONAL AUTHORS (100)

5. CORPORATE AUTHORS (101)

Northwestern Univ. Medical School

6. DOCUMENT DATE (110)
19807. NUMBER OF PAGES (120)
94p.8. ARC NUMBER (170)
301.32072.N879 - 1980

9. REFERENCE ORGANIZATION (130)

Northwestern

10. SUPPLEMENTARY NOTES (500)

(In compliance with contracts: AID/csd-3608 and AID/DSPE-C-0035)

11. ABSTRACT (950)

12. DESCRIPTORS (920)

Fertility
Contraceptives
ResearchBirth control
Sterilization

13. PROJECT NUMBER (150)

931054600

14. CONTRACT NO.(140)

AID/csd-3608

15. CONTRACT
TYPE (140)

16. TYPE OF DOCUMENT (180)

PARFR

SEMI-ANNUAL REPORT

(AID/csd-3608 and AID/DSPE-C-0035)

January 1, 1980 - June 30, 1980

**PROGRAM FOR APPLIED RESEARCH
ON FERTILITY REGULATION**

S E M I - A N N U A L R E P O R T
January 1, 1980 - June 30, 1980

Submitted to:

**Research Division
Office of Population
Development Support Bureau
Agency for International Development
USIDCA
Washington, D.C. 20523**

Submitted by:

**Program for Applied Research on
Fertility Regulation
Northwestern University Medical
School
1040 Passavant Pavilion
303 East Superior Street
Chicago, Illinois 60611**

**In compliance with Contract AID/csd-3608
and Contract AID/DSPE-C-0035**

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REPORT SUMMARY

Project Title and Contract Number:

Program for Applied Research on Fertility Regulation
AID/csd-3608
AID/DSPE-C-0035 (7/1/79 - 6/30/81)

Principal Investigator:

John J. Sciarra, M.D., Ph.D.
Professor and Chairman
Department of Obstetrics and Gynecology
Prentice Women's Hospital and Maternity Center
333 East Superior Street
Chicago, Illinois 60611

Contractor:

Northwestern University
c/o Sponsored Projects Administration
619 Clark Street
Evanston, Illinois 60201

Contract Period:

July 1, 1975 - June 30, 1979 -- AID/csd-3608
July 1, 1979 - June 30, 1981 -- AID/DSPE-C-0035

Reporting Period:

January 1, 1980 - June 30, 1980

Total Expenditures Through December 31, 1979:

AID/csd-3608	\$3,708,417.30
AID/DSPE-C-0035	<u>208,256.27</u>
TOTAL:	\$3,916,673.57

Total Expenditures January 1, 1980 Through June 30, 1980

AID/csd-3608	\$ 394,250.41
AID/DSPE-C-0035	<u>442,619.86</u>
TOTAL:	\$ 836,870.27

Commitments Through June 30, 1981

AID/csd-3608	\$ 393,898.80
AID/DSPE-C-0035	<u>815,423.08</u>
TOTAL:	\$1,209,321.88

CONTRACT OBJECTIVES

"The contractor shall establish a (Program for Applied Research on Fertility Regulation, PARFR) which will actively involve a panel of experts to solicit, evaluate, and assist in the development and monitoring of a series of studies which require modest funding both within the U.S. and in less developed countries. These studies will include work to develop improved means of male and female sterilization, studies of once-a-month means of fertility control, and evaluation of locally-effective male and female methods of contraception."

"...The contractor shall make available and employ its research and development facilities and personnel...(to) perform a research and development program directed toward actively pursuing a number of promising leads of goal directed research to develop a new means of fertility control."



PARFR's International workshop on "Research Frontiers in Fertility Regulation" was held in Mexico City at Hotel El Presidente Chapultepec, February 11-14, 1980. 155 participants attended, representing 25 countries. Ninety-three (93) of the 155 participants were from the following 18 LDCs: Argentina, Barbados, W.I., Brazil, Chile, Colombia, Dominican Republic, Egypt, El Salvador, Guatemala, India, Indonesia, Jamaica, Korea, Mexico, Peru, Philippines, Puerto Rico and Thailand. Proceedings of this workshop will be distributed during the next reporting period.

PARFR's clinical network, established at PARFR's Guatemala Workshop in April, 1979 by Drs. Connell and Pauerstein, met for the 2nd time in Mexico City. The clinical network, adding Drs. Flores and Gaitan from Mexico and eliminating Dr. Peralta from Chile, consists of the following seven (7) investigators:

- (1) Dr. Renzo Antonini, Universidade Estadual Paulista, Sao Paulo, Brazil
- (2) Dr. Marcos Paulo P. de Castro, Universidade Sao Paulo, Sao Paulo, Brazil
- (3) Dr. Emilio Fernandez, Hospital Barcos Luco, Santiago, Chile
- (4) Dr. Juan Flores, Veracruz, Mexico
- (5) Dr. Jose Gaitan, Scientific Research Institute, Juarez University, Durango, Mexico
- (6) Dr. Hugo Maia, Maternidade Climerio de Oliveira, Salvador, Bahia, Brazil
- (7) Dr. Jose Nasser, PROFAMILIA, Cali, Colombia

Participation in the MCA/FEMCEPT protocol as well as the Intravaginal Insert (IVI) protocol was discussed with these investigators. We also discussed participation in the MCA/FEMCEPT protocol with Dr. Nargesh Motashaw of Seth G.S. Medical College, Bombay, India. Of this group, the following have PARFR subcontracts:

Dr. Antonini - PARFR-215, Dr. Castro - PARFR-254 (terminated), and Dr. Maia - PARFR-201B and 213B. We never heard from Dr. Fernandez. Dr. Flores applied to PARFR for the IVI project and was not approved by the AID Mission in Mexico. Dr. Gaitan was not heard from during this reporting period. Dr. Nasser's participation in either protocol was not approved by Mr. Marvin Cernik of the USAID Mission in Bogota. Ms. Krier had set up a current MCA investigators meeting attended by Drs. Apelo (PARFR-200P); Argueta (86Sa - El Salvador); Baur (200G); Moran-Caceres (86Sb - El Salvador); and Hong (86K - Seoul, Korea). The presentation was by Drs. Neuwirth and Richart and Mr. Lee Bolduc (Population Research, Inc.).

Ms. Krier met with Dr. Apelo (Philippines), Dr. Alvarez-Sanchez (Dominican Republic) and Dr. Tawat Sukontipatipark (Thailand) regarding the TATUM IUD study. This study was not funded during this period because Dr. Tawat proposed that a third IUD be studied as well. PARFR is still awaiting the revised protocol from Dr. Tatum and the Population Council.

The following subcontracts in LDCs terminated as of 6/30/80:

- (1) PARFR-97K "Research on Instillation Techniques for Pregnancy Termination in Korea", Dr. Kwak, Principal Investigator, Seoul, Korea.
- (2) PARFR-98M "Norethisterone Microcapsule Injectable Contraceptive Study" Drs. Aznar/Zamera, Principal Investigators, Mexico City, Mexico.
- (3) PARFR-105N "A Study of a Parenterally Administered Progesterone-Cholesterol Formulation for Use as a Post-Partum Injectable Contraceptive", Dr. Harry Rudel, Principal Investigator, Mexico City, Mexico.

PROGRAM ACCOMPLISHMENTS

Scientific Summary

1. Staff and Scientific Advisory Committee (SAC) review of extension, formal, pilot study and informal research proposals. Please refer to the SAC section (Program Accomplishments) and SAC Minutes (Appendix) regarding specific determinations.
2. Staff, SAC and consultant monitoring of active research progress by review of technical reports (refer to SAC Minutes in the Appendix) and site visits to the following projects:
 - a. 1/17/80 - Drs. Chatterton and Scrimshaw, Albuquerque (PARFR-P19)
 - b. 1/21-23/80 - Dr. Roberts, Birmingham (PARFR-206SRI, 206UAB and 208)
 - c. 1/21-23/80 - Drs. Goldsmith and Zatuschni, Birmingham (PARFR-206SRI, 83N and 110N)
 - d. 4/23/80 - Dr. Goldsmith and Ms. Krier, New York (PARFR-86N)
 - e. 4/23/80 - Dr. Goldsmith and Ms. Krier, New York (PARFR-89N)
 - f. 4/23/80 - Dr. Goldsmith and Ms. Krier, New York (PARFR-200C)
 - g. 4/25/80 - Dr. Goldsmith, Birmingham (PARFR-P57)
 - h. 5/12-13/80 - Dr. Connell, Baltimore (PARFR-97N)
 - i. 5/27-29/80 - Dr. Goldsmith, Colombia (PARFR-P52)
 - j. 6/1-3/80 - Dr. Goldsmith, Brazil (PARFR-P54 and 215)
 - k. 6/4-6/80 - Dr. Goldsmith, Brazil (PARFR-201B and 213B)
3. PARFR staff initiated plans to partially sponsor an International Workshop on Advances in Fertility Regulation, December 18-20, 1980 in Surabaya, Indonesia at the Hyatt Hotel. The local coordinating group is Yayasan Kusuma Buana. The audience will approximate 400 physicians from Indonesia. PARFR will put together a soft-bound volume of the papers to be presented at the Workshop.
4. PARFR held a Workshop on Gossypol in Chicago, Illinois on March 11, 1980. There were 38 participants from six countries. The information will be disseminated in PARFR's newsletter, "Research Frontiers in Fertility Regulation" in 1981.

PROGRAM ACCOMPLISHMENTS

Administrative Summary

In addition to the routine management of the program, the efforts of the PARFR Administrative Staff were chiefly directed toward:

1. Closing out terminated subcontracts under PARFR's old prime contract, AID/csd-3608. The twenty-nine remaining subcontracts were all terminated on or before June 30, 1980, and should be closed out during the next reporting period.
2. Two Scientific Advisory Committee Agendas were coordinated and mailed during this period. The first SAC meeting was March 10, 1980, and the agenda included: 3 extension proposals; 5 formal proposals; 1 informal proposal; and project monitoring including 21 technical reports. The June 22, 1980, SAC meeting included: 5 extension proposals; 10 formal proposals; 4 informal proposals; and project monitoring including 18 technical reports.
3. Negotiations and execution of the following subcontracts and amendments:

AID/csd-3608: 10 No-Cost Extensions (86Sa, 89N, 90Np, 91N, 97N, 100N, 106N, 111N, 114N and P19)

1 Statement of Work Amendment (114N)

AID/DSPE-C-0035: 13 New Subcontracts (209NMH, 209NU, 210, 212(85N), 213B, 213T, 214(83N), 214(110N), 215, 216(P19), P54, P57 and P59)

1 Additional Funding Amendment 212(85N)

5 No-Cost Amendments (200G, 201B, 206UAB, 208 and 210)
4. The book published from the proceedings of the 1979 Guatemala Workshop, Vaginal Contraception: New Developments was distributed in January, 1980, to all workshop participants, AID mission personnel and selected LDC investigators (see appendix for Harper & Row brochure).
5. PARFR held its 9th workshop, Research Frontiers in Fertility Regulation, in Mexico City at the Hotel El Presidente Chapultepec on February 11-14, 1980. There were 155 participants from 25 countries. The manuscripts for the workshop and subsequent publication were copyedited before and after the workshop. The final manuscript will be submitted to Harper and Row in the next reporting period. Anticipated publication date is December, 1980.
6. PARFR held a workshop on Gossypol in Chicago, Illinois on March 11, 1980. There were 38 participants from six countries. PARFR pre-

6. (con't.)

pared manuscripts from the meeting which will be used for the fourth issue of PARFR's newsletter, "Research Frontiers in Fertility Regulation" in 1981.

7. Revision and up-date of our mailing list of 6,000 contacts.

8. The program staff during the reporting period was:

Program Director	John J. Sciarra, M.D., Ph.D.
Director of Administration	Diane H. Krier, M.B.A.
Director of Technical Assistance	Gerald I. Zutuchni, M.D., M.Sc.
Head, Research Project Development	Alfredo Goldsmith, M.D., M.P.H. (Start date: 4/1/80)
Research Development Coordinator	Elizabeth B. Connell, M.D.
Foreign Technical Project Coordinator	Aquiles J. Sobrero, M.D. (Terminated: 4/30/80)
Project Controller	Georgia L. Fackler (Terminated: 2/15/80)
	Ann Conner Nickle (Start date: 2/1/80)
Three Full-time Secretaries	Ruvenia Thomas
	Mary Rose Traylor
	Mirta Bucheli (Terminated: 3/7/80)
	Martha M. Rolon (Start date: 4/23/80)

1/1/80 - 6/30/80
AID/csd-3608

Subcontract Negotiations

PROJECT #	TITLE/INVESTIGATORS/INSTITUTION	ACTION	PERIOD	FUNDING
PARFR-86Sa	"Phase I Clinical Trial of Fallopian Tube Closure Using Methylcyanoacrylate (MCA) Tissue Adhesive Delivered Through the Single-Application Fertility Regulation (FEMCEPT) Device" Gustavo Argueta, M.D. Asociacion Demografica Salvadorena San Salvador, El Salvador	No-cost Extension (Amendment #1)	3/15/79- 6/30/80	- 0 -
PARFR-89N	"Fallopian Tube Cauterization and Closure by Silver Acetate - Alginate Formulations" Harry P. Gregor, Ph.D. Columbia University, New York, New York	No-cost Extension (Amendment #5)	1/15/77- 6/30/80	- 0 -
PARFR-90Np	"New Method for Obstructing the Vas Deferens by Direct Injection of Chemical Agents: A Non-Operative Technique of Male Sterilization" Joseph E. Davis, M.D. Planned Parenthood Federation of America, Inc. New York, New York	No-cost Extension (Amendment #1)	2/1/79- 6/30/80	- 0 -
PARFR-91N	"Preparation and Evaluation of Biodegradable Cylindrical Implants for Fertility Control" Donald L. Wise, Ph.D. Dynatech R/D Company, Cambridge, Massachusetts	No-cost Extension (Amendment #4)	6/1/77- 6/30/80	- 0 -
PARFR-97N	"Research on Instillation Techniques for Pregnancy Termination in Korea" Theodore M. King, M.D., Ph.D. The Johns Hopkins University, Baltimore, Maryland	No-cost Extension (Amendment #3)	8/1/78- 6/30/80	- 0 -

PROJECT #	TITLE/INVESTIGATORS/INSTITUTION	ACTION	PERIOD	FUNDING
PARFR-100N	"Investigation of New Compounds to Terminate Pregnancy" Leonard J. Lerner, Ph.D. Jefferson Medical College of the Thomas Jefferson University, Philadelphia, Pennsylvania	No-cost Extension (Amendment #2)	9/1/78- 6/30/80	- 0 -
PARFR-106N	"Effects of Tubal Sterilization on Menstruation: A Prospective Controlled Study" Gary S. Berger, M.D. University of North Carolina, Chapel Hill, North Carolina	No-Cost Extension (Amendment #2)	2/1/79- 2/29/80	- 0 -
ARFR-111N	"An Evaluation of the Efficacy of Fimbrial Enclosure with Silastic Devices as a Reversible Female Sterilization Technique" Carlton A. Eddy, Ph.D. The University of Texas Health Science Center at San Antonio, San Antonio, Texas	No-cost Extension (Amendment #2)	6/1/79- 6/30/80	- 0 -
PARFR-114N	"The Induction of Luteolysis and Ovulation Inhibition by LRF-Agonist" Samuel S.C. Yen, M.D. University of California, San Diego La Jolla, California	New Statement of Work (Amendment #1)	Same	- 0 -
		No-cost Extension (Amendment #2)	6/15/79- 6/30/80	- 0 -
PARFR-P19	"Identification and Evaluation of Herbs Used By Native Healers to Affect Fertility" John C. Slocumb, M.D. University of New Mexico, Albuquerque, New Mexico	No-cost Extension (Amendment #3)	2/1/79- 6/30/80	- 0 -

1/1/80 - 6/30/80
AID/DSPE-C-0035

Subcontract Negotiations

PROJECT #	TITLE/INVESTIGATORS/INSTITUTION	ACTION	PERIOD	FUNDING
PARFR-200G	"Phase I Clinical Trial of Fallopian Tube Closure Using Methylcyanoacrylate (MCA) Tissue Adhesive Delivered Through the Single-Application Fertility Regulation (FEMCEPT) Device" Hans Baur, M.D. Bureau Mengen, Cologne, West Germany	Change in Key Personnel (Amendment #1)	Same	- 0 -
PARFR-201B	"Effect of LH-RH Agonist on Ovulation and Corpus Luteum Function in Women" Hugo Maia, Jr., M.D. Maternidade Climerio de Oliveira Salvador, Bahia, Brazil	No-cost Extension (Amendment #1)	8/1/79- 11/30/80	- 0 -
PARFR-206UAB	"Baboon Studies to Evaluate Non-Biodegradable Medicated Fibers for the Controlled-Release of Contraceptive Steroids Related to Research Supported Under PARFR-206SRI" Lee R. Beck, Ph.D., University of Alabama in Birmingham, Birmingham, Alabama	Change in Budget (Amendment #1)	Same	- 0 -
PARFR-208	"Testing the Abortifacient Potential of CI and CII, 1 Beta-Oh Androstane Derivatives, in the Baboon" Lee R. Beck, Ph.D., University of Alabama in Birmingham, Birmingham, Alabama	Change in Level of Effort (Amendment #1)	Same	- 0 -
PARFR-209NMH	"Evaluation of A-Nor Steroids as Potential Once-A-Month Contraceptive Agents" Raksha Mehta, Ph.D. Northwestern Memorial Hospital, Chicago, Illinois	New Subcontract	1/1/80- 12/31/80	\$24,288

PROJECT #	TITLE/INVESTIGATORS/INSTITUTION	ACTION	PERIOD	FUNDING
PARFR-209NU	"Evaluation of A-Nor Steroids as Potential Once-A-Month Contraceptive Agents" Raksha Mehta, Ph.D. Northwestern University, Evanston, Illinois	New Subcontract	1/1/80- 12/31/80	\$29,361
PARFR-210	"Study of a Plant Product 'Gossypol' as a Reversible Contraceptive in Male Rabbits" M. C. Chang, Ph.D. Worcester Foundation for Experimental Biology Shrewsbury, Massachusetts	New Subcontract Change in Level of Effort (Amendment #1)	1/1/80- 12/31/80 Same	42,070 - 0 -
PARFR-212(85N)	"Development of Collagen Sponge Containing Spermicide" Milos Chvapil, M.D., Ph.D. The University of Arizona Health Sciences Center Tucson, Arizona	New Subcontract Additional Funding (Amendment #1)	3/1/80- 2/28/81 Same	49,810 2,181
PARFR-213B	"The Study of the Intravaginal Insert (IVI) - Acceptability and Side Effects" Hugo Maia, Jr., M.D. Maternidade Climerio de Oliveira Salvador, Bahia, Brazil	New Subcontract	6/1/80- 5/31/81	14,000
PARFR-213T	"The Study of the Intravaginal Insert (IVI) - Acceptability and Side Effects" Mohammed M. Ahmad, M.D., Ph.D. and Ricardo H. Asch, M.D. The University of Texas Health Science Center at San Antonio, San Antonio, Texas	New Subcontract	7/1/80- 6/30/81	59,618
PARFR-214(83N)	"Studies to Test an Injectable Delivery System for the Sustained Release of Norethisterone" Lee R. Beck, Ph.D., University of Alabama in Birmingham, Birmingham, Alabama	New Subcontract	4/1/80- 3/31/81	67,164

PROJECT #	TITLE/INVESTIGATORS/INSTITUTION	ACTION	PERIOD	FUNDING
PARFR-214(110N)	"Optimization of an Injectable Microcapsule Formulation for the 90-Day Delivery of Norethisterone" Danny H. Lewis, Ph.D. Southern Research Institute, Birmingham, Alabama	New Subcontract	4/1/80- 3/31/81	\$69,311
PARFR-215	"Chemical Sterilization in the Cebus Appella Monkey" Renzo Antonini Filho, M.D. Centro De Estudos De Reproducao Humana de Botucatu Botucatu, Sao Paulo, Brazil	New Subcontract	5/15/80- 5/14/81	16,775
PARFR-216(P19)	"Identification and Evaluation of Herbs Used By Native Healers to Affect Fertility" John C. Slocumb, M.D. University of New Mexico, Albuquerque, New Mexico	New Subcontract	5/1/80- 4/30/81	40,814
PARFR-P54	"Percutaneous Injection of Monoethanolamine Oleate as a Vas Deferens Sclerosing Agent" Marcos Paulo de Castro, M.D. Centro de Reproducao Humana, Sao Paulo, Brazil	New Subcontract	1/1/80- 6/30/80	9,350
PARFR-P57	"A Fibrous Polymer for the Delivery of Quinacrine to the Human Reproductive Tract" Richard L. Dunn, Ph.D. Southern Research Institute, Birmingham, Alabama	New Subcontract	1/1/80- 6/30/80	7,428
PARFR-P59	"The Development and Clinical Testing of an Estrogen Bromocryptine Regime as an Interceptive and/or Abortifacient Means of Fertility Regulation" Richard E. Blackwell, Ph.D. University of Alabama in Birmingham Birmingham, Alabama	New Subcontract	5/1/80- 10/31/80	7,500

PERSONNEL

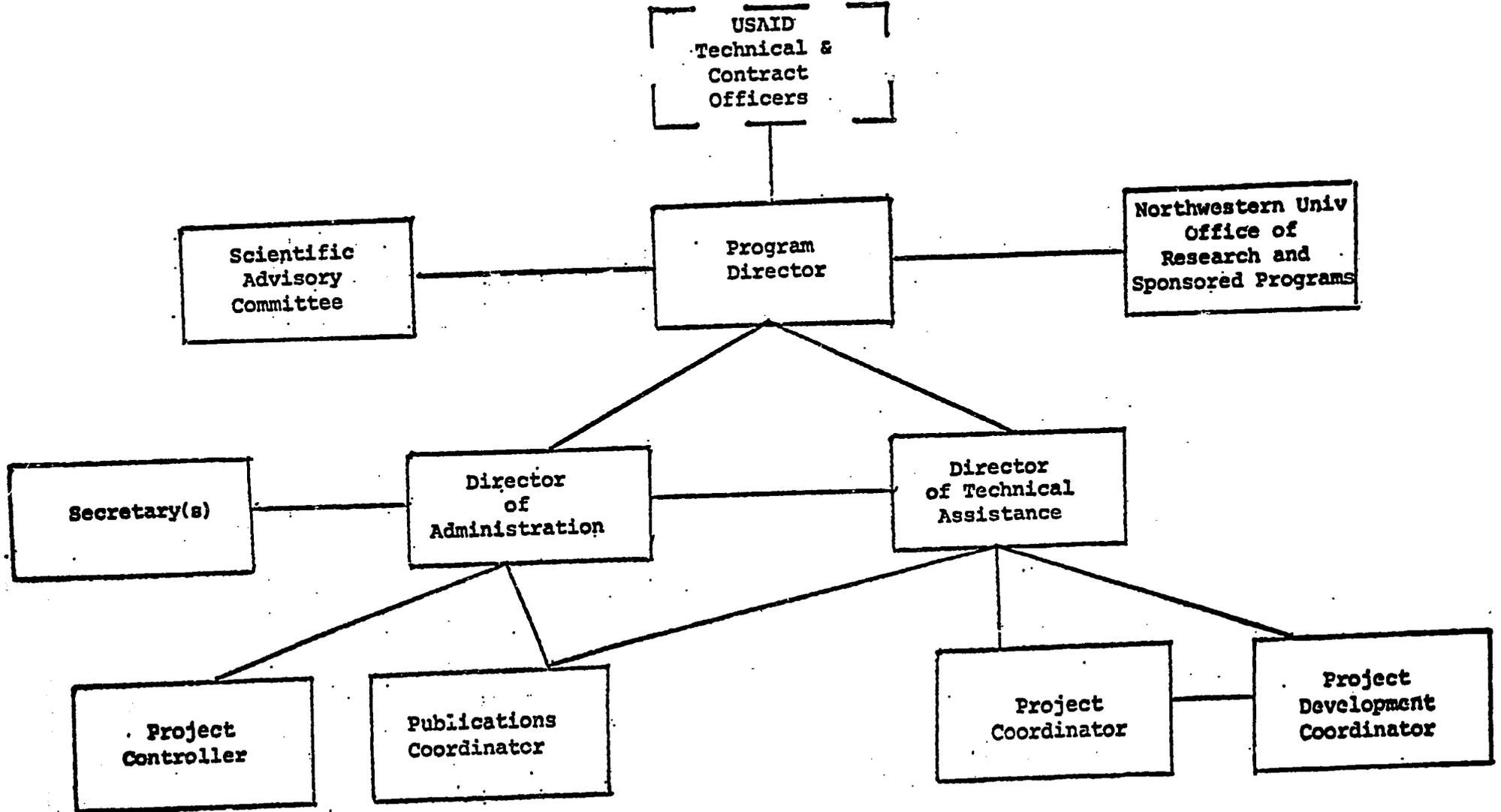
Effort and salary expenditures of PARFR personnel for this reporting period are listed below:

<u>Staff and Title</u>	<u>Effort in Man-Months</u>	<u>Salary</u>
John J. Sciarra, M.D., Ph.D. Director and Principal Investigator	.6	- 0 -
Gerald I. Zatuchni, M.D., M.Sc. Director of Technical Assistance	4.8	\$19,000.02
Alfredo Goldsmith, M.D., M.P.H. Head, Research Project Development	3.0	12,125.01
Elizabeth B. Connell, M.D. Research Development Coordinator	6.0	23,749.98
Aquiles J. Sobrero, M.D. Foreign Technical Project Coordinator	1.0	3,000.00
Diane H. Krier Director of Administration	6.0	11,235.00
Georgia L. Fackler Project Controller	2.8	3,626.66
Ann Conner Nickle Project Controller	5.1	6,360.20
Kelley Osborn Publications Coordinator	1.2	2,010.00
Ruvenia Thomas Secretary I	6.0	6,559.56
Mary Rose Traylor Secretary I	6.0	5,951.52
Mirta Bucheli Secretary I	2.5	2,491.65
Martha Rolon Secretary I	2.3	2,172.70
<u>Temporary Services</u> Temporary Secretaries	5.5	7,059.90
<u>Fringe Benefits</u>		\$14,427.12
<u>Indirect Costs</u>		39,346.71

Administrative Organization

The program staff is structured as indicated on the following page.

PARFR Organization



Scientific Advisory Committee

The membership of the Scientific Advisory Committee consisted of those individuals listed below during this reporting period:

John J. Sciarra, M.D., Ph.D., Chairman
Nancy J. Alexander, Ph.D.

Robert T. Chatterton, Ph.D.
Joseph E. Davis, M.D.
Edward C. Mather, D.V.M., Ph.D.
Kamran S. Moghissi, M.D.
Carl J. Pauerstein, M.D.

Ralph M. Richart, M.D.
Susan C.M. Scrimshaw, Ph.D.

Aquiles J. Sobrero, M.D.
Judith L. Vaitukaitis, M.D.
A. Albert Yuzpe, M.D.

Northwestern University
Oregon Regional Primate
Research Center
Northwestern University
New York Medical College
Michigan State University
Wayne State University
University of Texas Health
Science Center at San Antonio
Columbia University
University of California
at Los Angeles
Northwestern University
Boston University
University of Western Ontario,
Canada

The Scientific Advisory Committee (SAC) held two meetings during this period: March 10, 1980, in Chicago, Illinois, and June 22, 1980, in New York. Minutes of these meetings are included in the Appendix.

At these SAC meetings, the Committee reviewed 39 Technical Reports for presently funded projects of which 7 were Final Reports.

Extension Proposals

Eight extension proposals were reviewed by SAC of which two have been funded [PARFR-214(83N) and PARFR-214(110N)], three will be continued (PARFR-100N, PARFR-90Np and PARFR-107N), one project was not extended involving two subcontracts (PARFR-97N and 97K), and two are being negotiated (PARFR-91N and PARFR-114N).

Informal Proposals

Five informal proposals were reviewed by SAC, with the resultant recommendation that one formal proposal be solicited. The formal proposal requested was:

"The Mechanism of Prostaglandin Action in the Guinea Pig"
Arpad I. Csapo, M.D., Washington University, St. Louis, Missouri

Formal Proposals

Fifteen formal proposals were reviewed by SAC with resultant recommendations that the following five projects be funded:

"A Multi-Site Evaluation in Developed and Developing Countries of a Technique and Equipment for Transcutaneous Closure of the Vas Deferens by Electrocoagulation" Edwin L. Adair, M.D. and Michael J. Free, Ph.D., Medical Dynamics, Inc., Englewood, Colorado

Formal Proposals (continued)

"Identification and Evaluation of Herbs Used by Native Healers to Affect Fertility" - (supported Pilot Study PARFR-P19) John C. Slocumb, M.D., University of New Mexico, Albuquerque, New Mexico

"Prostaglandin Levels in the Human Follicular Fluid in Relation to the Moment of Ovulation" Hugo Maia, Jr., M.D. and Ione C. Barbosa, Ph.D., Maternidade Climerio de Oliveira, Salvador, Bahia, Brazil

"The Relationship Between Endometrial Dimensions and IUD Performance" - (supported Pilot Study PARFR-P51) Harrith M. Hasson, M.D., Chicago, Illinois

"A Fibrous Polymer for the Delivery of Quinacrine to the Human Reproductive Tract - PARFR-P57" Richard L. Dunn, Ph.D., Southern Research Institute, Birmingham, Alabama

In addition, the Committee made recommendations on the following proposals:

"Antigestational Effects of LH-RH Analogues" Joseph W. Goldzieher, M.D. and V. Daniel Castracane, Ph.D., Southwest Foundation for Research and Education (Dr. Goldzieher has been requested to rework the protocol to look at one LH-RH agonist at a much reduced level of funding.)

"Luteolysis in the Guinea Pig" Arpad I. Csapo, M.D., Washington University (PARFR's staff was directed to rework the protocol with Dr. Csapo.)

"Studies on Bioabsorbable Subdermal Contraceptive Pellet Implants" Gopi N. Gupta, Ph.D. and Brij B. Saxena, Ph.D., Cornell University (Budget must be reworked to be within PARFR range or study should not be approved.)

"Isolation, Characterization and Acute Toxicity of Spermicidal Agents Isolated from *Ecballium Elaterium*, Linn" Alan R. Buckpitt, Ph.D., University of California (SAC felt project should be further investigated but suggested pilot funding.)

Site Visits

The following site visits were reported on:

<u>Project</u>	<u>Site Visitor(s)</u>	<u>Date</u>
PARFR-P19, "Identification and Evaluation of Herbs Used by Native Healers to Affect Fertility" John C. Slocumb, M.D., University of New Mexico	Drs. Chatterton and Scrimshaw	1/17/80

Site Visits (continued)

<u>Project</u>	<u>Site Visitor(s)</u>	<u>Date</u>
PARFR-83N, "Studies to Test an Injectable Delivery System for the Sustained Release of Norethisterone" Lee R. Beck, Ph.D., University of Alabama	Drs. Goldsmith and Zatuchni	1/21-23/80
PARFR-110N, "Optimization of an Injectable Microcapsule Formulation for the 90-Day Delivery of Norethisterone" Danny H. Lewis, Ph.D., Southern Research Institute	Drs. Goldsmith and Zatuchni	1/21-23/80
PARFR-86N, "Phase I Clinical Trial of Fallopian Tube Closure Using Methylcyanoacrylate (MCA) Tissue Adhesive Delivered Through the Single-Application Fertility Regulation (FEMCEPT) Device" Robert S. Neuwirth, M.D. and Ralph M. Richart, M.D., The St. Luke's Institute for Health Sciences	Dr. Goldsmith and Ms. Krier	4/23/80
PARFR-200C, "Data Collection and Analysis for MCA/FEMCEPT Clinical Trials" Ralph M. Richart, M.D., Columbia University	Dr. Goldsmith and Ms. Krier	4/23/80
PARFR-89N, "Fallopian Tube Cauterization and Closure by Silver Acetate-Alginate Formulations" Harry P. Gregor, Ph.D., Columbia University	Dr. Goldsmith and Ms. Krier	4/23/80
PARFR-97N, "Research on Instillation Techniques for Pregnancy Termination in Korea" Theodore M. King, M.D., Ph.D., The Johns Hopkins University	Dr. Connell	5/12-13/80

Consultants

The following is a list of Program Consultants, indicating their areas of expertise, contributions to the program, and payment therefore. This list includes members of the Scientific Advisory Committee.

<u>Consultant</u>	<u>Purpose</u>	<u>Effort</u>	<u>Fee</u>
Nancy J. Alexander, Ph.D. Reproductive Physiology	SAC - 3/9-10/80	2 days	\$ 300
	SAC - 6/21-22/80	2 days	300
Ricardo H. Asch, M.D. Reproductive Endocrinology	Network Consultation 10/79 - 3/80	2 days	300
Gamal El Din Beheiry, M.D. Plastic and Urologic Surgery	Subcontract Consultation 2/2-9/80	8 days	1,200
Robert T. Chatterton, Ph.D. Steroid Biochemistry	Site Visit 1/16-18/80	3 days	450
	SAC - 3/9-10/80	2 days	300
	SAC - 6/21-22/80	2 days	300
Joseph E. Davis, M.D. Urology	SAC - 3/9-10/80	2 days	300
	SAC - 6/21-22/80	2 days	300
Erwin Goldberg, Ph.D. Reproductive Biology	Review 2/27/80		50
Alfredo Goldsmith, M.D. Research Program Development	Site Visit 1/21-23/80	3 days	549
	Network Consultation 1/24-25/80	2 days	366
	SAC - 3/9-10/80	2 days	366
	Network Consultation 3/11-15/80	5 days	915
Edward C. Mather, D.V.M., Ph.D. Animal Reproductive Physiology	SAC - 3/10/80	1 day	150
Kamran S. Moghissi, M.D. Obstetrics & Gynecology Reproductive Endocrinology	SAC - 6/21-22/80	2 days	300
Carl J. Pauerstein, M.D. Reproductive Biology	SAC - 3/9-10/80	2 days	300
	SAC - 6/21-22/80	2 days	300
Ralph M. Richart, M.D. Obstetrics and Gynecology Pathology	SAC - 3/9-10/80	2 days	300
	SAC - 6/21-22/80	2 days	300
Mary F. Roberts, Ph.D. Polymer Chemist	Site Visit 1/21-22/80	2 days	160
Susan C.M. Scrimshaw, Ph.D. Medical Anthropology	Site Visit 1/16-17/80	2 days	300
	SAC - 3/9-10/80	2 days	300
	SAC - 6/21-22/80	2 days	300

Consultants (con't.)

<u>Consultant</u>	<u>Purpose</u>	<u>Effort</u>	<u>Fee</u>
Aquiles J. Sobrero, M.D. Infertility	SAC - 6/21-22/80	2 days	\$ 366
Robert N. Taylor, Jr. Data Processing	Subcontract Consultation 4/80-5/80	4 days	536

TOTAL ----- \$9,608.



For Subcontracts Active During This Reporting Period
(January 1, 1980 to June 30, 1980)

FEMALE STERILIZATION

C. TRANSCERVICAL

"Phase I Clinical Trial of Fallopian Tube Closure Using Methylcyanoacrylate (MCA) Tissue Adhesive Delivered Through the Single-Application Fertility Regulation (FEMCEPT) Device"

PARFR-86N

Robert S. Neuwirth, M.D., The St. Luke's Institute for Health Sciences, New York, and Ralph M. Richart, M.D., Columbia Univ.

FUNDING PERIOD: 6/1/78 - 3/31/80 EXPENDED: \$36,490

PARFR-86K

Sung-bong Hong, M.D., Korea University College of Medicine, Seoul, Korea

FUNDING PERIOD: 5/1/79 - 4/30/80 BUDGET: \$16,080

PARFR-86Sa

Gustavo Argueta, M.D., Asociacion Demografica Salvadorena, San Salvador, El Salvador

FUNDING PERIOD: 3/15/79 - 6/30/80 BUDGET: \$12,410

PARFR-86Sb

Ernesto Moran, M.D., Instituto Salvadorena del Seguro Social, San Salvador, El Salvador

FUNDING PERIOD: 3/15/79 - 3/14/80 EXPENDED: \$ 1,360

PARFR-200G(86G)

Hans Baur, M.D., Evangelisches Krankenhaus, Cologne Germany

FUNDING PERIOD: 9/1/79 - 8/31/80 BUDGET: \$32,020 (200G)
9/1/78 - 8/31/79 EXPENDED: 22,097 (86G)
\$54,117 TOTAL

PARFR-200P

Ruben A. Apelo, Jose Fabella Memorial Hospital, Manila, Philippines

FUNDING PERIOD: 10/1/79 - 9/30/80 BUDGET: \$ 6,820

Objectives: To determine the safety and efficacy of the Single-Application Fertility Regulation (FEMCEPT) Device for the delivery of methylcyanoacrylate to the fallopian tubes of human volunteers.

Results: As of March, 1980, 148 patients seeking sterilization were treated; 80.3% of these women have shown bilateral tubal blockage. Thus far no pregnancies have been reported in these patients. The problems associated with the procedure have been restricted to a vagal type of reaction in about 20% of the patients. There have been 3 instances of transient fever, none requiring hospitalization. The data suggest that the system could be effective in excess of 95% if performed twice with a suitable interval between treatments. The patients enrolled in this phase of the study will be followed for two years.

1. FEMALE STERILIZATIONC. TRANSCERVICAL (cont'd)PARFR-200C

"Data Collection and Analysis of Phase I Clinical Trials of Fallopian Tube Closure Using MCA Delivered Through the FEMCEPT Device"

Ralph M. Richart, M.D., Columbia University, New York

FUNDING PERIOD: 7/1/79 - 6/30/81

BUDGET: \$30,715

Objectives: To develop a data system to store and summarize the information relating to the FEMCEPT/MCA Clinical Trials.

Results: Data collection instrument and standard protocol were prepared and computer software is being developed. Computer hardware is on site.

PARFR-89N

"Fallopian Tube Cauterization and Closure by Silver Acetate-Alginate Formulations"

Harry P. Gregor, Ph.D., Columbia University

FUNDING PERIOD: 1/15/77 - 6/30/80

\$112,073 (Columbia)

63,326 (St. Luke's)

\$175,399 TOTAL BUDGET

Objectives: To refine the formulation of silver acetate (an insoluble calcium salt) sodium alginate (a calcium sequestering agent) and distilled water so that it will be sufficiently fluid for administration into the fallopian tubes. To develop an improved technique for female sterilization which uses commercially available materials and is deliverable by a blind delivery system (FEMCEPT device).

Results: Several formulations have been developed of sufficiently low viscosity for clinical delivery by the FEMCEPT device. The substitution of silver nitrate for silver acetate when triacetin was used as part of the solvent mixture led to improved injectability and an improved efficiency of closure in both rabbits and monkeys. The substitution in the solvent mixture of ethylene glycol in place of triacetin to constitute a solvent system of 2 parts (volume) of propylene glycol, 5 of ethanol and 3 of ethylene glycol led to substantially improved results, with 100% closure efficiency in pigtail monkeys.

The investigator has always been concerned as to whether or not the formulations were consistently entering the isthmic and interstitial regions since it was observed on several trials that the formulation did not reach the interstitial region following retrograde injection. It appeared that a pre-existing bolus of material was pushed along by the

I. FEMALE STERILIZATION

C. TRANSCERVICAL (cont'd)

PARFR-89N

(cont'd)

formulation and this may have blocked the entrance of the formulation into the interstitial region. Thus it was concluded that retrograde injection cannot lead to truly unequivocal results. Therefore, the decision was made to initiate studies using either Langer or Cebus monkeys, introducing the formulation via transcervical injection, mimicking the action of the FEMCEPT device. Under these circumstances the insertion will be unequivocal for it will be possible to see the formulation leave the interstitial region and enter the Fallopian tube proper.

PARFR-215

"Chemical Sterilization in Cebus Appella Monkeys"

Renzo Antonini, M.D., Universidade Estadual Paulista,
Botucatu, Brazil

FUNDING PERIOD: 5/15/80 - 5/14/81

BUDGET: \$16,775

Objectives:

The objective of this study is to: a) evaluate the transcervical blind delivery of two different doses of silver acetate alginate, and b) study the time response to a quinacrine - IUD vector.

Results:

Supplies delivered, monkeys being held in quarantine.

PARFR-P57

"A Fibrous Polymer for the Delivery of Quinacrine to the Human Reproductive Tract"

Richard L. Dunn, Ph.D., Southern Research Institute

FUNDING PERIOD: 1/1/80 - 6/30/80

BUDGET: \$7,428

Objectives:

Selection of suitable fibers forming polymers as the matrix for a quinacrine delivery system, spinning of prototype loaded fibers and determination of the release characteristics of the prototype fibers in vitro and in vivo.

Preparation of an IUD vector with Q fibers for time response studies in the Cebus monkey.

Results:

The Pilot study (P-57) demonstrated that monolithic fibers loaded with quinacrine hydrochloride or as a free base can be developed which have a first order release rate. These fibers will be further tested. Dr. Leonard Laufe and Mr. Robert Wheeler (IFRP) will work on an IUD vector. When this is completed, it is planned that this IUD vector be tested in 10 cebus appella monkeys by Dr. Antonini in Brazil (see PARFR-215).

I. FEMALE STERILIZATION

D. REVERSIBLE

PARFR-79N

"A Method for Reversible Sterilization in the Female"

C. Irving Meeker, M.D., Maine Medical Center, Portland, Maine (9/1/77-6/30/80) and University of Vermont, Burlington, Vermont (2/1/77-8/31/77)

FUNDING PERIOD: 2/1/77 - 6/30/80

BUDGET: \$187,221

Objectives: The original objective was to fabricate a series of special devices designed for use in the stumptail macaque monkey and to insert them in 45 animals. Observations were to be carried out with regard to effectiveness against pregnancy with later removal of the devices and testing for fertility restoration.

The current overall objective of the project is to develop a reversible approach to female sterilization. The specific objective of the present phase of the project is to determine whether the clip modification of the device within the tube will solve the technical problems encountered, using suture material to secure the device. To this end, the devices are being tested for efficacy in a small series of baboons.

Results: Earlier studies with the stumptail macaque demonstrated that: 1) the plug must be placed as close to the uterine fundus as possible and no further laterally than the junction of the isthmic and ampullary portion of the tube, 2) the plug must be secured within the tube in a manner which will allow removal without disturbing the contiguity of the tube (suture or a fine clip will end up buried in fibrous material in the wall of the tube with inevitable extensive damage at the time of removal, so new teflon clips have been designed to deal with this issue), and 3) only an animal model very close to the human in anatomic and physiological function such as the baboon offers any hope of meeting the objectives.

On November 8, 1979, the 1 mm. plugs and clips were placed in the tubes of four adult female baboons of known fertility, either in the isthmic portion of the tube or at the junction of the isthmus and ampullary portion of the tube. There have been no untoward sequelae following surgery and no pregnancies to date with the devices in place. Breeding was continued until March at which time all animals were re-explored and the clips removed and the devices withdrawn from the tube. The animals were bred in April, May and June, 1980. Any pregnancies were documented and the patency of the tubes evaluated. Final exploration was carried out by the end of June 1980 with salpingectomy and microscopic examination of a portion of the tubes. PARFR is awaiting the final report, due August 15, 1980.

I. FEMALE STERILIZATION

D. REVERSIBLE (cont'd)

PARFR-94N

"Modern Modified Aldridge Procedure"

William Droegemueller, M.D., The University of Arizona

FUNDING PERIOD: 12/1/77 - 12/31/79

\$44,716 (Arizona)
 14,960 (U of Ill)
\$59,676 TOTAL EXPENDED

Objectives: To test in baboons a modern modification of the Aldridge procedure i.e., a surgical technique of enclosing the fimbria of the fallopian tubes in a stocking made of microporous expanded polytetrafluoroethylene. The animals have had the caps implanted and are being observed for fertility. At an appropriate time, the majority of the animals will be re-operated, the devices removed, and mating again carried out to establish the reversibility of the procedure.

Results: The fimbriae of the fallopian tubes of 20 baboons were placed in stockings made of the candidate material. None of the baboons became pregnant during the breeding cycles, and all baboons were bred a minimum of 4 cycles. Subsequently, the stockings were removed from the fimbriae, following which 9 pregnancies occurred in 7 of 16 remaining baboons. The normal pregnancy rate in this particular baboon colony is approximately 60%.

At the completion of the study, a third operation was performed and the tubes were removed for histological examination. Gross and microscopic examination of the tubes demonstrated that the stockings had protected the fimbriae from adhesion formation. Future studies are planned for human use of this new surgical procedure.

I. FEMALE STERILIZATION

D. REVERSIBLE (cont'd)

PARFR-P13

"An Evaluation of the Efficacy of Candidate Fimbrial Prosthesis in Female Rabbits and the Evaluation of Fimbrial Devices as a Reversible Technique of Female Sterilization"

Ivo Brosens, M.D., Ph.D. and Willem Boeckx, M.D., Catholic University of Leuven, Leuven, Belgium; Leonard Laufe, M.D., IFRP

FUNDING PERIOD: 5/1/78 - 4/30/80	BUDGET: \$11,681 (Belgium)
	EXPENDED: 2,750 (IFRP)
	<u>\$14,431</u> TOTAL

Objectives: To evaluate various biocompatible materials in rabbits for their potential use as tubal hoods.

Results: White New Zealand rabbits, 5 months of age, were selected. Candidate materials for the tubal hood were two thicknesses of silastic, and PTFE - a teflon polymer developed at the University of Arizona. The devices were made on suitable molds, and all devices were semi-permeable. A special instrument was developed for mounting the cap on the fimbriae of the tube. Because of the smallness of this anatomic structure in the rabbit, the surgery had to be performed with the use of an operating microscope.

The thin (.002 inch) silastic devices proved to be the easiest to apply. Thirty-three caps were placed in 17 rabbits using a 2-stitch fixation technique. Unfortunately, only 6 caps remained in place in 6 animals. All of the detachments occurred within 2 months of the procedure. In the animals in which the caps had remained in place, as seen by laparoscopic examination, challenges for pregnancy were negative.

Ten additional rabbits have had prostheses placed, using a continuous suture technique of 10-0 nylon. Recent results indicate that the continuous suture technique does result in permanent fixation of the cap to the tube.

Biopsies of the fimbrial ends of the tubes in those animals where the caps had remained in place indicated no damage to either the secretory or ciliated cells.

The results in the rabbits warranted the evaluation of this surgical technique in primates. Accordingly, another PARFR study was instituted to determine in the Rhesus monkey the efficacy of these ultra-thin silastic tubal hoods (see PARFR-111N).

1. FEMALE STERILIZATION

D. REVERSIBLE (cont'd)

PARFR-111N

"An Evaluation of the Efficacy of Fimbrial Enclosure With Silastic Devices as a Reversible Female Sterilization Technique"

Carlton A. Eddy, Ph.D., The University of Texas Health Science Center at San Antonio, Texas

FUNDING PERIOD: 6/1/79 - 6/30/80

BUDGET: \$58,290

Objectives: To determine in the Rhesus monkey the efficacy of ultra thin silastic tubal hoods as potentially reversible female sterilization devices.

Results: Silastic devices were fitted bilaterally in 20 subjects. The animals were followed via laparoscopic examination and breeding experiments. One animal became pregnant one month after the enclosure technique, due to spontaneous detachment of the device on one tube. An additional animal has died of causes not related to the surgery. Unfortunately, detachment of the devices occurred in a significant number of the animals, within approximately 2 months of the surgical procedure, despite the use of 6 to 8 interrupted 9-0 nylon suture. In the animals in which the device remained for a significant period of time, the silastic material has shown remarkable inertness and freedom from tissue reactivity. Adhesions, when present, have been minor. Histologic examination of the enclosed fimbriae revealed no tubal damage, even under electron microscopy.

The next step in the continued development of this procedure is to attempt a better fixation technique of cap to tube. Once this has been accomplished, the P.I. plans a Phase I clinical study.

I. FEMALE STERILIZATION

D. REVERSIBLE (cont'd)

PARFR-207(63N & B, 63)

"Hysteroscopic Sterilization by Using Uterotubal Blocking Devices"

(207) - Abdol H. Hosseinian, M.D., Cook County Hospital

(63N, & B, 63) - Abdol H. Hosseinian, M.D., The University of Chicago and Lourens J.D. Zaneveld, D.V.M., Ph.D., The University of Illinois at the Medical Center

(87N) - Abdol H. Hosseinian, M.D., Reza Pahlavi Medical Center, Tehran, Iran

FUNDING PERIOD:	11/1/79 - 10/31/80	BUDGET:	\$24,348 (207)
	7/1/75 - 9/30/79	EXPENDED:	63,502 (63N, B)
	11/1/76 - 8/31/77	IRAN:	17,310 (87N)
	4/1/74 - 6/30/75	MINNESOTA SUB:	54,063 (63)

Objectives: To determine, in selected volunteer women, the contraceptive efficacy of the Uterotubal Junction (UTJ) plug.

Results: Previous PARFR-supported studies in baboons (and preliminary human trials) have been conducted which showed the technique to be 100% effective in preventing pregnancies. Upon removal of the devices, 50% of the animals became pregnant. In that particular baboon colony, 60% fertility rate is the normal.

In this project extension, the protocol calls for the performance of the procedure in 25 women. Seven volunteers have had the devices inserted on an out-patient basis. The last patient developed pulmonary edema a few minutes after the procedure was terminated. She was hospitalized and responded well to medical therapy. The complication appeared to be related to the use of the distending medium, Dextran 40, for the hysteroscopic portion of the procedure. Due to this one complication, a different substance will be used - namely 5% dextrose in water. All seven patients have had bilateral obstruction of the tubes demonstrated by tubal insufflation at 3 months post procedure. These patients will be followed for as long as possible in order to determine efficacy of the procedure in preventing pregnancy.

I. FEMALE STERILIZATION

E. OTHER

PARFR-106N

"Effects of Tubal Sterilization on Menstruation: A Prospective Controlled Study"

Gary S. Berger, M.D., University of North Carolina at Chapel Hill

FUNDING PERIOD: 2/1/79 - 2/29/80

BUDGET: \$47,676

Objectives: To determine prospectively the menstrual cycle outcome following sterilization, using a unique data base of 3,885 women followed for approximately 40 years.

Results: Data were analyzed from the Menstruation and Reproduction History (MRH) Research Program, an ongoing study of the menstrual and reproductive histories of a cohort of 3885 American women. Before analyses could be conducted, it was necessary to accomplish several data processing tasks in order to have easy access to all the available MRH data for analysis, editing and review purposes.

The analytical problems involved were considerably more complex than anyone had envisioned at the onset of the study. The preliminary results showed that, in terms of menstrual changes (cycle length, flow length) following sterilization, there appeared to be differences with regard to the type of tubal occlusive procedure used (electrocoagulation or tubal ligation) and the timing of the sterilization relative to termination of the women's last pregnancy. By far the most significant variable was whether or not oral contraceptives (OCs) had been used before sterilization. Comparisons were made of menstrual cycle lengths and flow lengths for women who used OCs for one or more years before sterilization and for women who used OCs for one or more years and discontinued OC use but who were not sterilized. Both groups had similar menstrual patterns.

Whether the observed differences between the menstrual patterns of the sterilized and non-sterilized women can be attributed to the sterilization per se will require additional analyses. A similar analysis will need to be conducted to compare the menstrual patterns of women who have not used OCs prior to sterilization with those of an appropriate control group. The overall importance of this research is that it provides reassurance that the effects of tubal sterilization on menstruation are minimal and are not a cause for concern.

II. MALE STERILIZATION

B. OTHER (cont'd)

PARFR-90Np

"A New Method for Obstructing the Vas Deferens by Direct Injection of Chemical Agents: A Non-Operative Technique of Male Sterilization"

Joseph E. Davis, M.D.

FUNDING PERIOD: 2/1/79 - 6/30/80 BUDGET: \$54,007 (90Np-PPFA)
6/1/77 - 12/31/78 EXPENDED: 39,772 (90N-NYMC)

Objectives: The object of this study is to determine the effectiveness and safety of a non-surgical technique for achieving male sterilization by injecting a sclerosing solution of 4% formaldehyde in alcohol percutaneously into the vas deferens.

Results: Twenty-seven volunteers were treated by this technique; 13 became azoospermic. Three patients had a significant decrease in sperm count, but failed to return for follow-up. Seven of the failed cases underwent standard vasectomy. One of the other 4 failed cases was reinjected, but has not returned for follow-up. In a second group of 25 volunteers, 17 became azoospermic, 2 requiring reinjection. Four failures have undergone standard vasectomy and 3 are still pending reinjection. Three men have shown significantly decreased sperm counts, but have not returned for adequate follow-up. One procedure was technically unsuccessful due to retractile testes.

No patient who has become azoospermic has had return of sperm to the ejaculate. In several cases sperm counts went almost to zero, but then increased, probably due to only partial occlusion of the lumen and temporary edema.

A number of improvements of the Frisch-Davis vas clamp injector have been made during the course of these studies. Several instruments of the final design have been produced for use by an international network of investigators who will be doing further evaluation of this technique.

Under a new extension request, 25 additional volunteers will be recruited for the next study. These patients will receive an injection at two sites of each vas in an attempt to increase the efficacy of the procedure.

II. MALE STERILIZATION

B. OTHER (cont'd)

PARFR-205(95N)(P6)

"Development and Evaluation of a Reversible Vas Deferens Blocking Device"

Lourens J.D. Zaneveld, D.V.M., Ph.D., University of Illinois at the Medical Center

FUNDING PERIOD:	10/1/79 - 12/30/80	BUDGET: \$ 63,785 [205(95N)]
	7/1/77 - 9/30/79	113,348 (95N)EXPENDED
	9/1/76 - 8/31/77	5,985 (P6)EXPENDED

Objectives: To test in rabbits and primates a reversible vas deferens blocking device.

Results: Primates (cynomologus macaques) were selected for testing the device developed, after much experimentation in rabbits and in other primates. The most advanced prototype consists of two hollow rods, made out of medical grade silicone with a 1.75 cm external diameter, each of which is closed at one end. A small ethylon thread is incorporated in the closed end and runs through the center of the rod to the other rod where it is attached to the closed end. These devices were tested in a new group of primates. Unfortunately, the new group of animals were less mature than the previous group and hence, had smaller vasa deferentia.

In February, 1980, Dr. G. Beheri, a urologic surgeon from Egypt, participated with the investigator at the University of Illinois, investigating various types of fixation techniques for the device. The results in these few animals indicated that the devices were too large for the Macaque, although one of the animals proved that the procedure would be feasible in a larger animal.

Future plans call for the use of Rhesus monkeys which have larger vasa. These studies should be completed by early 1981.

II. MALE STERILIZATION

B. OTHER (cont'd)

PARFR-107N

"Is Sperm Antigen a Causative Agent for Atherosclerosis After Vasectomy"

Nancy J. Alexander, Ph.D., Oregon Regional Primate Research Center

FUNDING PERIOD: 4/1/79 - 6/30/80 BUDGET: \$83,318

Objectives: The goal of this study is to determine if there is a direct correlation between vasectomy and atherosclerosis and glomerulonephritis. It will be determined whether or not sperm-specific antigen-antibody complexes play a definitive role in plaque formation and whether or not post-vasectomy glomerulonephritis is associated with similar sperm-specific immune complexes.

Results: Two antigen preparations, rabbit sperm and human sperm, were made. Thirteen rabbits were placed on an atherogenic diet for two months before injections were begun. Group I received rabbit sperm plus Complete Freund's Adjuvant (CFA) (5 rabbits). Group II received rabbit sperm only (4 rabbits). Group III received human sperm plus CFA (2 rabbits). Group IV received human sperm only (2 rabbits). At the conclusion of the experiment it appeared that there was no difference between the CFA and non-CFA groups, 7/9 of the rabbit sperm group and 4/4 of the human sperm group exhibiting plaques in their arterial trees.

The testes of these animals showed no evidence of complexes with the exception of the testis of one of the rabbits injected with human sperm which showed tiny dot deposits when stained with anti-IgM. In contrast to an earlier study of 80 rabbits where there was evidence of leakage of sperm from the testes of non-vasectomized rabbits, this study suggested that a longer time interval may be necessary for such deposition to occur. Also, this seemed to indicate that there is a common antigen between rabbit testis and human sperm.

II. MALE STERILIZATION

B. OTHER (cont'd)

PARFR-211

"Study of Vas Occlusion in Animals Using Chemical Agents"

Joseph E. Davis, M.D.

FUNDING PERIOD: 12/1/79 - 11/30/80

BUDGET: \$13,540

Objectives: To study vas occlusion in mongrel dogs using MCA and silver acetate alginate (materials developed under subcontracts PARFR-86N & 89N), injected under direct vision to test their efficacy, the degree of occlusion and tissue effects.

Results: Five adult mongrel dogs have undergone bilateral vas occlusion attempts with methylcyanoacrylate (MCA). 0.3 cc of MCA was directly injected into the vas lumen after longitudinal vasotomy had been performed. Four of the five animals became azoospermic within 2 weeks. Histopathology indicated excellent closure of the lumen with minimal vas muscle damage and little change in the proximal reproductive tract, except for some dilatation of the proximal vas and epididymis. Spermatogenesis appeared to be unaffected.

These findings confirm the ability of MCA to obstruct the vas lumen sufficiently to block sperm passage, when injected directly into the lumen. The minimal tissue damage created by the agent suggests that whether or not percutaneous occlusion is possible with MCA, the use of MCA as a vasocclusive agent for open vasectomy may prove beneficial. Thus, the vas may be occluded in continuity, leading to a more reversible type of occlusion. Studies with the alginate formulation will be performed.

II. MALE STERILIZATION

B. OTHER (cont'd)

PARFR-P12

"Development of Microporous Materials for Thin Intravasal Implants"

David H. Frisch, Ph.D., Massachusetts Institute of Technology

FUNDING PERIOD: 7/1/78 - 6/30/80

BUDGET \$15,000

Objectives: To develop an intravasal implant capable of blocking the vas, which can be easily removed.

Results: Mylar plastic discs which had been electronically drilled with a large number of holes were placed in the vas deferens of dogs. Unfortunately, these hydrophilic plastics tend to be absorbed, and this was found to be true in the dog. Accordingly, microporous stainless steel discs were developed using a laser beam for the drilling of the minute holes. These devices were placed in Rhesus monkeys at the Oregon Regional Primate Center. Once again, many technical problems arose in the placement of the device in the vas deferens of the monkeys, their fixation, and their effectiveness. Accordingly, it has been decided to terminate this project.

PARFR-P56

"Efficacy Testing of Frisch Intravasal Implants"

Nancy J. Alexander, Ph.D., Oregon Regional Primate Research Center

FUNDING PERIOD: 11/1/79 - 10/31/80

BUDGET: \$14,665

Objectives: To determine the efficacy in cynomolgus monkeys of the microporous intravasal implants developed by Dr. David Frisch (MIT) under PARFR-P12.

Results: Six Cynomolgus monkeys were operated upon in March and implanted with various vas devices, following weekly ejaculations to establish base-line sperm counts. At the end of May, none of the animals had negative sperm counts. Their sperm counts were not continuing to decrease and those animals that appeared to have a marked decrease in sperm were once again observed to have sperm in their ejaculates. It is planned to vasectomize the animals and collect the tissue for histological evaluation.

II. MALE STERILIZATION

B. OTHER (cont'd)

PARFR-P54

"Percutaneous Injection of Monoethanolamine Oleate as a Vas Deferens Sclerosing Agent"

Marcos Paulo P. de Castro, M.D., M.S., Centro de Reproducao Humana, Brazil

FUNDING PERIOD: 1/1/80 - 6/30/80 \$4,529 EXPENDED

Objectives: This project would determine the feasibility and efficacy of the transcutaneous injection of monoethanolamine oleate as an agent for non-surgical sterilization of the male.

Results: In five volunteers seeking vasectomy, the sclerosing substance (monoethanolamine oleate) was injected into the vas bilaterally. In two of these men, another bilateral vas injection of the same substance was performed two months after the first procedure. In one man, the injection was performed under X-ray control, with the needle tip being located in the vas lumen. In all six men, semen analysis performed at one week, one month, two months, and three months after the vas injection showed no changes as compared with their pre-injection values. In view of these negative results, further volunteers were not recruited and the study was terminated.

PARFR-92N

"Contraception by Induction of Mild Uterine Inflammation"

Deborah J. Anderson, Ph.D., Medical Research Foundation of Oregon

FUNDING PERIOD: 6/1/77 - 12/31/79 \$85,524 EXPENDED

Objectives: To determine if pregnancy can be interrupted by the induction of mild uterine inflammation in the rat.

Results: Short-term and long-term studies on the effects of various types of glycogen-releasing intrauterine devices in rats and in primates have been accomplished. The results indicate that the glycogen-releasing matrix material (polyacrylamide and polyhydroxyethyl methacrylate) was tolerated by the uterus for periods of up to 6 months, and elicited a moderate inflammatory response. The matrix and glycogen release did not promote uterine infections, nor did they affect subsequent fertility in rats upon device removal. Unfortunately, the second phase of the rat study which was designed to determine if glycogen release enhances the effectiveness of IUDs was inconclusive because the control IUDs, which consisted of the inert matrix material alone, also caused markedly reduced fertility in most animals.

Rhesus monkeys bearing the glycogen-releasing IUDs for periods up to 6 months manifested mild to moderate intrauterine inflammatory responses, but not detectable uterine infections. The P.I. concludes that leukocytic agents such as glycogen may have applications as early abortifacient agents, but more studies are necessary.

III. INTRAUTERINE CONTRACEPTION

D. OTHER (cont'd)

PARFR-P21

"Development and Preliminary Human Testing of the Retention of a New Intracervical Device (ICD)"

Milos Chvapil, M.D., Ph.D., The University of Arizona

FUNDING PERIOD: 6/15/79 - 6/14/80 BUDGET: \$7,500

Objectives: Unique biocompatible material of teflon derivatives will be investigated to determine their retention characteristics when placed in the human cervix.

Results: In order to develop a soft, pliable ICD into which 100 mgs of progestin could be incorporated, 3 types of tissue-acceptable materials were tested: expanded tetrafluoroethylene membranes, collagen, and polyacrylonitrile hydrophilic gel, the last showing the best laboratory performance. It is similar to a Hydron polymer, glycolmethacrylate, used for soft contact lenses. However, this new polymer has superior mechanical properties; it can be molded, cast, sealed. Its water content is controllable, it is nonirritating to vaginal mucosa in rabbits, and progestins can be incorporated into the casting polymer before final stabilization. The investigator wished to use the new ICD molds to determine the retention rate of nonmedicated ICDs in hysterectomy patients and the study of progestin release rates in vivo and in vitro. However, upon careful review by SAC, the project was felt to have many problems with regard to its feasibility and was not approved for continuation.

PARFR-P51

"Graphic Assessment of Uterine Shape"

Harith M. Hasson, M.D., Chicago, Illinois

FUNDING PERIOD: 10/1/79 - 9/30/80 \$10,000 EXPENDED

Objectives: To determine the reliability of a new intrauterine measuring device that can provide a basis for more appropriate IUD fitting.

Results: The uterine measuring device, Wing Sound II, was developed in order to identify accurately uterine shape and dimensions. The device is a winged sound capable of successively holding stable wing spreads possessing transverse dimension of 12 and 30 millimeters respectively. Thirty-four fresh hysterectomy specimens were used in the study, and the comparison of measurements obtained in the patient as compared with the specimen was extremely close. Excellent correlation was noted between the

INTRAUTERINE CONTRACEPTIOND. OTH: ? (cont'd)PARFR-P51 (cont'd)

measured and computed fundal transverse dimensions and uterine angles. The results of the study suggest that it is possible to determine the general shape and dimensions of the endometrial cavity through the use of the Wing Sound II device.

The P.I. has proposed clinical studies to be done in several centers in which the device will be used to measure the interior dimensions of the uterine cavity. The clinician will then select and insert one of three standard IUDs. The event rates will be correlated with the uterine measurements obtained with the Wing Sound II. IFRP will select the centers and collate the standard IUD data. The P.I. will independently determine the size and shape of the uterine cavity from the obtained measurements. The objective of these correlations is to determine in the actual clinical situation whether or not "mis-fitted" IUDs cause a statistically significant increase in event rates, such as pregnancy, expulsion, and removals for bleeding/pain or other reasons.

PARFR-209NU/NMH

"Evaluation of A-Nor Steroids as Potential Once-A-Month Contraceptive Agents"

Raksha Mehta, Ph.D., Northwestern University Medical School

FUNDING PERIOD: 1/1/80 - 12/31/80

\$29,361 (NU)

24,288 (NMH)

\$53,649 TOTAL BUDGET

Objectives: 1) To evaluate the uterotrophic activity of Anordrin and Dinordrin by looking at uterine histology and cytology; 2) To measure the alterations in the circulating and uterine levels of estrogen and progesterone; 3) To establish a definite relationship between the steroids and their feedback mechanism by assaying serum LH levels; 4) To study their antiprogestosterone activity by determining competition for the estradiol and progesterone binding sites in the uterus; and 5) To look for specific side effects of the compounds by measuring organ weights, liver tests, blood coagulation rates, blood pressure, ova count in the subsequent cycles and other long term effects on fertility.

Results: Project recently started. Initial report due 9/15/80.

IV. SYSTEMIC CONTRACEPTION

B. INJECTABLES AND IMPLANTS

PARFR-214(83N) "Studies to Test an Injectable Delivery System for the Sustained Release of Norethisterone"
& 76

Lee R. Beck, Ph.D., University of Alabama

FUNDING PERIOD:	4/1/80 - 3/31/81	BUDGET: \$ 67,164 [214(83N)]
	4/1/76 - 3/31/80	257,849 (83N) EXPENDED
	7/1/75 - 9/30/75	9,338 (76N) EXPENDED
	10/1/74 - 6/30/75	33,502 (76) EXPENDED - MINNESOTA

Objectives: To develop and perfect a small particulate injectable system for the programmed delivery of the contraceptive steroid norethisterone.

PARFR-214(110N) "Optimization of an Injectable Microcapsule Formulation for the 90-day Delivery of Norethisterone"

Danny H. Lewis, Ph.D., Southern Research Institute, Birmingham, AL

FUNDING PERIOD:	4/1/80 - 3/31/81	BUDGET: \$69,311 [214(110N)]
	4/1/79 - 3/31/80	BUDGET: 65,972 (110N)

Objectives: To perform toxicology and metabolic studies, gather release rate information, and determine degradation rates of polymer and steroid in a three month injectable biodegradable system.

Results: The Department of Obstetrics and Gynecology at the University of Alabama in Birmingham (UAB) and the Biosystems Division of Southern Research Institute (SRI) have been engaged in a continuous program of research to develop and perfect a small particulate injectable system for the programmed delivery of the contraceptive steroid, norethisterone (NET). As a result of this effort, they have successfully developed polymeric microspheres that provide 6- and 3-month durations of NET release. Acceptable NET release profiles have been demonstrated in baboons for both the 3- and 6-month system and Phase I human trials on the 6-month system are nearing completion in Mexico (PARFR-98M). Detailed descriptions of the manufacturing process and the test results have been presented in previous progress reports, and most of this information has been published.

A decision was made April 1, 1979, to concentrate their efforts on the 3-month system. By the beginning of the current reporting period, they had completed dose-response studies on a prototype 3-month system. The dose-response studies suggested that there might be more than one type of contraceptive action. They found that doses which maintain blood levels of NET above 1 ng/ml inhibit ovulation for the full 3-month interval, whereas

IV. SYSTEMIC CONTRACEPTION

B. INJECTABLES AND IMPLANTS

Results: (cont'd)

doses which maintain blood levels of less than 1 ng/ml do not always inhibit ovulation. They did not know at that time if non-ovulatory inhibiting doses prevent pregnancy. If they did, this would be the preferred mechanism of contraceptive action because the non-ovulatory inhibiting doses do not interrupt normal menstrual bleeding patterns.

Accordingly, a major objective was to undertake a fertility study in primates to determine contraceptive effectiveness of a non-ovulatory inhibiting dose utilizing the prototype 3-month system. It was found in the early experiments that the microspheres biodegrade over a 12-month period of time. A 12-month period of biodegradation was chosen for the prototype system because initially a 6-month duration of NET release was wanted. Changing the size of the microspheres to achieve three months duration of NET release did not significantly change the duration of biodegradation. Accordingly, the prototype 3-month system has a 12-month duration of biodegradation which is not acceptable. The 3-month system should biodegrade between 4 and 5 months in order to prevent build up of the polymer in the body with repeated injections. Therefore, a second major objective was to find a way to shorten the duration of biodegradation of the microspheres without affecting the duration of NET release.

This could be done by using a copolymer of polylactic acid and polyglycolic acid in lieu of polylactic acid. Theoretically, changing the ratios of the two polymers will change the rate of biodegradation of the copolymer. In this manner different rates of biodegradation of the microspheres could be achieved.

SRI has succeeded in producing microcapsules of the copolymer, polylactic/glycolic acid, and in vivo studies confirm shorter biodegradation for the copolymer formulations. Moreover, primate studies on the rate and duration of norethisterone release from microspheres made of the copolymer demonstrate acceptable NET blood profiles. Although some of these experiments are still ongoing, they have sufficient evidence to show that it is possible to produce microspheres which provide three months of continuous norethisterone release in vivo which biodegrade within five months.

UAB completed fertility studies on the 3-month injectable system using a non-ovulatory inhibiting dose. They found evidence of impaired fertility; however, a number of pregnancies resulted, and it is clear on the basis of this study that a non-ovulatory inhibiting dose may not be acceptable for human use because pregnancy might not be prevented.

IV. SYSTEMIC CONTRACEPTION

B. INJECTABLES AND IMPLANTS

Results: (cont'd)

An unexpected finding from the fertility trial is that low constant blood levels of norethisterone caused early abortion in some animals. These results suggest a hitherto unknown mechanism of action of the minipill, subdermal implants, injectable steroid formulations, and other systems that provide constant blood levels of a progestogen that do not inhibit ovulation.

The 3-month polylactic/glycolic acid polymer preparation is the system of choice for IND/FDA application. Additional refinements of this system are necessary to qualify this system for Phase I human studies. The optimal ratios of the polymers have to be balanced against the size of the microspheres in order to achieve precise rates and duration of norethisterone release and biodegradation of the microspheres. SRI plans to optimize the 3-month system and carry out toxicology studies on the formulation selected for Phase I human studies. The UAB will evaluate the improved formulations in the primate model and will carry out in-depth preclinical studies on the formulation selected for human use.

PARFR-98M

"Norethisterone Microcapsule Injectable Contraceptive Study"

Ramon Aznar, M.D., and Gustavo Zamora, M.D., Centro de Investigaciones Sobre Fertilidad y Esterilidad, Mexico City

FUNDING PERIOD: 7/1/78 - 6/30/80

BUDGET: \$34,265 (98M)

BUDGET: 10,780 (UAB)

EXPENDED: 27,642 (SRI)

Objectives: Phase I Clinical Study, using two dosages, as a 6 month NET microcapsule injectable system.

Results: Acceptable NET release profiles have been demonstrated in 28 patients and 597 serum samples are undergoing radio-immunoassay at UAB.

Final technical report due on August 15, 1980.

SYSTEMIC CONTRACEPTIONB. INJECTABLES AND IMPLANTS (cont'd)PARFR-206SKI(104N & P9)

"A Fibrous Polymer for the Delivery of Contraceptive Steroids to the Female Reproductive Tract"

Danny H. Lewis, Ph.D., Southern Research Institute, Birmingham, Alabama

FUNDING PERIOD: 11/1/79 - 10/31/80 BUDGET: \$66,000 (206SRI)
 11/1/78 - 10/31/79 BUDGET: 66,000 (104N)
 6,000 (P9) EXPENDED

Objectives: Development of a fibrous system for long term delivery of contraceptive steroids in the uterus of the human female.

PARFR-206UAB

"Baboon Studies to Evaluate Non- Biodegradable Medicated Fibers for the Controlled-release of Contraceptive Steroids Related to Research Supported under PARFR-206SRI"

Lee R. Beck, Ph.D., University of Alabama in Birmingham

FUNDING PERIOD: 11/1/79 - 10/31/80 BUDGET: \$18,865

Objectives: To evaluate, in vivo, progesterone-releasing fibers as potential systems for contraception in the female.

Results: The major accomplishments have been the measurement of the basic mechanical properties of steroid-loaded fibers, the determination of the in vivo release characteristics of the fibers, the evaluation of a prototype fibrous contraceptive system in baboons, and the establishment of a correlation between the in vitro release characteristics and the in vivo effects upon the baboon endometrium.

The measurements of the basic mechanical properties of coaxial (sheath-core) fibers loaded with steroids show that their tensile strengths are controlled by the type of polymer used as the sheath material, the drug loading in the core, and the degree of drawing or orientation. Some of the initial fibers have low tensile strengths which may need improvement for long-term use as IUDs.

SRI has demonstrated zero-order (constant) release of progesterone in vitro from coaxial fibers. Several rates and durations of release have been obtained by variations in the polymer type and the drug loadings. With improved melt-spinning equipment, they expect to prepare fibers with even larger reservoirs of drug for extended durations of release.

IV. SYSTEMIC CONTRACEPTION

B. INJECTABLES AND IMPLANTS (cont'd)

Results: (cont'd)

The five doses of the prototype system placed in the uteri of normal-cycling female baboons have shown such a marked progestational effect upon the baboon endometrium that they have lowered the dosage to approximately 20 percent of the progesterone released by current medicated IUDs. No such effect was observed for control animals which received similar fibers with no drug. Additional evidence from the baboon studies indicates that the duration of drug release in vivo approximates that calculated from earlier in vitro experiments.

PARFR-91N

"Preparation and Evaluation of Biodegradable Cylindrical Implants for Fertility Control"

Donald L. Wise, Ph.D., Dynatech R/D Company, Cambridge, Ma.

FUNDING PERIOD: 6/1/77 - 6/30/80

BUDGET: \$177,141

Objectives: To demonstrate in baboons (supported by further testing in rats) that a small biodegradable cylindrical implant releasing d-norgestrel at approximately zero-order for a period of at least twelve months is feasible.

Results: Dynatech developed an implantable, biodegradable polymer system for the long term administration of levonorgestrel. The system exhibited excellent release rate characteristics but was too prolonged in its duration of action, the estimated duration of activity being approximately 5 years. Consequently, it was decided to manufacture similar implants that would exhibit quicker release rates and consequently shorter durations of activity by varying the molecular weight of the polymer, the percent drug loading of the levonorgestrel, and the percentage of polylactic and polyglycolic acid. Therefore, four systems were studied in rats, looking for the best system prior to implantation into baboons.

The immediate objective of the study in baboons is to develop the system most likely to be accepted by the FDA for Phase I clinical studies. The ultimate aim would be to have a short-acting system of 3 months total duration and a longer acting system of 12 months duration.

Preliminary work has now been completed on a 12-month rod. PARFR has suggested and Dynatech has agreed to apply for an IND for a Phase I study of this system. It is proposed to carry out such a study in Mexico. In addition, NIH plans to evaluate the new rods in small animals at their own expense.

SYSTEMIC CONTRACEPTION

B. INJECTABLES AND IMPLANTS (cont'd)

PARFR-105N "A Study of a Parenterally Administered Progesterone-Cholesterol Formulation for Use As a Post-Partum Injectable Contraceptive"

Harry W. Rudel, M.D., Centro de Investigacion Sobre Fertilidad y Esterilidad, Mexico City

FUNDING PERIOD: 5/1/79 - 4/30/80

BUDGET: \$56,236

Objectives: Phase I clinical trial to determine the rate of release of progesterone from the uniquely designed formulation in post-partum women, men and lactating women.

Results: Due to technical and administrative problems, this project was three months late in getting started. Thus far, the P.I. has completed studies on release characteristics, in vitro, using varying concentrations of steroid and cholesterol. The eutetic mixture of cholesterol and progesterone has the same dissolution rate as crystalline progesterone when used in the same particle size. This similar dissolution behavior indicates that the cholesterol is not behaving as a lipid membrane, but rather the characteristics are similar to an erosion system. The more regular release of the eutetic mixture of progesterone and cholesterol, as compared to a non-eutetic mixture (1:4), confirmed earlier in vitro findings. Increasing the concentration of alcohol leads to more rapid dissolution of progesterone and diminishes the differences among the various formulations.

Four formulations are currently being tested in human volunteers to correlate the in vitro dissolution rates with in vivo levels of plasma progesterone. Once these release rates have been compared, the optimum formulation will be selected for further clinical studies.

IV. SYSTEMIC CONTRACEPTION

C. OTHER

PARFR-P15

"Isolation of Effective Sperm Antigen for Use in Contraceptive Immunization"

Sidney Shulman, Ph.D., New York Medical College

FUNDING PERIOD: 3/1/79 - 2/29/80 BUDGET: \$7,500

Objectives: The objectives are: 1) to homogenize and solubilize human spermatozoa, 2) to demonstrate appropriate antigenic activity in the soluble product, as shown by inhibition studies, 3) to fractionate the soluble product, and 4) to obtain antigens that might be useful for contraceptive immunization.

Results: Using various disruption procedures, soluble antigen was liberated that was derived from the sperm head. This was verified by immunological testing by means of sperm agglutination. The Tube-slide Agglutination Test was used for antigenic evaluation, since it was believed that any soluble antigen would most likely derive from the head portions; this test is known to be more sensitive for the action of sperm-head antibody than the sperm-tail antibody. The data obtained showed that a liberation of soluble antigen had been achieved, and implicated the antigen of the sperm head.

PARFR-114N

"The Induction of Luteolysis and Ovulation Inhibition by LRF-Agonist"

Samuel S.C. Yen, M.D., University of California, San Diego

FUNDING PERIOD: 6/15/79 - 6/30/80 BUDGET: \$65,959

Objectives: To determine, in female volunteers, the efficacy of super analogs of LRF agonist to cause a luteolytic effect or ovulation inhibition.

Results: LRF-Ag was administered at an appropriate time of the luteal phase to make evaluation of the luteolytic effect possible. Preliminary clinical impressions suggest that luteolysis occurred as indicated by the onset of menses within 6 days. In no subject was ovulation disturbed in any of the treatment or recovery cycles. When hCG (100 IU or 5000 IU) was added to the LRF-Ag treatment, the onset of menses was delayed by 2-6 days. When women were treated with LRF-Ag in early pregnancy, no abortions occurred.

The studies to date have shown that LRF-Ag administration to normal women will consistently shorten the luteal phase. However, the presence of hCG at relatively low circulating levels, either administered or present as the result of an early pregnancy, will overcome the luteolytic action of LRF-Ag. The possibility remains that the use of higher doses of the agonist may overcome the luteotropic effect of hCG.

IV. SYSTEMIC CONTRACEPTION

C. OTHER (cont'd)

PARFR-201B "Effect of LH-RH Agonist on Ovulation and Corpus Luteum Function in Women"
 Hugo Maia, Jr., M.D., Federal University of Bahia, Brazil
 FUNDING PERIOD: 8/1/79 - 11/30/80 BUDGET: \$34,600

Objectives: To determine in female volunteers the effects of LH-RH agonist on ovulation and subsequent corpus luteum function.

Results: The initial results of this investigation suggest that high doses of LH-RH are effective in suppressing progesterone production by the corpus luteum. The earlier the drug is administered during the luteal phase, the more marked is this effect. The ideal time for LH-RH administration is at midcycle right after ovulation and before the corpus luteum is completely formed.

These data confirm previous observations that pharmacologic doses of LH-RH can exert an anti-fertility effect and they suggest that LH-RH might be used as post-coital contraceptive in women.

PARFR-216(P19) "Identification and Evaluation of Herbs Used by Native Healers to Affect Fertility"
 John C. Slocumb, M.D., University of New Mexico
 FUNDING PERIOD: 5/1/80 - 4/30/81 BUDGET: \$40,814 [216(P19)]
 2/1/79 - 6/30/80 BUDGET: 7,700 (P19)

Objectives: To identify herbs used by Navaho Indians as anti-fertility substances, to extract active ingredients and to determine in small animals the efficacy of the preparations.

Results: Cooperation with native healers has resulted in the identification of several plants utilized for the purposes of their supposed anti-fertility effect. Cotton root bark and pennyroyal herb have been shown to induce menses within 48 hours when taken between one and fourteen days after the day of missed menses. An herb used as a contraceptive, *Lithospermum* sp., inhibits LH, FSH, and TSH in laboratory animals and blocks luteotrophic effects of exogenous hCG. In addition, studies have been conducted yielding biomedical data from patients who have used herbs for fertility regulation. Although the early evidence of effectiveness of these agents is still far from conclusive, it continues to appear to be at least suggestive. Work, therefore, is being continued.

IV. SYSTEMIC CONTRACEPTION

C. OTHER (cont'd)

PARFR-P53 "Antifertility Effects of Luteinizing Hormone Releasing Hormone Analogue in the Female Rhesus Monkey"

Ricardo H. Asch, M.D., The University of Texas Health Science Center at San Antonio

FUNDING PERIOD: 11/1/79 - 10/31/80 BUDGET: \$7,500

Objectives: To provide information on the luteolytic action of LH-RH analogue and its effects on implantation and/or pregnancy interference in normally cycling female Rhesus monkeys.

Results: D-Trp-6-LH-RH induced luteolysis in regularly cycling rhesus monkeys when administered early during the luteal phase. When the super analogue of LHRH was administered during the mid-luteal phase or later, it failed to induce changes in corpus luteum function as evidenced by serum progesterone concentrations and luteal phase lengths. Administration of human chorionic gonadotropin (hCG) in doses similar to those occurring in early pregnancy overcame the effect of the antagonist.

In vitro studies were performed with dispersed cells from Rhesus monkey corpora lutea. The presence of the analogue in the incubation medium did not interfere with the basal or the hCG-stimulated progesterone production.

These findings suggest that LHRH analogue may be effective as a luteolytic agent when administered very early in the luteal phase but appears to be ineffective when administered at the mid- or late-luteal phase or during pregnancy. Moreover, its mechanism of action seems to be at the pituitary rather than at the gonadal level.

IV. SYSTEMIC CONTRACEPTION

C. OTHER - MALE PHARMACOLOGICAL METHODS (cont'd)

PARFR-210

"Study of a Plant Product "Gossypol" As a Reversible
Contraceptive in Male Rabbits"

M. C. Chang, Ph.D., Sc.D., Worcester Foundation for
Experimental Biology, Inc.

FUNDING PERIOD: 1/1/80 - 12/31/80

BUDGET: \$43,070

Objectives: To study, in laboratory animals, the efficacy and toxicity of
Gossypol.

Results: Gossypol acetate, obtained from the Shanghai Institute of Materia
Medica, People's Republic of China, was suspended in a steroid
suspending vehicle, obtained from the National Cancer Institute,
NIH. Male rabbits were force fed by means of a plastic tube in-
serted deep in their mouths. About 2.0 cc of the Gossypol suspen-
sion at different concentrations was fed daily to the rabbits, 5
days a week.

One rabbit died without obvious symptoms 3 days after feeding with
Gossypol at 10 mg per kg. The other 5 rabbits fed with varying
doses of 1.25 to 10 mgs per kg for 5 to 15 weeks were in good
health and their body weights were not affected. Semen analysis
demonstrated that feeding Gossypol acetate to male rabbits 5 times
weekly at a dose level of 1.25 to 10 mgs per kg had no or very
little effect on their sperm production. Sperm samples collected
from rabbits before or during treatment with Gossypol were used
for artificial insemination. No obvious differences were noted
in the proportion of rabbits becoming pregnant or in the number
of implantation sites. Accordingly, treatment of male rabbits
with Gossypol for 3 to 13 weeks had no or very little effect
on the fertilizing ability of sperm.

In general, male rats and hamsters were in good health and showed
no toxic symptoms during treatment with 5 to 10 mgs per kg per day
of Gossypol for 6 to 14 weeks. However, oral administration of
Gossypol at 15 mgs per kg per day was toxic to male rats but not
to male hamsters. Treated males caged with adult females of
proven fertility showed no disturbances in sex drive or mating
ability. Treatment of male rats with Gossypol at 5 mgs per kg
for 4 to 8 weeks did not affect their fertility. However, 3
out of 9 females mated to male rats treated with 10 mgs per kg
for 8 weeks were not pregnant. Four out of 6 females mated to
hamsters treated with Gossypol for 10 weeks at the same dose
were not pregnant and the two pregnant hamsters had a signifi-
cantly reduced number of implantation sites.

Autopsies performed at 6 to 14 weeks after the initiation of
treatment showed no changes in the weights of the reproductive
organs. Sperm recovered from the epididymis of both male rats
and hamsters treated with Gossypol were immotile.

IV. SYSTEMIC CONTRACEPTION

C. OTHER - MALE PHARMACOLOGICAL METHODS (cont'd)

PARFR-P52

"Effects of Gossypol on Pregnancy"

Jose' Perea-Sasiain, M.D., Universidad Nacional de Colombia,
Bogota, Colombia

FUNDING PERIOD: 10/1/79 - 9/30/80

BUDGET: \$7,000

Objectives: To determine the effects of gossypol when administered to pregnant animals at the time of fertilization, implantation and during early pregnancy.

Results: Gossypol in propylene glycol at all dosages administered subcutaneously was associated with female mice mortality. The lowest dose of 95 mg per kg of gossypol killed over 50% of the mothers. Pregnancy in the surviving mice progressed normally and no significant increase in death of these advanced embryos was seen.

Intragastric administration of a suspension of gossypol in propylene glycol was carried out in control, non-pregnant rats. The dose administered was 40 mg per kg, and all rats showed a decrease in weight gain with a high mortality.

PARFR-P58

"Immunologic Suppression of Fertility by a Synthetic Antigenic Determinant of Lactate Dehydrogenase C₄"

Erwin Goldberg, Ph.D., Northwestern University

FUNDING PERIOD: 12/1/79 - 11/30/80

BUDGET: \$7,500

Objectives: To determine if an antigenic fragment of lactate dehydrogenate C₄, a sperm specific isozyme, is capable of stimulating antibodies in rabbits with the peptide-carrier conjugate.

Results: An antigenic fragment of LDH-C₄, designated T-13, was synthesized commercially. The synthetic peptide has the following sequence: GLY-ILE-SER-GLY-PHE-PRO-VAL-GLY-ARG-VAL. Three rabbits were immunized with the peptide conjugated to bovine serum albumin. Antisera were elicited which are specific to T-13 and which also react with LDH-C₄. Further studies have determined that antibodies developed against a peptide fragment bearing an antigenic determinant will react with the native protein which contains that determinant.

The investigator has applied to PARFR for continuation of these most promising studies.

V. BARRIER CONTRACEPTION

B. FEMALE

PARFR-212(85N) "Development of Collagen Sponge Containing Spermicide"
and (P2 & 3)

Milos Chvapil, M.D., Ph.D., The University of Arizona

FUNDING PERIOD: 3/1/80 - 2/28/81 BUDGET: \$51,911 [212(85N)]
12/1/76 - 6/30/80 BUDGET: 98,124 (85N)
1/1/76 - 4/30/76 EXPENDED: 10,329 (P2 & 3)

Objectives: To develop and test a long-acting intravaginal contraceptive made of collagen sponge.

Results: The effectiveness of a collagen sponge (CS) as an intravaginal barrier contraceptive method was tested by postcoital tests. After establishing that the partner of every volunteer had an acceptable sperm count, the effect of CS alone, Ortho spermicidal cream alone, and the combination of both was tested on the presence of sperm in the cervical mucus during midcycle. While CS alone as well as spermicidal cream alone showed approximately 20% positive tests, the combination of both showed only one viable sperm/ high power magnification field in one volunteer and one viable sperm per whole slide for another volunteer. In both cases the mucus originated from the exocervix. Thus, it has been concluded that the maximum effectiveness is achieved by the combined use of CS with a spermicide.

PARFR-202 "Collagen Sponge Contraceptive -- Testing of Efficacy in Human Volunteers"

M. W. Heine, M.D., Texas Tech University School of Medicine

FUNDING PERIOD: 9/1/79 - 8/31/80 BUDGET: \$49,044

Objectives: To determine the safety, acceptability and effectiveness of a collagen sponge contraceptive.

Results: To date, approximately 50 volunteer couples have been enrolled in the study. Half of the women are using a collagen sponge containing nonoxynol-9, and other half are using the collagen sponge alone. After approximately 6 months of experience, 3 pregnancies have occurred; 2 in the group of women using the collagen sponge plus spermicide, and the other pregnancy occurred in a women using the collagen sponge alone. One pregnancy (sponge plus spermicide) was probably already present before inclusion in the study. Accordingly, these preliminary efficacy studies indicate that the collagen sponge alone is an effective method. Plans are to continue these volunteers for an additional 6 months of use and enroll additional couples to the study, probably using the collagen sponge alone as the method of choice. PARFR intends to confirm these data by establishing a multi-center trial involving a significant number of volunteer couples.

V. BARRIER CONTRACEPTIONB. FEMALE (cont'd)PARFR-204

"Development of Sperm Enzyme Inhibitors as Vaginal Contraceptives"

Lourens J.D. Zaneveld, D.V.M., Ph.D., University of Illinois at the Medical Center

FUNDING PERIOD: 10/1/79 - 6/30/81

BUDGET: \$116,431

Objectives: To evaluate in vitro and in vivo a number of sperm enzyme inhibitors for their vaginal contraceptive activity.

Results: Significant progress has been made in the development and testing of acrosin and hyaluronidase inhibitors. Both hyaluronidase and acrosin were purified from human spermatozoa. A total of 15 agents were tested for inhibition of hyaluronidase, of which 13 were purchased and 2 were synthesized. Nine of these are presently on the market and the others should be of low toxicity. Six of these agents inhibited hyaluronidase and have undergone vaginal contraceptive testing using the rabbit as an animal model. Three of these were shown to possess high vaginal contraceptive activity, much more so than Delfen cream. One of these is an FDA approved drug (Phenylbutazone) and is contraceptive in ug quantity.

The synthesis of guanidinobenzoic acid derivatives of FDA approved phenols, which should form effective and non-toxic acrosin inhibitors, has been worked out successfully and one compound has already been synthesized in gram quantities. This compound is a very active acrosin inhibitor. Another guanidinobenzoic acid derivative of an FDA approved phenol was shown to have very low toxicity and to prevent the in vitro fertilization of mouse gametes. Vaginal contraceptive studies are planned with both of these agents.

PARFR-P16

"Investigation of a New Vaginal Barrier Contraceptive"

Ernest B. Page, M.D., Ross, California

FUNDING PERIOD: 1/1/79 - 6/30/80

BUDGET: \$6,000

Objectives: To develop and test a new vaginal barrier contraceptive made of cellulose and spermicide.

Results: A tampon applicator was developed in which a spermicidal solution of nonoxynol-9 is stored in the plunger and released onto a disposable tampon just prior to insertion of the tampon. The experiences of 26 volunteers who used the device at the time of coitus suggest that the method is both acceptable and feasible, although some of the subjects experienced difficulty in removal of the tampon. Post-coital studies of the cervical mucus, at the time of ovulation, were conducted on 16 subjects and no motile spermatozoa were found, thus suggesting a high degree of theoretical effectiveness. Further developmental work consists of a redesign of the applicator in order to permit easier moistening of the tampon, and work directed toward making the tampon removal easier.

4. BARRIER CONTRACEPTIONB. FEMALE (cont'd)PARFR-P50

"Effect of Spermicidal Detergent, Nonoxynol-9, on Liver Function"

Milos Chvapil, M.D., Ph.D., The University of Arizona

FUNDING PERIOD: 7/1/79 - 6/30/80 \$8,000

Objectives: To determine, in female volunteers, the effects on liver function of daily intravaginal administration of standard doses of nonoxynol-9.

Results: Previous work by this investigator showed that nonoxynol-9 (N-9), administered as an aqueous solution into the vaginas of rats, is quickly absorbed. At certain doses of N-9 and after certain durations of administration, definite changes were demonstrated in the rat liver and kidney, indicating toxicity.

For this reason the effect of intravaginal N-9 containing spermicidal cream on various serum indicators of liver function was studied in ten volunteers. Four of the ten volunteers discontinued the testing because of vaginal irritation (two), infection of urinary tract (one), and vaginal infection (one).

The results of the study showed that the intravaginal use of spermicidal cream containing the surfactant Nonoxynol-9, did not result in abnormal patterns of liver function. Serum cholesterol values were significantly reduced, and SGOT and GGT values were found to be below normal limits.

V. BARRIER CONTRACEPTION

B. FEMALE (cont'd)

PARFR-213T "The Study of the Intravaginal Insert (IVI) - Acceptability and Side Effects"

Mohamed Ahmad, M.D., and Ricardo H. Asch, M.D., University of Texas Health Science Center at San Antonio

FUNDING PERIOD: 5/1/80 - 4/30/81 BUDGET: \$59,618

Objectives: This study was undertaken in order to determine and assess the safety, acceptability and effectiveness of a new barrier contraceptive, the intravaginal insert (IVI), inasmuch as PARFR-108N was terminated. The IVI is a polyester vaginal plug to which nonoxynol-9 is added. During coitus it is released in spermicidally-effective quantities into the vagina.

Results: This project was started recently.

PARFR-213B "The Study of the Intravaginal Insert (IVI) - Acceptability and Side Effects"

Hugo Maia, Jr., M.D., Maternidade Climerio de Oliveira, Bahia, Brazil

FUNDING PERIOD: 6/1/80 - 5/31/81 BUDGET: \$14,000

Objectives: SAME AS PARFR-213T.

Results: This project was recently started.

VII. PREGNANCY TERMINATION

C. MIDTRIMESTER

"Research Instillation Techniques for Pregnancy Termination in Korea"

PARFR-97N

Theodore M. King, M.D., Ph.D., The Johns Hopkins University

FUNDING PERIOD: 8/1/79 - 6/30/80

BUDGET: \$108,442

PARFR-97K

Hyun-Mo Kwak, M.D., Yonsei University College of Medicine, Seoul, Korea

FUNDING PERIOD: 7/1/78 - 6/30/80

BUDGET: \$ 66,550

Objectives:

To compare the results (safety, complications and effectiveness) of four different approaches to mid-trimester abortion using combinations of prostaglandins, urea, and oxytocin and laminaria.

Results:

This study is being carried out in four medical institutions located in Seoul, Korea - Yonsei University, Korea University, Ewha Women's University and Kyung Hee University. The Department of Obstetrics and Gynecology of The John Hopkins Hospital is responsible for the evaluation of the results of the study.

The patients have been randomly assigned to one of four treatment groups.

<u>Groups</u>	<u>Treatment</u>
Group 1	Urea (80 grams) + 15s-15m-PGF _{2a} (250 mu)
Group 2	Urea (80 grams) + 15s-15m-PGF _{2a} (250 mu) + Laminaria
Group 3	15s-15m-PGF _{2a} (2.5 mg)
Group 4	15s-15m-PGF _{2a} (2.5 mg) + Laminaria

The results to date are as follows:

<u>Group</u>	<u>Complete Abortion</u>	<u>Incomplete Abortion</u>	<u>Failure</u>	<u>Injection Abortion Time</u>
Group 1	72.2%	21.1%	6.7%	22.37 hours
Group 2	58.8%	36.8%	4.4%	16.95 hours
Group 3	67.2%	31.3%	1.5%	15.12 hours
Group 4	70.4%	26.8%	2.8%	15.45 hours
Average	67.6%	28.3%	4.1%	17.47 hours

There have been no maternal deaths in the study. In 129 cases (44%) no oxytocin was needed to complete the abortion process. The general complication rates are about the same as those reported from similar programs.

VII. PREGNANCY TERMINATION

D. OTHER

PARFR-100N

"Investigation of New Compounds to Terminate Pregnancy"

Leonard J. Lerner, Ph.D., Jefferson Medical College of
Thomas Jefferson University, Philadelphia, Pa.

FUNDING PERIOD: 9/1/78 - 6/30/80 \$109,384 EXPENDED

Objectives: To determine the efficacy of a series of new compounds on the pre-implantation period, using the golden hamster and rat.

Results: Thirty-four compounds were studied for pregnancy termination activity in hamsters. The most potent of these compounds were studied for dose-related effectiveness in single and multiple day subcutaneous and oral administration regimens, as well as for toxicity. Several of the most potent compounds were effective by both routes of administration and by single or multiple day dosage regimens. Generally, lower total dosage was effective when the treatment regimens were spread over five days instead of a single day. The most potent compound for all four treatment regimens was L-14105; however, the prolonged duration of action of this compound may make it less desirable for parenteral administration than several less potent compounds having shorter durations of action. The effectiveness of the compounds is greatest in the first third to first half of pregnancy. Studies of best candidate compounds were initiated in rats. The compound L-14105 was 100% effective when injected subcutaneously for five days at daily doses of 1 mg/kg in the rat compared to 0.0375 mg/kg in hamsters, demonstrating differences in sensitivity between these two rodent species to this series of compounds.

PARFR and Lepetit Research Laboratories in Milan, Italy have worked out a letter of agreement that will permit PARFR to continue mechanism of action studies with their most promising compound. Lepetit has completed the required toxicology studies in small animals, and will have completed toxicology studies in sub-human primates by October, 1980. If these studies validate the safety of the compound, Lepetit will ask PARFR support for Phase I clinical studies in one or more centers.

1. PREGNANCY TERMINATION

D. OTHER (cont'd)

PARFR-208

"Testing the Abortifacient Potential of CI and CII, 1 Beta-OH Androstane Derivatives, in the Baboon"

Lee R. Beck, Ph.D., The University of Alabama in Birmingham

FUNDING PERIOD: 11/1/79 - 10/31/80

BUDGET: \$19,406

Objectives:

To test the anti-fertility and abortifacient potential of compounds CI and CII (hydroxylated androstane derivatives) in the baboon, and to determine the mechanism of action.

Results:

In cooperation with Schering (Germany), the group at the University of Alabama has tested the utility of two new hydroxylated androstane derivatives which Schering has claimed induces early abortion.

Cycling female baboons were mated and serum samples obtained for the RIA of baboon chorionic gonadotropin. Initially, intramuscular injections of CII at a dose of 50 mg/day, or approximately 3.33 mg/kg were utilized. This treatment caused abortion two days following the last injection in one out of three baboons treated on days 21-25 of pregnancy. The two baboons that did not abort were given 75 mg/day of CI on days 41-45 of pregnancy. One of these baboons aborted 27 days following the second treatment. The other baboon was not affected and delivered uneventfully.

A fourth baboon treated with 75 mg/day of CII on days 22-26 of pregnancy aborted on day 35, and a fifth baboon treated with 100 mg/day of CI on days 21-25 of pregnancy aborted between days 32 and 35. Two other baboons treated with 75 mg/day of CII on days 45-48 of pregnancy did not abort. Abortion was confirmed in all baboons by hormone assays, and fetal tissues were recovered from the menstrual discharge in the baboons that aborted.

In summary, three abortions occurred in five baboons following a single series of injections administered between days 21 and 25 of pregnancy. One of these resulted from the 50 mg/day dose, and two occurred using a dose of 75 mg/day. Only one out of four baboons treated with the 75 mg/day dose late in the first trimester of pregnancy aborted. These results suggest that CI and CII are more effective when administered early in pregnancy.

Additional baboon studies are being carried out utilizing the CI compound at a minimum dose of 100 mg/day on days 21-25.

VII. PREGNANCY TERMINATION

D. OTHER (cont'd)

PARFR-P20 "Effect of the Estrogen-Bromocryptine Regimen in the Post-Implantation Phase in Baboons"

Joseph W. Goldzieher, M.D., Southwest Foundation for Research and Education, San Antonio, Tx

FUNDING PERIOD: 6/1/79 - 11/30/79 \$7,461 EXPENDED

Objectives: To determine, in baboons, whether a synergistic effect of estrogen and bromocryptine is effective in preventing implantation.

Results: Previous studies done by the P.I. demonstrated a synergism of estrogen and bromocryptine (CB-154) in the induction of luteolysis in the normally cycling cynomolgus monkey. There was no effect on menstrual cycle length in monkeys treated with CB-154 alone or animals treated with estrogen alone. Treatment with both agents resulted in significantly shortened menstrual cycles.

In this pilot study, the results have demonstrated a luteolytic effect of estrogen and CB-154 administered sequentially in the non-pregnant baboon. With the lower dosage of estrogen used, a depression of progesterone was seen in pregnant baboons, which rebounded after the cessation of treatment. With the higher estrogen dosage, an equivocal abortifacient effect is seen in pregnant baboons. None of the synergistic treatments have been associated with any adverse reactions.

Additional studies are being supported by PARFR among human volunteers. These studies are being carried out at the University of Alabama.

PARFR-P59 "The Development and Clinical Testing of an Estrogen Bromocryptine Regimen as an Interceptive and/or Abortifacient Means of Fertility Regulation"

Richard E. Blackwell, Ph.D., M.D., The University of Alabama in Birmingham

FUNDING PERIOD: 5/1/80 - 10/31/80 BUDGET: \$7,500

Objectives: To determine the efficacy of an estrogen-bromocryptine regimen as an interceptive means of fertility regulation.

Results: This Phase I clinical study to determine the luteolytic effectiveness of a combination of estrogen and CB-154 has just started.

Vii. PREGNANCY TERMINATION

D. OTHER (cont'd)

PARFR-P22 "A Preliminary Investigation of Fertility Regulation by South American Tribes"
Lindley A. Cates, Ph.D., University of Houston
FUNDING PERIOD: 6/15/79 - 6/14/80 BUDGET: \$7,688
EXPENDED: \$ -0-

Objectives: To collect, extract and test in suitable animal species certain plants that are known from anthropological studies to cause a contragestational effect.

Results: Project was never initiated by the investigator.

PARFR-P55 "1-Hydroxyestra-1,3,5(10-TRIEN-17B-OLS and Congeners as Contragestative Agents"
Vladimir Petrow, Ph.D., Duke University Medical Center
FUNDING PERIOD: 11/1/79 - 11/30/80 BUDGET: \$7,590

Objectives: To synthesize 1-hydroxyestra-1,3,5(10-TRIEN-17B-OLS and related compounds and determine their efficacy as contragestative agents.

Results: The preparation of the relevant compound - 3-desoxy-1-hydroxy-4-methylestradiol has been satisfactorily completed and the compound is presently undergoing biological evaluation. The development of a satisfactory synthesis route to the intermediate compound listed in the title has proved to be difficult and time-consuming. However, a recently discovered chromatographic technique has permitted the overcoming of this hurdle, so that a satisfactory laboratory preparation is now available. This compound has been submitted for biological evaluation. Conversion of this latter compound into 1-hydroxy estrone acetate has been achieved and a sample of the compound has been submitted for biological evaluation.

VII. PREGNANCY TERMINATIOND. OTHER (cont'd)**"Fertility Regulation by Control of Progesterone Clearance"**

PARFR-203NU/NMH Robert T. Chatterton, Ph.D., Northwestern University
Medical School

FUNDING PERIOD: 9/1/79 - 8/31/80	\$27,552 NU
	<u>34,127 NMH</u>
	\$61,679 TOTAL BUDGET

PARFR-102(P10) Robert T. Chatterton, Ph.D., The University of Illinois at
Medical Center

FUNDING PERIOD: 11/1/78 - 10/31/79	\$46,767 (102) BUDGET
11/1/77 - 10/31/78	6,049 (P10) EXPENDED

Objectives: To test the hypothesis that clearance of progesterone can be sufficiently increased by oral administration of encapsulated antiprogestosterone antibodies to bring about involution of the endometrium.

Results: Antiserum specific for progesterone (APA) has been produced. In its soluble form an i.p. injection of APA results in a rapid increase in gonadotropin secretion, an eventual decrease in uterine progesterone concentration (by 36 hours) and abortion in rats. Encapsulation in polysiloxane prevents release of APA, but allows entry and binding of progesterone; when given i.p., the encapsulated APA causes a decrease in serum progesterone and abortion in the midpregnant rat. Preparation of a more highly encapsulated form of APA for oral administration has begun.

Microcapsules of polysiloxane have been formed at the surface of aqueous droplets containing antiprogestosterone antibody. The size and uniformity of microcapsules have been closely controlled. Binding of progesterone with high affinity to the encapsulated antiserum has been observed in the presence of low affinity non-specific binding to the capsular material. The P.I. has determined that the IIT encapsulation process is inferior to the one developed at the Univ. of Illinois. Hence, future developmental studies for encapsulation will not include the IIT component.

On July 31, 1980 a site visit was conducted and the independent evaluators concluded "the strengths of the project to be the logical approach to the question of progesterone withdrawal." They recommended the following changes: a) use of pregnant rat instead of the pseudopregnant rat, and b) administration of the encapsulated antibody by mouth and if a positive result is obtained, a suitable primate model should be used. Dr. Chatterton will submit a continuation request for review at PARFR's November 16, 1980 Scientific Advisory Committee Meeting.

PREGNANCY TERMINATIOND. OTHER (cont'd)PARFR-203IIT "Microencapsulation of Progesterone Antibodies"

Kurt Gutfreund, IIT Research Institute, Chicago

FUNDING PERIOD: 11/1/79 - 10/31/80 BUDGET: \$21,905

Objectives: To develop suitable encapsulation processes that will permit the oral administration of progesterone antibody without being digested and that will permit the entrance of progesterone molecules into the capsule.

Results: Microcapsules of polysiloxane have been formed at the surface of aqueous droplets containing antiprogestosterone antibody. The size and uniformity of microcapsules has been closely controlled. Binding of progesterone with high affinity to the encapsulated antiserum has been observed in the presence of low affinity nonspecific binding to the capsular material. This subcontract will terminate 10/31/80 in that Dr. Chatterton's extension request will exclude IIT. He has found Dr. Duane Venton's (University of Illinois) encapsulation process to be superior to IIT's.



WORK PLAN

Anticipated Accomplishments

Negotiations are underway for clinical trials of the following PARFR supported developments:

- a) Collagen Sponge - The investigator and PARFR are interested in testing the sponge in a variety of socio-cultural settings in both developed and developing countries. PARFR is awaiting results of Dr. Heine's clinical trial at Texas Tech (PARFR-202).
- b) Spermicidal Condom - Additional PARFR support will be requested to permit the small scale manufacture of a suitable number of biodegradable condoms containing spermicide to be used in clinical studies of acceptability and effectiveness. These clinical studies are anticipated to be carried out in the U.S. and in developing countries. This study has been delayed since Schering has bought the previous subcontractor, the Emko Company (PARFR-P8). The budget request is still being formulated by Schering.
- c) The Utero-Tubal Junction Blocking Device - The investigator and PARFR are again working closely together on the equipment modifications required and the development of an appropriate protocol for Phase II human studies to be carried out in the United States, and possibly in Chile and Germany. Dr. Hosseinian has returned to the United States and has initiated clinical trials at Cook County Hospital in Chicago (PARFR-207). We are awaiting the first technical report in the next reporting period before LDC centers are initiated.
- d) MCA-FEMCEPT Project - PARFR currently has 5 clinical sites (2 in Salvador, 1 in Germany, 1 in Korea, and 1 in the Philippines) for the project entitled: "Phase I Clinical Trial of Fallopian Tube Closure Using Methylcyanoacrylate (MCA) as a Tissue Adhesive Delivered Through the Single Application Fertility Regulation (FEMCEPT) Device." An MCA clinical investigators meeting was held on February 12, 1980, in Mexico. During the next reporting period, centers in Brazil, Chile and Indonesia will be subcontracted for 150 patients each to participate in a randomized study of (1) one application of MCA (control group); (2) two applications of MCA separated by one month; and (3) a single application of MCA preceded by uterine lavage with a sterile saline solution.
- e) Intra-Vaginal Insert (IVI) - The protocol for this is the old PARFR-108N which terminated July 11, 1979, due to lack of patient enrollment by PPFA. During this reporting period, PARFR-213T (University of Texas Health Science Center at San Antonio) and PARFR-213B (Maternidade Climerio de Oliveira) were subcontracted. Results will be submitted during the next reporting period. PARFR plans to add additional centers during the next reporting period.

- f) Tatum IUD Study - Dr. Howard Tatum's (Population Council) IUD study (approved at PARFR's 9/5/79 SAC meeting) will be carried out in Brazil, Dominican Republic, Philippines, and Thailand. The investigators met in Mexico in February, 1980, to discuss the protocol and administrative procedures. PARFR received a suggestion to study a third IUD, from the Thailand group. Dr. Tatum had not submitted the revised protocol during this reporting period but PARFR expects the revised protocol during the next reporting period.

Publications:

- a) Published proceedings of PARFR's 8th Workshop entitled New Developments in Vaginal Contraception, held at the Camino Real Hotel in Guatemala City, Guatemala, April 25-27, 1979 were received from Harper and Row during this reporting period. Copies were sent to all participants and selected LDC investigators.
- b) PARFR held its 9th Workshop: Research Frontiers in Fertility Regulation, February 11-14, 1980, at Hotel El Presidente Chapultepec, Mexico City. Harper and Row will have the publication available and PARFR will distribute in the next reporting period.
- c) Fertility Regulation Research and Development Reports - PARFR is planning to establish a research technical information report which will review the latest R and D efforts on selected topics in a series of six issues per year. For each issue, a pertinent and knowledgeable investigator will be selected to review published and unpublished studies in a specific area of fertility regulation. The selected investigator consultant will be given adequate time and PARFR assistance to review the findings in the specified field. This material then will be submitted to PARFR for final review and editing, and subsequent publication. Each review will be about six to ten pages, prepared in a loose-leaf manner. PARFR will use its own mailing lists, domestic and foreign, and selected mailing from the Population Report series. Approximately 6,000 copies of each issue will be distributed internationally. Investigators who have been asked to submit reports are Lee R. Beck, Ph.D., Emil Steinberger, M.D., Robert T. Chatterton, Ph.D., Ralph Richart, M.D. and Samuel S.C. Yen, M.D. Dr. Beck's will be the first issue entitled: Long-Acting Steroidal Contraceptive Systems. The first issue will be completed and distributed in July of the next reporting period.

Procedures and Activities

- 1) The scheduled Scientific Advisory Committee meeting for the next reporting period is: November 16, 1980 (Sunday) Arlington Hyatt Hotel, Arlington, Virginia. PARFR, with AID approval, has changed from 4 to 3 meetings per year.
- 2) PARFR is planning on initiating a small symposium on Advances in Fertility Regulation in Indonesia, December 18-20, 1980.
- 3) PARFR is planning its annual workshop for May 11-13, 1981 in the Chicago area.

Summary Financial Reports

This section includes:

- A. AID/DSPE-C-0035 Monthly Financial Reports, 1/1/80 - 6/30/80
- B. AID/csd-3608 Quarterly Financial Report, 3/31/80 and Monthly Financial Reports 4/1/80 - 6/30/80
- C. AID/DSPE-C-0035 Current Subs - Budgeted and Expended
- D. AID/csd-3608 Current Subs - Budgeted and Expended
- E. LDC Research Budgeted and Expended Funds

	<u>AID/csd-3608</u> <u>(7/1/75-6/30/80)</u>	<u>AID/DSPE-C-0035</u> <u>(7/1/79-6/30/81)</u>	<u>Total</u> <u>(Both Contracts)</u>
Expenditures this Period	\$ 394,250.41	\$ 442,619.86	\$ 836,870.27
Expenditures through 12/31/79	<u>3,708,417.30</u>	<u>208,256.27</u>	<u>3,916,673.57</u>
Total Expenditures	4,102,667.71	650,876.13	4,753,543.84
Total Commitments	393,898.80	815,423.08	1,209,321.88
Uncommitted Balance	<u>15,945.99</u>	<u>1,533,700.79*</u>	<u>1,549,646.78*</u>
Total Budget	\$4,512,512.50	\$3,000,000.00	\$7,512,512.50

*AID/DSPE-C-0035 Uncommitted Balance of \$1,533,700.79 includes the \$1,500,000.00 just awarded for PARFR's next fiscal year 7/1/80 - 6/30/81. Therefore, the actual uncommitted balance for the past fiscal year is \$33,700.79.

		<u>Budget 7/1/79- 6/30/80</u>	<u>Expended 7/1/79- 12/31/79</u>	<u>Expended 1/1/80- 1/31/80</u>	<u>Total Cum. Exp. 7/1/79- 1/31/80</u>	<u>Outstand. Commits 2/1/80- 6/30/80</u>	<u>Uncommitted Balance</u>
Salaries	02	143,400.00	68,193.32	11,658.33	79,851.65	56,305.28	7,243.07
	03	46,425.00	17,208.08	3,081.84	20,289.92	15,363.20	10,771.88
Total Salaries		189,825.00	85,401.40	14,740.17	100,141.57	71,668.48	18,014.95
Fringe Benefits	13	27,145.00	12,124.20	2,107.84	14,232.04	10,103.64	2,809.32
Indirect Cost	88	74,035.00	32,424.53	5,748.67	38,173.20	27,555.38	8,306.42
Supplies	05	35,750.00	15,813.49	3,806.72	19,620.21	18,369.68	(2,239.89)
	09	1,300.00	575.72	82.49	658.21	---	641.79
	10	12,000.00	3,627.22	804.90	4,432.12	---	7,567.88
	12	850.00	451.20	70.30	521.50	405.50	(77.00)
	78	100.00	46.98	43.05	90.03	14.40	(4.43)
Total Supplies		50,000.00	20,514.61	4,807.46	25,322.07	18,789.58	5,888.35
Equipment	06	2,500.00	346.50	---	346.50	---	2,153.50
Consulting Fees	49	19,400.00	6,216.00	2,700.00	8,916.00	2,115.00	8,369.00
Travel	07	75,000.00	16,010.43	9,244.47	25,254.90	9,216.56	40,528.54
Workshop/Publ.	91	60,000.00	14,753.86	5,003.23	19,757.09	43,546.36	(3,303.45)
Subcontracts	90	927,095.00	11,160.00	---	11,160.00	626,375.00	289,560.00
Pilot Studies	92	75,000.00	9,304.74	1,000.00	10,304.74	68,728.26	(4,033.00)
TOTAL RESEARCH		1,002,095.00	20,464.74	1,000.00	21,464.74	695,103.26	285,527.00
TOTAL WORKSHOP		60,000.00	14,753.86	5,003.23	19,757.09	43,546.36	(3,303.45)
TOTAL ADMINIS.		437,905.00	173,037.67	39,348.61	212,386.28	139,448.64	86,070.08
TOTAL		1,500,000.00	208,256.27	45,351.84	253,608.11	878,098.26	368,293.63

ACN/art
4/1/80

REVISED

		<u>Budget</u> 7/1/79- 6/30/80	<u>Expended</u> 7/1/79- 1/31/80	<u>Expended</u> 2/1/80 - 2/29/80	<u>Total</u> <u>Cum. Exp.</u> 7/1/79 - 2/29/80	<u>Outstand.</u> <u>Commits</u> 3/1/80 - 6/30/80	<u>Uncommitted</u> <u>Balance</u>
Salaries	02	143,400.00	79,851.65	14,294.28	94,145.93	44,554.75	4,699.32
	03	46,425.00	20,289.92	3,036.96	23,326.88	12,281.36	10,816.76
Total Salaries		<u>189,825.00</u>	<u>100,141.57</u>	<u>17,331.24</u>	<u>117,472.81</u>	<u>56,836.11</u>	<u>15,516.08</u>
Frirge Benefits	13	27,145.00	14,232.04	2,478.37	16,710.41	8,046.80	2,387.79
Indirect Cost	88	74,035.00	38,173.20	6,759.18	44,932.38	21,945.83	7,156.79
Supplies	05	35,650.00	19,620.21	2,857.28	22,477.49	14,296.27	(1,123.76)
	09	1,300.00	658.21	124.49	782.70	---	517.30
	10	12,000.00	4,432.12	1,483.83	5,915.95	---	6,084.05
	12	850.00	521.50	88.30	609.80	317.20	(77.00)
	78	200.00	90.03	14.40	104.43	---	95.57
Total Supplies		<u>50,000.00</u>	<u>25,322.07</u>	<u>4,568.30</u>	<u>29,890.37</u>	<u>14,613.47</u>	<u>5,496.16</u>
Equipment	06	2,500.00	346.50	---	346.50	---	2,153.50
Consulting fees	49	19,400.00	8,916.00	2,115.00	11,031.00	1,810.00	6,559.00
Travel	07	75,000.00	25,254.90	3,392.91	28,647.81	9,833.26	36,518.93
Workshop/Publ.	91	60,000.00	19,757.09	(2,027.85)	17,729.24	31,708.76	10,562.00
Subcontracts	90	927,095.00	11,160.00	14,075.60	25,235.60	612,299.40	289,560.00
Pilot Studies	92	<u>75,000.00</u>	<u>10,304.74</u>	<u>5,928.34</u>	<u>16,233.08</u>	<u>62,799.92</u>	<u>(4,033.00)</u>
TOTAL RESEARCH		1,002,095.00	21,464.74	20,003.94	41,468.68	675,099.32	285,527.00
TOTAL WORKSHOP		60,000.00	19,757.09	(2,027.85)	17,729.24	31,708.76	10,562.00
TOTAL ADMINIS.		<u>437,905.00</u>	<u>212,386.28</u>	<u>36,645.00</u>	<u>249,031.28</u>	<u>113,085.47</u>	<u>75,788.25</u>
TOTAL		<u>1,500,000.00</u>	<u>253,608.11</u>	<u>54,621.09</u>	<u>308,229.20</u>	<u>819,893.55</u>	<u>371,877.25</u>

		<u>Budget</u> 7/1/79- 6/30/80	<u>Expended</u> 7/1/79- 2/29/80	<u>Expended</u> 3/1/80- 3/31/80	<u>Total</u> <u>Cum. Exp.</u> 7/1/79- 3/31/80	<u>Outstand.</u> <u>Commits</u> 4/1/80- 6/30/80	<u>Uncommitted</u> <u>Balance</u>
Salaries	02	143,400.00	94,145.93	11,047.50	105,193.43	35,302.50	12,904.07
	03	46,425.00	23,326.88	2,583.51	25,910.39	6,488.62	4,025.99
Total Salaries		<u>189,825.00</u>	<u>117,472.81</u>	<u>13,631.01</u>	<u>131,103.82</u>	<u>41,791.12</u>	<u>16,930.06</u>
Fringe Benefits	13	27,145.00	16,710.41	1,949.23	18,659.64	5,608.03	2,877.33
Indirect Cost	88	74,035.00	44,932.38	5,316.10	50,248.48	15,294.62	8,491.90
Supplies	05	35,650.00	22,477.49	2,281.28	24,758.77	15,021.69	(4,130.46)
	09	1,300.00	782.70	110.49	893.19	---	406.81
	10	12,000.00	5,915.95	866.24	6,782.19	---	5,217.81
	12	850.00	609.80	70.30	680.10	246.90	(77.00)
	78	200.00	104.43	4.75	109.18	---	90.82
Total Supplies		<u>50,000.00</u>	<u>29,890.37</u>	<u>3,333.06</u>	<u>33,223.43</u>	<u>15,268.59</u>	<u>1,507.98</u>
Equipment	06	2,500.00	346.50	---	346.50	---	2,153.50
Consulting Fees	49	19,400.00	11,031.00	2,860.00	13,891.00	1,581.00	3,928.00
Travel	07	75,000.00	28,647.81	3,054.09	31,701.90	11,007.81	32,290.29
Workshop/Publ.	91	60,000.00	17,729.24	39,720.50	57,449.74	(3,722.94)	6,273.20
Subcontracts	90	927,095.00	25,235.60	31,027.53	56,263.13	631,081.87	239,750.00
Pilot Studies	92	<u>75,000.00</u>	<u>16,233.08</u>	<u>2,148.74</u>	<u>18,381.82</u>	<u>60,651.18</u>	<u>(4,033.00)</u>
TOTAL RESEARCH		<u>1,002,095.00</u>	<u>41,468.68</u>	<u>33,176.27</u>	<u>74,644.95</u>	<u>691,733.05</u>	<u>235,717.00</u>
TOTAL WORKSHOP		<u>60,000.00</u>	<u>17,729.24</u>	<u>39,720.50</u>	<u>57,449.74</u>	<u>(3,722.94)</u>	<u>6,273.20</u>
TOTAL ADMINIS.		<u>437,905.00</u>	<u>249,031.28</u>	<u>30,143.49</u>	<u>279,174.77</u>	<u>90,551.17</u>	<u>68,179.06</u>
TOTAL		<u>1,500,000.00</u>	<u>308,229.20</u>	<u>103,040.26</u>	<u>411,269.46</u>	<u>778,561.28</u>	<u>310,169.26</u>

		<u>Budget</u> 7/1/79- 6/30/80	<u>Expended</u> 7/1/79- 3/31/80	<u>Expended</u> 4/1/80- 4/30/80	<u>Total</u> <u>Cum. Exp.</u> 7/1/79- 4/30/80	<u>Outstand.</u> <u>Commits</u> 5/1/80- 6/30/80	<u>Uncommitted</u> <u>Balance</u>
Salaries	02	153,400.00	105,193.43	12,762.01	117,955.44	22,119.74	13,324.82
	03	36,425.00	25,910.39	2,085.18	27,995.57	4,543.01	3,886.42
Total Salaries		<u>189,825.00</u>	<u>131,103.82</u>	<u>14,847.19</u>	<u>145,951.01</u>	<u>26,662.75</u>	<u>17,211.24</u>
Fringe Benefits	13	27,145.00	18,659.64	2,123.15	20,782.79	3,737.21	2,625.00
Indirect Cost	88	74,035.00	50,248.48	5,790.40	56,038.88	10,192.38	7,803.74
Supplies	05	35,650.00	24,758.77	2,657.09	27,415.86	19,379.49	(11,145.35)
	09	1,300.00	893.19	110.25	1,003.44	---	296.56
	10	12,000.00	6,782.19	1,022.00	7,804.19	---	4,195.81
	12	850.00	680.10	70.30	750.40	176.60	(77.00)
	78	200.00	109.18	21.25	130.43	---	69.57
Total Supplies		<u>50,000.00</u>	<u>33,223.43</u>	<u>3,880.89</u>	<u>37,104.32</u>	<u>19,556.09</u>	<u>(6,660.41)</u>
Equipment	06	2,500.00	346.50	---	346.50	---	2,153.50
Consulting Fees	49	19,400.00	13,891.00	2,181.00	16,072.00	---	3,328.00
Travel	07	75,000.00	31,701.90	4,772.88	36,474.78	1,870.49	36,654.73
Map/Publ.	91	60,000.00	57,449.74	(16,564.96)	40,884.78	10,195.27	8,919.95
Subcontracts	90	927,095.00	56,263.13	14,472.04	70,735.17	616,609.83	239,750.00
Pilot Studies	92	<u>75,000.00</u>	<u>18,381.82</u>	<u>1,609.09</u>	<u>19,990.91</u>	<u>59,042.09</u>	<u>(4,033.00)</u>
TOTAL RESEARCH		1,002,095.00	74,644.95	16,081.13	90,726.08	675,651.92	235,717.00
TOTAL WORKSHOP		60,000.00	57,449.74	(16,564.96)	40,884.78	10,195.27	8,919.95
TOTAL ADMINISTRATION		<u>437,905.00</u>	<u>279,174.77</u>	<u>33,595.51</u>	<u>312,770.28</u>	<u>62,018.92</u>	<u>63,115.80</u>
TOTAL		1,500,000.00	411,269.46	33,111.68	444,381.14	747,866.11	307,752.75

		<u>Budget 7/1/79- 6/30/80</u>	<u>Expended 7/1/79- 4/30/80</u>	<u>Expended 5/1/80- 5/31/80</u>	<u>Total Cum. Exp. 7/1/79- 5/31/80</u>	<u>Outstanding Commits 6/1/80- 6/30/80</u>	<u>Uncommitted Balance</u>
Salaries	02	153,400.00	117,955.44	19,205.58	137,161.02	15,039.17	1,199.81
	03	36,425.00	27,995.57	3,456.44	31,452.01	3,279.73	1,693.26
Total Salaries		189,825.00	145,951.01	22,662.02	168,613.03	18,318.90	2,893.07
Fringe Benfts	13	27,145.00	20,782.79	3,240.67	24,023.46	2,581.05	540.49
Indirect Costs	88	74,035.00	56,038.88	8,838.19	64,877.07	7,039.22	2,118.71
Supplies	05	50,650.00	27,415.86	8,680.51	36,096.37	14,228.43	325.20
	09	1,300.00	1,003.44	76.14	1,079.58	---	220.42
	10	12,000.00	7,804.19	329.09	8,133.28	---	3,866.72
	12	850.00	750.40	106.30	856.70	70.30	(77.00)
	78	200.00	130.43	3.10	133.53	---	66.47
Total Supplies		65,000.00	37,104.32	9,195.14	46,299.46	14,298.73	4,401.81
Equipment	06	2,500.00	346.50	---	346.50	---	2,153.50
Conslt. Fees	49	19,400.00	16,072.00	---	16,072.00	---	3,328.00
Travel	07	60,000.00	36,474.78	2,515.26	38,990.04	5,566.51	15,443.45
Wksp/Publ.	91	60,000.00	40,884.78	405.25	41,290.03	10,437.80	8,272.17
Subcontracts	90	927,095.00	70,735.17	58,955.33	129,690.50	768,746.50	28,658.00
Pilot Studies	92	75,000.00	19,990.91	13,498.15	33,489.06	53,043.94	(11,533.00)
TOTAL RESEARCH		1,002,095.00	90,726.08	72,453.48	163,179.56	821,790.44	17,125.00
TOTAL WORKSHOP		60,000.00	40,884.78	405.25	41,290.03	10,437.80	8,272.17
TOTAL ADMINIS.		437,905.00	312,770.28	46,451.28	359,221.56	47,804.41	30,879.03
TOTAL		1,500,000.00	444,381.14	119,310.01	563,691.15	880,032.65	56,276.20

		Budget 7/1/79- 6/30/81	Expended 7/1/79- 5/31/80	Expended 6/1/80- 6/30/80	Total Cum. Exp. 7/1/79- 6/30/80	Outstanding Commits 7/1/80- 6/30/81	Uncommitted Balance
Salaries	02	268,400.00	137,161.02	14,289.17	151,450.19	1,050.00	115,899.81
	03	117,734.00	31,452.01	3,388.19	34,840.20	(31.04)	82,924.84
Total Salaries		386,134.00	168,613.03	17,677.36	186,290.39	1,018.96	198,824.65
Fringe Benefits	13	55,217.00	24,023.46	2,527.86	26,551.32	(4.44)	28,670.12
Indirect Costs	88	150,596.00	64,877.07	6,894.17	71,771.24	(12.10)	78,836.86
Supplies	05	89,100.00	36,096.37	9,173.31	45,269.68	13,670.37	30,159.95
	09	2,600.00	1,079.58	89.61	1,169.19	----	1,430.81
	10	24,000.00	8,133.28	260.09	8,393.37	----	15,606.63
	12	1,700.00	856.70	70.30	927.00	----	773.00
	78	400.00	133.53	----	133.53	----	266.47
Total Supplies		117,800.00	46,299.46	9,593.31	55,892.77	13,670.37	48,236.86
Equipment	06	2,600.00	346.50	----	346.50	----	2,253.50
Consult. Fees	49	35,200.00	16,072.00	536.00	16,608.00	1,566.00	17,026.00
Travel	07	115,000.00	38,990.04	2,573.70	41,563.74	9,018.63	64,417.63
Wkshp./Publ.	91	135,000.00	41,290.03	672.78	41,962.81	15,085.02	77,952.17
Subcontracts	90	1,852,453.00	129,690.50	41,568.64	171,259.14	727,177.86	954,016.00
Pilot Studies	92	150,000.00	33,489.06	5,141.16	38,630.22	47,902.78	63,467.00
TOTAL RESEARCH		2,002,453.00	163,179.56	46,709.80	209,889.36	775,080.64	1,017,483.00
TOTAL WORKSHOP		135,000.00	41,290.03	672.78	41,962.81	15,085.02	77,952.17
TOTAL ADMINISTRATION		862,547.00	359,221.56	39,802.40	399,023.96	25,257.42	438,265.62
TOTAL		3,000,000.00	563,691.15	87,184.98	650,876.13	815,423.08	1,533,700.79

		<u>Budget</u> 7/1/75- 6/30/80	<u>Expended</u> 7/1/75- 12/31/79	<u>Expended</u> 12/31/79- 3/31/80	<u>Total</u> <u>Cum. Exp.</u> 7/1/75- 3/31/80	<u>Outstand.</u> <u>Commits</u> <u>Through</u> 6/30/80	<u>Balance</u>
Salaries	02	267,128.89	269,218.89	---	269,218.89	---	(2,090.00)
	03	112,224.14	103,708.02	---	103,708.02	---	8,516.12
Total Salaries		<u>379,353.03</u>	<u>372,926.91</u>	<u>---</u>	<u>372,926.91</u>	<u>---</u>	<u>6,426.12</u>
Fringe Benefits	13	52,354.04	51,269.43	---	51,269.43	---	1,084.61
Indrt. Costs	88	133,140.46	131,094.58	---	131,094.58	---	2,045.88
Supplies	05	108,057.16	130,175.54	1,750.00	131,925.54	20.00	(23,888.38)
	09	1,600.00	527.81	---	527.81	---	1,072.19
	10	36.13	5,931.81	---	5,931.81	---	(5,895.68)
	12	1,537.00	1,591.00	---	1,591.00	---	(54.00)
	78	2,091.89	1,567.39	---	1,567.39	---	524.50
Total Supplies		<u>113,322.18</u>	<u>139,793.55</u>	<u>1,750.00</u>	<u>141,543.55</u>	<u>20.00</u>	<u>(28,241.37)</u>
Equipment	06	15,755.55	27,790.56	204.60	27,995.16	---	(12,239.61)
Consulting Fees	49	50,944.00	40,973.11	---	40,973.11	---	9,970.89
Travel	07	135,321.02	143,860.20	---	143,860.20	461.00	(9,000.18)
Moving Expense	18	6,846.17	2,963.91	---	2,963.91	---	3,882.26
Remodel & Maint	52	16,249.30	11,249.30	---	11,249.30	---	5,000.00
Missp/Publ.	91	203,404.33	183,852.77	8,500.00	192,352.77	---	11,051.56
Subcontracts	90	3,077,193.92	2,509,196.96	199,005.25	2,708,202.21	628,374.48	(259,382.77)
Pilot Studies	92	<u>125,347.00</u>	<u>93,446.02</u>	<u>10,260.75</u>	<u>103,706.77</u>	<u>37,330.06</u>	<u>(15,699.83)</u>
TOTAL RESEARCH		3,202,540.92	2,602,642.98	209,266.00	2,811,908.98	665,704.54	(275,072.60)
TOTAL WORKSHOP		203,404.33	183,852.77	8,500.00	192,352.77	---	11,051.56
TOTAL ADMIN		903,285.75	921,921.55	1,954.60	923,876.15	481.00	(21,071.40)
TOTAL		4,309,231.00	3,708,417.30	219,720.60	3,928,137.90	666,185.54	(285,092.44)

		Budget 7/1/75- 6/30/80	Expended 7/1/75- 3/31/80	Expended 3/31/80- 4/30/80	Total Cum. Exp. 7/1/75- 4/30/80	Outstanding Commits Through 6/30/80	Balance
Salaries	02	267,128.89	269,218.89	---	269,218.89	---	(2,090.00)
	03	112,224.14	103,708.02	---	103,708.02	---	8,516.12
Total Salaries		379,353.03	372,926.91	---	372,926.91	---	6,426.12
Fringe Benefits	13	52,354.04	51,269.43	---	51,269.43	---	1,084.61
Indrt. Costs	88	133,140.46	131,094.58	---	131,094.58	---	2,045.88
Supplies	05	108,057.16	131,925.54	---	131,925.54	20.00	(23,888.38)
	09	1,600.00	527.81	---	527.81	---	1,072.19
	10	36.13	5,931.81	---	5,931.81	---	(5,895.68)
	12	1,537.00	1,591.00	---	1,591.00	---	(54.00)
	78	2,091.89	1,567.39	---	1,567.39	---	524.50
Total Supplies		113,322.18	141,543.55	---	141,543.55	20.00	(28,241.37)
Equipment	06	15,755.55	27,995.16	---	27,995.16	---	(12,239.61)
Consulting Fees	49	50,944.00	40,973.11	---	40,973.11	---	9,970.89
Travel	07	135,321.02	143,860.20	---	143,860.20	461.00	(9,000.18)
Moving Expense	18	6,846.17	2,963.91	---	2,963.91	---	3,882.26
Remodel & Maint	52	16,249.30	11,249.30	---	11,249.30	---	5,000.00
Wksp/Publ.	91	203,404.33	192,352.77	---	192,352.77	---	11,051.56
Subcontracts	90	3,077,193.92	2,708,202.21	29,008.41	2,737,210.62	587,040.76	(247,057.46)
PfTot Studies	92	125,347.00	103,706.77	---	103,706.77	37,597.37	(15,957.14)
TOTAL RESEARCH		3,202,540.92	2,811,908.98	29,008.41	2,840,917.39	624,638.13	(263,014.60)
TOTAL WORKSHOP		203,404.33	192,352.77	---	192,352.77	---	11,051.56
TOTAL ADMIN.		903,285.75	923,876.15	---	923,876.15	481.00	(21,071.40)
TOTAL		4,309,231.00	3,928,137.90	29,008.41	3,957,146.31	625,119.13	(273,034.44)

		Budget 7/1/75- 6/30/80	Expended 7/1/75- 4/30/80	Expended 5/1/80- 5/31/80	Total Cum. Exp. 7/1/75- 5/31/80	Outstanding Commits Through 6/30/80	Balance
Salaries	02	267,128.89	269,218.89	---	269,218.89	---	(2,090.00)
	03	112,224.14	103,708.02	---	103,708.02	---	8,516.12
Total Salaries		379,353.03	372,926.91	---	372,926.91	---	6,426.12
Fringe Benfts.	13	52,354.04	51,269.43	---	51,269.43	---	1,084.61
Indrt. Costs	88	133,140.46	131,094.58	---	131,094.58	---	2,045.88
Supplies	05	108,057.16	131,925.54	---	131,925.54	20.00	(23,888.38)
	09	1,600.00	527.81	---	527.81	---	1,072.19
	10	36.13	5,931.81	---	5,931.81	---	(5,895.68)
	12	1,537.00	1,591.00	---	1,591.00	---	(54.00)
	78	2,091.89	1,567.39	---	1,567.39	---	524.50
Total Supplies		113,322.18	141,543.55	---	141,543.55	20.00	(28,241.37)
Equipment	06	15,755.55	27,995.16	---	27,995.16	---	(12,239.61)
Consult. Fees	49	50,944.00	40,973.11	---	40,973.11	---	9,970.89
Travel	07	135,321.02	143,860.20	---	143,860.20	451.00	(9,000.18)
Moving Exp.	18	6,846.17	2,963.91	---	2,963.91	---	3,882.26
Remod. & Maint.	52	16,249.30	11,249.30	---	11,249.30	---	5,000.00
Wksp/Publ.	91	203,404.33	192,352.77	(690.00)	191,662.77	---	11,741.56
Subcontracts	90	3,077,193.92	2,737,210.62	54,636.65	2,791,847.27	532,404.11	(247,057.46)
Pilot Studies	92	125,347.00	103,706.77	1,764.55	105,471.32	35,832.82	(15,957.14)
TOTAL RESEARCH		3,202,540.92	2,840,917.39	56,401.20	2,897,318.59	568,236.93	(263,014.60)
TOTAL WORKSHOP		203,404.33	192,352.77	(690.00)	191,662.77	---	11,741.56
TOTAL ADMIN.		903,285.75	923,876.15	---	923,876.15	481.00	(21,071.40)
TOTAL		4,309,231.00	3,957,146.31	55,711.20	4,012,857.51	568,717.93	(272,344.44)

		Budget 7/1/75- 6/30/80	Expended 7/1/75- 5/31/80	Expended 6/1/80- 6/30/80	Total Cum. Exp. 1/1/75- 6/30/80	Outstanding Commits Through 6/30/80	Balance
Salaries	02	269,218.89	269,218.89	----	269,218.89	----	----
	03	103,708.02	103,708.02	----	103,708.02	----	----
Total Salaries		372,926.91	372,926.91	----	372,926.91	----	----
Fringe Benefits	13	51,269.43	51,269.43	----	51,269.43	----	----
Indirect Costs	88	131,094.58	131,094.58	----	131,094.58	----	----
Supplies	05	131,925.54	131,925.54	----	131,925.54	----	----
	09	527.81	527.81	----	527.81	----	----
	10	5,931.81	5,931.81	----	5,931.81	----	----
	12	1,591.00	1,591.00	----	1,591.00	----	----
	78	1,567.39	1,567.39	----	1,567.39	----	----
Total Supplies		141,543.55	141,543.55	----	141,543.55	----	----
Equipment	16	27,995.16	27,995.16	----	27,995.16	----	----
Consulting Fees	49	40,973.11	40,973.11	----	40,973.11	----	----
Travel	07	143,860.20	143,860.20	----	143,860.20	461.00	(461.00)
Moving Exp.	18	2,963.91	2,963.91	----	2,963.91	----	----
Remodl. & Maint.	52	11,249.30	11,249.30	----	11,249.30	----	----
Wksp./Publ.	91	192,352.77	191,662.77	----	191,662.77	----	690.00
Subcontracts	90	3,253,038.11	2,791,847.27	83,461.19	2,875,308.46	367,012.64	10,717.01
Pilot Studies	92	143,245.47	105,471.32	6,349.01	111,820.33	26,425.16	4,999.98
TOTAL RESEARCH		3,396,283.58	2,897,318.59	89,810.20	2,987,128.79	393,437.80	15,716.99
TOTAL WORKSHOP		192,352.77	191,662.77	----	191,662.77	----	690.00
TOTAL ADMINISTRATION		923,876.15	923,876.15	----	923,876.15	461.00	(461.00)
TOTAL		4,512,512.50	4,012,857.51	89,810.20	4,102,667.71	393,898.80	15,945.99

Report(8/5/80)

CURRENT SUBCONTRACTS
Budgeted and Expended Funds (4263-404-90)
AID/DSPE-C-0035

<u>Subcontract</u>	<u>Budget/Period</u>	<u>Expended/Period*</u>
200C Richart/Columbia U.	\$30,715 7/1/79-6/30/81	\$ 2,206.50 1/1/80-4/30/80
200G Zinser/Germany	\$32,020 9/1/79-8/31/80	\$12,908.07 9/1/79-3/31/80
200P Apelo/Philippines	\$ 6,820 10/1/79-9/30/80	\$ 1,675.94 12/1/79-4/30/80
201B Mafa/Brazil	\$34,600 8/1/79-11/30/80	\$26,210.00 8/1/79-4/30/80
202 Heine/Maine Med. Ctr.	\$49,044 9/1/79-8/31/80	\$19,837.19 9/1/79-4/30/80
203IIT Gutfreund/IIT	\$21,905 11/1/79-10/31/80	\$ 5,701.63 12/1/79-4/30/80
203NMH Chatterton/Northwestern	\$34,127 9/1/79-8/31/80	\$20,426.16 9/1/79-4/30/80
203NU Chatterton/Northwestern	\$27,552 9/1/79-8/31/80	\$ 9,188.17 9/1/79-4/30/80
204 Zaneveld/U. of IL	\$116,431 10/1/79-6/30/81	- 0 -
205(95N) Zaneveld/U. of IL	\$45,443 10/1/79-9/30/80	- 0 -
206SRI Lewis/SRI	\$66,000 11/1/79-10/31/80	\$23,673.79 11/1/79-5/31/80
206UAB Beck/U. of AL	\$18,865 11/1/79-10/31/80	\$11,547.34 11/1/79-3/31/80
207 Hosseinian/Cook County	\$24,348 11/1/79-10/31/80	\$ 7,681.62 11/1/79-5/31/80
208 Beck/U. of AL	\$19,406 11/1/79-10/31/80	\$ 6,755.22 11/1/79-3/31/80
209NMH Mehta/Northwestern	\$24,288 1/1/80-12/31/80	\$ 3,008.11 2/1/80-4/30/80
209NU Mehta/Northwestern	\$29,361 1/1/80-12/31/80	\$ 5,478.73 1/1/80-4/30/80

* Expenditure TOTALS are taken from dates on invoices because of the lag time before expenditures show up on NU Budget Statements.

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CURRENT SUBCONTRACTS
Budgeted and Expended Funds (4263-404-90)
AID/DSPE-C-0035

<u>Sucontract</u>	<u>Budget/Period</u>	<u>Expended/Period</u> *
210 Chang/Morchester Foundation	\$43,070 1/1/80-12/31/80	\$11,944.41 1/1/80-5/31/80
211 Davis	\$13,540 12/1/79-11/30/80	\$ 950 12/1/79-4/30/80
212(85N) Chvapil/U. of AZ	\$51,991 3/1/80-2/28/81	- 0 -
213B Maia/Brazil	\$14,000 6/1/80-5/31/81	- 0 -
213T Ahmad/UTHSCSA	\$59,618 5/1/80-4/30/81	- 0 -
214(83N) Beck/U. of AL	\$67,164 4/1/80-3/31/81	- 0 -
214(110N) Lewis/SRI	\$69,311 4/1/80-3/31/81	\$ 7,839.34 4/1/80-5/31/80
215 Antonini/Brazil	\$16,775 5/15/80-5/14/81	\$ 6,507.60 5/15/80-6/14/80
216(P19) Slocumb/U. of NM	\$40,814 5/1/80-4/30/81	- 0 -

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CURRENT SUBCONTRACTS
Budgeted and Expended Funds (Pilots 4263-404-92)
AID/DSPE-C-0035

<u>Subcontract</u>	<u>Budget/Period</u>	<u>Expended/Period*</u>
P50 Chvapil/U. of AZ	\$ 8,000 7/1/79-6/30/80	\$ 2,078.37 12/1/79-3/31/80
P51 (final) Hasson	\$10,000 10/1/79-9/30/80	\$10,000.00 10/1/79-3/31/80
P52 Perea Sasiain/Colombia	\$ 7,000 10/1/79-9/30/80	\$ 4,321.72 10/1/79-3/31/80
P53 Asch/UTHSCSA	\$ 7,500 11/1/79-10/31/80	\$ 1,906.21 2/1/80-4/30/80
P54 (final) de Castro/Brazil	\$ 9,350 1/1/80-6/30/80	\$ 4,529.00 1/1/80-4/30/80
P55 Petrow/Duke U.	\$ 7,590 11/1/79-11/30/80	\$ 2,013.05 11/1/79-4/30/80
P56 Alexander/Med. Rsch. Foundation	\$14,665 11/1/79-10/31/80	\$ 6,242.73 12/1/79-4/30/80
P57 Dunn/SRI	\$ 7,428 1/1/80-6/30/80	\$ 7,132.15 1/1/80-5/31/80
P58 Goldberg/Northwestern	\$ 7,500 12/1/79-11/30/80	\$ 1,286.99 12/1/79-4/30/80
P59 Blackwell/U. of AL	\$ 7,500 5/1/80-10/31/80	- 0 -

* Expenditure TOTALS are taken from dates on invoices because of the lag time before expenditures show up on NU Budget Statements.

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CURRENT SUBCONTRACTS
Budgeted and Expended Funds (4263-401-90)
AID/csd-3608

<u>Subcontract</u>	<u>Budget/Period</u>	<u>Expended/Period</u> *
79N Meeker/ Maine Med. Ctr.	\$187,220.60 2/1/77-6/30/80	\$136,061.82 2/1/77-5/31/80
83N Beck/U. of AL	\$257,849.00 4/1/76-3/31/80	\$249,498.17 4/1/76-2/29/80
85N Chvapil/U. of AZ	\$ 98,124.00 12/1/76-6/30/80	\$ 97,349.45 12/1/76-4/30/80
86N (final) Neuwirth/St. Luke's	\$ 36,602.00 6/1/78-3/31/80	\$ 36,489.98 6/1/78-3/31/80
86K Hong/Korea	\$ 16,080.00 5/1/79-4/30/80	\$ 6,939.59 6/1/79-4/30/80
86Sa Argueta/Salvador	\$ 12,410.00 3/15/79-6/30/80	\$ 7,326.00 3/15/79-2/14/80
86Sb Moran/Salvador	\$ 8,000.00 3/15/79-3/14/80	\$ 1,360.00 5/1/79-1/31/80
89N Gregor/Columbia	\$112,073.00 1/15/77-6/30/80	\$107,981.07 1/15/77-4/14/80
89N St. Luke's	\$ 63,326.00 11/1/77-6/30/80	\$ 52,664.02 11/1/77-4/30/80
90Np Davis/Planned Parenthood	\$ 54,007.00 2/1/79-6/30/80	\$ 31,098.59 2/1/79-11/30/79
91N Wise/Dynatech	\$177,141.00 6/1/77-6/30/80	\$160,496.54 6/1/77-4/30/80
92N (final) Anderson/OR Primate Rsch. Ctr.	\$ 86,107.65 6/1/77-12/31/79	\$ 85,524.48 6/1/77-12/31/79
94N (final) DroegemueLLer/U. of AZ	\$ 62,061.92 12/1/77-12/31/79	\$ 44,715.58 12/1/77-12/31/79
97N King/Johns Hopkins U.	\$108,442.00 8/1/78-6/30/80	\$ 43,127.59 8/1/78-5/31/80
97K Kwak/Korea	\$ 66,550.00 7/1/78-6/30/80	\$ 24,170.02 7/1/78-5/31/80
98M Aznar/CIFE-Mexico	\$ 34,265.00 7/1/78-6/30/80	\$ 29,310.38 7/1/78-3/31/80

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CURRENT SUBCONTRACTS
Budgeted and Expended Funds (4263-401-90)
AID/csd-3608

<u>Subcontract</u>	<u>Budget/Period</u>	<u>Expended/Period</u> *
98M U. of Alabama	\$ 10,780.00 7/1/78-6/30/80	\$ 8,438.63 7/1/78-4/30/80
98M (final) Southern Research Institute	\$ 27,642.00 7/1/78-6/30/79	\$ 27,642.00 7/1/78-6/30/79
100N (final) Lerner/Jefferson Med. College	\$109,384.00 9/1/78-6/30/80	\$109,384.00 9/1/78-5/31/80
102N(P10) Chatterton/U. of IL	\$ 46,767.00 11/1/78-10/31/79	\$ 24,209.56 11/1/78-6/31/79
104N(P9) Lewis/SRI	\$ 66,000.00 11/1/78-10/31/79	\$ 60,103.39 11/1/78-10/31/79
105N Rudel/CIFE Mexico	\$ 56,236.00 5/1/79-4/30/80	\$ 15,600.23 5/1/79-3/31/80
106N Berger/U. of NC	\$ 47,676.00 2/1/79-2/29/80	\$ 37,503.53 2/1/79-1/31/80
107N Alexander/OR Primate Rsch. Ctr.	\$ 83,318.00 4/1/79-9/30/80	\$ 60,569.41 4/1/79-5/31/80
110N Lewis/SRI	\$ 65,972.00 4/1/79-3/31/80	\$ 65,396.85 4/1/79-3/31/80
111N Eddy/U. of TX	\$ 58,290.00 6/1/79-6/30/80	\$ 30,670.74 6/1/79-4/30/80
114N Yen/U. of CA	\$ 65,959.00 6/15/79-6/30/80	43,018.60 6/15/79-4/30/80

* Expenditure TOTALS are taken from dates on invoices because of the lag time before expenditures show up on NU Budget Statements.

CURRENT SUBCONTRACTS
Budgeted and Expended Funds (Pilots 4263-401-92)

<u>Subcontract</u>	<u>Budget/Period</u>	<u>Expended/Period</u> *
P12 Frisch/MIT	\$15,000.00 7/1/78-6/30/80	\$11,729.86 7/1/78-4/30/80
P13 Brosens/Leuven	\$11,680.59 5/1/78-4/30/80	\$ 6,425.41 5/1/78-11/30/79
P13 (final) IFRP	\$ 2,750.00 5/1/78-4/30/80	\$ 2,750.00 5/1/78-9/79
P15 Shulman/NY Med. College	\$ 7,500.00 3/1/79-2/29/80	\$ 6,947.53 3/1/79-1/31/80
P16 Page/U. of CA	\$ 6,000.00 1/1/79-6/30/80	\$ 1,636.61 1/1/79-3/31/80
P19 Slocumb/U. of NM	\$ 7,700.00 2/1/79-6/30/80	\$ 7,414.17 2/1/79-4/30/80
P20 (final) Goldzieher/Southwest Fdn.	\$ 7,500.00 6/1/79-11/30/79	\$ 7,461.45 6/1/79-11/30/79
P21 Chvapil/U. of AZ	\$7,500.00 6/15/79-6/14/80	\$ 3,721.49 9/1/79-4/30/80
P22 Cates/U. of Houston	\$ 7,688.00 6/15/79-6/14/80	Never initiated - 0 -

* Expenditure TOTALS are taken from dates on invoices because of the lag time before expenditures show up on NU Budget Statements.

LDC Research Funds
1/1/80-6/30/80

<u>PARFR #</u> <u>(AID/csd-3608)</u>	<u>Budget (Dollars)</u>	<u>Spent (Dollars)</u>
86K Hong-Korea	\$16,080	\$ 6,939.59 (6/1/79-4/30/80)
86Sa Argueta-Salvador	\$12,410	\$ 7,326.00 (3/15/79-2/14/80)
86Sb Moran-Salvador	\$ 8,000	\$ 1,360.00 (5/1/79-1/31/80)
97K Kwak-Korea	\$66,550	\$24,170.02 (7/1/78-5/31/80)
98M Aznar-Mexico	\$34,265	\$29,310.38 (7/1/78-3/31/80)
105N Rudel-Mexico	\$56,236	\$15,600.23 (5/1/79-3/31/80)
(AID/DSPE-C-0035)		
200P Apelo-Philippines	\$ 6,820	\$ 1,675.94 (12/1/79-4/30/80)
201B Maia-Brazil	\$34,600	\$26,210.00 (8/1/79-4/30/80)
213B Maia-Brazil	\$14,000	- 0 -
215 Antonini-Brazil	\$16,775	\$ 6,507.60 (5/15/80-6/14/80)
P52 Perea Sasiain-Colombia	\$ 7,000	\$ 4,321.72 (10/1/79-3/31/80)
P54 (final) deCastro-Brazil	\$ 9,350	\$ 4,529.00 (1/1/80-4/30/80)

PARFR SCIENTIFIC ADVISORY COMMITTEE

MEETING XXXII

PALMER HOUSE
Chicago, Illinois
March 10, 1980

MINUTES

VOTING SAC MEMBERS PRESENT

John J. Sciarra, M.D., Ph.D.
Nancy J. Alexander, Ph.D.
Robert T. Chatterton, Ph.D.
Joseph E. Davis, M.D.
Edward C. Mather, D.V.M., Ph.D.
Carl J. Pauerstein, M.D.
Ralph M. Richart, M.D.
Susan C.M. Scrimshaw, Ph.D.

VOTING SAC MEMBERS ABSENT

Kamran S. Moghissi, M.D.
Judith L. Vaitukaitis, M.D.
A. Albert Yuzpe, M.D.

PARFR STAFF PRESENT

Elizabeth B. Connell, M.D.
Alfredo J. Goldsmith, M.D.
Diane H. Krier, M.B.A.
Ann Conner Nickle
Aquiles J. Sobrero, M.D.
Gerald I. Zatuchni, M.D., M.Sc.

USAID MEMBERS PRESENT

Miriam H. Labbok, M.D., M.P.H.

The thirty-second meeting of PARFR's Scientific Advisory Committee convened on Monday, March 10, 1980 at 8:00 A.M. at the Palmer House, Chicago, Illinois. Dr. John J. Sciarra presided as Chairman. Minutes of the December 3, 1979 meeting were approved with no voiced corrections.

I. ANNOUNCEMENTS

- A. Dr. Gerald Zatuchni reported on PARFR's International Workshop: Research Frontiers in Fertility Regulation, February 11-14, 1980, Mexico City. There were 155 individuals in attendance, representing 25 countries.
- B. PARFR's "Research Frontiers in Fertility Regulation" (note the title is the same as the Mexico Workshop) - a series designed to present a comprehensive review of past and current research information and experience on selected major topics in fertility regulation and contraceptive development, will be distributed this spring/summer. The premier issue is on "Long-Acting Steroidal Contraceptive Systems" and will be authored by Lee R. Beck, Ph.D., Donald R. Cowsar, Ph.D. and Valerie Z. Pope, M.S.
- C. Scheduled Meeting dates for PARFR's SAC are:

June 22, 1980 (Sunday) - New York Statler Hotel
September 7, 1980 (Sunday) - Washington, D.C.
December 8, 1980 (Monday) - Chicago, Illinois

(Note - the September and December SAC Meetings were cancelled in May, 1980 and the new SAC date is November 16, 1980 (Sunday) at the Arlington Hyatt House.)

II. NEW BUSINESS

A. EXTENSION PROPOSAL REVIEW

1. PARFR-83N -- Lee R. Beck, Ph.D., University of Alabama

"Studies to Test an Injectable Delivery System for the Sustained Release of Norethisterone"

Funding Requested: \$66,975 Length of Project: One Year

Drs. Goldsmith and Zatuchni reported on 1/21-23/80 site visit. In this continuing PARFR development, the P.I. and SRI plan to perform all necessary studies in order to obtain an FDA-IND by October, 1980. The system will be a three-month system in which the rate of NET-release will be sufficient to maintain blood levels between 1 and 2 ng/ml throughout the three-month treatment interval, and the microsphere should be completely biodegraded between four and five months post-injection. The major task will be to evaluate the rates and duration of NET-release from the improved microsphere formulations provided by SRI. These experiments will require a minimum of five baboons for each new formulation. The optimum formulation will be selected for use in clinical trials to be conducted at the UAB and at other institutions. Additional baboons (15) will be utilized for the optimal formulation. Various types of dose regimens and interval treatments will be examined, including post-treatment fertility studies. Currently, Dr. Aznar (CIFE - Mexico City) is completing a clinical trial of the 6-month system on 26 patients (13 each on two different doses).

The Committee voted unanimously to approve the continuation of PARFR-83N; however, requested that Dr. Beck clarify certain points raised and that this clarification be submitted in the next SAC Agenda.

2. PARFR-110N -- Danny H. Lewis, Ph.D., Southern Research Institute

"Optimization of an Injectable Microcapsule Formulation for the 90-day Delivery of Norethisterone"

Funding Requested: \$69,311 Length of Project: One Year

Drs. Goldsmith and Zatuchni reported on 1/21-23/80 site visit of this companion proposal of PARFR-83N. In close cooperation with the in vivo (baboon) testing at the UAB, and the Phase I clinical trials in Mexico, SRI has been most successful in developing a six-month biodegradable system of contraception steroid (NET) release. During the present year of support a whole range of technical studies have been completed with the objective of optimizing a three-month system and putting the final manufacturing touches on the six-month system. Co-polymers have been examined in varying proportion and it now appears that the addition of glycolic acid to the polylactic acid

- A. EXTENSION PROPOSAL REVIEW (cont'd)
2. PARFR-110N -- Danny H. Lewis, Ph.D. (cont'd)

provides more rapid biodegradation. Apparently the optimal proportion for a three-month system of release which would biodegrade over a five-month period is the mixture of 75% polylactic acid and 25% glycolic acid. Additional studies have convinced SRI that based on the proportion of polymer and the steroid loading dose, a highly reproducible preparation can be made to provide for a thirty-day total release system up to a two-year releasing system. Particle size has a great deal to do with released rates, and SRI has spent considerable effort in formulating capsules within defined and prescribed diameter limits. The extension proposal covers six main areas: 1) Completion of the ongoing evaluation of the kinetics of biodegradation of the ¹⁴C-poly(lactide-co-glycolide) microcapsules in rats. 2) Selection of the specific lactide/glycolide copolymer to be used in the 90-day NET-releasing microcapsules, looking for one which will provide constant, predictable blood levels of NET for approximately 90 days and is thus completely resorbed within 180 days post-treatment. 3) Further optimization of the microencapsulation process, investigating the batch-to-batch reproducibility and the preparation of larger batches of microcapsules. 4) Standardization of materials, processes, analyses, quality-control procedures, and compositions in accordance with the FDA Guidelines for Good Manufacturing Practices. 5) Development of a suitable vehicle for the administration of the 90-day system by means of a conventional syringe and needle. 6) Determination of the biodegradation kinetics in rats of the final co-polymer selected.

The Committee voted unanimously to approve continuation of PARFR-110N.

3. PARFR-100N -- Leonard J. Lerner, Ph.D., Jefferson Medical College

"Investigation of New Compounds to Terminate Pregnancy"

Funding Requested: \$67,342 Length of Project: One Year

Drs. Chatterton and Zatuschni report on 11/29/79 site visit to Dr. Lerner. After a year of study, the PI has been successful in screening over 30 compounds in hamsters, and partly in rats, that have pregnancy termination activity. The two best compounds are designated DL-111-IT and DL-105-IT. The former compound is active only via injection, or perhaps vaginal administration, while the latter compound appears to have oral activity. Both compounds are patented by Lepetit Laboratories and are under development and toxicological studies at Inverness Research Institute in Scotland. Lerner proposes to study the effects of compounds on prostaglandin levels, thromboxane levels in organs and plasma of the pregnant rat. Additionally, a prostaglandin synthetase inhibitor will be administered to determine if reduction of endogenous prostaglandins influences the efficacy and/or unwanted biological activities of the compound.

A. EXTENSION PROPOSAL REVIEW (cont'd)

3. PARFR-100N -- Leonard J. Lerner, Ph.D. (cont'd)

DL-111-IT will be administered in different doses and tissue analysis for histamine concentration in designated organs will be studied. The effects of DL-111-IT on blood flow in various organs systems will be determined by using radioactive means. Standard immunological responses will be studied to determine the effects of DL-111-IT on the rat immune response. Finally, the effectiveness of DL-111-IT and DL-105-IT will be studied using the pregnant guinea pig as the model. The results in this animal will be compared with those obtained in other species, including the subhuman primate (rhesus monkey).

Dr. Zatuchni reported that in early summer he and Dr. Lerner plan to travel to Italy to discuss further development of abortifacient components patented by Lepetit and Carlo Erba. The Committee unanimously approved continuation of this project.

B. FORMAL PROPOSAL REVIEW

1. Edwin L. Adair, M.D., Medical Dynamics, Englewood, Colorado and Michael J. Free, Ph.D., PIACT

"A Multi-site Evaluation in Developed and Developing Countries of a Technique and Equipment for Transcutaneous Closure of the Vas Deferens by Electrocoagulation"

Funding Requested: \$64,000 Length of Project: Three Years

On his own and at his own expense Dr. Adair has developed a percutaneous approach to vas occlusion by bipolar electrocoagulation. He uses standard electrical generating equipment, and a bipolar needle probe that is used in neurosurgery. He has had experience with the technique since 1976. Basically, the procedure is simple and done under local anesthesia. He reports that patients exhibit azoospermia within four to six weeks following the burn. In his latest series of twelve patients done in September, 1979, all patients became azoospermic within this time interval, and he is continuing to follow them for the possibilities of spontaneous recanalization. Some members of the SAC saw a videotape of the procedure at the recent Mexico Workshop. Certainly, if the results are as good as the PI suggests, this procedure would supplant standard vasectomy.

The SAC had suggestions in terms of qualifying Free's involvement; limiting number of centers - 2 U.S. and 2 LDC's. Dr. De Castro (Brasil) was recommended for participation.

The SAC voted unanimously to approve this multi-center clinical trial.

B. FORMAL PROPOSAL REVIEW (cont'd)

2. Sidney Shulman, Ph.D., New York Medical College

"Isolation of Effective Sperm Antigen for Use in Contraceptive Immunization" - (Supported Pilot Study PARFR-P15)

Funding Requested: \$49,725 Length of Project: One Year

PARFR's Staff requested external review of this proposal from Dr. Erwin Goldberg. The investigator proposes a study which essentially has already been done in certain other laboratories. The objective of this work is to isolate cell membranes from human spermatozoa, dissociate and fractionate these membranes, and isolate "antigenic" constituents. A major part of this study is to test the best method of disruption of spermatozoa. Recently, Tumboh-Oeri and Koide (The Population Council, Rockefeller University) isolated plasma membranes (86-92% pure) from human spermatozoa, solubilized these membranes with Triton X-100 and fractionated the solution through a Biogel column. They found 3 of 6 column fractions to possess antigenic activity and are in the process of characterizing these fractions.

In addition, SAC felt that the contraceptive aspects were too far into the future for further PARFR support. SAC voted unanimously to not approve this proposal. When Dr. Shulman was notified of such, he proceeded to write the PARFR Staff, as well as each SAC Member. PARFR has responded to his letter. His Technical Report is overdue.

3. John C. Slocumb, M.D., University of New Mexico

"Identification and Evaluation of Herbs Used by Native Healers to Affect Fertility" - (Supported Pilot Study PARFR-P19)

Funding Requested: \$53,686.60 Length of Project: One Year

Drs. Chatterton and Scrimshaw reported on their 1/17/80 site visit. The PI is proposing a series of separate studies: 1) A detailed clinical study among women taking herbs especially cotton root and/or pennyroyal. 2) Chemical extraction studies on lithospermum. 3) Gossypol assays on herbs taken by the women. The PI and his assistants have been most fortunate in developing working relationships with rural health clinics and herbalists, although the results of the previous pilot survey regarding the possible useful effects of these herbs in producing menstruation is questionable.

SAC approved the project but suggested the Staff assist Dr. Slocumb in another rewrite of the protocol that would eliminate the studies on Lithospermum.

B. FORMAL PROPOSAL REVIEW (cont'd)

4. Richard E. Blackwell, Ph.D., M.D., University of Alabama

"Microencapsulation of a Luteinizing Hormone Releasing Factor (LRF) Analogue and Its Evaluation as a Long-acting Injectable Contraceptive Agent"

Funding Requested: \$59,835 Length of Project: One Year

The PI proposes to microencapsulate an LHRH analog which is agonistic at a potency level of more than 144 times the native peptide. The technical aspects of doing this microencapsulation will be handled by Southern Research Institute in Alabama.

SAC did not approve this project in that they felt the project is premature, with respect to the possible contraceptive potential of the LRF analogues.

5. Gary D. Friedman, M.D., Kaiser Foundation Research Institute

"Surveillance of the Health Effects of Vasectomy"

Funding Requested: \$100,695 Length of Project: Two Years

This is an unsolicited proposal for an epidemiological study of a retrospective cohort study to examine the possible risks regarding hospitalized illnesses among vasectomized men. The PI proposes to identify about 6,200 men who have indicated at an annual health check-up during the period from July, 1977 through December, 1980 that they have previously had a vasectomy. A control group will be selected on the basis of age and race in a two to one ratio. The NIH has funded a classic case control study in the Boston area, and this study was previously proposed to PARFR. Additionally, NIH is funding a large epidemiologic study in Los Angeles and Rochester, Minnesota which should provide relative risk measurements of vasectomy regarding later health hazards. Finally, another study has been funded by NIH in Milwaukee, in which a large group of men have had coronary angiograms performed. These men will have a medical history search to determine who among them have had vasectomy.

SAC voted not to approve this project due to all the NIH interest in the possible risks of vasectomy.

C. INFORMAL PROPOSAL REVIEW

1. Arpad I. Csapo, M.D., Washington University, St. Louis, Missouri

"The Mechanism of Prostaglandin Action in the Guinea Pig"

Funding Requested: \$60,000

Length of Project: One Year

The PI proposes to study in great depth the reproductive endocrinology of the guinea pig in order to better utilize the guinea pig as a model for the future screening of compounds intended for the effects of luteolysis or pregnancy termination by some other mechanism. Once these basic research questions are answered (may require two to three years), the PI proposes to modify the regulatory balance at different stages of gestation either surgically or pharmacologically.

SAC approved solicitation of Dr. Csapo's formal proposal for the next Meeting.

D. TECHNICAL REPORTS

PARFR-79N -- C. Irving Meeker, M.D., Maine Medical Center
"A Method for Reversible Sterilization in the Female"

PARFR 85N -- Milos Chvapil, M.D., Ph.D., The University of Arizona
"Collagen Sponge Contraceptive -- Testing of Efficacy in Human Volunteers"

PARFR-86N -- Robert S. Neuwirth, M.D., The St. Luke's Institute for Health Sciences
"Phase I Clinical Trial of Fallopian Tube Closure Using Methylcyanoacrylate (MCA) Tissue Adhesive Delivered Through the Single-Application Fertility Regulation (FEMCEPT) Device"

PARFR-200C -- Ralph M. Richart, M.D., Columbia University
"Data Collection and Analysis for MCA/FEMCEPT Clinical Trials"

Dr. Ralph Richart reported on MCA/FEMCEPT clinical investigators meeting on 2/12/80 in Mexico and that the tubal closure rate is currently 80.5%.

PARFR-90Np -- Joseph E. Davis, M.D., Planned Parenthood Federation of America
"New Method for Obstructing the Vas Deferens by Direct Injection of Chemical Agents: A Non-Operative Technique of Male Sterilization"

Dr. Connell reported on 11/28/79 site visit.

D. TECHNICAL REPORTS (cont'd)

PARFR-91N -- Donald L. Wise, Ph.D., Dynatech R/D Company
"Preparation and Evaluation of Biodegradable Cylindrical Implants
for Fertility Control"

Drs. Connell and Zatuschni reported on Dr. Wise's 1/10/80 visit to PARFR. They will submit an extension request for consideration at the next SAC Meeting.

PARFR-92N -- Deobrah J. Anderson, Ph.D., Oregon Regional Primate Research Center
"Contraception by Induction of Mild Uterine Inflammation"
(FINAL) Publication

PARFR-98M -- Ramon Aznar, M.D., Centro de Investigacion Sobre Fertilidad y Esterilidad (CIFE), Mexico City
"Norethisterone Microcapsule Injectable Contraceptive Study"

PARFR-101N -- Joseph W. Goldzieher, M.D., Southwest Foundation for Research and Education
"Metabolism and Pharmacokinetics of Ethynyl Estrogens"
(FINAL) Publication

PARFR-105N -- Harry W. Rudel, M.D., Centro de Investigacion Sobre Fertilidad y Esterilidad (CIFE), Mexico City
"A Study of a Parenterally Administered Progesterone-Cholesterol Formulation for Use as A Post-Partum Injectable Contraceptive"

PARFR-111N -- Carlton A. Eddy, Ph.D., The University of Texas Health Science Center at San Antonio
"An Evaluation of the Efficacy of Fimbrial Enclosure with Silastic Devices as a Reversible Female Sterilization Technique"

PARFR-114N -- Samuel S.C. Yen, M.D., University of California, San Diego
"The Induction of Luteolysis and Ovulation Inhibition by LRF-Agonist"

PARFR-201B -- Hugo Maia, Jr., M.D., Federal University of Bahia
"Effect of LH-RH Agonist on Ovulation and Corpus Luteum Function in Women"

PARFR-202 -- M. W. Heine, M.D., Texas Tech University School of Medicine
"Collagen Sponge Contraceptive -- Testing of Efficacy in Human Volunteers"

PARFR-205(95N) -- Lourens J.D. Zaneveld, D.V.M., Ph.D., University of Illinois at the Medical Center
"Development and Evaluation of a Reversible Vas Deferens Blocking Device"

D. TECHNICAL REPORTS (cont'd)

PARFR-206SRI -- Danny H. Lewis, Ph.D., Southern Research Institute
"A Fibrous Polymer for the Delivery of Contraceptive Steroids
to the Female Reproductive Tract"

PARFR-P13 -- Ivo Brosens, M.D., Ph.D. and Willem Boeckx, M.D.,
Catholic University of Leuven, Belgium
"An Evaluation of the Efficacy of Candidate Fimbrial Prosthesis
in Female Rabbits and the Evaluation of Fimbrial Devices as a
Reversible Technique of Female Sterilization"

PARFR-P18 -- Marion M. Bradford, Ph.D., University of Georgia
"Evaluation of Acrosin-Acrolysin Inhibitors as Male Contraceptive Agents"
(FINAL)

PARFR-P22 -- Lindley A. Cates, Ph.D., University of Houston
"A Preliminary Investigation of Fertility Regulation by South
American Tribes"

PARFR-P50 -- Milos Chvapil, M.D., Ph.D., The University of Arizona
"Effect of Spermicidal Detergent, Nonoxynol-9, on Liver Function"
(Publication)

PARFR-P51 -- Harrieth M. Hasson, M.D.
"Graphic Assessment of Uterine Shape"

III. ADMINISTRATIVE

A. Pending from 9/5/79 SAC Meeting:

1. Howard J. Tatum, M.D., Ph.D., The Population Council
"Use Effectiveness of the Nova-T Postpartum and the TCu 380Ag
When Inserted During the Immediate Post-Placental Period of
the Puerperium"
 - a. NU Human Subjects Board approved consent form on 12/14/79.
 - b. Awaiting budget request from the Population Council.
 - c. Protocol changed to 4 LDC centers, 250 patients each (Sweden
center deleted) - met with 3 clinicians, Drs. Alvarez-Sanchez
(Dominican Republic), Apelo (Philippines) and Tawat (Thailand)
in Mexico on 2/12/80 to negotiate budgets. Dr. Faundes (Brazil)
unable to attend.
 - d. All centers will be subcontracted to individually.

B. Pending from 12/3/79 SAC Meeting:

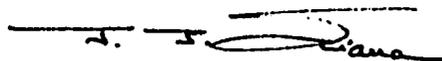
1. No subcontracts were written from proposals reviewed at this meeting.
2. Drs. Chatterton and Scrimshaw site visit generated a revision of the Slocumb proposal to narrow the focus to the human fertility trials. A companion for the laboratory studies will be submitted by Dr. Slocumb for the 6/22/80 SAC Agenda.
3. Dr. Matthew Freund (S.I.U.) will submit his revised proposal for consideration at the 6/22/80 SAC Meeting.

IV. MISCELLANEOUS

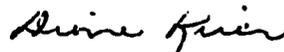
1. PARFR's 1981 Workshop was discussed in terms of topic and location.

There being no further business, the Meeting adjourned at 4:00 P.M.

Respectfully submitted,



John J. Sciarra, M.D., Ph.D.
Program Director, PARFR
Chairman, Scientific Advisory Committee



Diane H. Krier, M.B.A.
Director of Administration, PARFR

PARFR SCIENTIFIC ADVISORY COMMITTEE

MEETING XXXIII

NEW YORK STATLER HOTEL
New York, New York
June 22, 1980

MINUTES

VOTING SAC MEMBERS PRESENT

John J. Sciarra, M.D., Ph.D.
Nancy J. Alexander, Ph.D.
Robert T. Chatterton, Ph.D.
Joseph E. Davis, M.D.
Kamran S. Moghissi, M.D.
Carl J. Pauerstein, M.D.
Ralph M. Richart, M.D.
Susan C.M. Scrimshaw, Ph.D.
Aquiles J. Sobrero, M.D.

VOTING SAC MEMBERS ABSENT

Edward C. Mather, D.V.M., Ph.D.
Judith L. Vaitukaitis, M.D.
A. Albert Yuzpe, M.D.

PARFR STAFF PRESENT

Elizabeth B. Connell, M.D.
Alfredo J. Goldsmith, M.D., M.P.H.
Diane H. Krier, M.B.A.
Gerald I. Zatuchni, M.D., M.Sc.

USAID MEMBERS PRESENT

James D. Shelton, M.D., M.P.H.

The thirty-third meeting of PARFR's Scientific Advisory Committee convened on Sunday, June 22, 1980 at 8:30 A.M. at the New York Statler Hotel. Dr. John J. Sciarra presided as Chairman. Minutes of the March 10, 1980 meeting were approved with no voiced corrections.

I. ANNOUNCEMENTS

- A. Dr. Aquiles Sobrero was introduced as a SAC member. Dr. Sobrero had served on the PARFR staff as Research Development Coordinator since 1976.
- B. Dr. Sciarra announced that Dr. Elizabeth Connell will be leaving the PARFR staff on August 31, 1980.
- C. The scheduled meeting dates for PARFR SAC are:
 - November 16, 1980 at the Arlington Hyatt House near Washington, D.C.
 - March 8, 1981 at Chicago's O'Hare Hilton
 - November, 1981 to be scheduled
- D. PARFR's series entitled: "Research Frontiers in Fertility Regulation" will have issues distributed to our mailing list of 6,000, including SAC members. The premiere issue entitled Long-Acting Steroidal Contraceptive Systems is authored by Lee R. Beck, Ph.D., Donald R. Cowsar, Ph.D. and Valerie Z. Pope, M.S.

I. ANNOUNCEMENTS (continued)

- E. Dr. Zatuchni reported on PARFR's March 11, 1980 Workshop on Gossypol. He mentioned that a summary of this workshop will be the fourth issue of PARFR's Research Frontiers in Fertility Regulation. This workshop was by invitation only and included 38 participants representing 6 countries.
- F. Dr. Goldsmith reported that the Portugese Proceedings of the partially, PARFR-supported Workshop entitled: "Temas De Contracepcao," (editors: C. A. Salvatore, W. D. P. Carvalho, M. P. P. Castro, A. Goldsmith) were mailed by Dr. de Castro (Brasil).

II. NEW BUSINESS

A. EXTENSION PROPOSAL REVIEW

- 1. PARFR-90Np -- Joseph E. Davis, M.D., Planned Parenthood Federation of America
"New Method for Obstructing the Vas Deferens by Direct Injection of Chemical Agents: A Non-Operative Technique of Male Sterilization"

FUNDING REQUESTED: \$54,012

LENGTH OF PROJECT: One Year

The objective of this study is to determine the effectiveness and safety of a non-surgical technique for achieving male sterilization by injecting a sclerosing solution of 4% formaldehyde and alcohol percutaneously into the vas deferens. Dr. Connell reported that 27 volunteers had been treated by this technique; 13 became azoospermic. Three patients had a significant increase in serum count but failed to return for follow-up. Seven of the failed cases underwent standard vasectomy. One of the other failed cases was reinjected, but was not returned for follow-up. In a second group of 25 volunteers, 17 became azoospermic, 2 requiring reinjection. Four failures have undergone standard vasectomy and 3 are still pending reinjection. Three men had shown significantly decreased sperm counts but have not returned for adequate follow-up. One procedure was technically unsuccessful due to retractal testis. No patient who has become azoospermic has had return of sperm to the ejaculate. In several cases, sperm counts went almost to zero but then increased probably due to other only partial occlusion of the lumen and temporary edema. A number of improvements of the Frisch-Davis vas clamp injector had been made during the course of these studies. The initial funding for Dr. Davis on this technique was June 1, 1977. The committee voted to approve the continuation of Dr. Davis' research. Twenty-five additional volunteers will be recruited for the next phase of the study. These patients will receive an injection at two sites of each vas in an attempt to increase the efficacy of the procedure. Depending upon the results of these 25 patients, IFRP would be willing to support larger-scale clinical studies in several developing countries.

A. EXTENSION PROPOSAL REVIEW (continued)

2. PARFR-91N -- Donald L. Wise, Ph.D., Dynatech R/D Company
"Preparation and Evaluation of Biodegradable Cylindrical Implants
for Fertility Control"

FUNDING REQUESTED: \$132,208

LENGTH OF PROJECT: Two Years

The objective of this proposal is to demonstrate in baboons that a small biodegradable cylindrical implant releasing d-norgestrel at approximately zero order for a period of at least twelve months is feasible. This proposal had a second component that wished to investigate two other dosage forms - an injectable levonorgestrel - polymer preparation, and an implantable norethisterone polymer preparation. These latter components were not approved. SAC did approve that the baboon studies be funded in order to develop the system most likely to be acceptable by FDA for Phase I clinical studies. PARFR will suggest that Dynatech apply for an IND for a Phase I study of the twelve month system.

3. "Research on Instillation Techniques for Pregnancy Termination in Korea"

PARFR-97N -- Theodore M. King, M.D., Ph.D., The Johns Hopkins University

FUNDING REQUESTED: \$33,956

LENGTH OF PROJECT: One Year

PARFR-97K -- Hyun Mo Kwak, M.D., Yonsei University College of Medicine,
Seoul Korea

FUNDING REQUESTED: \$43,290

LENGTH OF PROJECT: One Year

Dr. Connell reported on her site visit to Baltimore on May 12-13, 1980. The original proposal called for 600 cases over a two-year period to compare the results - safety, complications and effectiveness of four different approaches to mid-trimester abortion using combinations of prostaglandins, urea, oxytocin and laminaria. The study was initiated in four medical institutions in Seoul, Korea - Yonsei University, Korea University, Ewha Women's University and Kyung Hee University. The Department of Obstetrics and Gynecology of The Johns Hopkins Hospital is responsible for the evaluation of the results of this study. At the time of this proposal a total of 293 cases had been assessed in the first year. Preliminary results indicated that the four procedures were relatively safe; a high incidence of incomplete procedures was noted in each of the four groups; and apparently small differences among the four treatment modalities. SAC voted not to approve continuation of this project in that additional cases enrolled probably would provide the same results.

A. EXTENSION PROPOSAL REVIEW (continued)

4. PARFR-107N -- Nancy J. Alexander, Ph.D., Medical Research Foundation of Oregon, Portland, Oregon
"Is Sperm Antigen A Causative Agent for Atherosclerosis After Vasectomy"

FUNDING REQUESTED: \$17,789

LENGTH OF PROJECT: 6 Months

Dr. Alexander reported that the objective of her project was to determine if there is a direct correlation between vasectomy and atherosclerosis and glomerulonephritis. Sperm antigens had been identified within the renal glomeruli and arterial walls of rabbits. Now that the techniques have been perfected, she requests an additional six months to complete the studies of vasectomized rabbits and vasectomized monkeys both with and without an atherogenic diet. SAC voted to approve continuation of the project and to review the final technical report at the March, 1981 SAC Meeting.

5. PARFR-114N -- Samuel S.C. Yen, M.D., University of California, San Diego
"The Induction of Luteolysis and Ovulation Inhibition by LRF-Agonist"

FUNDING REQUESTED: \$65,959

LENGTH OF PROJECT: One Year

Dr. Connell reported that Dr. Yen wishes to continue the second year of this project with the objective being to determine, in female volunteers, the efficacy of super analogues of LRF agonists to cause a luteolytic effect on ovulation inhibition. Studies to date have shown that LRF-Ag administration to normal women will consistently shorten the luteal phase. However, the presence of hCG at relatively low circulating levels, either administered or present as the results of an early pregnancy, will overcome the luteolytic action of the LRF agonist. The possibility remains that the use of higher doses of the agonist may overcome the luteotropic effect of hCG. SAC voted to approve the clinical studies involving the use of the LRF agonist and antagonist and did not approve the proposed non-clinical studies.

B. FORMAL PROPOSAL REVIEW

- i. Joseph W. Goldzieher, M.D. and V. Daniel Castracane, Southwest Foundation for Research and Education, San Antonio, Texas
"Antigestational Effects of LHRH Analogues"

FUNDING REQUESTED: \$64,251

LENGTH OF PROJECT: One Year

Dr. Zatuchni reported that the investigators proposed to study 3 LRF analogues - 1) agonist, obtained from Salk Institute; 2) Syntex agonist; and 3) Wyeth agonist. It is proposed that the compounds will be administered to pregnant baboons on the 20th day post-conception, initially utilizing a single injection at high dose. Should that particular group of baboons respond by aborting, then the dosage will be decreased in an attempt to find a practical dose response level. SAC voted not to approve the project as written. It was suggested that Dr. Goldzieher be requested to rework the protocol and look at one LH-RH agonist, at a much reduced level of funding.

B. FORMAL PROPOSAL REVIEW (continued)

2. Arpad I. Csapo, M.D., Washington University School of Medicine,
St. Louis, Missouri
"Luteolysis in the Guinea-Pig"

FUNDING REQUESTED: \$64,908

LENGTH OF PROJECT: One Year

This proposal purports to develop a combined LRH/prostaglandin regimen that theoretically would be more potent in intercepting pregnancies than the component parts, thereby allowing a reduction in the effective dosage of both drugs and a reduction of some side effects noted with prostaglandins. Dr. Csapo has been instrumental in the development of PGE₂-analog (sulproston) which has been reported in clinical studies to be 95% effective, although many patients suffered the well-known side effects of prostaglandins. Additionally, the investigator would like to determine, with finality, whether or not the guinea pig is the most suitable animal model for studying possible luteolysis and early abortion. Dr. Csapo proposes to study a super agonist and a super antagonist provided gratis from the Salk Institute. Two prostaglandin analogs will be provided by Pfizer and Searle. Dr. Chatterton reported that in contrast to studies in the rat, the guinea pig does not abort in response to depletion of progesterone, and therefore a luteolytic effect of LRH analogs will not have the complimentary effects sought. He, as well as other committee members, felt that the guinea pig was not a suitable animal model for this investigation. PARFR's staff was directed to rework the protocol with Dr. Csapo to determine the effects of two orally active PGE₁ analogs provided by Pfizer and Searle, at three different stages of pregnancy in the guinea pig.

3. Hugo Maia, Jr., M.D. and Ione C. Barbosa, Ph.D., Maternidade Climerio de Oliveira, Federal University of Bahia, Brazil
"Prostaglandin Levels in the Human Follicular Fluid in Relation to the Moment of Ovulation"

FUNDING REQUESTED: \$20,000

LENGTH OF PROJECT: One Year

Dr. Goldsmith reported that the investigators proposed to study the levels of PGF_{2a} and PGE₂ in human follicular fluid in relation to the time of LH surge and the moment of follicular rupture. It was suggested by Dr. Moghissi that Dr. Maia choose a prostaglandin inhibitor currently in use in the United States which seems to have fewer side effects than the one proposed. It was suggested that he study Motrin. SAC voted unanimously to support this project.

B. FORMAL PROPOSAL REVIEW (continued)

4. Gopi N. Gupta, Ph.D. and Brij B. Saxena, Ph.D., Cornell University
Medical College, New York
"Studies on Bioabsorbable Subdermal Contraceptive Pellet Implants"

FUNDING REQUESTED: \$268,499 LENGTH OF PROJECT: Two Years

Dr. Zatuchni reported that the investigators proposed to prepare fused norethindrone/cholesterol pellets for Phase I clinical studies on ten female volunteers. These studies are for the purposes of determining absorption and elimination of the contraceptive and measuring endocrine parameters during the menstrual cycles. The SAC stated that if the investigators were unable to rework their budget, within the PARFR range, that this study should not be approved.

5. M. R. Sairam, M.Sc., Ph.D., Clinical Research Institute of Montreal
"Characterization of Human Inhibin and Application to the Male"

FUNDING REQUESTED: \$128,310 LENGTH OF PROJECT: Three Years

The principal investigator proposes to isolate human inhibin, characterize it and hopefully synthesize it. This proposal was reviewed by the Committee and unanimously not approved in that they felt the scope of work was much too basic for PARFR support at this stage.

6. Milos Chvapil, M.D., Ph.D., University of Arizona, Arizona Health
Sciences Center
"Testing of a New Intracervical Device - PARFR-P21"

FUNDING REQUESTED: \$64,377 LENGTH OF PROJECT: One Year

Dr. Zatuchni reported that in the presently supported pilot study, PARFR-P21, Dr. Chvapil has investigated three different materials proposed for use as an intracervical device that would release steroids. Dr. Chvapil proposes to expand these preliminary studies by studying manufacturing reproducibility with regard to shape and thickness of the polymer and the inclusion of progestin. The Committee voted unanimously not to approve funding of this formal proposal.

7. Harrith M. Hasson, M.D.
"The Relationship Between Endometrial Dimensions and IUD
Performance - PARFR-P51"

FUNDING REQUESTED: \$45,749 LENGTH OF PROJECT: Two Years

Dr. Zatuchni reported that with PARFR pilot support (PARFR-P51) a prototype Wing Sound II was used on fresh hysterectomy specimens and has permitted Dr. Hasson to accurately measure total uterine length as well as two different uterine width measurements. From these raw data, the P.I. has constructed nomograms which permit the determination of the endometrial cavity shape, including the angles where the tubal ostia are located. An excellent correlation was noted between the data derived from the Wing Sound II measurement and those obtained by direct measurement. The P.I.

B. FORMAL PROPOSAL REVIEW (continued)

7. Harrith M. Hasson, M.D. (continued)

now seeks PARFR support to manufacture sufficient plastic Wing Sound II devices in order to carry out a multi-center study along the following lines: each center will be requested to insert, in a normal fashion, either the Lippes Loop or a Copper-T device. The patients will be closely followed for twelve months, and all event rates carefully noted. The P.I. will be furnished all these data. Statistically, about 525 insertions with each IUD are required. These raw data will then be analyzed in conjunction with the measurements of the patient's uterus obtained by the individual investigator using the Wing Sound II. This study will be the first to demonstrate whether the unwanted characteristics of an IUD expulsion, removal for bleeding and/or pain - are correlated with the IUD's dimensions in the particular uterus into which it has been inserted. If a strong correlation can be determined, then a mechanism will exist to tailor-fit an IUD to a particular patient, thereby resulting in superior continuation rates. The SAC voted unanimously to approve funding.

8. Richard L. Dunn, Ph.D., Southern Research Institute
"A Fibrous Polymer for the Delivery of Quinacrine to the Human Reproductive Tract - PARFR-P57"

FUNDING REQUESTED: \$66,000

LENGTH OF PROJECT: One Year

SRI has been successful in developing a first order release system for quinacrine from either biodegradable or nonbiodegradable polymers. In view of the promising results obtained during the pilot study, PARFR-P57, SRI proposed to continue the ongoing program of research to develop a fibrous polymer for the delivery of quinacrine into the female reproductive tract. Some of these candidate fibers have mechanical properties which would permit them to be used as intrauterine devices. However, the maximum loading of these fibers with quinacrine or its salt has not been determined. Dr. Len Laufe and Mr. Robert Wheeler (IFRP) will be consulted to work with SRI on the IUD vector. Once the IUD vector is available, PARFR will utilize the Cebus monkey colony of Dr. Antonini in Brazil (PARFR-215). The SAC voted to approve this project, as modified by Dr. Goldsmith's presentation of the proposed work plan.

B. FORMAL PROPOSAL REVIEW (continued)

9. KLI

"Investigation of a Technique for Voluntary Male Sterilization Utilizing a Unique Silicone Rubber Device for Extravasal Occlusion of the Vas Deferens - Phase II Trial"

FUNDING REQUESTED:

LENGTH OF PROJECT: One Year

Dr. Connell has worked with Mr. Arthur Hontz, Administrative Director, Research and Development, KLI, Inc., in developing this proposal which plans to verify the safety, efficacy and practicality of a unique silicone rubber device - Azusperm™ - a delivery system for occlusion of the vas deferens. The SAC voted not to approve support of this project.

10. Alan R. Buckpitt, Ph.D., University of California, Irvine
"Isolation, Characterization and Acute Toxicity of Spermicidal Agents Isolated from Ecaballium Eleterium, Linn"

FUNDING REQUESTED: \$63,719

LENGTH OF PROJECT: One Year

Dr. Zatuchni reported that Dr. Nasser, while working in Lebanon, performed some studies in rats, rabbits and man utilizing a crude extract of a plant, Ecaballium Eleterium, Linn, commonly known as the "squirting cucumber." As an orally administered agent, in extremely small doses, semen is rapidly converted - within one hour of oral ingestion - to a hyperacidic state, the pH at about 1.5 to 2.0, resulting in loss of motility of over 90% of the sperm, without the development of abnormal forms. SAC voted that the plant extract should be further investigated for efficacy and suggested that it be done with pilot funding.

C. INFORMAL PROPOSAL REVIEW

The following informal proposals were reviewed and SAC voted not to request formal proposals:

1. Gary L. Curtis, Ph.D., University of Nebraska Medical Center
"Sperm Immunization - Method, Route and Effect on Reproduction"
2. M. Yusoff Dawood, M.D., University of Illinois
"Development of a Self-Dissolvable Contraceptive Steroid Pellet and Its Effect in Monkeys"
3. Mohamed B. Abou-Donia, Ph.D., Duke University Medical Center
"Toxicology and Mechanisms of Antifertility Action of Gossypol"
4. C. Alex Shivers, University of Tennessee and and Vernon C. Stevens, Ph.D., Ohio State University
"Contraceptive Potential in Active Immunization of Female Baboons With Zona Pellucida Antigens"

D. TECHNICAL REPORTS

The following technical reports were reviewed by SAC:

PARFR-83N -- Lee R. Beck, Ph.D., University of Alabama in Birmingham
"Studies to Test an Injectable Delivery System for the Sustained Release of Norethisterone"
Clarification presented as Addendum to extension request proposal in 3/10/80 Agenda.

PARFR-86N(FINAL) -- Robert S. Neuwirth, M.D., The St. Luke's Institute for Health Sciences
"Phase I Clinical Trial of Fallopian Tube Closure Using Methylcyanoacrylate (MCA) Tissue Adhesive Delivered Through the Single-Application Fertility Regulation (FEMCEPT) Device"
Dr. Alfredo Goldsmith reported on his and Ms. Krier's 4/23/80 site visit.

PARFR-89N -- Harry P. Gregor, Ph.D., Columbia University
"Fallopian Tube Cauterization and Closure by Silver Acetate-Alginate Formulations"
Dr. Alfredo Goldsmith reported on 4/23/80 site visit and June, 1980 Brasil trip to Antonini who will be testing SA/A in Cebus monkeys.

PARFR-94N(FINAL) -- William Droegemueller, M.D., The University of Arizona
"Modern Modified Aldridge Procedure"

PARFR-105N -- Harry W. Rudel, M.D., Centro de Investigacion Sobre Fertilidad y Esterilidad (CIFE), Mexico City, Mexico
"A Study of a Parenterally Administered Progesterone-Cholesterol Formulation for Use as a Post-Partum Injectable Contraceptive"

PARFR-106N(FINAL) -- Gary S. Berger, M.D., University of North Carolina at Chapel Hill
"Effects of Tubal Sterilization on Menstruation: A Prospective Controlled Study"

PARFR-200P -- Ruben A. Apelo, M.D., JFMH Comprehensive Family Planning Center
"Phase I Clinical Trial of Fallopian Tube Closure Using Methylcyanoacrylate (MCA) Tissue Adhesive Delivered Through the Single-Application Fertility Regulation (FEMCEPT) Device"

PARFR-203NU & NMH -- Robert T. Chatterton, Ph.D., Northwestern University Medical School
"Fertility Regulation by Control of Progesterone Clearance"
Dr. Chatterton will have a PARFR site visit and reported that he plans to submit an extension request at the 11/16/80 SAC Meeting.

PARFR-203IIT -- Kurt Gutfreund, IIT Research Institute
"Microencapsulation of Progesterone Antibodies"

PARFR-204 -- Lourens J.D. Zaneveld, D.V.M., Ph.D., University of Illinois at the Medical Center
"Development of Sperm Enzyme Inhibitors as Vaginal Contraceptives"

D. TECHNICAL REPORTS (continued)

PARFR-207 -- Abdol H. Hosseinian, M.D., Cook County Hospital
"Hysteroscopic Sterilization by Using Uterotubal Blocking Devices"

PARFR-208 -- Lee R. Beck, Ph.D., University of Alabama in Birmingham
"Testing the Abortifacient Potential of CI and CII, 1 Beta-Oh
Androstane Derivatives, in the Baboon"

PARFR-211 -- Joseph E. Davis, M.D., New York, New York
"Study of Vas Occlusion in Animals Using Chemical Agents"
Dr. Joseph Davis reported that 4 out of 5 dogs injected with MCA
became azoospermic in 2 weeks.

PARFR-P12 -- David H. Frisch, Ph.D., Massachusetts Institute of Technology
"Development of Microporous Materials for Thin Intravasal Implants"

PARFR-P16 -- Ernest W. Page, M.D., Ross, California
"Investigation of a New Vaginal Barrier Contraceptive"

PARFR-P53 -- Ricardo H. Asch, M.D., The University of Texas Health
Science Center at San Antonio
"Antifertility Effects of Luteinizing Hormone Releasing Analogue
in the Female Rhesus Monkey"

PARFR P54(FINAL) -- Marcos Paulo P. de Castro, M.D., M.S., Universidade
de Sao Paulo, Brasil
"Percutaneous Injection of Monoethanolamine Oleate As a Vas
Deferens Sclerosing Agent"

PARFR-P55 -- Vladimir Petrow, Ph.D., D.Sc., FRIC, Duke University Medical
Center
"1-Hydroxyestra-1,3,5(10)-TRIEN-17B-OLS and Congeners as
Contragestative Agents"

III. ADMINISTRATIVE

A. Ms. Krier reported that the following project is still pending contract development (project approved at the 9/5/79 SAC Meeting):

Howard J. Tatum, M.D., Ph.D., The Population Council
"Use Effectiveness of the Nova-T Postpartum and the TCU 380Ag
When Inserted During the Immediate Post-Placental Period of the
Puerperium"

a. Awaiting protocol revisions from Dr. Tatum.

b. Once revised protocol is received and reviewed by PARFR, each
of the 4 centers involved must redo human subjects documentation
for review and must resubmit budget requests.

III. ADMINISTRATIVE (continued)

B. Ms. Krier reported on administrative matters involving previous SAC approvals from the March 10, 1980 SAC Meeting:

1. The following four subcontracts have been executed:

- a. PARFR-214(83N) -- Lee R. Beck, Ph.D., University of Alabama
"Studies to Test an Injectable Delivery System for
the Sustained Release of Norethisterone"
4/1/80 - 3/31/81 \$67,164
- b. PARFR 214(110N) -- Danny H. Lewis, Ph.D., Southern Research
Institute
"Optimization of an Injectable Microcapsule Formulation
for the 90-day Delivery of Norethisterone"
4/1/80 - 3/31/81 \$69,311
- c. PARFR-215 -- Renzo Antonini, M.D., Centro de Estudos de
Reproducao Humana de Botucatu, Sao Paulo, Brasil
"Chemical Sterilization in the Cebus Appella Monkeys"
5/15/80 - 5/14/81 \$16,775
- d. PARFR-216(P19) -- John C. Slocumb, M.D., University of New Mexico.
"Identification and Evaluation of Herbs Used by Native
Healers to Affect Fertility"
5/1/80 - 4/30/81 \$40,814

2. Pending from the March 10, 1980 SAC Meeting:

- a. PARFR-100N -- Leonard J. Lerner, Ph.D., Jefferson Medical College
"Investigation of New Compounds to Terminate Pregnancy"

A no cost extension to June 30, 1980 was requested by Dr. Lerner. Dr. Zatuschni reported on his June 3-7, 1980 trip to Italy to discuss negotiations with Lepetit and Carlo Erba Pharmaceutical companies.
- b. Edwin L. Adair, M.D., Medical Dynamics, and Michael J. Free, Ph.D.,
PIACT
"A Multi-site Evaluation in Developed and Developing
Countries of a Technique and Equipment for Transcutaneous
Closure of the Vas Deferens by Electrocoagulation"

Dr. Goldsmith reported on his site visit to Dr. De Castro in Brasil, as one of the potential clinical centers for this multi-center clinical trial. Protocol and data collection forms are under development.

III. ADMINISTRATIVE (continued)

3. Of the reviewed technical reports at the March 10, 1980 SAC Meeting, the following subcontract was brought to the attention of the SAC:

PARFR-P22 Lindley A. Cates, Ph.D., University of Houston, Texas,
"A Preliminary Investigation of Fertility Regulation by South
American Tribes"

Funding Level: \$7,688

Period: 6/15/79 - 6/14/80

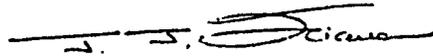
Dr. Cates never initiated the above study.

IV. MISCELLANEOUS

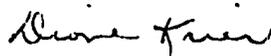
1. PARFR's 1981 Workshop was discussed in terms of dates, topic and location. The current dates considered are April 8-10, 1981; location in Chicago or San Antonio; and the topic is expected to be on LH-RH analogs as contraceptives.
2. Dr. Alfredo Goldsmith reported that PARFR may co-sponsor (with IFRP) a meeting in Brazil on IUDs.

There being no further business, the meeting adjourned at 3:30 P.M.

Respectfully submitted,



John J. Sciarra, M.D., Ph.D.
Program Director, PARFR
Chairman, Scientific Advisory Committee



Diane H. Krier, M.B.A.
Director of Administration, PARFR

Contraception... The old ways are the best ways! Fact? Fiction?



Read . . .

Vaginal Contraception: New Developments

. . . for significant, timely information about fertility control that answers many important questions about this age-old problem.

Edited by:

Gerald I. Zatzuchni, M.D., M.Sc.

Aquiles J. Sobrero, M.D.

J. Joseph Speidel, M.D., M.P.H.

John J. Sciarra, M.D., Ph.D.

94 Contributors.

Update on Contraception

Vaginal contraceptives, overshadowed for the past two decades by the wide acceptance of oral contraceptives, the intrauterine device, male and female sterilization and abortion, are experiencing a resurgence of interest as individuals search for a safe, reversible contraceptive method.

This renewal of interest has prompted a complete reassessment of vaginal contraception, the oldest method of fertility control known to man. To that end, physicians, family-planning administrators, researchers, and social scientists from 42 countries attended the International Workshop on New Developments in Vaginal Contraception. This volume contains information garnered from that 3-day workshop, and in it you will find details about:

- The basic physiology of reproduction
- The current status of vaginal contraception research and development

- Spermicidal formulation
- Current methods of evaluating vaginal contraceptives in the laboratory and in clinical trials
- New developments in barrier and spermicide methods
- International perspectives on vaginal contraception

Vaginal Contraceptive Devices Discussed

Evidence indicates that vaginal methods of contraception continue to offer considerable advantages with regard to safety and reversibility in fertility control, and that efforts should be made to increase their effectiveness. Among the devices discussed in this volume are:

- Barrier Methods
- Collagen Sponge
- Contraceptive Foaming Tablet
- Intravaginal Contraceptive Device (IVCD)
- Intravaginal Spermicidal Sponge
- Medicated Polyurethane Sponge
- Nonoxynol 9
- Patentex Oval
- Polyurethane Spermicide Contraceptive Sponge
- Vaginal Rings Releasing Spermicide
- Water-Soluble Condom and Vaginal Film Insert

Counseling Effectiveness Enhanced

You will find this informative volume invaluable when counseling persons who seek safe, effective methods of contraception. You will be able to provide them with details about the latest methods, and how they have been tested and evaluated throughout the world. **VAGINAL CONTRACEPTION: NEW DEVELOPMENTS** is available to you on a free 30-day examination basis. You will find it a valuable addition to your reference library. Complete and return the enclosed order form to obtain your copy.

About the Editors.

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389 Pages 58 Illustrations 14-29018 \$17.50

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION



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PROGRAM DESCRIPTION

The Program for Applied Research on Fertility Regulation (PARFR) at Northwestern University, in association with the United States Agency for International Development, provides scientific and technical assistance and funding support to foreign and United States institutions for applied research in the field of fertility regulation. Priority is given to proposals for the development of new or improved methods of fertility control appropriate for use in developing countries. Collaborative efforts between United States and foreign institutions are particularly encouraged.

Of major interest to PARFR are fertility control methods which:

- * Do not require physician services;
- * Do not require frequent administration;
- * Do not require high levels of motivation;
- * Can be self-administered;
- * Can be effective on a post-coital or hindsight basis;
- * Can minimize supply and distribution problems.

RESEARCH AREAS

Specific research areas which can be supported include animal or human investigations leading to the development of methods that:

- * Interfere with the maturation processes of sperm or ova either at the local or central level;
- * Interfere with the transport of gametes;
- * Interfere with the process of fertilization;
- * Interfere with the process of implantation;
- * Provide for long-acting sustained release of antifertility agents.

TYPES OF PROPOSALS

- * **Pilot Studies:** Research proposals for short-term studies are designed to produce preliminary results from which formal research proposals may develop. These projects may receive maximum support of \$7,500, with funds provided through a cost-reimbursable contract for a period not to exceed one year.
- * **Informal Proposals:** Brief research proposals are reviewed by PARFR Staff and its Scientific Advisory Committee. Those investigators whose proposals met PARFR objectives will then be requested to submit formal proposals for further review and consideration.

- * **Formal Proposals:** Proposals for extended research are reviewed by PARFR Staff and its Scientific Advisory Committee. Approved proposals may receive maximum support of \$66,000 annually, with funds provided through a cost-reimbursable contract. Subsequent support is dependent upon satisfactory progress and PARFR review. PARFR Guidelines for proposal preparation are obtained by writing the Director of Administration.

EXAMPLES OF PRIOR AND CURRENT PROJECTS

- * Biodegradable contraceptive drug release systems
- * Contraception intervention methods
- * Intrauterine delivery systems
- * Intravaginal chemical and barrier methods
- * Luteolytic contraceptive agents
- * Male pharmacological methods
- * Pharmacological, mechanical, and surgical methods of male and female sterilization
- * Reversible occlusive devices for male and female sterilization

SCIENTIFIC WORKSHOPS & PUBLICATIONS

PARFR supports 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 fertility regulation. The proceedings of each workshop are published by Harper and Row, Publishers, Inc. and are available from Lippincott/Harper; P.O. Box 7777-R0200, Philadelphia, Pennsylvania 19175 — Control of Male Fertility; Advances in Female Sterilization Techniques; Risks, Benefits, and Controversies in Fertility Control; Reversal of Sterilization; Pregnancy Termination: Procedures, Safety, and New Developments; Animal Models for Research on Contraception and Fertility; Vaginal Contraception: New Developments; and Research Frontiers in Fertility Regulation.

PARFR also publishes and distributes internationally a bi-monthly research review entitled "Research Frontiers in Fertility Regulation". Each issue deals separately with a specific area of research in the field of fertility regulation. Copies of these publications, if available, can be obtained at no charge by written request to PARFR's Director of Administration.