

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, 1981 - June 30, 1981

Submitted to: Research Division
 Office of Population
 Development Support Bureau
 Agency for International Development
 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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<u>Research Frontiers in Fertility Regulation</u>	
Volume 1, Number 3 February, 1981	
Volume 1, Number 4 May, 1981	

REPORT SUMMARY

Project Title and Contract Number:

Program for Applied Research on Fertility Regulation
AID/csd-3608
AID/DSPE-C-0035

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, 1981 - June 30, 1981

Total Expenditures Through December 30, 1980:

AID/csd-3608	\$4,308,527.43
AID/DSPE-C-0035	<u>1,292,337.66</u>
TOTAL:	\$5,600,865.09

Total Expenditures January 1, 1981 Through June 30, 1981:

AID/csd-3608	\$ 23,719.56
AID/DSPE-C-0035	<u>942,411.58</u>
TOTAL:	\$ 966,131.14

Commitments Through June 30, 1982:

AID/DSPE-C-0035	\$1,178,838.99
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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."

PROGRAM ACCOMPLISHMENTS

LDC Involvement

An International Seminar on IUDs was held June 8-9, 1981 in Salvador, Bahia, Brasil which was mutually developed by the Federal University of Bahia, IFRP and PARFR. PARFR supported the following speakers: Elizabeth B. Connell, M.D., Howard J. Tatum, M.D. and Gerald I. Zatuchni, M.D.

During this period (1/1/81 - 6/30/81), the following subcontracts in LDCs terminated due to a high failure rate:

1. PARFR-221Ba -- "A Multi-Site Evaluation in Developed and Developing Countries of a Technique and Equipment for Transcutaneous Closure of the Vas Deferens by Electrocoagulation"
Jose Freitas-Melo, M.D., Maternidade Climerio de Oliveira Salvador, Bahia, Brasil
2. PARFR-221Bb -- "A Multi-Site Evaluation in Developed and Developing Countries of a Technique and Equipment for Transcutaneous Closure of the Vas Deferens by Electrocoagulation"
Marcos Paulo P. de Castro, M.D., M.S., PROPATER Sao Paulo, Brasil

The following subcontracts and amendments to existing subcontracts in LDCs were completed during this reporting period (1/1/81 - 6/30/81):

1. Amendment #1 to PARFR-215 --
"Chemical Sterilization in the Cebus Appella Monkeys"
Renzo Antonini, M.D., Universidade Estadual Paulista, Botucatu, SP, Brasil
2. PARFR-225B -- "Clinical Trials of the Norethisterone Microcapsule Injectable Contraceptive System"
Elsimar Coutinho, M.D., Maternidade Climerio de Oliveira, Salvador, Bahia, Brasil
3. PARFR-225M -- "Preparation of Norethisterone Microcapsules"
Roberto Rivera, M.D., Instituto de Investigacion Cientifica, Durango, Durango, Mexico
4. PARFR-225Ma -- "Clinical Trials of the Norethisterone Microcapsule Injectable Contraceptive System"
Roberto Rivera, M.D., Instituto de Investigacion Cientifica, Durango, Durango, Mexico
5. PARFR-226C -- "Clinical Trial of Fallopian Tube Closure Using MCA"
Rene Guzman-Serani, M.D., Universidad Austral, Santiago, Chile

LDC Involvement (cont'd)

6. PARFR-227B -- "Prostaglandin Levels in the Human Follicular Fluid in Relation to the Moment of Ovulation"
Hugo Maia, Jr., M.D., Maternidade Climerio de Oliveira,
Salvador, Bahia, Brasil
7. PARFR-229B -- "Studies on Bioabsorbable Subdermal Contraceptive Norethindrone Pellet Implants"
Elismar Coutinho, M.D., Maternidade Climerio de Oliveira,
Salvador, Bahia, Brasil
8. PARFR-229M -- "A Clinical Evaluation of the Bioabsorbable Subdermal Contraceptive Norethindrone Pellet Implant"
Roberto Rivera, M.D., Instituto de Investigacion Cientifica,
Durango, Durango, Mexico
9. PARFR-238C -- "Radio-Opaque MCA - Cineflouorography Study"
Rene Guzman-Serani, M.D., Universidad Austral, Santiago, Chile

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. 2/9-13/81 - Dr. Goldsmith, Durango, Durango, Mexico (PARFR-225M)
 - b. 3/25-28/81 - Dr. Sobrero, San Antonio, Texas [PARFR-213T and PARFR-217(111N)]
 - c. 5/6/81 - Dr. Goldsmith and Mrs. Krier-Morrow, New York, New York (PARFR-200C)
 - d. 5/18-23/81 - Dr. Goldsmith, Albuquerque, New Mexico and Tucson, Arizona [PARFR-216(P19) and PARFR-212(85N)]
 - e. 6/5-10/81 - Dr. Zatuchni, Salvador, Bahia, Brasil (PARFR-221Ba, PARFR-226B and PARFR-229B)
3. PARFR staff participated in the following medical and scientific meetings:
 - a. 2/21-23/81 - Dr. Zatuchni, Asian congress on Gynecological Endoscopy, Bombay, India
 - b. 3/16-18/81 - Drs. Goldsmith and Zatuchni, American Fertility Society Meeting, Atlanta, Georgia
 - c. 3/22-26/81 - Dr. Goldsmith, World Congress of Human Reproduction, Berlin, West Germany
 - d. 6/5-7/81 - Dr. Zatuchni, IUD Seminar, Salvador, Bahia, Brasil
 - e. 6/18-19/81 - Drs. Goldsmith and Zatuchni, Non-Surgical Sterilization Meeting at IFRP, Raleigh-Durham, North Carolina.
4. PARFR held its 11th International Workshop on LHRH Peptides as Female and Male Contraceptives in Chicago, Illinois on May 13-15, 1981. The workshop was attended by 68 participants representing 11 countries.

Scientific Summary (cont'd)

5. PARFR staff initiated plans for the 12th International Workshop to be held June ~~2~~4, 1982 on Nonsurgical Female Tubal Occlusion in Chicago.
6. PARFR has established a research technical information report which reviews the latest R and D efforts on selected topics in a series of four to six issues per year. For each issue, a pertinent and knowledgeable investigator is selected to review published and unpublished studies in a specific area of fertility regulation. The selected investigator consultant is given adequate time and PARFR assistance to review the findings in the specified field. This material is submitted to PARFR for final review, editing, and subsequent publication. Each review will be about 10 to 15 pages, prepared in a loose-leaf manner. This series is entitled, "Research Frontiers in Fertility Regulation." Volume 1, No. 3 - Inhibition of Progestational Activity for Fertility Regulation, and Volume 1, No. 4 - Gossypol: A Possible Male Antifertility Agent, Report of a Workshop, were produced during this reporting period (see Appendix).

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. Termination of PARFR's old prime contract, AID/csd-3608. All sub-contracts under this contract are now closed. Details are summarized in the Financial Section of this report.
2. PARFR's contract current during this reporting period, AID/DSPE-C-0035, terminated at the end of the period, June 30, 1981 though prior research commitments will continue to be monitored and expended through June 30, 1982. PARFR's staff will continue to pursue the contract objectives under PARFR's new Cooperative Agreement, DPE-0546-A-00-1003-00.
3. One Scientific Committee Agenda was coordinated and mailed during this period. The SAC meeting was held on March 15, 1981 and the Agenda included: 2 extension proposals; 2 formal proposals; 5 informal proposals; 2 pilot study reviews; and 25 technical reports.
4. Negotiations and execution of the following subcontracts and amendments:
 - 21 new subcontracts [207M, 225B, 225M, 225Ma, 225UAB, 226C, 228, 229B, 229M, 232, 233, 235SRI, 235UAB, 236IIT, 237, 238C, 239, 240, 241, P62 and P63].
 - 16 additional funding amendments [200C, 200P, 203NMH, 203NU, 204, 205(95N), 209NMH, 209NU, 212(85N), 214(83N), 214(110N), 217(111N), 219, 225, 226B and 229] and 3 decreased funding amendments [213T, 216(P19), and 220].
 - 12 no-cost extension amendments [203IIT, 207, 211, 212(85N), 215, 218, 219, 225, 225M, 230 and P55, Amendment 2 and Amendment 3] and 2 change of funding period amendments [225M and 227B].
5. Six thousand copies of the third and fourth issues of PARFR's series entitled Research Frontiers in Fertility Regulation (see Appendix) were mailed.

Volume 1, No. 3 -- Inhibition of Progestational Activity for Fertility Regulation

Volume 1, No. 4 -- Gossypol: A Possible Male Antifertility Agent, Report of a Workshop

Administrative Summary (cont'd)

6. PARFR held its 11th International Workshop, LHRH Peptides as Female and Male Contraceptives, in Chicago, Illinois at the Ambassador East Hotel on May 13-15, 1981. There were 68 participants representing 11 countries. The manuscripts were copyedited and the final manuscript will be submitted to Harper and Row in July 1981. Publication of the book is anticipated during the next reporting period.
7. The book published from the proceedings of the 1980 Mexico Workshop, Research Frontiers in Fertility Regulation was distributed during this period to all workshop participants, AID Mission personnel and selected LDC investigators.
8. Revision and update of our mailing list of 6,000 contacts.
9. The program staff during the reporting period was:

Program Director	John J. Sciarra, M.D., Ph.D.
Director of Administration	Diane Krier-Morrow, M.B.A.
Director of Technical Assistance	Gerald I. Zatuchni, M.D., M.Sc.
Head, Research Project Development	Alfredo Goldsmith, M.D., M.P.H.
Project Controller	Ann Conner Nickle
Three Full-time Secretaries	Ruvenia Thomas
	Mary Rose Traylor
	Elizabeth Pereyra (started 4/8/81)

1/1/81 - 6/30/81

AID/DSPE-C-0035

Subcontract Negotiations

PROJECT #	TITLE/INVESTIGATORS/INSTITUTION	ACTION	PERIOD	FUNDING
200C	"Data Collection and Analysis for MCA/FEMCEPT Clinical Trials" Ralph M. Richart, M.D. and Robert S. Neuwirth, M.D. Columbia University New York, New York	Additional Funding (Amendment #1)	7/1/79- 6/30/81	\$ 5,117.67
200P	"Phase I Clinical Trial of Fallopian Tube Closure Using Methylcyanoacrylate (MCA) Tissue Adhesive Delivered Through the Single-Application Fertility Regulation (FEMCEPT) Device" Ruben A. Apelo, M.D. JFMH Comprehensive Family Planning Center Manila, Philippines	Additional Funding (Amendment #2)	10/1/79- 9/30/81	\$ 2,240.00
203IIT	"Microencapsulation of Progesterone Antibodies" Kurt Gutfreund IIT Research Institute Chicago, Illinois	No-cost Extension (Amendment #2)	11/1/79 6/30/81	- 0 -
203NMH	"Fertility Regulation by Control of Progesterone Clearance" Robert T. Chatterton, Ph.D. Northwestern Memorial Hospital Chicago, Illinois	Additional Funding and Time (Amendment #3)	9/1/79- 12/31/81	\$ 8,767.00

PROJECT #	TITLE/INVESTIGATORS/INSTITUTION	ACTION	PERIOD	FUNDING
203NU	"Fertility Regulation by Control of Progesterone Clearance" Robert T. Chatterton, Ph.D. Northwestern University Medical School Chicago, Illinois	Additional Funding and Time (Amendment #3)	9/1/79 12/31/81	\$56,893.00
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 Chicago, Illinois	Additional Funding and Time (Amendment #1)	10/1/79- 12/31/81	\$33,174.00
205(95N)	"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 Chicago, Illinois	Additional Funding and Time (Amendment #2)	10/1/79- 12/31/81	\$44,763.00
207	"Hysteroscopic Sterilization by Using Uterotubal Blocking Devices" Abdol H. Hosseinian, M.D. Hektoen Institute for Medical Research Chicago, Illinois	No-cost Extension (Amendment #2)	11/1/79- 12/31/81	- 0 -
207M	"Hysteroscopic Sterilization by Using Uterotubal Blocking Devices" Rodolfo Quinones, M.D. Mexico D.F., Mexico	New Subcontract (Subsequently cancelled due to delays in obtaining necessary equipment)	2/1/81- 1/31/82	\$21,175.00

PROJECT #	TITLE/INVESTIGATORS/INSTITUTION	ACTION	PERIOD	FUNDING
209NMH	"Evaluation of A-Nor Steroids as Potential Once-A-Month Contraceptive Agents" Raksha Mehta, Ph.D. Northwestern Memorial Hospital Chicago, Illinois	Additional Funding and Time (Amendment #1)	1/1/80- 12/31/81	\$27,011.00
209NU	"Evaluation of A-Nor Steroids as Potential Once-A-Month Contraceptive Agents" Raksha Mehta, Ph.D. Northwestern University Medical School Chicago, Illinois	Additional Funding and Time (Amendment #1)	1/1/80- 12/31/81	\$29,380.00
211	"Study of Vas Occlusion in Animals Using Chemical Agents" Joseph E. Davis, M.D. New York, New York	No-cost Extension (Amendment #2)	12/1/79- 9/30/81	- 0 -
212(85N)	"Development of Collagen Sponge Containing Spermicide and Post-Coital Testing of Collagen Sponge Diaphragm" Milos Chvapil, M.D., Ph.D. and William Droegemueller, M.D. The University of Arizona Health Sciences Center Tucson, Arizona	No-cost Extension (Amendment #2)	3/1/80- 8/31/81	- 0 -
		Additional Funding and Time (Amendment #3)	3/1/80- 12/14/81	\$23,026.00
213T	"The Study of the Intravaginal Insert (IVI) - Acceptability and Side Effects" Mohamed Mitwalli Ahmad, M.D., Ph.D. and Ricardo H. Asch, M.D. The University of Texas Health Science Center at San Antonio San Antonio, Texas	Decreased Funding (Amendment #2)	7/1/80- 6/30/81	(\$44,867.00)

PROJECT #	TITLE/INVESTIGATORS/INSTITUTION	ACTION	PERIOD	FUNDING
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	Additional Funding and Time (Amendment #1)	4/1/80- 9/30/81	\$29,773.00
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	Additional Funding and Time (Amendment #1)	4/1/80- 7/31/81	\$43,734.00
215	"Chemical Sterilization in the Cebus Appella Monkey" Renzo Antonini, M.D. Universidade Estadual Paulista Sao Paulo, Brasil	No-cost Extension (Amendment #1)	5/15/80- 12/31/81	- 0 -
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	Decreased Funding & Additional Time (Amendment #1)	5/1/80- 8/31/81	(\$ 4,080.00)
217(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	Additional Funding and Time (Amendment #2)	7/1/80- 5/31/82	\$19,698.00

PROJECT #	TITLE/INVESTIGATORS/INSTITUTION	ACTION	PERIOD	FUNDING
218	"Development and Mechanism of Activity Studies With the Pregnancy Termination Compounds DL-111-IT and DL-105-IT" Leonard J. Lerner, Ph.D. Jefferson Medical College of Thomas Jefferson University Philadelphia, Pennsylvania	No-cost Extension (Amendment #1)	7/1/80- 9/30/81	- 0 -
219	"A Fibrous Polymer for the Delivery of Quinacrine to the Human Reproductive Tract" Richard L. Dunn, Ph.D. Southern Research Institute Birmingham, Alabama	No-cost Extension (Amendment #1)	9/1/80- 6/30/81	- 0 -
		Additional Funding and Time (Amendment #2)	9/1/80- 9/30/81	\$14,999.00
220	"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. New York, New York	Decreased Funding & Additional Time (Amendment #1)	9/1/80- 12/31/81	(\$13,519.00)
225	"Preparation of Norethisterone Microcapsules" Danny H. Lewis, Ph.D. Southern Research Institute Birmingham, Alabama	No-cost Extension (Amendment #1)	11/1/80- 4/30/81	- 0 -
		Additional Funding and Time (Amendment #2)	11/1/80- 8/31/81	\$ 5,107.00
225B	"Clinical Trials of Norethisterone Microcapsule Injectable Contraceptive System" Elsimar Metzker Coutinho, M.D. and Jose Carlos de Souza, M.D. Maternidade Climerio de Oliveira Salvador, Bahia, Brasil	New Subcontract	4/1/81- 3/31/82	\$39,226.00

PROJECT #	TITLE/INVESTIGATORS/INSTITUTION	ACTION	PERIOD	FUNDING
225M	"Preparation of Norethisterone Microcapsules" Roberto Rivera, M.D. Instituto de Investigacion Cientifica Durango, Durango, Mexico	New Subcontract	12/1/80- 2/28/81	\$ 4,693.00
		Change of Funding Period (Amendment #1)	2/1/81- 5/31/81	- 0 -
		No-cost Extension	2/1/81- 12/31/81	- 0 -
225Ma	"Clinical Trials of the Norethisterone Microcapsule Injectable Contraceptive System" Roberto Rivera, M.D. Instituto de Investigacion Cientifica Durango, Durango, Mexico	New Subcontract	4/1/81- 3/31/82	\$41,063.00
225UAB	"Clinical Trials of the Norethisterone Injectable Contraceptive System" Charles E. Flowers, Jr., M.D. and Lee R. Beck, Ph.D. University of Alabama in Birmingham Birmingham, Alabama	New Subcontract	4/1/81- 3/31/82	\$12,825.00
226B	"Clinical Trial of Fallopian Tube Closure Using MCA" (Randomized Protocol) Elsimar Metzker Coutinho, M.D. and Manuel Bomfim de Souza Filho, M.D. Maternidade Climerio de Oliveira Salvador, Bahia, Brasil	Additional Funding and Time (Amendment #1)	9/15/80- 6/30/82	\$12,485.00

PROJECT #	TITLE/INVESTIGATORS/INSTITUTION	ACTION	PERIOD	FUNDING
226C	"Clinical Trial of Fallopian Tubal Closure Using MCA" (Randomized Protocol) Rene Guzman-Serani, M.D. Universidad Austral de Chile Valdivia, Chile	New Subcontract	4/1/81- 3/31/82	\$24,145.00
227B	"Prostaglandin Levels in the Human Follicular Fluid in Relation to the Moment of Ovulation" Hugo Maia, Jr., M.D. Maternidade Climerio de Oliveira Salvador, Bahia, Brasil	Change of Funding Period (Amendment #1)	3/1/81- 11/30/81	- 0 -
228	"Induction of Luteolysis and Ovulation Inhibition by LHF-Analogues" Samuel S.C. Yen, M.D. University of California, San Diego La Jolla, California	New Subcontract	4/1/81- 3/31/82	\$34,977.00
229	"A Clinical Evaluation of the Subdermal Contraceptive Norethindrone Pellet" Brij B. Saxena, Ph.D., D.Sc. and Gopi Gupta, Ph.D. The Cornell University Medical College New York, New York	Additional Funding (Amendment #1)	1/1/81- 12/31/81	\$23,668.00
229B	"Studies on Bioabsorbable Subdermal Contraceptive Norethindrone Pellet Implants" Elsimar Metzker Coutinho, M.D. Maternidade Climerio de Oliveira Salvador, Bahia, Brasil	New Subcontract	3/1/81- 2/28/82	\$32,461.00

PROJECT #	TITLE/INVESTIGATORS/INSTITUTION	ACTION	PERIOD	FUNDING
229M	"A Clinical Evaluation of the Bioabsorbable Subdermal Contraceptive Norethindrone Pellet Implant" Roberto Rivera, M.D. Instituto de Investigacion Cientifica Durango, Durango, Mexico	New Subcontract	3/1/81- 2/28/82	\$36,843.00
230	"Design and Manufacture of 1500 - 2000 Wing Sound II Devices" [Harrith M. Hasson, M.D.] H.F.D. Design Crystal Lake, Illinois	No-cost Extension (Amendment #1)	1/1/81- 12/15/81	- 0 -
232	"Immunologic Suppression of Fertility by Synthetic Antigenic Determinants of Lactate Dehydrogenase-C ⁴ " Erwin Goldberg, Ph.D. Northwestern University Evanston, Illinois	New Subcontract	3/1/81- 2/28/82	\$60,018.00
233	"Potentially Antifertility Activity of LH/HCG Peptide Fragments" Joseph W. Goldzieher, M.D. and V. Daniel Castracane, Ph.D. Southwest Foundation for Research and Education San Antonio, Texas	New Subcontract	4/15/81- 10/14/81	\$44,090.00
235SRI	"A Fibrous Polymer for the Delivery of Contraceptive Steroids to the Female Reproductive Tract - Continuation of PARFR-206SRI" Danny H. Lewis, Ph.D. Southern Research Institute Birmingham, Alabama	New Subcontract	4/1/81- 12/31/81	\$24,487.00

PROJECT #	TITLE/INVESTIGATORS/INSTITUTION	ACTION	PERIOD	FUNDING
235UAB	"A Fibrous Polymer for the Delivery of Contraceptive Steroids to the Female Reproductive Tract - Continuation of PARFR-206UAB" Lee R. Beck, Ph.D. University of Alabama in Birmingham Birmingham, Alabama	New Subcontract	4/1/81- 12/31/81	\$29,789.00
236IIT	"Retinoids and Male Contraception" Rajendra G. Mehta, Ph.D. IIT Research Institute Chicago, Illinois	New Subcontract	6/1/81- 5/31/82	\$61,908.00
237	"Detection of Pregnancy in Women Before Implantation" Nancy J. Alexander, Ph.D. Medical Research Foundation of Oregon Portland, Oregon	New Subcontract	6/1/81- 11/30/81	\$ 9,391.00
238C	"Radio-Opaque MCA-Cineflourography Study" Rene Guzman-Serani, M.D. Universidad Austral de Chile Valdivia, Chile	New Subcontract	6/15/81- 12/14/81	\$ 6,985.00
239	"Clinical Trial of the Collagen Sponge as a Contraceptive" Gary S. Berger, M.D. Center for the Advancement of Reproductive Health, Inc. Chapel Hill, North Carolina	New Subcontract	6/1/81- 5/31/82	\$31,890.00

PROJECT #	TITLE/INVESTIGATORS/INSTITUTION	ACTION	PERIOD	FUNDING
240	"Data Collection and Analysis of MCA/FEMCEPT Clinical Trials (Previously PARFR-200C)" Ralph M. Richart, M.D. and Robert S. Neuwirth, M.D. Presbyterian Hospital New York, New York	New Subcontract	7/1/81- 6/30/82	\$24,440.00
241	"Measurements of Electrical Characteristics of Equipment for Transcutaneous Electrocoagulation of the Vas Deferens" Michael J. Free, Ph.D. PIACT Seattle, Washington	New Subcontract	7/20/81- 8/31/82	\$ 8,243.00
P55	"1-Hydroxyestra-1,3,5(10)-TRIEN-17B-OLS and Congeners as Contraceptive Agents" Vladimir Petrow, Ph.D., D.Sc. Duke University Medical Center Durham, North Carolina	No-cost Extension (Amendment #2)	11/1/79- 4/30/81	- 0 -
		No-cost Extension (Amendment #3)	11/1/79- 6/30/81	- 0 -
P62	"Testing A New Polymer Sheet Typan", To Be Used As A Hood for Modified Aldrich Reversible Sterilization Method" Milos Chvapil, M.D., Ph.D. and William Droegemueller, M.D. The University of Arizona Health Sciences Center Tucson, Arizona	New Subcontract	3/1/81- 9/30/81	\$ 7,479.00
P63	"Prostaglandin Antagonists as Local Antifertility Agents" Antonio Scommegna, M.D. Michael Reese Hospital and Medical Center Chicago, Illinois	New Subcontract	6/15/81- 12/14/81	\$ 7,504.53

PERSONNEL

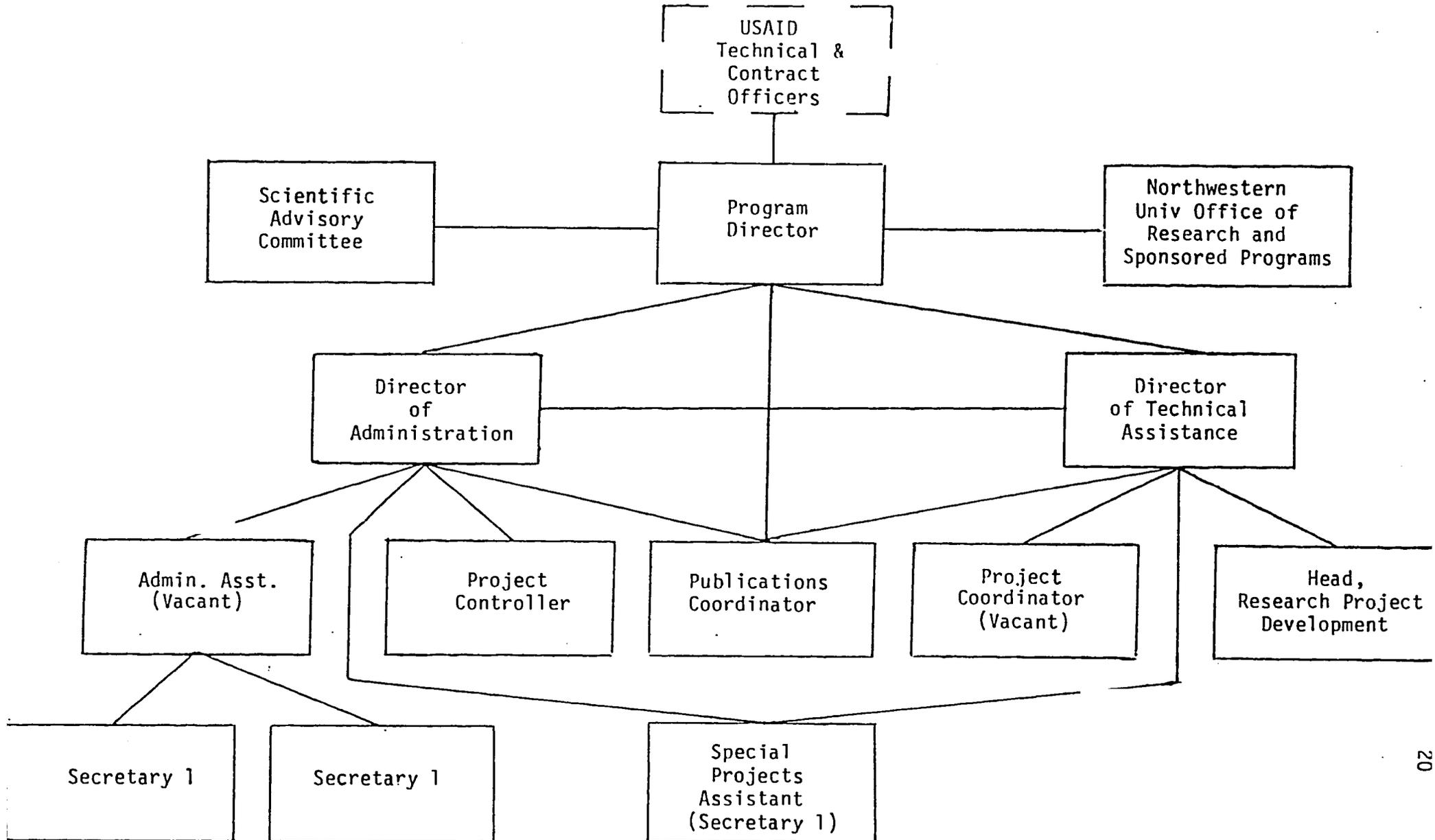
Effort and salary expenditures of PARFR personnel for this reporting period are listed below:

<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	\$ 835.16
Gerald I. Zatuchni, M.D., M.Sc. Director of Technical Assistance	4.8	\$19,999.88
Alfredo Goldsmith, M.D., M.P.H. Head, Research Project Development	5.8	24,183.52
Diane Krier Morrow Director of Administration	6.0	12,499.98
Ann Conner Nickle Project Controller	6.0	8,100.00
Kelley Osborn Publications Coordinator	2.0	5,250.00
Ruvenia Thomas Secretary I	6.0	7,305.00
Mary Rose Traylor Secretary I	5.3	5,734.92
Elizabeth Pereyra (Start 4/8/81) Secretary I	2.8	2,764.41
<u>Temporary Services</u> Temporary Secretaries	2.6	2,695.50
<u>Fringe Benefits</u>		\$13,495.45
<u>Indirect Costs</u>		35,495.52

Administrative Organization

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

PARFR Organization Chart



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	Northwestern University
Nancy J. Alexander, Ph.D.	Oregon Regional Primate Research Center
Robert T. Chatterton, Ph.D.	Northwestern University
Elizabeth B. Connell, M.D.	
Joseph E. Davis, M.D.	New York Medical College
Edward C. Mather, D.V.M., Ph.D.	Michigan State University
Kamran S. Moghissi, M.D.	Wayne State University
Carl J. Pauerstein, M.D.	University of Texas Health Science Center at San Antonio
Ralph M. Richart, M.D.	Columbia University
Susan C.M. Scrimshaw, Ph.D.	University of California at Los Angeles
Aquiles J. Sobrero, M.D.	Northwestern University
Judith L. Vaitukaitis, M.D.	Boston University
A. Albert Yuzpe, M.D.	University of Western Ontario, Canada

The Scientific Advisory Committee (SAC) held one meeting during this reporting period: March 15, 1981, in Atlanta, Georgia. Minutes of this meeting are included in the Appendix.

At this SAC meeting, the Committee reviewed 25 Technical Reports of which 3 were Final Reports.

Extension Proposals

Two extension proposals were reviewed by SAC, both of which were approved [PARFR-214(110N) and PARFR-214(83N)].

Informal Proposals

Five informal proposals were reviewed and SAC voted not to request any formal proposals.

Formal Proposals

Four formal proposals were reviewed by SAC with the resultant recommendation that the following two projects be funded:

"Investigation of a Potent Orally Active Luteolytic Prostaglandin that has Significantly Reduced Effects on Smooth Muscles"

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

"Detection of Pregnancy in Women Before Implantation"

Nancy J. Alexander, Ph.D., Medical Research Foundation of Oregon, Portland, Oregon

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 3/14-15/81	2 days	\$ 300.00
Robert T. Chatterton, Ph.D. Steroid Biochemistry	RFFR #3 12/80 SAC 3/14-15/81	9 days	1,350.00
Elizabeth B. Connell, M.D. Obstetrics and Gynecology	SAC 3/14-15/81	2 days	385.48
Joseph E. Davis, M.D. Urology	SAC 3/14-15/81	2 days	300.00
Harvey Dershin Statistician	Project Development 2/16-17/81	2 days	385.48
David A. Edelman, Ph.D. Biostatistician	Project Development between 4/4/81 and 5/24/81	3 1/2 days	570.50
Harrith M. Hasson, M.D. IUDs	Project Development between 1/3/81 and 2/25/81	14 1/2 days	2,794.73
Leonard E. Laufe, M.D. Obstetrics and Gynecology	Project Development between 3/20/81 and 3/30/81	1 day	173.00
Edward C. Mather, D.V.M., Ph.D. Animal Reproductive Physiology	SAC 3/14-15/81	2 days	300.00
Kenneth McKerns, Ph.D. Reproductive Biology	Project Development 1/13-14/81	2 days	320.00
Kamran S. Moghissi, M.D. Obstetrics and Gynecology Reproductive Endocrinology	SAC 3/14-15/81	2 days	300.00
Carl J. Pauerstein, M.D. Reproductive Biology	SAC 3/14-15/81	2 days	300.00
Ralph M. Richart, M.D. Obstetrics and Gynecology Pathology	RFFR #5 5/81 SAC 3/14-15/81	9 days	1,350.00

Consultants (cont'd)

Susan C.M. Scrimshaw, Ph.D. Medical Anthropology	SAC 3/14-15/81	2 days	300.00
Aquiles J. Sobrero, M.D. Infertility	SAC 3/14-15/81 Site Visit - 3/25-28/81	3 days	549.00
Robert G. Wheeler Engineer	Project Development 5/1/81	1 day	153.85
A. Albert Yuzpe, M.D. Obstetrics and Gyneecology	SAC 3/14-15/81	2 days	300.00
		TOTAL	<hr/> \$10,132.04

For Subcontracts Active During This Reporting Period
(January 1, 1981 to June 30, 1981)

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-86Sa

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

FUNDING PERIOD: 3/15/79 - 6/30/80 EXPENDED: \$ 9,911

PARFR-200G(86G)

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

FUNDING PERIOD: 9/1/79 - 8/31/80 EXPENDED: \$24,478 (200G)
9/1/78 - 8/31/79 EXPENDED: 22,097 (86G)
\$46,575 TOTAL

PARFR-200K(86K)

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

FUNDING PERIOD: 5/1/80 - 8/31/82 BUDGET: \$ 2,598 [200K(86K)]
5/1/79 - 4/30/80 BUDGET: \$16,080 (86K)

PARFR-200P

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

FUNDING PERIOD: 10/1/79 - 9/30/81 BUDGET: \$14,385

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.

"Clinical Trial of Fallopian Tubal Closure Using MCA"

PARFR-226B

Elsimar Metzker Coutinho, M.D., Maternidade Climerio de Oliveira, Bahia, Brasil

FUNDING PERIOD: 9/15/80 - 9/14/81 BUDGET: \$28,820

PARFR-226C

Rene Guzman-Serani, M.D., Universidad Austral de Chile, Valdivia, Chile

FUNDING PERIOD: 4/1/81 - 3/31/82 BUDGET: \$24,145

Objectives: The objective of this randomized study of a nonsurgical method of female sterilization is to determine if the tubal occlusion rate obtained by a single application of methylcyanoacrylate (MCA) delivered through the FEMCEPT device can be improved by either uterine lavage prior to application and/or using two consecutive monthly applications.

FEMALE STERILIZATION

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. and Robert S. Neuwirth, M.D.,
Columbia University, New York

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

BUDGET: \$35,832.67

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 are being revised and computer software is being developed. Computer hardware is on site.

PARFR-240

"Data Collection and Analysis of MCA/FEMCEPT Clinical Trials"

Ralph M. Richart, M.D. and Robert S. Neuwirth, M.D.,
Presbyterian Hospital, Obstetrical and Gynecological Service,
New York, New York

FUNDING PERIOD: 7/1/81 - 6/30/82

BUDGET: \$24,440

Objectives: To provide technical service in the form of monitoring data processing and statistical analysis of the PARFR-supported clinical trials with the MCA/FEMCEPT system of non-surgical female sterilization.

Results: As of June, 1981, 454 patients seeking sterilization were treated. The data indicate that the overall bilateral closure rate is approximately 71%. The closure rates from the more recent series, however, is still approximately 80%, and the bilateral closure rate from patients having a second application is approximately 75%. Certain factors strongly affect the closure rate - for example, if the balloon is visible at the cervix during the injection, the closure rate is only 57%. Although the number of cases is small (19 with hysterosalpingograms), the uterine lavage prior to MCA application appears to exert no significant effects since the closure rate bilaterally is approximately 79%. The stage of the cycle at which treatment was performed is also important. The bilateral closure rate was 85% when the FEMCEPT device was used at menstrual dates 0-6 (N=106), 68% at dates 7-10 (N=157), 61% at dates 11-15 (N=31), and 70% at dates 16+ (N=40). Only two pregnancies have been seen to date. One in Manila occurred in a patient who became pregnant before the first follow-up visit. This was presumably a condom failure. The second occurred in a patient who was

FEMALE STERILIZATION

TRANSCERVICAL (cont'd)

Results: (cont'd)

retreated and returned pregnant (presumably due to a condom failure nine months later but prior to her repeat hysterosalpingogram).

Again all numbers are small, but there is a clearcut trend suggesting that performing the hysterosalpingogram too early may diminish closure rates. It is possible that performing the HSG even later than four months post-treatment may be beneficial.

All the data derived from the tests of the FEMCEPT/MCA system are sent to the Obstetrical and Gynecological Division of Columbia-Presbyterian Medical Center where they are entered into the computer and the data analyzed periodically. There have been a number of problems with the program, most of which have been resolved, and tables can now be produced on a routine basis.

New data collection instruments were developed and all centers will start to use them in the second half of 1981.

PARFR 238C

"Radio-Opaque MCA - Cineflourography Study"

Rene Guzman-Serani, M.D., Universidad Austral de Chile, Valdivia, Chile

FUNDING PERIOD: 6/15/81 - 12/14/81 BUDGET: \$ 6,985

Objectives: Recently, an inhibitor of MCA polymerization which is also radio-opaque was synthesized, opening up the possibility of measuring the penetration of MCA into the Fallopian tubes shortly after a FEMCEPT application. In order to test whether the behavior of the MCA is different with the addition of this new inhibitor and to better understand the dynamics of the FEMCEPT application process, a limited number of patients will be studied using cine flouroscopy at the time of the FEMCEPT/MCA treatment.

Results: This project recently started and results will not be available until the next reporting period.

FEMALE STERILIZATIONC. TRANSCERVICAL (cont'd)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)
50,617 (St. Luke's)
<u>\$162,690</u> TOTAL EXPENDED

- 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.

FEMALE STERILIZATIONC. TRANSCERVICAL (cont'd)

PARFR-215 "Chemical Sterilization in Cebus Appella Monkeys"
 Renzo Antonini, M.D., Universidade Estadual Paulista,
 Botucatu, Brasil
 FUNDING PERIOD: 5/15/80 - 12/31/81 BUDGET: \$16,775

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

Results: Transcervical delivery of silver acetate alginate was completed. This substance is toxic when spillage into the peritoneal cavity occurs. Fabrication of the IUD-quinacrine vector (objective b.) is completed and Dr. Antonini is in process of testing. A technical report is due during the next reporting period.

PARFR-219(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 EXPENDED: \$ 7,401.43 (P57)
 9/1/80 - 9/30/81 BUDGET: \$47,999 (219)

Objectives: In view of the promising results obtained during the pilot study PARFR-P57, Southern Research Institute proposes to continue the ongoing program of research to develop a fibrous polymer for the delivery of quinacrine to 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. With high loadings of quinacrine, less fiber is required to deliver the drug. These loading values become important since relatively high doses of quinacrine appear to be required for tubal occlusion.

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) have developed an IUD vector. This IUD vector is in process of being tested in 10 cebus appella monkeys by Dr. Antonini in Brasil (see PARFR-215).

FEMALE STERILIZATIOND. REVERSIBLE (cont'd)PARFR-217(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: 7/1/80 - 5/31/82 BUDGET: \$56,252 [217(111N)]
6/1/79 - 6/30/80 EXPENDED: \$55,258 (111N)

Objectives: To determine the reversibility of sterilization by fimbrial enclosure with specially designed silastic fimbrial hoods in adult female Rhesus monkeys.

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.

PARFR-P62

"Testing a New Polymer Sheet Hypan", to be Used As a Hood for Modified Aldrich Reversible Sterilization Method"

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

FUNDING PERIOD: 3/1/81 - 9/30/81 BUDGET: \$ 7,479

Objectives: To prepare tubal hoods from a new polymer sheet Hypan™.

Results: Project recently started. The final technical report is due 10/15/81.

FEMALE STERILIZATIOND. 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 - 12/31/81	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.

During this reporting period, the further enrollment of patients in Chicago and the initiation of the Mexico study were postponed due to problems with equipment modification.

MALE STERILIZATIONB. OTHER (cont'd)PARFR-220(90Np) (90N)

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

Joseph E. Davis, M.D.

FUNDING PERIOD:	9/1/80 - 12/31/81	BUDGET:	\$13,721 (220)
	2/1/79 - 6/30/80	EXPENDED:	52,215 (90Np-PPFA)
	6/1/77 - 12/31/78	EXPENDED:	39,772 (90N-NYMC)

Objectives: To determine the effectiveness and safety of a non-surgical technique for achieving male sterilization by injecting a sclerosing solution of 4 per cent formaldehyde in alcohol percutaneously into two separate areas of 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.

These patients will be continued to be followed, however, no further clinical trials are planned.

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 - 12/31/81	BUDGET:	\$108,548 [205(95N)]
	7/1/77 - 9/30/79	EXPENDED:	113,348 (95N)
	9/1/76 - 8/31/77	EXPENDED:	5,985 (P6)

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.

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, hence studies in the Rhesus monkeys which have larger vasa have been initiated.

MALE STERILIZATION

B. OTHER (cont'd)

PARFR-222(107N)

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

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

FUNDING PERIOD: 7/1/80 - 12/31/80	EXPENDED: \$17,598 [222(107N)]
4/1/79 - 6/30/80	EXPENDED: 78,806 (107N)
	<u>\$96,404</u> TOTAL

Objectives: To further define the role, if any, of immune complexes in atherosclerosis and glomerulonephritis developing in vasectomized monkeys fed an atherogenic diet.

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.

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 - 9/30/81 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 silver acetate alginate. Up to .3 cc of the agent was directly injected into the vas lumen after vasotomy had been performed during scrotal exploration. The straight portion of the vas was utilized for each injection. Two of the animals became azoospermic within a week. Two became oligospermic. One animal died from a generalized unrelated infection. Histopathology is to be done on all animals, and is pending.

Five adult mongrel dogs have undergone vas occlusive attempts by the indirect percutaneous injection of methylcyanoacrylate (MCA). These procedures were tolerated satisfactorily. Post-operative semen analyses and subsequent histologic study are under way and planned.

Three adult mongrel dogs have undergone indirect percutaneous injection of silver acetate alginate. The procedures were performed uneventfully, and semen analyses and histopathology are underway.

MALE STERILIZATION

B. OTHER (cont'd)

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

PARFR-221Ba

Jose Freitas-Melo, M.D., Maternidade Climerio de Oliveira, Bahia, Brasil

FUNDING PERIOD: 9/15/80 - 9/14/81 EXPENDED: \$ 2,954

PARFR-221Bb

Marcos Paulo P. de Castro, M.D., M.S., PROPATER-Promacao da Paternidade Responsavel, Sao Paulo, Brasil

FUNDING PERIOD: 9/15/80 - 9/14/81 EXPENDED: \$10,018

PARFR-221C

Edwin L. Adair, M.D., Medical Dynamics, Inc., Englewood, Colorado

FUNDING PERIOD: 9/1/80 - 8/31/81 EXPENDED: \$ 4,400

Objectives: To determine the effectiveness and safety of a transcutaneous vas closure technique using a bipolar electrical source.

Results: This project was terminated due to equipment problems and failure to sterilize the men enrolled. Refer to PARFR-241 below where arrangements are made for testing the equipment and redesign of the needle.

PARFR-241

"Measurement of Electrical Characteristics of Equipment for Transcutaneous Electrocoagulation of the Vas Deferens"

Michael J. Free, Ph.D., PIACT, Seattle Washington

FUNDING PERIOD: 7/20/81 - 8/31/81 BUDGET: \$ 8,243.44

Objectives: The technique of transcutaneous closure of the vas deferens by electrocoagulation has been suggested as a method with possible technical and programmatic advantages in a developing world setting. However, existing prototypical equipment has not been thoroughly characterized with respect to its electrical characteristics under load. Before further biological or clinical investigation of this method is carried out, we propose to 1) describe existing equipment in precise electrical terms; 2) compare it to a known bipolar vas cautery system used for standard vasectomy by cutting and electrocoagulation; and 3) recommend trial power settings and burn times ranges based on existing systems.

Results: This project began and a report is being prepared for the next reporting period.

MALE STERILIZATION

B. OTHER (cont'd)

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 EXPENDED: \$13,361

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.

PARFR-230

"Design and Manufacture of 1,500 - 2,000 Wing Sound II Devices"

H.F.D. Design, Crystal Lake, Illinois

FUNDING PERIOD: 1/1/81 - 12/15/81 BUDGET: \$33,000

Objectives: Design and coordinate manufacture of 1,500 to 2,000 Wing Sound II Devices

Results: Upon execution of the subcontract, half payment was made. The design has been completed and approved. It is expected that the Wing Sound II's will be delivered during the next reporting period and clinical trials are planned in Chile, England and other countries. Protocol is being written and arrangements with IFRP for data analysis are completed.

SYSTEMIC CONTRACEPTION

B. INJECTABLES AND IMPLANTS

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

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

FUNDING PERIOD: 4/1/80 - 9/30/81 BUDGET: \$ 96,937 [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 - 7/31/81 BUDGET: \$113,045 [214(110N)]
4/1/79 - 3/31/80 EXPENDED: 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

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.

SYSTEMIC CONTRACEPTION

B. INJECTABLES AND IMPLANTS

Results: (cont'd)

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. An IND/FDA was granted and Phase I clinical studies in four centers are planned for late 1981.

PARFR-225

"Preparation of Norethisterone Microcapsules"

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

FUNDING PERIOD: 11/1/80 - 8/31/81

BUDGET: \$34,217

Objectives: Preparation of the 180 NET delivery system for Phase I clinical trials.

Results: Project completed. Awaiting quality control results to initiate Phase I clinical studies.

SYSTEMIC CONTRACEPTIONB. INJECTABLES AND IMPLANTSPARFR-225M

"Preparation of Norethisterone Microcapsules"

Roberto Rivera, M.D., Instituto de Investigacion Cientifica,
Durango, Mexico

FUNDING PERIOD: 2/1/81 - 12/31/81 BUDGET: \$ 4,693

Objectives: To provide suitable laboratory space and facilities for the
preparation of the Norethisterone Microcapsule Injectable
Contraceptive System by the Staff of Southern Research Institute.Results: Preparation of the microcapsules in Mexico City is completed;
quality control is underway.PARFR-225UAB"Clinical Trials of the Norethisterone Injectable Contraceptive
System"Charles E. Flowers, Jr., M.D. and Lee R. Beck, Ph.D.,
University of Alabama in Birmingham, Birmingham, Alabama

FUNDING PERIOD: 4/1/81 - 3/31/82 BUDGET: \$12,825

Objectives: To monitor the Phase I clinical trials of the 180-day NET
microcapsule system.Results: Study not initiated due to delay in initiation of Phase I
clinical trials in Mexico and Brasil.

SYSTEMIC CONTRACEPTIONB. INJECTABLES AND IMPLANTS

"Clinical Trials of the Norethisterone Microcapsule Injectable Contraceptive System"

PARFR-225B

Elsimar Metzker Coutinho, M.D., Maternidade Climerio de Oliveira, Salvador, Bahia, Brasil

FUNDING PERIOD: 4/1/81 - 3/31/82

BUDGET: \$39,226

PARFR-225Ma

Roberta Rivera, M.D., Instituto de Investigacion Cientifica, Durango, Mexico

FUNDING PERIOD: 4/1/81 - 3/31/82

BUDGET: \$41,063

Objectives:

Clinical Trials of a long-acting injectable contraception system which provides continuous release of norethisterone for a precise period of six months following a single intramuscular injection. The system consists of microcapsules made of the biodegradable polymer d,l-poly(lactide), in which micronized crystals of NET are homogeneously dispersed.

The NET system has been shown to be effective in the suppression of ovulation over a 180-day period, to have a virtually constant rate of release of NET into the system, to have no significant side effects, and to have minimal adverse impact on menstrual function other than amenorrhea during the period of contraceptive coverage. In a preliminary clinical trial microcapsule doses containing between 7.25 and 94.5 mg of NET were tested. On the basis of this study it was determined that larger doses are necessary to inhibit ovulation for the full six months. Patients in the Mexico study will be treated with 800 mg of microcapsules containing 200 mg of NET and patients in the Brasil study will be treated with 600 mg of microcapsules containing 150 mg of NET.

Results:

Clinical trials of 180-day NET microcapsules were postponed due to manufacturing delays and will be initiated in early fall, 1981.

SYSTEMIC CONTRACEPTIONB. INJECTABLES AND IMPLANTSPARFR-229

"A Clinical Evaluation of the Subdermal Contraceptive Norethisterone Pellet"

Brij B. Saxena, Ph.D., The Cornell University Medical College, New York, New York

FUNDING PERIOD: 1/1/81 - 12/31/81

BUDGET: \$77,813

Objectives: To prepare fused norethindrone pellets for Phase I clinical studies on 10 female volunteers. These studies are for the purposes of determining absorption and elimination of the contraceptive and measuring endocrine parameters during the menstrual cycles.

Results: Implantation of the subdermal NET pellets have been completed in 9 subjects. After insertion of two small NET pellets into each subject, the serum NET levels were found to be between 0.4 ng to 1.0 ng/ml so far observed in three subjects over an extended period of 47 to 50 days. The sustained levels were fairly constant over this period.

The preliminary results of the present study indicate that the sustained serum NET levels of 0.4 ng/ml to 1.0 ng/ml brought about suppression of P in two subjects, either as a result of direct action on ovary or through affecting pituitary LH and FSH. However, in the third subject, low and sustained serum NET levels distinctly affected LH and FSH but not the P.

PARFR-229B

"Studies on Bioabsorbable Subdermal Contraceptive Norethindrone Pellet Implants"

Elsimar Metzker Coutinho, M.D., Maternidade Climerio de Oliveira, Bahia, Brasil

FUNDING PERIOD: 3/1/81 - 2/28/82

BUDGET: \$32,461

PARFR-229M

"A Clinical Evaluation of the Bioabsorbable Subdermal Contraceptive Norethindrone Pellet Implant"

Roberto Rivera, M.D., Instituto de Investigacion Cientifica, Durango, Mexico

FUNDING PERIOD: 3/1/81 - 2/28/82

BUDGET: \$36,843

Objectives: To study fused norethindrone pellets for Phase I clinical studies on 10 female volunteers. These studies are for the purposes of determining absorption and elimination of the contraceptive and measuring endocrine parameters during the menstrual cycles.

Results: The Brasil center has enrolled two patients. The Mexico center has enrolled six patients. All centers have reported problems with breakage of the implants. Plans are in process to initiate centers in USA and Chile.

SYSTEMIC CONTRACEPTIONB. INJECTABLES AND IMPLANTS (cont'd)PARFR-235SRI(206SRI, 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: 4/1/81 - 12/31/81	BUDGET: \$24,487 (235SRI)
11/1/79 - 12/31/80	EXPENDED: \$65,092 (206SRI)
11/1/78 - 10/31/79	EXPENDED: 66,000 (104N)
	EXPENDED: 6,000 (P9)

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

PARFR-235UAB (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: 4/1/81 - 12/31/81	BUDGET: \$29,789 (235UAB)
11/1/79 - 10/31/80	EXPENDED: \$18,865 (206UAB)

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.

SYSTEMIC CONTRACEPTIONB. 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.

An expert meeting was held at PARFR headquarters to discuss clinical application of these fibers, several alternatives were discussed including the fabrication of an IUD, intra-cervical device, and a biodegradable pellet prepared from fibers, for use in the post-partum period.

SYSTEMIC CONTRACEPTION

B. INJECTABLES AND IMPLANTS (cont'd)

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 - 8/31/81 BUDGET: \$36,734 [216(P19)]
2/1/79 - 6/30/80 EXPENDED: 7,694 (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.

The project has 192 women encounters seeking remedies for either a missed period and/or for "feeling pregnant". Of these, 102 (53%) were evaluated and found not to be pregnant (negative urine pregnancy test).

Of the 90 women pregnant, 47 were excluded because they did not fit into the study criteria (more than 42 days post last menstrual period), were not willing to complete the records or sign the permit or were excluded for reasons that they would not or did not take the herbal preparation.

The remaining 43 women who then fulfilled the study criteria, 7 were lost to follow-up, 36 completed the study with only 4 (11%) having evidence of a spontaneous abortion in response to the herbs and 32 (89%) seeking therapeutic abortion services (clinical) elsewhere.

It is interesting to note that 9 of 10 patients with negative pregnancy tests were found to have onset of menses within 48 hours after taking the same herbal preparations.

Assays for Gossypol were completed. Project will terminate in the next reporting period.

SYSTEMIC CONTRACEPTIONOTHER

"Fertility Regulation by Control of Progesterone Clearance"

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

FUNDING PERIOD: 9/1/79 - 12/31/81	\$ 92,535 NU
	48,636 NMH
	<u>\$141,171</u> TOTAL BUDGET

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

FUNDING PERIOD: 11/1/78 - 10/31/79	\$40,127 (102N)EXPENDED
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: During this reporting period the PI has prepared a new steroid conjugate for immunization and started collecting antisera for testing from two new sheep. Additional antisera has been purified and characterized for in vitro and in vivo studies. Significant improvements have been made in the polymer entrapment method for immobilizing and protecting antiprogestosterone antisera (APA). Using different combinations of monomers, a matrix that has high entrapment capacity with relatively low nonspecific binding of steroids, and with good retention of high affinity binding of progesterone by the entrapped APA has been obtained. An attempt to compare the APA entrapped by the new procedure with previous preparations by intraperitoneal injection of the material in rats was unsuccessful because of the inflammatory response that it produces. The inflammatory response was not specific for polymer containing APA, but also occurred with polymer containing nonspecific immunoglobulins. Although considerably more APA will be required for testing, comparisons will now be made exclusively by the oral route of administration.

Mircoencapsulation has also been tested as a means of immobilization of APA. While this may have some theoretical advantages of protecting the antibody, the binding capacity of ³H-progesterone in current preparations is not considered for in vivo studies.

SYSTEMIC CONTRACEPTION

C. OTHER (cont'd)

Results: (cont'd)

A good primate model has been tested for use in evaluating entrapped APA. Monitoring uterine contractions after administration of EAPA provides an initial response, in addition to measuring serum levels of progesterone, for determining an adequate dose and frequency of administration for maintaining uterine reactivity. This project will not continue beyond 12/31/81.

PARFR-203IIT "Microencapsulation of Progesterone Antibodies"

Kurt Gutfreund, IIT Research Institute, Chicago

FUNDING PERIOD: 11/1/79 - 6/30/81 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 and polyamide 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. Dr. Chatterton, under PARFR-203NU/NMH, has provided Dr. Gutfreund with the antibody preparations. Dr. Gutfreund will determine the loading capacity of the microcapsules for the antibody preparation and will add Lithophilic materials to the surface of the microcapsules to protect the antibody from pH changes in the stomach.

SYSTEMIC CONTRACEPTIOND. OTHER (cont'd)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 - 12/31/81	\$ 58,741 (NU)
	51,299 (NMH)
	<u>\$110,040</u> 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: The investigators have had success in synthesizing Anordrin and compared this product with that obtained from the WHO which indicated that the PI's product was as potent as the comparison sample.

Anordrin does not have any androgenic or anabolic potency, but when administered to the animals along with TP, it shows antiandrogenic properties. The mechanism of antiandrogenic action is yet to be studied.

Antiestrogenic characteristics of Anordrin causes luteolysis of corpora lutea resulting in decreased serum progesterone levels.

Preparation of a large amount of Anordrin for the toxicity studies is being processed at the moment.

Experiments on acute toxicity will begin in the next reporting period.

SYSTEMIC CONTRACEPTIONOTHERPARFR-227B

"Prostaglandin Levels in the Human Follicular Fluid in Relation to the Moment of Ovulation"

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

FUNDING PERIOD: 3/1/81 - 11/30/81

BUDGET: \$13,613

Objectives:

To study the level of prostaglandins in the human follicular fluid in relation to the LH surge and the moment of follicular rupture. The effects of PG's antagonist on PG's synthesis in the follicle and on the ovulation process will also be assessed.

Results:

This study was initiated using Motrin and results will not be available until the next reporting period.

PARFR-228

"Induction of Luteolysis and Ovulation Inhibition by LRF-Analogues"

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

FUNDING PERIOD: 4/1/81 - 3/31/82

BUDGET: \$34,977

Objectives:

To determine the effectiveness of LRF-agonist in the induction of luteolysis in the presence of luteotropic effect of exogenously administered human chorionic gonadotropin.

Results:

This project recently started and a technical report is not due until the next reporting period (10/1/81).

PARFR 233

"Potentially Antifertility Activity of LH/HCG Peptide Fragments"

Joseph W. Goldzieher, M.D. and Daniel Castracane, M.D., Southwest Foundation for Research and Education, San Antonio, Texas

FUNDING PERIOD: 4/15/81 - 10/14/81

BUDGET: \$44,090

Objectives:

To study in the female baboon the ability of certain unique peptides to inhibit the action of endogenously secreted gonadotropin and determine the anti-fertility potential of the McKern's peptide (E2).

Results:

This project recently started and a technical report is not due until the next reporting period (9/1/81).

SYSTEMIC CONTRACEPTIONOTHER - 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 - 3/31/81

EXPENDED: \$43,070

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

Results: The effects on different doses of orally administered polyphenolic
compound "Gossypol" on semen quality, circulating testosterone
(T) and fertility of Dutch-belted male rabbits were studied.
Following gossypol treatment at 80, 40 or 20 mg/kg/day, animals
lost appetite and body weight, developed hind limb paralysis,
breathing difficulties and collapsed while sitting in their cages.
At autopsy, the liver and lungs were found congested while the
stomach and intestines contained gases. On the other hand,
rabbits fed daily with 10 mg/kg/day gossypol exhibited a survival
time ranging from 77 to 250 days. Despite the severe side effects
resulting in eventual deaths, weekly semen samples from all
treated animals did not show any apparent change in sperm motility,
morphology or population. Likewise, gossypol treated males mated
to estrous does exhibit a fertility comparable to vehicle treated
controls. Gossypol fed at a dose of 10 mg/kg/day for up to 35
weeks failed to induce sterility.

Male rabbits, fed with either 20 or 10 mg/kg/day gossypol, that
survived for longer periods of time had substantially reduced
T levels by 12-20 weeks depending upon dose but were fertile at
all times. When the in vitro release of T from the rat testes
mince in the presence of hCG and gossypol was evaluated, an
inhibition of T release was recorded. Although gossypol has
been shown to be an effective antifertility agent in several
mammalian species, it failed to exhibit such an affect in
Dutch-belted rabbits, although serum T levels were reduced.

Fertile mature male syrian hamsters fed daily either 10 or 15 mg/kg
of gossypol (Gossypol acetic acid; Sigma Chemical Co., #G-4382)
for 5 weeks, no changes occurred in the relative organ weights
of testis, epididymis or seminal vesicles as compared to vehicle
treated controls. Likewise circulating PRL, LH and T remained
unaltered, and the total sperm population along the reproductive
tract was significantly reduced in the 15 mg/kg gossypol treated
group (74 ± 24 vs 297 ± 44 millions). After 10 weeks of treat-
ment, males receiving 10 mg/kg became sterile with a signifi-
cant decrease in the relative weights of the epididymis but no
difference in the weights of testis and seminal vesicles. A
significant reduction was recoded in testosterone levels and
sperm count.

SYSTEMIC CONTRACEPTIONC. OTHER - MALE PHARMACOLOGICAL METHODS (cont'd)

Results: (cont'd)

The vehicle treated control hamsters were found fertile when periodically mated to proestrous females. On the other hand, females mated to 10 or 15 mg/kg gossypol treated males showed 3/6 and 2/6 pregnancies, respectively. By 7-8 weeks of treatment all males in the 15 mg/kg gossypol treated group were sterile (treatment terminated) while males treated with 10 mg/kg gossypol, 50% were found sterile. After 12 weeks of treatment, the 10 mg/kg gossypol treated males were 100 percent sterile and their treatment was also stopped. At 20 weeks after the initiation of treatment, 3/5 (15 mg/kg and 6/6 (10 mg/kg), the gossypol induced sterility started showing reversibility and by the 22nd week even those male which were treated with 15 mg/kg/day gossypol were found fertile.

Histological studies during and after gossypol induced sterility and changes in the testicular morphology are in progress.

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 - 2/28/81 BUDGET: \$7,500

Objectives: To determine if an antigenic fragment of lactate dehydrogenase 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 had applied to PARFR for continuation of these most promising studies and was funded under PARFR-232 listed below.

SYSTEMIC CONTRACEPTIONC. OTHER - MALE PHARMACOLOGICAL METHODS (cont'd)

PARFR-P61 "Immunologic Suppression of Fertility In Vitro by Antisera to a Synthetic Antigenic Determinant of Lactate Dehydrogenase-C₄"

Erwin Goldberg, M.D., Northwestern University, Evanston, Illinois

FUNDING PERIOD: 8/1/80 - 7/31/81 BUDGET: \$7,500

Objectives: To evaluate the immunologic suppression of fertility using the peptide T-13, in rabbits, mice and hamsters.

Results: Refer to PARFR-232 below.

PARFR-232 "Immunologic Suppression of Fertility by Synthetic Antigenic Determinants of Lactate Dehydrogenase-C₄"

Erwin Goldberg, Ph.D., Northwestern University, Evanston, Illinois

FUNDING PERIOD: 3/1/81 - 2/28/82 BUDGET: \$60,018

Objectives: To develop a contraceptive vaccine consisting of a synthesizable antigenic peptide that will provoke antibodies against the LDH-C₄ enzyme of spermatozoa.

Results: Four peptide fragments of LDH-C₄ which bind antibody to the native protein, have been isolated by HPLC from tryptic digests. Each of these peptides has been subjected to sequence analysis and placed in the overall sequence of LDH-C₄. Two of these peptides representing residues 5-16 and residues 211-220 were selected for custom synthesis by Peninsula Laboratories, Inc.

The synthetic product will be conjugated to BSA as indicated in the proposal, and tested for immunogenicity. The peptides have proven difficult to synthesize.

The peptide, T-13, will now be designated MC₁₅₂₋₁₅₉. It has been used as a model to verify the validity of this strategy for development of a synthetic antigen useful in a contraceptive vaccine. As reported previously, rabbits immunized with BSA-MC₁₅₂₋₁₅₉ produced antibody which bound to the peptide. This binding was inhibited by free peptide and by the BSA-peptide conjugate. These antibodies were purified and tested for binding to ¹²⁵I-LDH-C₄. The results, show that purified anti-MC₁₅₂₋₁₅₉ does indeed bind to LDH-C₄. Furthermore, the

SYSTEMIC CONTRACEPTIONC. OTHER - MALE PHARMACOLOGICAL METHODS (cont'd)

Results: (cont'd)

specificity of this binding is confirmed by competition of unlabelled LDH-C₄. As expected, only a small portion of the antibodies elicited by the BSA-peptide conjugate bind to LDH-C₄. From these data, it can be concluded that peptide MC₁₅₂₋₁₅₉ contains an antigenic determinant of LDH-C₄. Furthermore, the strategy for development of synthetic determinants which provoke an immune response to native LDH-C₄ has proven to be sound.

PARFR-236IIT "Retinoids and Male Contraception"

Rajendra G. Mehta, Ph.D., IIT Research Institute, Chicago, Illinois

FUNDING PERIOD: 6/1/81 - 5/31/82

BUDGET: \$61,908

Objectives: To investigate the possible use of six retinoids as effective non-toxic and reversible male contraceptives in rats.

Results: The project recently started. A technical report is not due until 9/1/81, the next reporting period.

BARRIER CONTRACEPTIONFEMALE

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

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

FUNDING PERIOD: 3/1/80 - 12/14/81 BUDGET: \$75,017 [212(85N)]
12/1/76 - 6/30/80 EXPENDED: 97,896 (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.

A clinical trial with the plain collagen sponge is initiated (see PARFR-239). Post-coital testing of a disposable collagen sponge diaphragm containing nonoxynol-9 was initiated as an amendment.

PARFR-239 "Clinical Trial of the Collagen Sponge As A Contraceptive"

Gary S. Berger, M.D., Center for the Advancement of Reproductive Health, Inc., Chapel Hill, North Carolina

FUNDING PERIOD: 6/1/81 - 5/31/82 BUDGET: \$31,890

Objectives: To determine the clinical efficacy and acceptability of the collagen sponge vaginal contraceptive.

Results: Project recently started.

BARRIER CONTRACEPTIONB. FEMALEPARFR-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 - 12/31/80 EXPENDED: \$37,336

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

Results: To date, 57 volunteer couples have been enrolled in the study. Half of the women are using a collagen sponge containing nonoxynol-9 and the other half are using the collagen sponge alone. After 6 months of experience, 6 pregnancies have occurred; 2 in the group of women using the collagen sponge plus spermicide, and 4 pregnancies occurred in women using the collagen sponge alone. Of these 4, 2 cases were women not using the sponge at mid cycle. 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. Due to problems of cost of follow-up and poor patient criteria selection, PARFR intends to confirm these data by establishing a multi-center trial involving a larger number of volunteer couples.

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 - 12/31/81 BUDGET: \$149,605

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.

BARRIER CONTRACEPTION

B. FEMALE (cont'd)

Results: (cont'd)

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-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: 7/1/80 - 6/30/81

BUDGET: \$14,751

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: Eleven patients were enrolled; side effects and participant complaints were minimal; a few smears showed inflammation and blood chemistry did not change except in one out of eleven patients. Evidence of spermicidal effect has been shown consistently in post-coital tests after the removal of the IVI. The inventor has made arrangements with a major drug company for Phase II and Phase III clinical trials.

PREGNANCY TESTSPARFR-237

"Detection of Pregnancy in Women Before Implantation"

Nancy J. Alexander, Ph.D., Medical Research Foundation of
Oregon, Portland, Oregon

FUNDING PERIOD: 6/1/81 - 11/30/81

BUDGET: \$ 9,391

Objectives: To test lymphocytes and sera of women attending an artificial insemination clinic and correlate rosette inhibition findings with other tests for pregnancy.

Results: This project recently started. A technical report is due during the next reporting period.

WORK PLANAnticipated Accomplishments

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

- a. MCA/FEMCEPT Project - Straight baseline studies were completed and only follow-up data is being collected in Korea (PARFR-200K), El Salvador (PARFR-86Sa), Germany (PARFR-200K) and the Philippines (PARFR-200P). Randomized studies are underway in Brasil (PARFR-226B) and Chile (PARFR-226C). Radio-opaque MCA was developed and prepared by Population Research, Inc. Clinical trials with radio-opaque MCA will be initiated in Brasil, Chile, India and Venezuela. Cine flouroscopy and x-ray studies will be initiated in Chile (PARFR-238C) and other centers.
- b. Collagen Sponge - Post-coital tests were completed and clinical trials with the plain collagen sponge were initiated in North Carolina (PARFR-239) and a non-AID supported study in Hungary. Post-coital testing of a disposable collagen sponge diaphragm containing nonoxynol-9 were initiated [Amendment to PARFR-212(85N)].
- c. Intravaginal Insert - The post-coital tests were completed (PARFR-213T). The inventor has made arrangements with a major drug company for Phase II and III clinical trials.
- d. The Utero-Tubal Junction Blocking Device - Clinical studies in Chicago and Mexico City were postponed due to problems with equipment modification.
- e. NET-fused Pellets - Patient enrollment was completed in the US center (PARFR-229) and partially in the two LDC centers (PARFR-229B and PARFR-229M). During the next reporting period, two additional sites - one in San Antonio and one in Santiago are planned to be initiated.
- f. 180-day NET Microcapsules - Preparation of the microcapsules in Mexico City was completed; quality control is underway and postponed clinical studies will be initiated during the next reporting period (PARFR-225MA and PARFR-225B).
- g. 90-day NET Microcapsules - The principal investigator obtained an FDA-IND. During the next reporting period, microcapsules will be prepared and clinical trials will be initiated in San Antonio, Alabama, Rome, Santiago and Alexandria.
- h. NET Rods - A manufacturing capability was located in England and in the next reporting period, we plan to manufacture the rods and conduct a Phase I study in England.

Anticipated Accomplishments (cont'd)

- i. Prostaglandin Inhibition: Effects on Ovulation - Studies using Motrin will be completed in the next reporting period (PARFR-227B).
- j. LHRH - An LHRH studied was initiated; results are not yet available. It is expected that the trial will be completed in March, 1982; a technical report is not due until the next reporting period (PARFR-228). We plan to initiate another study with an antagonist in San Antonio.
- k. Transcutaneous Bipolar Vasectomy Techniques - Due to a high failure rate, clinical trials in Brasil (PARFR-221Ba and 221Bb) and Colorado (PARFR-221C) were terminated. Arrangements were made for testing the equipment and redesign of the needle (PARFR-241). Follow-up continues of the Davis technique (PARFR-220); however, no further clinical trials are planned.
- l. Wing Sound II - The modified prototype was developed; the competitive bid obtained and during the next reporting period the Wing Sound II will be manufactured (PARFR-230). During the next reporting period, clinical trials, supported by IFRP and PARFR, will be initiated in Europe and LDCs.

Publications:

Planned Volume 1, No. 5 entitled: "Fallopian Tube Occlusion by Pharmacologic Agents" of our series, Research Frontiers in Fertility Regulation is in process and will be submitted for editorializing and publication next reporting period. Issue No. 6 is planned on "Plants and Antifertility Agents."

Procedures and Activities

- 1) The scheduled Scientific Advisory Committee meeting for the next reporting period is: July 8, 1981 at the Sheraton Plaza, Chicago and October 14, 1981 at the Camelback Inn, Scottsdale, Arizona.
- 2) PARFR is planning our next workshop on Non-Surgical Female Tubal Occlusion in June, 1982 in Chicago.

Summary Financial Reports

This section includes:

- A. AID/DSPE - C-0035 Monthly Financial Reports,
1/1/81 - 6/30/81
- B. AID/csd-3608 Monthly Financial Reports,
1/1/81 - 6/30/81
- C. AID/DSPE-C-0035 Subcontracts, Budget and Total Expenditures
when Terminated
- D. AID/csd-3608 Subcontracts, Budget and Total Expenditures
when Terminated
- E. LDC Research Funds, Budget and Expenditures Through 6/30/81

	<u>AID/csd-3608</u> <u>(7/1/75-6/30/80)</u>	<u>AID/DSPE-C-0035</u> <u>(7/1/79-6/30/82)</u>	<u>Total</u> <u>(Both Contracts)</u>
Expenditures this period	\$ 23,719.56	\$ 942,411.58	\$ 966,131.14
Expenditures through 12/31/80	<u>4,308,527.43</u>	<u>1,292,337.66</u>	<u>5,600,865.09</u>
Total Expenditures	\$4,332,246.99	\$2,234,749.24	\$6,566,996.23
Total Commitments	<u> </u>	1,178,838.99	1,178,838.99
Uncommitted Balance	<u>180,265.51</u>	<u>(3,588.23)</u>	<u>176,677.28</u>
Total Budget	\$4,512,512.50	\$3,410,000.00	\$7,922,512.50

		Budget 7/1/79- 6/30/81	Expended 7/1/79- 12/31/80	Expended 1/1/81- 1/31/81	Total Cum. Exp. 7/1/79- 1/31/81	Outstanding Commits 2/1/81- 6/30/81	Uncommitted Balance
Salaries	02	310,400.00	227,941.85	13,498.33	241,440.18	55,941.89	13,017.93
	03	75,734.00	51,883.47	2,561.92	54,445.39	11,765.60	9,523.01
TOTAL SALARIES		386,134.00	279,825.32	16,060.25	295,885.57	67,707.49	22,540.94
Fringe Benefits	13	55,217.00	39,926.81	2,296.62	42,223.43	9,460.34	3,533.23
Indirect Cost	88	150,596.00	108,249.87	6,263.50	114,513.37	25,800.93	10,281.70
Supplies	05	129,100.00	76,784.53	18,927.47	95,712.00	14,754.47	18,633.53
	09	6,900.00	3,982.70	187.92	4,170.62	---	2,729.38
	10	19,700.00	13,148.66	444.25	13,592.91	(23.00)	6,130.09
	12	2,200.00	1,067.60	---	1,067.60	1,094.10	38.30
	78	400.00	237.58	---	237.58	---	162.42
TOTAL SUPPLIES		158,300.00	95,221.07	19,559.64	114,780.71	15,825.57	27,693.72
Equipment	06	2,100.00	346.50	---	346.50	---	1,753.50
Consultant Fees	49	35,200.00	23,871.44	1,435.48	25,306.92	705.48	9,187.60
Travel	07	115,000.00	68,460.63	7,120.23	75,580.86	10,018.67	29,400.47
Workshop/Publ.	91	135,000.00	50,508.17	9,990.84	60,499.01	12,711.15	61,789.84
Subcontracts	90	2,262,453.00	567,644.35	135,618.38	703,262.73	876,994.04	682,196.23
Pilot Studies	92	110,000.00	58,283.50	5,265.46	63,548.96	22,210.41	24,240.63
TOTAL RESEARCH		2,372,453.00	625,927.85	140,883.84	766,811.69	899,204.45	706,436.86
TOTAL WORKSHOP		135,000.00	50,508.17	9,990.84	60,499.01	12,711.15	61,789.84
TOTAL ADMINISTRATION		902,547.00	615,901.64	52,735.72	668,637.36	129,518.48	104,391.16
TOTAL		3,410,000.00	1,292,337.66	203,610.40	1,495,948.06	1,041,434.08	872,617.86

PARFR Financial Report, January 31, 1981

AID/DSPE-C-0035 (4263-404)

DN/mrt
'20/81

		Budget 7/1/79- 6/30/81	Expended 7/1/79- 1/31/81	Expended 2/1/81- 2/28/81	Total Cum. Exp. 7/1/79- 2/28/81	Outstanding Commits 3/1/81- 6/30/81	Uncommitted Balance
Salaries	02	310,400.00	241,440.18	12,208.57	253,648.75	44,783.32	11,967.93
	03	75,734.00	54,445.39	2,693.92	57,139.31	9,388.18	9,206.51
Total Salaries		386,134.00	295,885.57	14,902.49	310,788.06	54,171.50	21,174.44
Per Diem Benefits	13	55,217.00	42,223.43	2,131.06	44,354.49	7,568.28	3,294.23
Indirect Cost	88	150,596.00	114,513.37	5,811.97	120,325.34	20,640.74	9,629.92
Supplies	05	129,100.00	95,712.00	7,360.51	103,072.51	9,279.87	16,747.62
	09	6,900.00	4,170.62	274.85	4,445.47	---	2,454.53
	10	19,700.00	13,592.91	709.68	14,302.59	---	5,397.41
	12	2,200.00	1,067.60	---	1,067.60	---	1,132.40
	78	400.00	237.58	1.66	239.24	---	160.76
TOTAL SUPPLIES		158,300.00	114,780.71	8,346.70	123,127.41	9,279.87	25,892.72
Equipment	06	2,100.00	346.50	---	346.50	---	1,753.50
Consultant Fees	49	35,200.00	25,306.92	705.48	26,012.40	---	9,187.60
Travel	07	115,000.00	75,580.86	7,103.32	82,684.18	8,136.64	24,179.18
Workshop/PUBL.	91	135,000.00	60,499.01	11,510.18	72,009.19	---	62,990.81
Subcontracts	90	2,262,453.00	703,262.73	55,692.90	758,955.63	967,704.17	535,793.20
Pilot Studies	92	110,000.00	63,548.96	9,327.23	72,876.19	26,649.08	10,474.73
TOTAL RESEARCH		2,372,453.00	766,811.69	65,020.13	831,831.82	994,353.25	546,267.93
TOTAL WORKSHOP		135,000.00	60,499.01	11,510.18	72,009.19	---	62,990.81
TOTAL ADMINISTRATION		902,547.00	668,637.36	39,001.02	707,638.38	99,797.03	95,111.59
TOTAL		3,410,000.00	1,495,948.06	115,531.33	1,611,479.39	1,094,150.28	704,370.33

PARFR Financial Report, February 28, 1981
AID/DSPE-C-0035 (4263-404)

CN/mrt
1/17/81

		<u>Budget 7/1/79- 6/30/81</u>	<u>Expended 7/1/79- 2/28/81</u>	<u>Expended 3/1/81- 3/31/81</u>	<u>Total Cum. Exp. 7/1/79- 3/31/81</u>	<u>Outstanding Commits 4/1/81- 6/30/81</u>	<u>Uncommitted Balance</u>
Salaries	02	310,400.00	253,648.75	11,983.33	265,632.08	33,099.99	11,667.93
	03	75,734.00	57,139.31	2,159.32	59,298.63	7,130.76	9,304.61
Total Salaries		386,134.00	310,788.06	14,142.65	324,930.71	40,230.75	20,972.54
Range Benefits	13	55,217.00	44,354.49	2,135.54	46,490.03	5,993.76	2,733.21
Indirect Cost	88	150,596.00	120,325.34	5,515.63	125,840.97	15,480.55	9,274.48
Supplies	05	129,100.00	103,072.51	5,468.72	108,541.23	7,668.01	12,890.76
	09	6,900.00	4,445.47	210.54	4,656.01	---	2,243.99
	10	19,700.00	14,302.59	607.12	14,909.71	---	4,790.29
	12	2,200.00	1,067.60	----	1,067.60	1,094.10	38.30
	78	400.00	239.24	----	239.24	---	160.76
Total Supplies		158,300.00	123,127.41	6,286.38	129,413.79	8,762.11	20,124.10
Equipment	06	2,100.00	346.50	---	346.50	359.23	1,394.27
Consultant Fees	49	35,200.00	26,012.40	1,638.29	27,650.69	3,536.96	4,012.35
Travel	07	115,000.00	82,684.18	3,997.23	86,681.41	13,514.29	14,804.30
Workshop/Publ.	91	135,000.00	72,009.19	3,528.00	75,537.19	20,594.26	38,868.55
Subcontracts	90	2,262,453.00	758,955.63	92,918.91	851,874.54	1,045,526.59	365,051.87
Pilot Studies	92	110,000.00	72,876.19	5,083.12	77,959.31	29,044.96	2,995.73
TOTAL RESEARCH		2,372,453.00	831,831.82	98,002.03	929,833.85	1,074,571.55	368,047.60
TOTAL WORKSHOP		135,000.00	72,009.19	3,528.00	75,537.19	20,594.26	38,868.55
TOTAL ADMINISTRATION		902,547.00	707,638.38	33,715.72	741,354.10	87,877.65	73,315.25
TOTAL		3,410,000.00	1,611,479.39	135,245.75	1,746,725.14	1,183,043.46	480,231.40

		BUDGET 7/1/79- 6/30/81	EXPENDED 7/1/79- 3/31/81	EXPENDED 4/1/81- 4/30/81	TOTAL CUM. EXP. 7/1/79- 4/30/81	OUTSTANDING COMMITTS 5/1/81 6/30/81	UNCOMMITTED BALANCE
Salaries	02	310,400.00	265,632.08	11,233.33	276,865.41	21,866.66	11,667.93
	03	75,734.00	59,298.63	3,305.33	62,603.96	6,712.84	6,417.20
TOTAL SALARIES		386,134.00	324,930.71	14,538.66	339,469.37	28,579.50	18,085.13
Fringe Benefits	13	55,217.00	46,490.03	2,195.34	48,685.37	4,296.93	2,234.70
Indirect Cost	88	150,596.00	125,840.97	5,670.08	131,511.05	11,098.02	7,986.93
Supplies	05	129,100.00	108,541.23	3,793.46	112,334.69	9,252.37	7,512.94
	09	6,900.00	4,656.01	326.11	4,982.12	---	1,917.88
	10	19,700.00	14,909.71	886.23	15,795.94	---	3,904.06
	12	2,200.00	1,067.60	740.54	1,808.14	704.31	(312.45)
	78	400.00	239.24	---	239.24	---	160.76
TOTAL SUPPLIES		158,300.00	129,413.79	5,746.34	135,160.13	9,956.68	13,183.19
Equipment	06	2,100.00	346.50	205.00	551.50	154.23	1,394.27
Consultant Fees	49	35,200.00	27,650.69	3,536.96	31,187.65	953.96	3,058.39
Travel	07	115,000.00	86,681.41	12,997.53	99,678.94	2,434.92	12,886.14
Workshop/Publ.	91	135,000.00	75,537.19	7,194.00	82,731.19	45,787.90	6,480.91
Subcontracts	90	2,262,453.00	851,874.54	95,202.04	947,076.58	1,134,979.71	180,396.71
Pilot Studies	92	110,000.00	77,959.31	4,529.92	82,489.23	26,404.04	1,106.73
TOTAL RESEARCH		2,372,453.00	929,833.85	99,731.96	1,029,565.81	1,161,383.75	181,503.44
TOTAL WORKSHOP		135,000.00	75,537.19	7,194.00	82,731.19	45,787.90	6,480.91
TOTAL ADMINISTRATION		902,547.00	741,354.10	44,889.91	786,244.01	57,474.24	58,828.75
TOTAL		3,410,000.00	1,746,725.14	151,815.87	1,898,541.01	1,264,645.89	246,813.10

		Budget 7/1/79 6/30/81	Expended 7/1/79- 4/30/81	Expended 5/1/81- 5/31/81	Total Cum. Exp. 7/1/79- 5/31/81	Outstanding Commits 6/1/81- 6/30/81	Uncommitted Balance
Salaries	02	310,400.00	276,865.41	11,965.08	288,830.49	11,360.24	10,209.27
	03	75,734.00	62,603.96	3,686.42	66,290.38	3,645.92	5,797.70
TOTAL SALARIES		386,134.00	339,469.37	15,651.50	355,120.87	15,006.16	16,006.97
Per Diem Benefits	13	55,217.00	48,685.37	2,363.38	51,048.75	2,086.82	2,081.43
Indirect Costs	88	150,596.00	131,511.05	6,104.08	137,615.13	5,389.79	7,591.08
Supplies	05	129,100.00	112,334.69	10,070.78	122,405.47	5,380.75	1,313.78
	09	6,900.00	4,982.12	201.63	5,183.75	---	1,716.25
	10	19,700.00	15,795.94	492.82	16,288.76	---	3,411.24
	12	2,200.00	1,808.14	162.14	1,970.28	542.17	(312.45)
	78	400.00	239.24	---	239.24	---	160.76
TOTAL SUPPLIES		158,300.00	135,160.13	10,927.37	146,087.50	5,922.92	6,289.58
Equipment	06	2,100.00	551.50	---	551.50	154.23	1,394.27
Consultant Fees	49	35,200.00	31,187.65	953.96	32,141.61	153.85	2,904.54
Travel	07	115,000.00	99,678.94	3,206.43	102,885.37	10,987.49	1,127.14
Workshop/Publ.	91	135,000.00	82,731.19	20,307.14	103,038.33	39,849.92	(7,888.25)
Subcontracts	90	2,262,453.00	947,076.58	57,990.59	1,005,067.17	1,116,366.62	141,019.21
Pilot Studies	92	110,000.00	82,489.23	13,338.95	95,828.18	13,065.09	1,106.73
TOTAL RESEARCH		2,372,453.00	1,029,565.81	71,329.54	1,100,895.35	1,129,431.71	142,125.94
TOTAL WORKSHOP		135,000.00	82,731.19	20,307.14	103,038.33	39,849.92	(7,888.25)
TOTAL ADMINISTRATION		902,547.00	786,244.01	39,206.72	825,450.73	39,701.26	37,395.01
TOTAL		3,410,000.00	1,898,541.01	130,843.40	2,029,384.41	1,208,982.89	171,632.70

PARFR Financial Report, May 31, 1981
AID/DSPE-C-0035 (4263-404)

		Budget 7/1/79- 6/30/81	Expended 7/1/79- 5/31/81	Expended 6/1/81- 6/30/81	Total Cum. Exp. 7/1/79- 6/30/81	Outstanding Commitments	Uncommitted Balance
Salaries	02	310,400.00	288,830.49	11,777.82	300,608.31	---	9,791.69
	03	75,734.00	66,290.38	3,940.79	70,231.17	132.00	5,370.83
TOTAL SALARIES		386,134.00	355,120.87	15,718.61	370,839.48	132.00	15,162.52
Fringe Benefits	13	55,217.00	51,048.75	2,373.51	53,422.26	63.05	1,731.69
Indirect Cost	88	150,596.00	137,615.13	6,130.26	143,745.39	162.85	6,687.76
Supplies	05	129,100.00	122,405.47	11,730.49	134,135.96	12,602.00	(17,637.96)
	09	6,900.00	5,183.75	245.88	5,429.63	---	1,470.37
	10	19,700.00	16,288.76	653.76	16,942.52	---	2,757.48
	12	2,200.00	1,970.28	162.14	2,132.42	324.28	(256.70)
	78	400.00	239.24	1.20	240.44	---	159.56
TOTAL SUPPLIES		158,300.00	146,087.50	12,793.47	158,880.97	12,926.28	(13,507.25)
Equipment	06	2,100.00	551.50	---	551.50	4,149.23	(2,600.73)
Consultant Fees	49	35,200.00	32,141.61	724.35	32,865.96	1,223.00	1,111.04
Travel	07	115,000.00	102,885.37	2,381.28	105,266.65	2,744.43	6,988.92
Workshop/Publ.	91	135,000.00	103,038.33	32,006.75	135,045.08	18,259.55	(18,304.63)
Subcontracts	90	2,262,453.00	1,005,667.17	132,332.56	1,137,399.73	1,119,413.02	5,640.25
Pilot Studies	92	110,000.00	95,828.18	904.04	96,732.22	19,765.58	(6,497.80)
TOTAL RESEARCH		2,372,453.00	1,100,895.35	133,236.60	1,234,131.95	1,139,178.60	(857.55)
TOTAL WORKSHOP		135,000.00	103,038.33	32,006.75	135,045.08	18,259.55	(18,304.63)
TOTAL ADMINISTRATION		902,547.00	825,450.73	40,121.48	865,572.21	21,400.84	15,573.95
TOTAL		3,410,000.00	2,029,384.41	205,364.83	2,234,749.24	1,178,838.99	(3,588.23)

		Budget 7/1/75- 6/30/80	Expended 7/1/75- 12/31/80	Expended 1/1/81- 1/31/81	Total Cum. Exp. 7/1/75- 1/31/81	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	06	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	---	---
Moving Expense	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	3,069,342.85	---	3,069,342.85	62,483.26	121,212.00
Pilot Studies	92	143,245.47	123,645.66	---	123,645.66	---	19,599.81
TOTAL RESEARCH		3,396,283.58	3,192,988.51	---	3,192,988.51	62,483.26	140,811.81
TOTAL WORKSHOP		192,352.77	191,662.77	---	191,662.77	---	690.00
TOTAL ADMINISTRATION		923,876.15	923,876.15	---	923,876.15	---	---
TOTAL		4,512,512.50	4,308,527.43	---	4,308,527.43	62,483.26	141,501.81

PARFR Financial Report, January 31, 1981

[Funds committed prior to 6/30/80]

AID/csd-3608 (4263-401)

ACN/mrt
2/18/81

		Budget 7/1/75- 6/30/80	Expended 7/1/75- 1/31/81	Expended 2/1/81 2/28/81	Total Cum. Exp. 7/1/75- 2/28/81	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	06	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	---	---
Moving Expense	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	3,069,342.85	---	3,069,342.85	2,499.00	181,196.20
Pilot Studies	92	143,245.47	123,645.66	---	123,645.66	---	19,599.80
TOTAL RESEARCH		3,396,283.58	3,192,988.51	---	3,192,988.51	2,499.00	200,796.00
TOTAL WORKSHOP		192,352.77	191,662.77	---	191,662.77	---	690.00
TOTAL ADMINISTRATION		923,876.15	923,876.15	---	923,876.15	---	---
TOTAL		4,512,512.50	4,308,527.43	---	4,308,527.43	2,499.00	201,486.00

		Budget 7/1/75- 6/30/80	Expended 7/1/75- 2/28/81	Expended 3/1/81- 3/31/81	Total Cum. Exp. 7/1/75- 3/31/81	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	06	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	---	---
Moving Expense	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	3,069,342.85	---	3,069,342.85	26,218.56	157,476.70
Pilot Studies	92	143,245.47	123,645.66	---	123,645.66	---	19,599.81
TOTAL RESEARCH		3,396,283.58	3,192,988.51	---	3,192,988.51	26,218.56	177,076.51
TOTAL WORKSHOP		192,352.77	191,662.77	---	191,662.77	---	690.00
TOTAL ADMINISTRATION		923,876.15	923,876.15	---	923,876.15	---	---
TOTAL		4,512,512.50	4,308,527.43	---	4,308,527.43	26,218.56	177,766.51

		Budget 7/1/75- 6/30/80	Expended 7/1/75- 3/31/81	Expended 4/1/81- 4/30/81	Total Cum. Exp. 7/1/75- 4/30/81	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	---	---
Per Diem	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	06	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	---	---
Printing Expense	18	2,963.91	2,963.91	---	2,963.91	---	---
Recomodl. & Maint.	52	11,249.30	11,249.30	---	11,249.30	---	---
Workshop/Publ.	91	192,352.77	191,662.77	---	191,662.77	---	690.00
Subcontracts	90	3,253,038.11	3,069,342.85	23,719.56	3,093,062.41	2,499.00	157,476.70
Pilot Studies	92	143,245.47	123,645.66	---	123,645.66	---	19,599.81
TOTAL RESEARCH		3,396,283.58	3,192,988.51	23,719.56	3,216,708.07	2,499.00	177,076.51
TOTAL WORKSHOP		192,352.77	191,662.77	---	191,662.77	---	690.00
TOTAL ADMINISTRATION		923,876.15	923,876.15	---	923,876.15	---	---
TOTAL		4,512,512.50	4,308,527.43	23,719.56	4,332,246.99	2,499.00	177,766.51

PARFR Financial Report, April 30, 1981
(Funds Committed prior to 6/30/80)
AID/csd-3608 (4263-401)

		<u>Budget 7/1/75- 6/30/80</u>	<u>Expended 7/1/75- 4/30/81</u>	<u>Expended 5/1/81- 5/31/81</u>	<u>Total Cum. Exp. 7/1/75- 5/31/81</u>	<u>Outstanding Commits Through 6/30/80</u>	<u>Balance</u>
Salaries	02	269,218.89	269,218.89	----	269,218.89	----	----
	03	<u>103,708.02</u>	<u>103,708.02</u>	<u>----</u>	<u>103,708.02</u>	<u>----</u>	<u>----</u>
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	<u>1,567.39</u>	<u>1,567.39</u>	<u>----</u>	<u>1,567.39</u>	<u>----</u>	<u>----</u>
TOTAL SUPPLIES		141,543.55	141,543.55	----	141,543.55	----	----
Equipment	06	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	----	----
Duplicating Expense	18	2,963.91	2,963.91	----	2,963.91	----	----
Remodl. & Maint.	52	11,249.30	11,249.30	----	11,249.30	----	----
Workshop/Publ.	91	192,352.77	191,662.77	----	191,662.77	----	690.00
Subcontracts	90	3,253,038.11	3,093,062.41	----	3,093,062.41	2,499.00	157,476.70
Pilot Studies	92	<u>143,245.47</u>	<u>123,645.66</u>	<u>----</u>	<u>123,645.66</u>	<u>----</u>	<u>19,599.81</u>
TOTAL RESEARCH		3,396,283.58	3,216,708.07	----	3,216,708.07	2,499.00	177,076.51
TOTAL WORKSHOP		192,352.77	191,662.77	----	191,662.77	----	690.00
TOTAL ADMINISTRATION		<u>923,876.15</u>	<u>923,876.15</u>	<u>----</u>	<u>923,876.15</u>	<u>----</u>	<u>----</u>
TOTAL		4,512,512.50	4,332,246.99	----	4,332,246.99	2,499.00	177,766.51

PARFR Financial Report, May 31, 1981
(Funds Committed prior to 6/30/80)
AID/csd-3608 (4263-401)

		<u>Budget 7/1/75- 6/30/80</u>	<u>Expended 7/1/75- 4/30/81</u>	<u>Expended 6/1/81- 6/30/81</u>	<u>Total Cum. Exp. 7/1/75- 6/30/81</u>	<u>Outstanding Commits Through 6/30/80</u>	<u>Balance</u>
Salaries	02	269,218.89	269,218.89	----	269,218.89	----	----
	03	<u>103,708.02</u>	<u>103,708.02</u>	----	<u>103,708.02</u>	----	----
TOTAL SALARIES		372,926.91	372,926.91	----	372,926.91	----	----
fringe Benefits	13	51,269.43	51,269.43	----	51,269.43	----	----
direct 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	<u>1,567.39</u>	<u>1,567.39</u>	----	<u>1,567.39</u>	----	----
TOTAL SUPPLIES		141,543.55	141,543.55	----	141,543.55	----	----
equipment	06	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	----	----
living Expense	18	2,963.91	2,963.91	----	2,963.91	----	----
modl. & Maint.	52	11,249.30	11,249.30	----	11,249.30	----	----
shop/Publ.	91	192,352.77	191,662.77	----	191,662.77	----	690.00
contracts	90	3,253,038.11	3,093,062.41	----	3,093,062.41	----	159,975.70
lot Studies	92	<u>143,245.47</u>	<u>123,645.66</u>	----	<u>123,645.66</u>	----	<u>19,599.81</u>
TOTAL RESEARCH		3,396,283.58	3,216,708.07	----	3,216,708.07	----	179,575.51
TOTAL WORKSHOP		192,352.77	191,662.77	----	191,662.77	----	690.00
TOTAL ADMINISTRATION		<u>923,876.15</u>	<u>923,876.15</u>	----	<u>923,876.15</u>	----	----
TOTAL		4,512,512.50	4,332,246.99	----	4,332,246.99	----	180,265.51

PARFR Financial Report, June 30, 1981
(Funds Committed prior to 6/30/80)
AID/csd-3608 (4263-401)

PARFR/NORTHWESTERN UNIVERSITY

SUBCONTRACTS: AID/DSPE-C-0035
7/1/79-6/30/82

<u>PARFR #</u>	<u>INSTITUTION</u>	<u>PRINCIPAL INVESTIGATOR</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>TOTAL EXPENDITURES WHEN TERMINATED</u>
200C	Columbia University New York, New York	Ralph M. Richart, M.D.	"Data Collection and Analysis for MCA/FEMCEPT Clinical Trials"	7/1/79- 6/30/81	\$35,832.67	
200G	Bureau Mengen Cologne, West Germany (Continuation of PARFR-86G)	Hans Baur, M.D.	"Phase I Clinical Trial of Fallopian Tube Closure Using Methylcyanoacrylate (MCA) Tissue Adhesive Delivered Through the Single-Application Fertility Regulation (FEMCEPT) Device"	9/1/79- 8/31/80	32,020	\$24,478.41
200K	Korea University College of Medicine Seoul, Korea	Sung-bong Hong, M.D. C-I Soo Cong Lee, M.D.	(SAME AS ABOVE)	5/1/80- 8/31/82	2,598	
200P	JFMH Comprehensive Family Planning Center Manila, Philippines	Ruben A. Apelo, M.D.	(SAME AS ABOVE)	10/1/79- 9/30/81	14,385	
201B	Maternidade Climerio de Oliveira Salvador, Bahia, Brasil	Hugo Maia, Jr., M.D.	"Effect of LH-RH Agonist on Ovulation and Corpus Luteum Function in Women"	8/1/79- 11/30/80	34,600	\$34,600.00
202	Texas Tech University Lubbock, Texas	M. W. Heine, M.D.	"Collagen Sponge Contraceptive -- Testing of Efficacy in Human Volunteers"	9/1/79- 12/31/80	49,044	37,336.33
203NU	Northwestern University Evanston, Illinois	Robert T. Chatterton, Ph.D.	"Fertility Regulation by Control of Progesterone Clearance"	9/1/79- 12/31/81	92,535	
203NMH	Northwestern Memorial Hospital	Robert T. Chatterton, Ph.D.	(SAME AS ABOVE)	9/1/79- 12/31/81	48,636	

PARFR/NORTHWESTERN UNIVERSITY

SUBCONTRACTS: AID/DSPE-C-0035
7/1/79-6/30/82

<u>PARFR #</u>	<u>INSTITUTION</u>	<u>PRINCIPAL INVESTIGATOR</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>TOTAL EXPENDITURES WHEN TERMINATED</u>
203IIT	IIT Research Institute Chicago, Illinois	Kurt Gutfreund	"Microencapsulation of Progesterone Antibodies"	11/1/79- 6/30/81	\$ 21,905	
204	University of Illinois at the Medical Center Chicago, Illinois	Lourens J.D. Zaneveld, D.V.M., Ph.D.	"Development of Sperm Enzyme Inhibitors as Vaginal Contraceptives"	10/1/79- 12/31/81	149,605	
205(95N)	University of Illinois at the Medical Center Chicago, Illinois	Lourens J.D. Zaneveld, D.V.M., Ph.D.	"Development and Evaluation of a Reversible Vas Deferens Blocking Device"	10/1/79- 12/31/81	108,548	
206UAB	University of Alabama in Birmingham, Birmingham, Alabama	Lee R. Beck, Ph.D.	"Baboon Studies to Evaluate Non-Biodegradable Medicated Fibers for the Controlled-Release of Contraceptive Steroids Related to Research Supported under PARFR-206SRI"	11/1/79- 10/31/80	18,865	\$ 18,865
206SRI	Southern Research Institute Birmingham, Alabama	Danny H. Lewis, Ph.D.	"A Fibrous Polymer for the Delivery of Contraceptive Steroids to the Female Reproductive Tract"	11/1/79- 12/31/80	66,000	\$ 65,091.53
207	Hektoen Institute for Medical Research Chicago, Illinois	Abdol H. Hosseinian, M.D.	"Hysteroscopic Sterilization by Using Uterotubal Blocking Devices"	11/1/79- 12/31/81	24,348	
207M	PROJECT NEVER STARTED -----					
208	University of Alabama in Birmingham Birmingham, Alabama	Lee R. Beck, Ph.D.	"Testing the Abortifacient Potential of CI and CII, 1 Beta-Oh Androstane Derivatives, in the Baboon"	11/1/79- 1/31/81	27,358	\$ 27,323.94

PARFR/NORTHWESTERN UNIVERSITY

SUBCONTRACTS: AID/DSPE-C-0035
7/1/79-6/30/82

<u>PARFR #</u>	<u>INSTITUTION</u>	<u>PRINCIPAL INVESTIGATOR</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>TOTAL EXPENDITURES WHEN TERMINATED</u>
209NU	Northwestern University Evanston, Illinois	Raksha Mehta, Ph.D.	"Evaluation of A-Nor Steroids as Potential Once-A-Month Contraceptive Agents"	1/1/80- 12/31/81	\$ 58,741	
209NMH	Northwestern Memorial Hospital Chicago, Illinois	Raksha Mehta, Ph.D.	"Evaluation of A-Nor Steroids as Potential Once-A-Month Contraceptive Agents"	1/1/80- 12/31/81	51,299	
210	Worcester Foundation for Experimental Biology Shrewsbury, Massachusetts	M. C. Chang, Ph.D.	"Study of a Plant Product 'Gossypol' as a Reversible Contraceptive in Male Rabbits"	1/1/80 3/31/81	43,070	\$ 43,070
211	-----Joseph E. Davis, M.D.----- New York, New York		"Study of Vas Occlusion in Animals Using Chemical Agents"	12/1/79- 9/30/81	13,540	
212(85N)	The University of Arizona Health Sciences Center Tucson, Arizona	Milos Chvapil, M.D., Ph.D.	"Development of Collagen Sponge Containing Spermicide and Post-Coital Testing of Collagen Sponge Diaphragm"	3/1/80- 12/14/81	75,017	
213T	The University of Texas Health Science Center at San Antonio, San Antonio, Texas	Mohammed M. Ahmad, M.D., Ph.D. and Ricardo H. Asch, M.D.	"The Study of the Intravaginal Insert (IVI) - Acceptability and Side Effects"	7/1/80- 6/30/81	14,751	
213B	PROJECT NEVER STARTED -----					

PARFR/NORTHWESTERN UNIVERSITY

SUBCONTRACTS: AID/DSPE-C-0035
7/1/79-6/30/82

<u>PARFR #</u>	<u>INSTITUTION</u>	<u>PRINCIPAL INVESTIGATOR</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>TOTAL EXPENDITURES WHEN TERMINATED</u>
214(83N)	University of Alabama in Birmingham Birmingham, Alabama	Lee R. Beck, Ph.D.	"Studies to Test an Injec- table Delivery System for the Sustained Release of Norethisterone"	4/1/80 9/30/81	\$ 96,937	
214(110N)	Southern Research Institute Birmingham, Alabama	Danny H. Lewis, Ph.D.	"Optimization of an In- jectable Microcapsule Formulation for the 90- day Delivery of Norethisterone"	4/1/80- 7/31/81	113,045	
215	Centro De Estudos De Re- producao Humana de Botucatu Botucatu, Sao Paulo, Brazil	Renzo <u>Antonini</u> Filho, M.D.	"Chemical Sterilization in the Cebus Appella Monkeys"	5/15/80- 12/31/81	16,775	
216(P19)	University of New Mexico Albuquerque, New Mexico	John C. Slocumb, M.D.	"Identification and Eval- uation of Herbs Used by Native Healers to Affect Fertility"	5/1/80- 8/31/81	36,734	
217(111N)	The University of Texas Health Science Center at San Antonio San Antonio, Texas	Carlton A. Eddy, Ph.D. Len Laufe, M.D. (IFRP)	"An Evaluation of the Efficacy of Fimbrial Enclosure With Silastic Devices as a Reversible Female Sterilization Technique"	7/1/80- 5/31/82 IFRP	56,252 4,534.88 (IFRP)	\$ 4,534.88
218	Jefferson Medical College of Thomas Jefferson University Philadelphia, Pennsylvania	Leonard J. Lerner, Ph.D.	"Development and Mechanism of Activity Studies With the Pregnancy Terminating Compounds DL-111-IT and DL-105-IT"	7/1/80- 9/30/81	67,807	

PARFR/NORTHWESTERN UNIVERSITY

SUBCONTRACTS: AID/DSPE-C-0035

7/1/79-6/30/82

<u>PARFR #</u>	<u>INSTITUTION</u>	<u>PRINCIPAL INVESTIGATOR</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>TOTAL EXPENDITURES WHEN TERMINATED</u>
219	Southern Research Institute Birmingham, Alabama	Richard L. Dunn, Ph.D.	"A Fibrous Polymer for Delivery of Quinacrine to the Human Reproductive Tract -- Related to PARFR-P57"	9/1/80- 9/30/81	\$ 47,999	
220	-----Joseph E. Davis, M.D.----- New York, New York		"New Method for Obstructing the Vas Deferens by Direct Injection of Chemical Agents: A Non-Operative Technique of Male Sterilization"	9/1/80- 12/31/81	13,721	
221C	Medical Dynamics, Inc. Englewood, Colorado	Edwin L. Adair, M.D.	"A Multi-Site Evaluation in Developed and Developing Countries of a Technique and Equipment for Transcutaneous Closure of the Vas Deferens by Electro Coagulation"	9/1/80- 8/31/81	15,960	\$ 4,400.00
221Ba	Maternidade Climerio de Oliveira, Salvador, Bahia, Brasil	Jose Freitas-Melo, M.D.	(SAME AS ABOVE)	9/15/80- 9/14/81	13,970	2,953.50
221Bb	PROPATER Sao Paulo, Brasil	Marcos Paulo P. de Castro, M.D.	(SAME AS ABOVE)	9/15/80- 9/14/81	14,245	10,017.70
222(107N)	Medical Research Foundation of Oregon Portland, Oregon	Nancy J. Alexander, Ph.D.	"Is Sperm Antigen a Causative Agent for Atherosclerosis After Vasectomy"	7/1/80- 12/31/80	17,601	17,597.53
223	Southwest Foundation for Research and Education San Antonio, Texas	Joseph W. Goldzieher, M.D.	"Antigestational Effects of LHRH Analogues"	9/1/80- 8/31/81	35,948	

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<u>PARFR #</u>	<u>INSTITUTION</u>	<u>PRINCIPAL INVESTIGATOR</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>TOTAL EXPENDITURES WHEN TERMINATED</u>
224	Washington University St. Louis, Missouri	Arpad I. Csapo, M.D.	"Luteolysis in the Guinea Pig"	10/1/80- 3/31/81	\$34,959	\$ 18,081.36
225	Southern Research Institute, Birmingham, Alabama	Danny H. Lewis, Ph.D.	"Preparation of Nore- thisterone Microcapsules"	11/1/80- 8/31/81	34,217	
225B	Maternidade Climerio de Oliveira Bahia, Brasil	Elsimar Metzker Coutinho, M.D.	"Clinical Trials of the Norethisterone Microcap- sule Injectable Contra- ceptive System"	4/1/81- 3/31/82	39,226	
225M	Instituto de Investi- gacion Cientifica, Durango, Mexico	Roberto Rivera, M.D.	"Preparation of Nore- thisterone Microcapsules"	2/1/81- 12/31/81	4,693	
225Ma	Instituto de Investi- gacion Cientifica Durango, Mexico	Roberto Rivera, M.D.	"Clinical Trials of the Norethisterone Micro- capsule Injectable Con- traceptive System"	4/1/81 3/31/82	41,063	
225UAB	University of Alabama in Birmingham Birmingham, Alabama	Charles E. Flowers, Jr., M.D.	"Clinical Trials of the Norethisterone Injectable Contraceptive System"	4/1/81- 3/31/82	12,825	
226B	Maternidade Climerio de Oliveira, Salvador, Bahia, Brasil	Elsimar Metzker Coutinho, M.D.	"Clinical Trial of Fallopian Tube Closure Using MCA"	9/15/80- 6/30/82	41,305	
226C	Instituto de Obstetricia y Ginecologia, Facultad de Medicina, Universidad Austral de Chile Valdivia, Chile	Rene Guzman-Serani, M.D.	"Clinical Trials of Fallopian Tubal Closure Using MCA"	4/1/81- 3/31/82	24,145	

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227B	Maternidade Climerio de Oliveira, Salvador, Bahia, Brasil	Hugo Maia, M.D.	"Prostaglandin Levels in the Human Follicular Fluid in Relation to the Moment of Ovulation"	3/1/81-11/30/81	13,613	
228	University of California-San Diego, La Jolla, California	Samuel S.C. Yen, M.D.	"Induction of Luteolysis and Ovulation Inhibition by LRF-Analogues"	4/1/81-3/31/82	34,977	
229	The Cornell University Medical College, New York, New York	B. Saxena, Ph.D., D.Sc. Gopi N. Gupta, Ph.D. William Ledger, M.D.	"A Clinical Evaluation of the Subdermal Contraceptive Norethindrone Pellet"	1/1/81-12/31/81	77,813	
229B	Maternidade Climerio de Oliveira Bahia, Brasil	Elsimar Metzker Coutinho, M.D.	"Studies on Bioabsorbable Subdermal Contraceptive Norethindrone Pellet Implants"	3/1/81-2/28/82	32,461	
229M	Instituto de Investigacion Cientifica Durango, Mexico	Roberto Rivera, M.D.	"A Clinical Evaluation of the Bioabsorbable Subdermal Contraceptive Norethindrone Pellet Implant"	3/1/81-2/28/82	36,843	
230	H.F.D. Design Crystal Lake, Illinois	N/A	"Design and Manufacture of 1500-2000 Wing Sound II Devices"	1/1/81-12/15/81	33,000	
232	Northwestern University Evanston, Illinois	Erwin Goldberg, Ph.D.	"Immunologic Suppression of Fertility by Synthetic Antigenic Determinants of Lactate Dehydrogenase-C ₄ "	3/1/81-2/28/82	60,018	
233	Southwest Foundation for Research and Education San Antonio, Texas	Joseph W. Goldzieher, M.D. Daniel Castracane, Ph.D.	"Potentially Antifertility Activity of LH, HCG Peptide Fragments"	4/15/81-10/14/81	44,090	

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235SRI	Southern Research Institute Birmingham, Alabama	Danny H. Lewis, Ph.D.	"A Fibrous Polymer for the Delivery of Contraceptive Steroids to the Female Reproductive Tract - Continuation of PARFR-206SRI"	4/1/81- 12/31/81	\$ 24,487	
235UAB	University of Alabama in Birmingham Birmingham, Alabama	Lee R. Beck, Ph.D.	"A Fibrous Polymer for the Delivery of Contraceptive Steroids to the Female Reproductive Tract - Continuation of PARFR-206UAB"	4/1/81- 12/31/81	29,789	
236IIT	IIT Research Institute Chicago, Illinois	Rejendra G. Mehta, Ph.D.	"Retinoids and Male Contraception"	6/1/81- 5/31/82	61,908	
237	Medical Research Foundation of Oregon Portland, Oregon	Nancy J. Alexander, Ph.D.	"Detection of Pregnancy in Women Before Implantation"	6/1/81- 11/30/81	9,391	
238C	Universidad Austral de Chile Valdivia, Chile	Rene Guzman-Serani, M.D.	"Radio-Opaque MCA - Cineflourography Study"	6/15/81- 12/14/81	6,985	
239	Center for the Advancement of Reproductive Health, Inc. Chapel Hill, North Carolina	Gary S. Berger, M.D.	"Clinical Trial of the Collagen Sponge As A Contraceptive"	6/1/81- 5/31/82	31,890	
240	Presbyterian Hospital, Obstetrical and Gynecological Service, New York, New York	Ralph M. Richart, M.D. Robert S. Neuwirth, M.D.	"Data Collection and Analysis of MCA/FEMCEPT Clinical Trials (Previously PARFR-200C)"	7/1/81- 6/30/82	24,440	

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241	PIACT Seattle, Washington	Michael J. Free, Ph.D.	"Measurements of Electrical Characteristics of Equipment for Transcutaneous Electrocoagulation of the Vas Deferens"	7/20/81- 8/31/81	8,243.44	

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P50	The University of Arizona Tucson, Arizona	Milos Chvapl, M.D. Ph.D.	"Effect of Spermicidal Detergent, Nonoxynol-9 on Liver Function"	7/1/79- 6/30/80	\$ 8,000	\$ 2,078.37
P51	----- Harrith M. Hasson, M.D. ----- Chicago, Illinois	-----	"Graphic Assessment of Uterine Shape"	10/1/79- 9/30/80	10,000	10,000.00
P52	Corporacion Centro Regional de Poblacion, Bogota, Colombia	Jose Perea-Sasiain, M.D.	"Effects of Gossypol on Pregnancy"	10/1/79- 9/30/80	7,000	4,548.80
P53	The University of Texas Health Science Center at San Antonio, Texas	Ricardo H. Asch, M.D.	"Antifertility Effects of Luteinizing Hormone Releasing Hormone Ana- logue in the Female Rhesus Monkey"	11/1/79- 10/31/80	7,500	7,485.77
P54	Centro de Reproducao Humana - Sao Paulo, Brasil	Marcos Paulo P. de Castro, M.D.	"Percutaneous Injection of Monoethanolamine Oleate as a Vas Deferens Sclerosing Agent"	1/1/80- 6/30/80	9,350	4,529.00
P55	Duke University Durham, North Carolina	Vladimir Petrow, Ph.D.	"1-Hydroxyestra-1,3,5(10)- TRIEN-17B-OLS and Con- geners as Contragestative Agents"	11/1/79- 6/30/81	7,590	
P56	Medical Research Foun- dation of Oregon Portland, Oregon	Nancy J. Alexander, Ph.D.	"Efficacy Testing of Frisch Intravasal Implants"	11/1/79- 10/31/80	14,665	13,360.90
P57	Southern Research Institute Birmingham, Alabama	Richard L. Dunn, Ph.D.	"A Fibrous Polymer for the Delivery of Quina- crine to the Human Reproductive Tract"	1/1/80- 6/30/80	7,428	7,401.43

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P58	Northwestern University Evanston, Illinois	Erwin Goldberg, Ph.D.	"Immunologic Suppression of Fertility by a Synthetic Antigenic Determinant of Lactate Dehydrogenase-C ₄ "	12/1/79- 2/28/81	\$ 7,500	
P59	University of Alabama in Birmingham Birmingham, Alabama	Richard E. Blackwell, Ph.D.	"The Development and Clinical Testing of an Estrogen Bromocryptine Regime as an Interceptive and/or Abortifacient Means of Fertility Regulation"	5/1/80- 10/31/80	7,500	\$7,500.00
P60	Michael Reese Hospital and Medical Center Chicago, Illinois	Antonio Scommegna, M.D.	"Prostaglandin Antagonists as Local Antifertility Agents"	8/1/80- 1/31/81	6,850	6,850.00
P61	Northwestern University Evanston, Illinois	Erwin Goldberg, Ph.D.	"Immunologic Suppression of Fertility <u>In Vitro</u> by Antisera to a Synthetic Antigenic Determinant of Lactate Dehydrogenase-C ₄ "	8/1/80- 7/31/81	7,500	
P62	University of Arizona Tucson, Arizona	Milos Chvapil, M.D., Ph.D. William Droegemuller, M.D.	"Testing a New Polymer Sheet Hypan™, to be Used As a Hood for Modified Aldrich Reversible Sterilization Method"	3/1/81- 9/30/81	7,479	
P63	Michael Reese Hospital and Medical Center Chicago, Illinois	Antonio Scommegna, M.D.	"Prostaglandin Antagonists as Local Antifertility Agents"	6/15/81- 12/14/81	7,504.53	

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 PARFR SUBCONTRACTS SUPPORTED AT MINNESOTA: 30 Subcontracts(29 projects)
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 PARFR-50 to PARFR-80 (inclusive) excluding PARFR-79

<u>PARFR #</u>	<u>INSTITUTION</u>	<u>PRINCIPAL INVESTIGATOR</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>TOTAL EXPENDITURES WHEN TERMINATED</u>
50	University of Minnesota Minneapolis, Minnesota Jichi University, Japan	Takashi Okagaki, M.D., Ph.D. Taro Tamada, M.D.	"Acceptability and Use- Effectiveness of Condoms"	10/1/72- 5/30/75	\$80,000	\$83,755.28
51	Johns Hopkins University Baltimore, Maryland	Donald S. Coffey, Ph.D.	"A New and Rapid Method for Obstructing the Vas Deferens by Direct Injec- tion of Chemical Agents"	6/1/73- 5/31/75	67,521	67,182.77
52	Washington State Univ. Pullman, Washington	William M. Dickson, Ph.D.	"The Effect of Certain Indonesian Herbs on Early Pregnancy"	5/1/73- 4/10/74	1,841	1,642.93
53	University of Minnesota Minneapolis, Minnesota	Edmund F. Graham, Ph.D.	"The Use of Physiologic- ally Non-Toxic Organo- siloxane and Fluoro- chemical Liquids as Intravaginal Spermatozoon Trapping Mechanisms"	5/15/73- 6/30/75	75,110	75,858.95
54	Planned Parenthood, Buffalo Jamaica Family Planning Association, Ltd. St. Ann's Bay, Jamaica	Jack Lippes, M.D. Lenworth Jacobs, M.D.	"An Evaluation of Loops C and D with Copper Com- paring Results in a Developed and a Developing Country"	2/1/74- 6/30/75	28,668	10,602.49 (Buffalo) 8,464.00 (Jamaica)
55	University of California San Francisco, California	Alan Margolis, M.D.	"Clinical Evaluation of a Long-Term Intrauterine Drug Delivery System Based on Fluid-Filled IUD"	3/1/74- 6/30/75	51,992	11,296.37
56	University of Texas - San Antonio San Antonio, Texas	Carl J. Pauerstein, M.D.	"Pharmacologic Accelera- tion of Ovum Transport as a Contraceptive Method"	9/1/73- 6/30/75	96,589	96,578.27

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 PARFR SUBCONTRACTS SUPPORTED AT MINNESOTA: 30 Subcontracts(29 projects)
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PARFR #	INSTITUTION	PRINCIPAL INVESTIGATOR	TITLE	DATES	BUDGET	TOTAL
						EXPENDITURES WHEN TERMINATED
57	University of Chicago Chicago, Illinois	Joseph Swartwout, M.D.	"Development of a Reversible Male Contraceptive Technique"	9/1/73- 2/28/75	\$64,772.44	\$52,259.68
58	University of Chicago Chicago, Illinois	Lourens J.D. Zaneveld, D.V.M., Ph.D. (Transferred to IIT 7/1/74) Refer to PARFR-72	"Improving Effectiveness of Vaginal Contraceptive Creams or Jellies by Addition of Sperm Enzyme Inhibitors"	8/1/73 6/30/74 ---(Continued Under PARFR-72)---	83,782	33,300.43
59	New York Medical College Valhalla, New York	Delphine Bartosik, M.D.	"Bio-assay of Luteolytic Agents Using Human Corpora Lutea"	12/1/73- 12/31/74	28,671	26,033.17
60	University of Illinois Chicago, Illinois	Jerzy Jozef Bienzenski, M.D.	"Fertility Control by Thyrotropin Releasing Hormone"	3/15/74- 6/30/75	51,049	44,314.88
61	Michael Reese Hospital Chicago, Illinois	Paul Dmowski, M.D., Ph.D.	"Development of a Hysteroscopic Technic for Permanent Sterilization"	1/15/74- 6/30/75	70,085	44,856.06
62	Worcester Foundation for Experimental Biology, Inc. Shrewsbury, Massachusetts	R. H. Hooker, M.D.	"Reversible Suppression of Male Fertility by Implants Located at the Vas Deferens"	6/1/74- 6/30/75	41,020	41,642.83
63	University of Chicago Chicago, Illinois	A.H. Hosseinian, M.D.	"Development of a Reversible and Permanent Uterotubal Blocking Technique by Hysteroscopy"	4/1/74- 6/30/75	58,987	54,062.69

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64A	Oak Ridge Associated Universities Oak Ridge, Tennessee (In collaboration with the Southwest Foundation for Research and Education San Antonio, Texas)	Melvin M. Ketchel, Ph.D.	"Contraceptive Action of Diethylaminoethanol"	1/1/75-6/30/75	\$31,931	\$31,456.09
65	Boston University Boston, Massachusetts	Herbert Wotiz, Ph.D.	"Synthesis, Biochemistry and Biological Testing of End-Organ Specific Anti-Fertility Agents"	1/1/74-6/30/75	75,000	74,114.66
66	Columbia University New York, New York	Ralph M. Richart, M.D.	"Collaborative Study on Hysteroscopic Sterilization Procedures"	4/1/74-6/30/75	24,897	21,648.27
67	Oklahoma State University Stillwater, Oklahoma	Richard J. Orts, Ph.D.	"Effects of a Pineal Antigonadotropin on Ovulation, Implantation and Pregnancy"	4/1/74-6/1/75	34,329	34,556.78
68	Medical College of Georgia Augusta, Georgia	R.B. Greenblatt, M.D.	"The Potential Role of Crystalline Estradiol Implants for Sustained Ovarian Inhibition in Humans"	5/1/74-6/30/75	21,150	21,013.30
69	Michael Reese Medical Center Chicago, Illinois	Antonio Scommegna, M.D.	"Contraceptive Action of 6-Dehydroretroprogesterone Delivered to the Uterine Cavity Via a Silastic T"	5/1/74-6/30/75	46,751	17,460.90
70	Medical Research Foundation of Oregon Portland, Oregon	Nancy J. Alexander, Ph.D.	"Vasectomy: Role of Antibodies"	6/1/74-6/30/75	53,904	51,800.54

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 PARFR SUBCONTRACTS SUPPORTED AT MINNESOTA: 30 Subcontracts(29 projects)
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71	University of California San Francisco, California	Pentti Siiteri, Ph.D.	"Inhibitors of Estrogen Biosynthesis in Fertility Regulation"	10/1/74- 6/30/75	\$36,326	\$36,278.05
72	IIT Research Institute Chicago, Illinois	Lourens J.D. Zaneveld, D.V.M., Ph.D.	[Zaneveld (PARFR-58) transferred from Univ. of Chicago to IIT Research] "Improving the Effectiveness of Vaginal Contraceptive Creams of Jellies by Addition of Sperm Enzyme Inhibitors"	7/1/74- 6/30/75	57,466	56,267.38
73	Battelle Columbus Laboratories Columbus, Ohio	Richard D. Falb, Ph.D.	"Development of a Temperature Sensing Electrocautery Probe for Transcervical Sterilization"	11/1/74- 6/30/75	34,257	26,478.18
74	University of Minnesota Minneapolis, Minnesota	Kailash Kedia, M.D.	"Pharmacological Male Contraception"	12/1/74- 6/30/75	33,265	17,000.00 (Approx.)
75	Medical College of Georgia Augusta, Georgia	Edwin Bransome, M.D. Virendra Mahesh, D.Sc., Ph.D.	"Testing the Anti-Fertility Effects of Equilenin and Derivatives <u>In Vivo</u> "	11/1/74- 6/30/75	35,368	32,680.35
76	University of Alabama Birmingham, Alabama	Lee R. Beck, Ph.D.	"Studies to Test an Injectable Delivery System for the Sustained Release of Norethisterone"	10/1/74- 6/30/75	31,308	33,502.28
77	University of Hawaii Honolulu, Hawaii	Milton Diamond, Ph.D.	"Development of an Intra-Uterine Sterilizing Device"	12/1/74- 6/30/75	20,068	10,789.76

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78	Abcor, Inc. Cambridge, Massachusetts	Elie S. Nuwayser, Ph.D.	"Development of An Injectable Polymer System for Tubal Occlusion"	12/15/74- 6/30/75	\$21,459	\$19,776.21
80	Washington University St. Louis, Missouri	David W. Keller, M.D.	"Fertility Control Through Local Cervical Injection of Micro- encapsulated Progestins"	4/16/75- 6/30/75	13,474	12,479.38

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<u>PARFR #</u>	<u>INSTITUTION</u>	<u>PRINCIPAL INVESTIGATOR</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>TOTAL EXPENDITURES WHEN TERMINATED</u>
51N	Johns Hopkins University Baltimore, Maryland	Donald S. Coffey, Ph.D.	"A New and Rapid Method for Obstructing the Vas Deferens by Direct Injection of Chemical Agents"	7/1/75- 3/24/76	\$ 44,058	\$ 26,493.62
54N	Planned Parenthood-Buffalo Jamaica Family Planning Association, Ltd. St. Ann's Bay, Jamaica	Jack Lippes, M.D. Lenworth Jacobs, M.D.	"An Evaluation of Loops C and D with Copper Comparing Results in a Developed and a Developing Country"	7/1/75- 12/31/77	50,247	47,566.67
60N	University of Illinois Chicago, Illinois	Jerzy Jozef Bienzenski, M.D.	"Fertility Control by Thyrotropin Releasing Hormone"	7/1/75 9/30/75	2,800	2,806.50
63N	University of Chicago Chicago, Illinois	A.H. Hosseinian, M.D.	"Development of a Reversible and Permanent Uterotubal Blocking Technique by Hysteroscopy"	7/1/75- 9/30/75	17,383	17,382.79
63B	University of Illinois Chicago, Illinois	Lourens J.D. Zaneveld D.V.M., Ph.D.	"Baboon Studies for PARFR-63N"	10/1/75- 6/30/79	35,938	35,926.19
-----Additional costs related to 63N, 63B-----			Sollie Lucero -----			\$ 3,114.92
			Univ. of Chicago-Central Shop -----			5,877.85
			Zaneveld (Consultant) -----			1,200.00
65N	Boston University Boston, Massachusetts	Herbert H. Wotiz, Ph.D.	"Synthesis, Biochemistry and Biological Testing of End-Organ Specific Anti-Fertility Agents"	7/1/75- 12/31/76	78,346	77,705.06
66N	Columbia University New York, New York	Ralph M. Richart, M.D.	"Collaborative Study on Hysteroscopic Sterilization Procedures"	7/1/75- 8/31/75	2,730	2,390.40

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 PARFR SUBCONTRACTS SUPPORTED AT NORTHWESTERN UNIVERSITY
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<u>PARFR #</u>	<u>INSTITUTION</u>	<u>PRINCIPAL INVESTIGATOR</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>TOTAL EXPENDITURES WHEN TERMINATED</u>
57N	Oklahoma State University Stillwater, Oklahoma	Richard J. Orts, Ph.D.	"Effects of a Pineal Antigonadotropin on Ovulation, Implantation and Pregnancy"	7/1/75- 6/30/77	\$ 80,300	\$ 80,267.77
58N	Medical College of Georgia Augusta, Georgia	R.B. Greenblatt, M.D.	"The Potential Role of Crystalline Estradiol Implants for Sustained Ovarian Inhibition in Humans"	7/1/75- 10/31/76	41,953	40,489.20
69N	Michael Reese Medical Center Chicago, Illinois	Antonio Scommegna, M.D.	"Contraceptive Action of 6-Dehydroretroprogesterone Delivered to the Uterine Cavity via a Silastic T"	7/1/75- 9/30/76	53,263	53,082.64
70N	Medical Research Foundation of Oregon Portland, Oregon	Nancy J. Alexander, Ph.D.	"Vasectomy: Role of Antibodies"	7/1/75- 6/30/77	93,460	93,028.38
71N	University of California San Francisco, California	Pentti Siiteri, Ph.D.	"Inhibitors of Estrogen Biosynthesis in Fertility Regulation"	7/1/75- 3/31/76	15,061	15,053.99
73N	Battelle Columbus Laboratories Columbus, Ohio	Richard D. Falb, Ph.D.	"Development of a Temperature Sensing Electrocautery Probe for Transcervical Sterilization"	7/1/75- 6/30/76	17,161	17,161.00
74N	University of Minnesota Minneapolis, Minnesota	Kailash Kedia, M.D.	"Pharmacological Male Contraception"	7/1/75- 12/31/75	29,044	21,178.04
75N	Medical College of Georgia Augusta, Georgia	Edwin Bransone, M.D. Virendra Mahesh, D.Sc., Ph.D.	"Testing the Anti-Fertility Effects of Equilenin and Derivatives In Vivo"	7/1/75- 3/1/76	39,252	39,252.00

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 PARFR SUBCONTRACTS SUPPORTED AT NORTHWESTERN UNIVERSITY
 July 1, 1975 - June 30, 1980

<u>PARFR #</u>	<u>INSTITUTION</u>	<u>PRINCIPAL INVESTIGATOR</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>TOTAL EXPENDITURES WHEN TERMINATED</u>
76N	University of Alabama Birmingham, Alabama	Lee R. Beck, Ph.D.	"Studies to Test an Injectable Delivery System for the Sustained Release of Norethisterone"	7/1/75- 9/30/75	\$ 11,729	\$ 9,337.94
77N	University of Hawaii Honolulu, Hawaii	Milton Diamond, Ph.D.	"Development of an Intra-Uterine Sterilizing Device"	7/1/75- 1/31/76	9,279	9,275.64
78N	Abcor, Inc. Cambridge, Massachusetts	Elie S. Nuwayser, Ph.D.	"Development of an Injectable Polymer System for Tubal Occlusion"	7/1/75- 2/29/76	33,287.10	33,287.10
79N	University of Vermont Burlington, Vermont Maine Medical Center Portland, Maine	C. Irving Meeker, M.D.	"A Method for Reversible Sterilization in the Female"	2/1/77- 8/31/77 9/1/77- 6/30/80	81,090 106,131	32,369.51 104,924.21
80N	Washington University St. Louis, Missouri	David W. Keller, M.D.	"Fertility Control Through Local Cervical Injection of Microencapsulated Progestins"	7/1/75- 7/11/78	168,526	159,380.31
81N	University Hospitals Essen, Germany	Peter F. Tauber, M.D.	"Clinical Evaluation of Intrauterine Devices Containing Epsilon Aminocaproic Acid (EACA)"	5/1/76- 9/30/78	62,595	60,297.23
82N	Al-Azhar University Cairo, Egypt	Fouad Hefnawi, M.B., M.S.	"Measurement of Blood Loss of Women Fitted With Copper-Clad Lippes Loops"	11/1/75- 4/30/79	74,300	71,120.79

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83N	University of Alabama Birmingham, Alabama	Lee R. Beck, Ph.D.	"Studies to Test an Injectable Delivery System for the Sustained Release of Norethisterone"	4/1/76- 3/31/80	\$257,849	\$257,848.66
84N	Planned Parenthood of Buffalo, Inc.	Jack Lippes, M.D.	"Evaluation of the Copper-T IUD as a Post-Coital Method of Contraception"	10/1/77- 8/15/78	2,600	2,568.63
85N	The University of Arizona Tucson, Arizona	Milos Chvapil, M.D., Ph.D.	"Development of Collagen Sponge Containing Spermicide"	12/1/76- 6/30/80	98,124	97,895.49
86N	The St. Luke's Institute for Health Sciences New York, New York	Robert S. Neuwirth, M.D. Ralph M. Richart, M.D.	"Phase I Clinical Trial of Fallopian Tube Closure Using Methylcyanoacrylate (MCA) Tissue Adhesive Delivered Through the Single-Application Fertility Regulation (FEMCEPT) Device"	6/1/78- 3/31/80	36,602	36,489.98
86G	Bureau Mengen Cologne, Germany	Prof. H.K. Zinser Evangelisches Krankenhaus	---(SAME TITLE AS 86N)---	9/1/78- 8/31/79	27,159	22,096.53
86K	Korea University College of Medicine Seoul, Korea	Sung-bong Hong, M.D.	---(SAME TITLE AS 86N)---	5/1/79- 4/30/80	16,080	6,939.59
86Sa	Asociacion Demografica Salvadorena San Salvador, El Salvador	Gustavo Argueta, M.D.	---(SAME TITLE AS 86N)---	3/15/79- 3/14/80	12,410	9,911.00
86Sb	Instituto Salvadorena del Seguro Social San Salvador, El Salvador	Ernesto Moran, M.D.	---(SAME TITLE AS 86N)---	3/15/79- 3/14/80	8,000	1,360.00
------(Dr. Moran Caceres left El Salvador - This subcontract will not receive a final invoice.)-----						

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87N	Reza Pahlavi Medical Center Tehran, Iran	Abdol Hosseinian, M.D.	"Development of a Safe and Effective Hysteroscopic Sterilization Technique by Using Uterotubal Blocking Devices"	11/1/76- 8/31/77	\$ 17,300	\$ 17,310.48
88N	Planned Parenthood Federation of America, Inc. New York, New York	Louise B. Tyrer, M.D.	"Study to Determine the Safety and Efficacy of Copper-Releasing IUDs as a Method of Post-Coital Contraception"	4/1/77- 8/31/78	83,020	44,162.00
89N	Columbia University New York, New York	Harry P. Gregor, Ph.D.	"Fallopian Tube Cauterization and Closure by Silver Acetate - Alginate Formulations"	1/15/77- 6/30/80	112,073	112,073.00
	-----St. Luke's Medical Center Agreement (animal work)-----			11/1/77- 6/30/80	63,326	50,617.49
90N	New York Medical College Valhalla, New York	Joseph E. Davis, M.D.	"New Method for Obstructing the Vas Deferens by Direct Injection of Chemical Agents: A Non-Operative Technique of Male Sterilization"	6/1/77 12/31/78	59,305	39,772.26
90Np	Planned Parenthood Federation of America, Inc. New York, New York	Joseph E. Davis, M.D.	---(SAME TITLE AS 90N)---	2/1/79- 6/30/80	54,007	52,215.03
91N	Dynatech R/D Company Cambridge, Massachusetts	Donald L. Wise, Ph.D.	"Preparation and Evaluation of Biodegradable Cylindrical Implants for Fertility Control"	6/1/77- 6/30/80	177,141	175,116.33

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92N	Medical Research Foundation of Oregon Portland, Oregon	Deborah J. Anderson, Ph.D.	"Contraception by Induction of Mild Uterine Inflammation"	6/1/77- 12/31/79	\$ 86,108	\$ 85,524.48
93N	National Academy of Sciences Washington, D.C.	Nancy Muckenhirn, Ph.D.	"Workshop on Animal Models For Research on Fertility and Contraception"	8/1/77- 6/30/79	50,500	50,362.22
94N	University of Arizona Tucson, Arizona	William Droegemueller, M.D.	"Modern Modified Aldridge Procedure"	12/1/77- 12/31/79	62,062	44,715.58
	-----University of Illinois Agreement (Animal Work)-----			10/1/78- 12/31/79	17,850	14,960.75
95N	University of Illinois Chicago, Illinois	Lourens J.D. Zaneveld, D.V.M., Ph.D.	"Development and Evaluation of a Reversible Vas Deferens Blocking Device"	7/1/77- 9/30/79	113,348	113,348.00
96N	PROJECT NEVER STARTED -----					
97N	The Johns Hopkins University Baltimore, Maryland	Theodore M. King, M.D., Ph.D.	"Research on Instillation Techniques for Pregnancy Termination in Korea"	8/1/78- 6/30/80	108,442	46,528.38
97K	Yonsei University College of Medicine Seoul, Korea	Hyun-Mo Kwak, M.D.	---(SAME TITLE AS 97N)---	7/1/78- 6/30/80	66,550	37,066.39
98M	Centro de Investigacion Sobre Fertilidad y Esterilidad (CIFE) Mexico City, Mexico	Ramon Aznar, M.D.	"Norethisterone Microcapsule Injectable Contraceptive Study"	7/1/78- 6/30/80	34,265	33,076.12
	-----UAB Agreement-----			7/1/78- 6/30/80	10,780	10,779.63
	-----SRI Agreement-----			7/1/78- 6/30/79	27,642	27,642.00

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99N	Oklahoma State University Stillwater, Oklahoma	Duane Garner, Ph.D.	"Immunoabsorbent Isolation of Specific Spermatozoal Antigens for Use as Anti-Fertility Immunogens"	7/1/78- 3/31/79	\$ 30,233	\$ 25,752.43
100N	Jefferson Medical College of The Thomas Jefferson University Philadelphia, Pennsylvania	Leonard J. Lerner, Ph.D.	"Investigation of New Compounds to Terminate Pregnancy"	9/1/78- 6/30/80	109,384	109,384.00
101N	Southwest Foundation for Research and Education San Antonio, Texas	Joseph W. Goldzieher, M.D.	"Metabolism and Pharmacokinetics of Ethynyl Estrogens"	9/1/78- 2/28/79	23,994	23,958.65
102N (P10)	University of Illinois Chicago, Illinois	Robert T. Chatterton, Ph.D.	"Fertility Regulation by Control of Progesterone Clearance"	11/1/78- 10/31/79	46,767	40,126.85
103N	IIT Research Institute Chicago, Illinois	Allan P. Gray, Ph.D.	"Microencapsulation of Progesterone Antibodies"	11/1/78- 10/31/79	28,108	28,108.00
-----Companion Project to PARFR-102N(P10)-----						
104N (P9)	Southern Research Institute Birmingham, Alabama	Danny H. Lewis, Ph.D.	"A Fibrous Polymer for the Delivery of Contraceptive Steroids to the Female Reproductive Tract"	11/1/78- 10/31/79	66,000	66,000.00
105N	Centro de Investigacion Sobre Fertilidad y Esterilidad (CIFE) Mexico City, Mexico	Harry Rudel, M.D.	"A Study of a Parenterally Administered Progesterone- Cholesterol Formulation for Use as a Post-Partum Injectable Contraceptive"	5/1/79- 4/30/80	56,236	26,924.23

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106N	University of North Carolina Chapel Hill, North Carolina	Gary S. Berger, M.D.	"Effects of Tubal Sterilization on Menstruation: A Prospective Controlled Study"	2/1/79- 2/29/80	\$ 47,676	\$ 47,672.38
107N	Medical Research Foundation of Oregon Portland, Oregon	Nancy J. Alexander, Ph.D.	"Is Sperm Antigen a Causative Agent for Atherosclerosis After Vasectomy"	4/1/79- 6/30/80	83,318	78,806.18
108N	Planned Parenthood Federation of America, Inc. New York, New York	Louise B. Tyrer, M.D.	"Study to Determine the Safety, Acceptability and Effectiveness of the Female Contraceptive Barrier Intra-Vaginal Device (IVD)"	3/1/79- 7/11/79	62,600	4,717.73
109	NUMBER NOT ASSIGNED -----					
110N	Southern Research Institute Birmingham, Alabama	Danny H. Lewis, Ph.D.	"Optimization of an Injectable Microcapsule Formulation for the 90-Day Delivery of Norethisterone"	4/1/79- 3/31/80	65,972	65,972.00
111N	The University of Texas Health Science Center at San Antonio San Antonio, Texas	Carlton A. Eddy, Ph.D.	"An Evaluation of the Efficacy of Fimbrial Enclosure With Silastic Devices as a Reversible Female Sterilization Technique"	6/1/79- 6/30/80	58,290	55,258.15
	-----IFRP Agreement -----				3,340	3,340.00
112	NUMBER NOT ASSIGNED -----					

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 PARFR SUBCONTRACTS SUPPORTED AT NORTHWESTERN UNIVERSITY
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113	NUMBER NOT ASSIGNED					
114N	University of California- San Diego La Jolla, California	Samuel S.C. Yen, M.D.	"The Induction of Luteo- lysis and Ovulation Inhibition by LRF-Agonist"	6/15/79- 6/30/80	\$ 65,959	\$ 62,282.59

----- PARFR-114N is the Last Subcontract Committed on AID/csd-3608 -----

PARFR/Northwestern University Executed Pilot Studies: AID/csd-3608

November 1, 1975 - June 30, 1980

21 Subcontracts (2 never started)

<u>PARFR #</u>	<u>INSTITUTION</u>	<u>PRINCIPAL INVESTIGATOR</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>TOTAL EXPENDITURES WHEN TERMINATED</u>
P1	University of Nebraska Omaha, Nebraska	James E. McClurg, Ph.D.	"Secretory Immune Response of the Female Genital Tract"	11/1/75- 1/15/77	\$ 6,000	\$6,000
P2	University of Arizona Tucson, Arizona	Milos Chvapil, M.D. Ph.D.	"Zinc-Collagen Sponge Com- plex as a Contraceptive, Section I - Lab Studies"	1/31/76- 3/31/76	6,000	5,322.44
P3	University of Arizona Tucson, Arizona	Milos Chvapil, M.D. Ph.D.	"Zinc-Collagen Sponge Com- plex as a Contraceptive, Section II - Clinic Studies"	2/1/76- 4/30/76	6,000	5,006.50
P4	Harbor General Hospital Torrance, California	A.F. Parlow, Ph.D.	"Active Immunization of the Human Follicle Stimu- lating Hormone to Inhibit Gonadal Function"	1/1/77- 12/31/77	6,000	- 0 -
P5	University of Minnesota Minneapolis, Minnesota	Bo G. Crabo, Ph.D.	"Contraceptive Effect of Low Oral Doses of 2,6-cis- Diphenylhexanethylcyclote- trasiloxane in the Male"	9/1/76- 8/31/77	5,850	5,850
P6	University of Illinois at the Medical Center Chicago, Illinois	Lourens J.D. Zaneveld, D.V.M., Ph.D.	"Development and Evalua- tion of a Reversible Vas Deferens Blocking Device"	9/1/76- 8/31/77	5,985	5,985
P7	NEVER EXECUTED -----					
P8	The Emko Company St. Louis, Missouri	Charles Salivar Ray Belsky	"Water Soluble Condom Feasibility Study"	9/15/77- 6/15/78	5,789.78	5,468.07

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P9	Southern Research Institute Birmingham, Alabama	Danny H. Lewis, Ph.D.	"A Fibrous Polymer for the Delivery of Contraceptive Steroids to the Female Reproductive Tract"	1/1/78- 6/30/78	\$ 6,000	\$6,000.00
P10	University of Illinois Chicago, Illinois	Robert T. Chatterton, Ph.D.	"Fertility Regulation by Control of Progesterone Clearance"	1/1/78- 10/31/78	7,216.78	6,048.62
P11	Columbia University New York, New York	Ralph M. Richart, M.D.	"Evaluation of Carbohexo- xymethyl-2-Cyanoacrylate as a Tube Blocking Agent"	2/1/78- 3/31/79	7,004.01	7,004.03
P12	Massachusetts Institute of Technology Cambridge, Massachusetts	David Frisch, Ph.D.	"Development of Micro- porous Materials for Thin Intravasal Implants"	7/1/78- 6/30/80	15,000	14,035.55
P13	Catholic University of Leuven, Leuven, Belgium	Ivo Brosens, M.D., Ph.D. Len Laufe, M.D. (IFRP)	"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"	5/1/78- 4/30/80	11,680.59 (Belgium) 2,750.00 (IFRP)	11,377.53 2,750.00 (IFRP)
P14	-----Stanwood Schmidt, M.D.----- Eureka, California		"The Bipolar Needle for Percutaneous Vas Obstruction"	7/1/78- 6/30/79	2,350	- 0 -
P15	New York Medical College Valhalla, New York	Sidney Shulman, Ph.D.	"Isolation of Effective Sperm Antigen for Use in Contraceptive Immuniza- tion"	3/1/79- 2/29/80	7,500	7,500.00

PARFR/Northwestern University Executed Pilot Studies: AID/csd-3608

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P16	University of California San Francisco, California	Ernest W. Page, M.D.	"Investigations of a New Vaginal Barrier Contraceptive"	1/1/79- 6/30/80	\$ 6,000	\$2,750.11
P17	Southern Illinois University Carbondale, Illinois	Matthew Freund, Ph.D.	"Development and Testing of a New Intravaginal Contraceptive Method and Device (IVCD)"	2/1/79- 9/30/79	7,500	6,791.60
P18	University of Georgia Athens, Georgia	Marion M. Bradford, Ph.D.	"Evaluation of Acrosin-Acrolysin Inhibitors as Male Contraceptive Agents"	2/1/79- 10/31/79	7,500	7,499.73
P19	University of New Mexico Albuquerque, New Mexico	John C. Slocumb, M.D.	"Identification and Evaluation of Herbs Used by Native Healers to Affect Fertility"	2/1/79- 6/30/80	7,700	7,693.96
P20	Southwest Foundation for Research and Education San Antonio, Texas	Joseph Goldzieher, M.D.	"Effect of the Estrogen-Bromocryptine Regimen in the Post-Implantation Phase in Baboons"	6/1/79 11/30/79	7,500	7,461.45
P21	University of Arizona Tucson, Arizona	Milos Chvapil, M.D. Ph.D.	"Development and Preliminary Human Testing of the Retention of a New Intra-cervical Device (ICD)"	6/15/79- 6/14/80	7,500	5,151.06
P22	University of Houston Houston, Texas	Lindley A. Cates, Ph.D.	"A Preliminary Investigation of Fertility Regulation by South American Tribes"	6/15/79- 6/14/80	7,688	- 0 -

LDC RESEARCH FUNDS

<u>PARFR #</u>	<u>BUDGET (DOLLARS)</u>	<u>TOTAL EXPENDITURES TO DATE</u>
<u>AID/csd-3608</u>		
PARFR-54 Jamaica	\$ 8,464	\$ 8,464.00 (Total)
PARFR-54N Jamaica	35,859	24,809.00 (Total)
PARFR-82N Egypt	74,300	71,120.79 (Total)
PARFR-86K Korea	16,080	6,939.59 (Total)
PARFR-86Sa El Salvador	12,410	9,911.00 (Total)
PARFR-86Sb El Salvador	8,000	1,360.00 (Total)
PARFR-87N Iran	17,300	17,310.48 (Total)
PARFR-97K Korea	66,550	37,066.39 (Total)
PARFR-98M Mexico	34,265	33,076.12 (Total)
PARFR-105N Mexico	56,236	26,924.23 (Total)
<u>AID/DSPE-C-0035</u>		
PARFR-200K(86K) Korea	\$ 2,598	\$ 1,648.00
PARFR-200P Philippines	14,385	8,281.29
PARFR-201b Brasil	34,600	34,600.00 (Total)
PARFR-215 Brasil	16,775	14,309.90
PARFR-221Ba Brasil	13,970	2,953.50 (Total)
PARFR-221Bb Brasil	14,245	10,017.70 (Total)
PARFR-225B Brasil	39,226	-0-
PARFR-225M Mexico	4,693	2,352.90
PARFR-225Ma Mexico	41,063	-0-
PARFR-226B Brasil	41,305	15,899.18
PARFR-226C Chile	24,145	3,271.59
PARFR-227B Brasil	13,613	3,547.50
PARFR-229B Brasil	32,461	7,775.90
PARFR-229M Mexico	36,843	-0-
PARFR-238C Chile	6,985	-0-
PARFR-P52 Colombia	7,000	4,548.80 (Total)
PARFR-P54 Brasil	9,350	4,529.00 (Total)

PARFR SCIENTIFIC ADVISORY COMMITTEE

MEETING XXXV

The Peachtree Plaza
Atlanta, Georgia
Sunday, March 15, 1981

MINUTES

VOTING SAC MEMBERS PRESENT

John J. Sciarra, M.D., Ph.D.
Nancy J. Alexander, Ph.D.
Robert T. Chatterton, Ph.D.
Elizabeth B. Connell, M.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.
A. Albert Yuzpe, M.D.

VOTING SAC MEMBERS ABSENT

Judith L. Vaitukaitis, M.D.

PARFR STAFF PRESENT

Alfredo Goldsmith, M.D., M.P.H.
Diane Krier-Morrow, M.B.A.
Gerald I. Zatuschni, M.D., M.Sc.

USAID MEMBERS PRESENT

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

The thirty-fifth meeting of PARFR's Scientific Advisory Committee convened on Sunday, March 15, 1981 at 8:30 A.M. at The Peachtree Plaza in Atlanta, Georgia. Dr. John J. Sciarra presided as Chairman. Minutes of the November 16, 1980 meeting were approved.

I. ANNOUNCEMENTS

- A. Dr. Connell reported on AID's Research Advisory Committee (RAC) review of PARFR's site visit (Dec. 1980) team report. The report was most positive (a copy is included at the end of the agenda). RAC recommended that a site visit be scheduled for Dec., 1982.
- B. The scheduled dates for PARFR/SAC meetings are:

July 8, 1981 (Wednesday) - Chicago, Illinois
October 14, 1981 (Wednesday) - Phoenix, Arizona
- C. The following SAC members will be rotating off the SAC Committee as of this meeting: Edward C. Mather, D.V.M., Ph.D., Judith L. Vaitukaitis, M.D., and A. Albert Yuzpe, M.D. Their support during their tenure is appreciated.

NEW BUSINESS

A. EXTENSION PROPOSAL REVIEW

1. PARFR-214(110N) -- Danny H. Lewis, Ph.D., Southern Research Institute
"Optimization of an Injectable Microcapsule Formulation for
the 90-Day Delivery of Norethisterone"
Funding Requested: \$69,808 Length of Project: One Year
2. PARFR-214(83N) -- Lee R. Beck, Ph.D., University of Alabama
"Studies to Test an Injectable Delivery System for the Sustained
Release of Norethisterone"
Funding Requested: \$66,803 Length of Project: One Year

Dr. Zatuschni reported that UAB and SRI are submitting a physician-sponsored IND for the 90-day Injectable system this month. Assuming FDA approval, the continuation of this development will require support to SRI for the standardization of materials, methods, quality control procedures, etc. Also, additional pharmacokinetic studies in baboons at UAB will be necessary to further refine the release rate systems, both of polymer and drug. Finally, the supply of copolymer that has been utilized thusfar has been exhausted and new polymer will have to be synthesized. SAC voted to approve continuation of this project.

B. FORMAL PROPOSAL REVIEW

1. Rajendra G. Mehta, Ph.D., IIT Research Institute, Chicago
"Retinoids and Male Contraception"
Funding Requested: \$61,908 - 1st yr. Length of Project: Two Years
\$68,223 - 2nd yr.

Dr. Goldsmith reported that Dr. Rajendra Mehta (no relation to Dr. Raksha Mehta of Northwestern University) submitted a formal proposal at the request of PARFR in that his informal proposal was reviewed and approved for consideration of a formal proposal at our last SAC meeting. Dr. Mehta proposes to study six retinoids in order to determine which retinoid best inhibits spermatogenesis in rats at non-toxic doses, and to determine if the noted retinoid effects are reversible. The Committee consensus was to fund for one year and to analyze the results before awarding the 2nd year of funding.

2. Leonard J. Lerner, Ph.D., Jefferson Medical College of The Thomas
Jefferson University, Philadelphia
"Investigation of a Potent Orally Active Luteolytic Prostaglandin
That has Significantly Reduced Effects on Smooth Muscles"
Funding Requested: Approximately \$35,000 Length of Project: Six Months

Dr. Zatuschni reported that Dr. Lerner proposed to study the Farmitalia Carlos Erba FCE 20430 compound in the pregnant guinea pig as a luteolytic agent and with a separate submission UAB would look at the effects in the baboon. Dr. Connell stated that she felt this project to be "politically unfundable." The Committee voted to approve the project but felt it might be wise to focus on luteolysis.

E. TECHNICAL REPORTS

PARFR-105N (FINAL) -- Harry Rudel, M.D., Centro de Investigacion Sobre Fertilidad y Esterilidad, Mexico City, Mexico

"A Study of a Parenterally Administered Progesterone Cholesterol Formulation for Use as a Post-Partum Injectable Contraceptive"

PARFR-105N terminated on April 30, 1980. Dr. Rudel is nearly a year late with submission of a Final Technical report. The Committee commented as to the below average quality of the research. Mrs. Krier-Morrow commented on Dr. Rudel's statement (page 7) that he was unable to purchase a scintillation counter due to "administrative constraints." Unfortunately, he did not submit a proper request including three competitive bids. PARFR did not deem it appropriate to purchase a \$17,000 item of equipment at the end of the subcontract.

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

Dr. Richart distributed his report at the meeting and presented the current status.

PARFR-200P -- Ruben A. Apelo, M.D., JFMH Comprehensive Family Planning Center, Manila, Philippines

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

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

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

PARFR-207 -- Abdol H. Hosseinian, M.D., Cook County Hospital/Hektoen Research Institute, Chicago

"Hysteroscopic Sterilization by Using Uterotubal Blocking Devices"

PARFR-209NU/NMH - Raksha Mehta, Ph.D., Northwestern University Medical School, Chicago, Illinois

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

PARFR-210 (INC. PUBLICATION) -- M. C. Chang, Ph.D., Sc.D., The Worcester Foundation for Experimental Biology, Inc., Shrewsbury, Massachusetts

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

PARFR-211 -- Joseph E. Davis, M.D., New York, New York

"Study of Vas Occlusion in Animals Using Chemical Agents"

E. TECHNICAL REPORTS (continued)

PARFR-213T -- Mohammed M. Ahmad, M.D., Ph.D. and Ricardo H. Asch, M.D.,
The University of Texas Health Science Center at San Antonio
"The Study of the Intravaginal Insert (IVI) - Acceptability and
Side Effects"

PARFR-217(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-218 -- Leonard J. Lerner, Ph.D., Jefferson Medical College of The
Thomas Jefferson University, Philadelphia, Pennsylvania
"Development and Mechanism of Activity Studies With the Pregnancy
Terminating Compounds DL-111-IT and DL-105-IT"

PARFR-220 -- Joseph E. Davis, M.D., New York, New York
"A New Method for Obstructing the Vas Deferens by Direct Injection
of Chemical Agents: A Non-Operative Technique of Male Sterilization"

PARFR-221Ba -- Jose Freitas-Melo, M.D., Maternidade Climerio de Oliveira,
Salvador, Bahia, Brasil
"A Multi-Site Evaluation in Developed and Developing Countries of a
Technique and Equipment for Transcutaneous Closure of the Vas
Deferens by Electrocoagulation"

PARFR-221Bb -- Marcos Paulo P. de Castro, M.D., M.S., PROPATER, Sao Paulo,
Brasil
"A Multi-Site Evaluation in Developed and Developing Countries of a
Technique and Equipment for Transcutaneous Closure of the Vas
Deferens by Electrocoagulation"

PARFR-221C -- Edwin L. Adair, M.D., Medical Dynamics, Inc., Englewood,
Colorado
"A Multi-Site Evaluation in Developed and Developing Countries of a
Technique and Equipment for Transcutaneous Closure of the Vas
Deferens by Electrocoagulation"

PARFR-223 -- Joseph W. Goldzieher, M.D., Southwest Foundation for Research
and Education, San Antonio, Texas
"Antigestational Effects of LHRH Analogues"

PARFR-225 -- Danny H. Lewis, Ph.D., Southern Research Institute, Birmingham,
Alabama
"Preparation of Norethisterone Microcapsules"

PARFR-P51 (PUBLICATION) -- Harrieth M. Hasson, M.D., Chicago, Illinois
"Graphic Assessment of Uterine Shape"

E. TECHNICAL REPORTS (continued)

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

PARFR-P56 (FINAL) -- Nancy J. Alexander, Ph.D., Medical Research Foundation
of Oregon, Portland
"Efficacy Testing of Frisch Intravascular Implants"

PARFR-P58 -- Erwin Goldberg, Ph.D., Northwestern University,
Evanston, Illinois
"Immunologic Suppression of Fertility by a Synthetic Antigenic
Determinant of Lactate Dehydrogenase C₄"

PARFR-P61 -- Erwin Goldberg, Ph.D., Northwestern University,
Evanston, Illinois
"Immunologic Suppression of Fertility In Vitro by Antisera to a
Synthetic Antigenic Determinant of Lactate Dehydrogenase-C₄"

PARFR-P59 (FINAL) (INC. PUBLICATION) -- Richard E. Blackwell, Ph.D., M.D.,
University of Alabama in Birmingham
"The Development and Clinical Testing of an Estrogen Bromocryptine
Regimen as an Interceptive and/or Abortifacient Means of Fertility
Regulation"

PARFR-P60 -- Antonio Scommegna, M.D., Michael Reese Hospital and Maternity
Center, Chicago, Illinois
"Prostaglandin Antagonists as Local Antifertility Agents"

III. ADMINISTRATIVE

- A. PARFR's 5 year proposal was approved by AID and a Cooperative Agreement is being negotiated for the period of 7/1/81-6/30/86.
- B. PARFR is in the process of keeping up-to-date with project activity on current contract AID/DSPE-C-0035. PARFR is able to amend current sub-contracts to 6/30/82 and able to consider requests for additional funding on active projects only through 6/30/81.
- C. From the November 16, 1980 SAC meeting, the following extension proposals that had been reviewed and approved by SAC, were extended via amendment: PARFR-209NU/NMH Mehta, PARFR-203NU/NMH Chatterton and PARFR-205(95N) Zaneveld. PARFR-206SRI and 206UAB terminated and Drs. Lewis and Beck's approved continuation were rewritten as PARFR-235SRI and 235UAB.

ADMINISTRATIVE (continued)

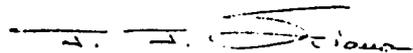
- D. The following approved formal proposals from the 11/16/80 SAC were sub-contracted:
1. PARFR-232 -- Erwin Goldberg, Ph.D., Northwestern University, Evanston
"Immunologic Suppression of Fertility by Synthetic Antigenic Determinants of Lactate Dehydrogenase-C₄"
Funding: \$60,018 Funding Period: 3/1/81-2/28/82
 2. PARFR-233 -- Joseph W. Goldzieher, M.D., Southwest Foundation for Research and Education, San Antonio, Texas
"Potential Antifertility Activity of LH/HCG Peptide Fragments"
Funding: \$44,090 Funding Period: 4/15/81-10/14/81

MISCELLANEOUS

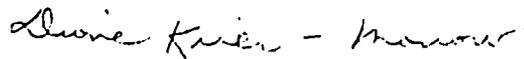
- A. Dr. Zatuchni reported on the upcoming PARFR Workshop, "LHRH Peptides as Female and Male Contraceptives" to be held May 13-15, 1981 at the Ambassador East Hotel in Chicago.

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 Krier-Morrow, M.B.A.
Director of Administration, PARFR



RESEARCH FRONTIERS IN FERTILITY REGULATION

INHIBITION OF PROGESTATIONAL ACTIVITY FOR FERTILITY REGULATION

Robert T. Chatterton, Ph.D.
*Professor, Department of Obstetrics and Gynecology
Northwestern University Medical School
Chicago, Illinois*

This review will describe some of the areas of current research on postovulatory contragestational techniques, and will mention certain factors that must be considered in the evaluation of potential new contragestational agents. It is not an exhaustive review; rather, it focuses upon some of the more promising new antiproggestational agents.

This is becoming one of the most important areas of research in the field of fertility regulation. The development of a safe and effective early postconceptive method is highly desirable, and holds considerable promise for providing control of fertility with relatively few untoward side-effects. Such a method could be self-administered; it would not require physician intervention; it would be effective on a postcoital or hindsight basis; it would not require high levels of motivation; and supply and distribution problems would be minimal.

POINTS OF ATTACK

Pregnancy depends on the availability of progesterone to the uterus; withdrawal of progesterone results in breakdown of the secretory endometrium. After implantation, the decidua which develops from the endometrial stroma is shed, along with the embryo, in the absence of sufficient progesterone. Progesterone is also required to maintain quiescence of the myometrium; a deficiency results in an increase in the amplitude of spontaneous contractions and a greater sensitivity of the uterus to oxytocin and prostaglandins. Progesterone has also been shown to diminish immunological recognition of histocompatibility antigens; this action of progesterone may serve to prevent cell-mediated rejection of fetal tissues, which are derived in part from the paternal genotype.

Availability of progesterone may be interfered with at sev-

eral levels (*Figure 1*). Pregnancy may be terminated at an early stage by substances that inhibit progesterone biosynthesis; increase the clearance of progesterone from the blood; compete with progesterone for receptors in the uterus; or indirectly oppose the action of progesterone on the myometrium.

Some advances have been made in recent years in all of these areas, however evaluation of new methods of progesterone inhibition is not a simple process. Many aspects of the action of new substances must be considered, in order to select one that has a low failure rate, while at the same time producing minimal residual and side effects. In addition to its contragestational activity, each compound must be tested for its uterotropic, androgenic, and glucocorticoid activities, and for antagonism of the biologic effects of estradiol, testosterone, and progesterone. Since many compounds that inhibit the effects of progesterone have opposing activities of their own, it is important that these compounds be tested for possible defeminizing properties and for some of the deleterious side-effects of estrogens, such as the tendency to increase blood pressure and clotting.

During the first trimester of pregnancy, when the contribution of the ovary is essential, and while the ovary depends on gonadotropins for progesterone secretion, disruption of pregnancy may be achieved in several ways:

- 1) Binding of gonadotropins to their receptors may be interfered with by compounds that compete for binding or cause a loss of available receptors (down-regulation).
- 2) The biosynthesis of progesterone in the corpus luteum may be interfered with by inhibitors of steroidogenesis or of conversion of pregnenolone to progesterone.

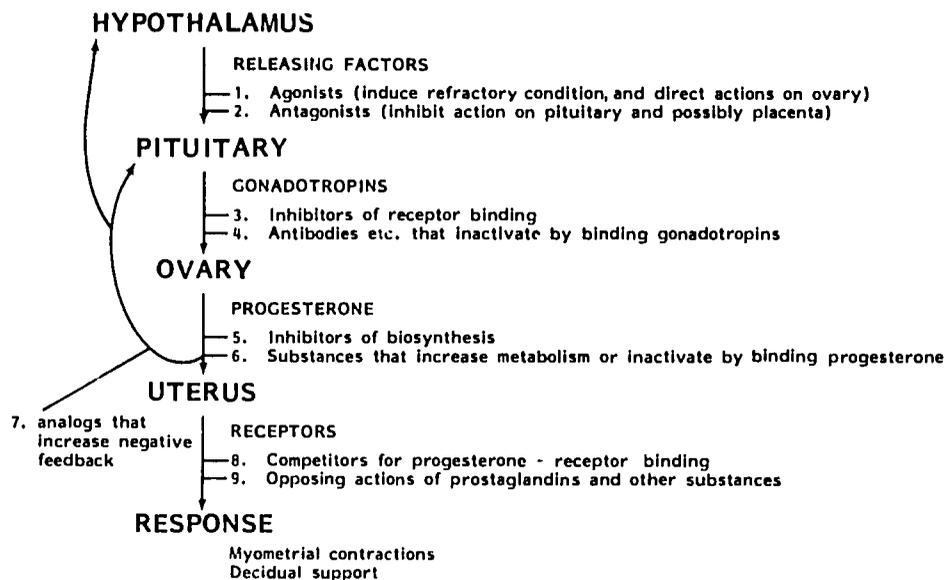


Figure 1. Points of interference with progesterone actions.

- 3) Progesterone may be removed from the circulation before it reaches its target organs, by increasing its metabolism or clearance from the body.
- 4) Progesterone may be interfered with at the cellular level by inhibitors that compete for receptor binding, and in this way progesterone is unable to exert its effects on its target cells.
- 5) Progesterone may be interfered with by substances or compounds that exert opposing actions. Typically, the substance would be an estrogen or prostaglandin, but compounds with fewer side-effects and greater specificity are being sought.

FACTORS IN TESTING CONTRAGESTATIONAL AGENTS

The following section will touch upon some of the problems associated with carrying out the evaluation and testing of new contragestational agents, providing an overview of the procedures and citing selected examples. A more detailed consideration of individual compounds will be presented in a later section.

Assessment of biological activities

With respect to the utility of a given animal species to serve as a model for studying the effects of candidate substances in the human, no single species is adequate to demonstrate effectively the quantitative relationships between dose and response, or even the relative potencies of the substances for the several biological effects being examined. Small laboratory animals probably should be used only to gain information about which organs are affected by a substance, and eventually about the molecular biology of the response. Laboratory animals can be used to provide information about the specificity and the mechanism of action of a compound. For example, is the compound a

competitive inhibitor of progesterone in the uterus or an inhibitor of steroid biosynthesis?

The irrelevance of extrapolating quantitative drug responses among species is obvious when one considers the extreme sensitivity of the rat to estrogens, an effect that has been related to the levels of circulating estradiol. At the preovulatory period, estradiol levels in the rat are only one-tenth those of women. The hamster is probably a better animal model for studying estrogen-related effects.

Predicting responses to pharmacologically modified steroids may be particularly difficult because, in addition to prolonging the half-life of the compound, structural modifications may result in altered binding to receptor molecules. There is evidence that the synthetic steroids produce different receptor complexes (1) and exert effects that may be intermediate between, or different from, those of any of the natural steroids. The way that an animal of any given species responds to a modified compound may differ significantly from the responses of other species; for example, the response to medroxyprogesterone acetate in rabbits differs from that of guinea pigs (24).

Dose requirements and mode of action

After the biological characteristics of the contragestational steroid are established, the minimal effective dose, or the dose to which 50% of the test animals respond (ED_{50}) should be established, along with the dose that is lethal to 50% of the animals (LD_{50}). Further elucidation of the time of pregnancy (rat) during which the substance is most effective provides information about whether the substance acts to interfere with the reproductive process before implantation, during implantation, while the pituitary is still required for gestation, or later.

If concomitant administration of progesterone, in doses that sustain pregnancy in the ovariectomized animal, is

capable of overcoming the contragestational activity, the substance may be interfering with the biosynthesis of progesterone. This interference may occur either by blocking the action of luteotropic hormones, or by inhibiting an enzyme in the biosynthesis of progesterone. Assays of serum progesterone will assist in the interpretation of the effects. LH assays will not be of value in pregnancy. Prolactin assays may be useful if the extreme diurnal variation is taken into account (59), but the applicability of this information to the human is questionable. In primates, a useful procedure for evaluation of luteolytic factors is determination of the ability of the substance to shorten the luteal phase of the menstrual cycle with and without administration of human chorionic gonadotropin (hCG). Not all compounds that interfere with corpus luteum function appear to be able to overcome the sustaining effect of hCG, as exemplified by studies of oxymetholone (32) and LH-RH (11).

If the substance being tested acts during implantation and thereafter, and is not associated with a decrease in serum progesterone, or if the action of the substance is not reversed by doses of progesterone that normally maintain pregnancy, a competitive inhibitor may be involved that prevents the progesterone from exerting its effects on maintenance of the decidua or on myometrial quiescence. However, the substance could also act as an estrogen to promote excitability of the myometrium, or it could stimulate synthesis of prostaglandins (or inhibit their catabolism), which would stimulate uterine contractions.

The rat is not the best model for such studies, because it does not respond to progesterone withdrawal or to prostaglandins with expulsion of the conceptus, as is the response in the human. In the rat, fetuses are resorbed, a process that takes about 4 days. Fetal death in the rat after progesterone withdrawal or prostaglandin administration in fact may be the result of uterine contractions, but the fetuses are retained.

The effects of progesterone withdrawal and prostaglandin administration can be most readily monitored in the rabbit or guinea pig, respectively, as these species have sufficiently pliable cervixes to allow expulsion of the fetuses during pregnancy. The guinea pig may be particularly useful for studying direct actions of prostaglandins on the uterus, since there is only a short span, from days 12 to 28 of the 60-day gestation period, during which the influence of the ovary is required to maintain pregnancy. An abortifacient action that is independent of the ovary can be readily studied either during the first 12 days or after midgestation. Conversely, the guinea pig is not a good model for studying actions of substances that decrease progesterone secretion, because in this species, suppression of uterine contractility is largely reliant upon relaxin and does not depend upon the influence of progesterone.

By contrast, in the rabbit, rat, mouse, and hamster,

maintenance of pregnancy depends upon ovarian progesterone until very late in gestation. None of these species may be considered good models for studies of prostaglandins as contragestational substances, however, because their ovaries are much more sensitive than are human ovaries to the luteolytic activity of prostaglandins. Inferences about contragestational substances, relative to the phase of human gestation in which pregnancy is dependent upon the ovary as a source of progesterone, can probably be made only from studies using other primates, particularly if the substance is known to have a direct action on the ovary.

Duration of effect

The next consideration in the testing of a contragestational substance is the duration of the effect. The plasma half-life ($T_{1/2}$) can be calculated in several animal species using the radioactively labeled compound. Obviously, a compound with a very short half-life will not be effective unless it is administered frequently. The half-life of a steroid may be improved in some cases by adding an ethinyl group, for example. Lan and Katzenellenbogen (38) have shown that, by the addition of an ethinyl group, estriol is made as active as estradiol-17 β in the assay in which uterine dry weight is the end-point. In evaluating the half-life of a compound that causes a decrease in serum progesterone, assessing the concentration of unbound (free) progesterone may be important. It is particularly important to measure the free steroid, when the possibility exists that the treatment may alter the serum concentration of corticosteroid-binding globulin (CBG), a property common to compounds possessing estrogenic activity. In the case of agents that act by causing a decrease in serum progesterone, it is apparent from several studies that for effectiveness, the duration of depletion of the progesterone is just as important as the degree of depletion.

The active form of the substance being tested is often not the form that is administered. Esters and even ethers are frequently cleaved *in vivo*, to give the form of the compound that is capable of binding to a receptor protein in a target cell. For example, the methoxy group of mestranol must be cleaved to a hydroxyl to produce ethinyl estradiol before it will become capable of exerting its effect. In studying properties of the contragestational agent, knowing the form of the compound that is active at the cellular level may be important; implants of the compound may be completely inactive if placed in a target tissue that does not have the enzymes necessary for conversion of the compound to its active form.

Route of administration

The active form and the half-life of the compound are considerations in establishing the optimal route of administration and the most appropriate vehicle in which to give the compound. The oral route may be most desirable to

the patient, but if the compound is metabolized to inactive products by the flora of the intestine, or is poorly absorbed or rapidly metabolized by the liver, using this route may not be feasible.

Drug tolerance and side-effects

Development of resistance to the medication is also obviously an important deterrent to continued use, especially with substances that must be administered frequently. Polypeptides, especially those with molecular weights greater than 10,000, can be immunogenic. The developing antibody titer against the substance will not only inactivate it, but the recipient could experience an anaphylactic reaction to the material.

The body may develop other kinds of compensatory reactions which may decrease the effectiveness of the administered compounds. An increase in the patient's tolerance to some drugs may involve the development of mixed function oxidases in the liver that inactivate the drug as part of the general detoxification process.

Side-effects of the contragestational drugs are most frequently related to vascular, gastrointestinal, and psychogenic actions. Certainly, organ weights and careful autopsies should be obtained in conjunction with toxicity studies.

For consideration of specific agents, contragestational substances have been divided into two groups: 1) those substances that act in some way to decrease the concentration of the progesterone that reaches the uterus; and 2) those substances that either directly antagonize the progesterone at the receptor site, or indirectly oppose the action of progesterone.

SUBSTANCES THAT INHIBIT PROGESTERONE SECRETION OR PROMOTE ITS CLEARANCE

Failure to maintain progesterone in the blood at levels required for maintenance of early pregnancy may be caused by a decrease in progesterone secretion by the ovary, or by an increased rate of metabolism and excretion of circulating progesterone. When the mechanism of action of a drug is well understood, there is no ambiguity about the cause of progesterone withdrawal, as detected by a decrease in the serum concentration of the hormone. However, even when a compound is known to decrease the rate of secretion of progesterone, the process by which it does this may not be known.

Prostaglandins

Although there is considerable evidence that prostaglandins (PG) produced by the uterus or administered to sheep or rats are luteolytic (46), that is, they bring about regression of the corpus luteum, there is little evidence that they

have a similar effect in the human, at least not with doses of prostaglandins that can be tolerated. In some studies, transient decreases in progesterone have been observed, when $\text{PGF}_{2\alpha}$ was given during the luteal phase of the menstrual cycle, but the extension of the menstrual cycle caused by injection of hCG was not abolished by $\text{PGF}_{2\alpha}$ administration (2). Serum 17-hydroxyprogesterone, which is indicative of ovarian secretion, decreased before serum progesterone levels declined, when women were given $\text{PGF}_{2\alpha}$ in early pregnancy. Nevertheless, some derivatives of the prostaglandins may have selective effects on the ovary. McCracken, Einer-Jensen, and Fried concluded that some 13-dehydro analogs of $\text{PGF}_{2\alpha}$ have very weak smooth muscle-stimulating activity, but are potent luteolytic agents in both the sheep and monkey (47). If these compounds can be shown to prevent progesterone secretion by the human ovary in the presence of hCG, they may be effective in menstrual induction, without causing the gastrointestinal side effects typical of the primary natural prostaglandins. However, altering the dosage and route of administration may also reduce the vomiting and diarrhea that are common side-effects of some of the analogs that apparently act on the myometrium.

The 15-methyl $\text{PGF}_{2\alpha}$ methyl ester is effective in 68% to 97% of cases, with an "acceptable" degree of side-effects, when given intravaginally or by intrauterine instillation (10), but gastrointestinal effects are reduced to a greater extent by 16,16-dimethyl PGE_2 , and even more by 16,16-dimethyl-*trans*- Δ^2 - PGE_1 methyl ester and 16-phenoxy- ω -tetranor- PGE_2 methylsulphonylamide, without a loss of effectiveness (10).

The primary, if not exclusive, action of the prostaglandins that have been tested clinically appears to be the effect of the prostaglandins on myometrial contraction, since doses that fail to affect ovarian function result in abortion. Continued tonic contraction of the myometrium may result in ischemia, which deprives the conceptus of essential nutrients and oxygen. In this respect, the prostaglandins used as contragestational agents should be classified as indirect antagonists of progesterone. Nevertheless, it is possible that local concentrations in the ovary are elevated to luteolytic levels. Prostaglandin levels may be increased locally in the ovary by analogs that have a particular affinity for the ovary, by substances that stimulate ovarian PG production, or by substances, such as the triazole compounds that are considered later, that inhibit PG catabolism.

LRF agonists

Interestingly, luteinizing hormone releasing hormone (LRF), and particularly its more potent agonists (11), as well as antibodies to LRF (36), are both capable of interfering with normal ovarian function in somewhat similar ways. The LRF "super" agonists can inhibit steroid produc-

tion by the ovary of hypophysectomized rats (45) and by luteal cells *in vitro* (16); however, apparently by interfering with binding of LH to its receptor, the agonists also induce a refractory state in which the pituitary *in situ* fails to produce LH after an initial response (18). Casper and associates studied the contragestational properties of the LRF agonist [D-Trp¹,Pro²NEt³]-LRF (11). This peptide, (LRF-Ag), is 144 times more potent in stimulating LH and FSH release than is natural LRF, because of its resistance to enzymatic degradation, and its increased uptake and retention by pituitary tissue. It was tested by the subcutaneous administration of 50 μ g of LRF on 2 successive days during the luteal phase of the menstrual cycle in 5 normal women. Luteolysis, judged by serum progesterone and onset of menses, was hastened in 17 of 28 cycles. The LRF agonist was effective when given 6 or more days from the LH surge, in agreement with other studies (12, 41). Unfortunately, the luteolytic effect was completely overcome in the presence of hCG at levels of 85 mIU/ml or less. When tested in women who were less than 8 weeks pregnant, LRF was also not effective (11). It would seem, at least with the agonists that have been tested so far, that LRF analogs do not offer a means of inducing menstruation in the presence of hCG. Other applications for LRF agonists, such as inhibition of ovulation by administration as a nasal spray, have shown promise, however (5).

Immunization against hCG

The immunological approach has been used to prevent rescue of the corpus luteum after conception. Immunization of the female against hCG would appear to be the most successful of the immunological methods. It has the advantage over methods that utilize antigens associated with ova (58) or sperm (29) in that humeral antibodies are available to combine with an antigen that passes through the blood. To combine with the fertilized ovum or sperm, the antibodies must be secreted into the lumen of the reproductive tract. Antibodies directed against antigens characteristic of the ovum may interfere with the development or even the survival of primary oocytes in the ovary, and thus bring about permanent sterilization. Another risk is that the induction of antibodies to antigens from ova or other specific cell types may result in development of an autoimmune disease that is not restricted to the particular cell or tissue that was the origin of the antigen. A third danger is that immune complexes deposited in the kidney can cause kidney failure. In the case of hCG, this problem is minimal, although it is still a concern, since many normal cells apparently produce very small amounts of this glycoprotein (15). Only the syncytiotrophoblast produces amounts having biological significance, however.

Active immunization with hCG has been studied extensively by Talwar and associates in New Delhi (63), and by Stevens in Columbus, Ohio (62). In a study of baboons actively immunized with partially purified baboon

chorionic gonadotropin (bCG), Stevens found that pregnancies were not sustained. Evidently, the bCG reaching the ovary was insufficient to promote the necessary steroid production. Curiously, when a highly purified bCG was used as the antigen, no effect on fertility was observed. One explanation is that the large amount of bCG secreted by the trophoblast in early pregnancy was more than sufficient to neutralize the circulating antibody. High titers of antibody are obviously required.

Specificity of the antigen is important to eliminate cross-reaction with LH. If the method is to be practicable, pituitary LH should not be neutralized. This is important from two points of view. First, LH is a "self" antigen produced constantly, albeit at different rates, and antigen-antibody complexes may become deposited in the kidney and vasculature if antibody titers remain elevated. Second, normal menstrual cycles probably would not continue, and reversal of the sterilizing effect may be impossible. Ideally, the active immunization procedure would be reversible, if progesterone were provided to maintain pregnancy once conception had occurred until the placenta had begun to produce sufficient progesterone. To allow for normal menstrual cycles and potentially, conception, baboons (61) and women (64) have been immunized with the β -subunit of hCG. In some cases, animals have been immunized with only the C-terminal 45 amino acid residues of the β -subunit, in order to produce antisera that are specific for the part of hCG that is most distinct from hLH (23). Methods using the hCG fragment conjugated to tetanus toxoid, or methods using Freund's adjuvant, have produced highly specific antisera. So far, successful contragestational immunizations have not been achieved in the few women who have been treated, but the β -hCG immunization has been successful in baboons (61).

Lithospermic acid

Other methods for interfering with gonadotropin support of the ovary have some potential as well, although none has been studied sufficiently to characterize its effectiveness, particular benefits, or risks. One such substance is extracted from *Lithospermum ruderale*, and has been used as a "tea" by Indians of the Shoshone tribe to reduce fertility (26). In rats and chicks, cold water extracts, especially those allowed to oxidize in the crude extract, have caused a reduction in gonadotropic effects. When studying the dose response of extracts in the chick, Breneman and Zeller found that with increasing doses, the pituitary content of gonadotropin increased, but at the highest dose of the extract, the pituitary content was reduced to levels below those seen in control animals (8). This was interpreted as inhibition of gonadotropin release with suppression of gonadotropin synthesis at the highest doses. Cold water extracts of *L. ruderale* also impaired development of gonads and accessory sex organs of the immature rat (26).

Such extracts can also inhibit the ovarian and uterine

weight increases caused by pregnant mare serum gonadotropin. The extract may act by inhibiting gonadotropin binding or by direct effects on the ovary. Either the active principle has effects on both the pituitary and the ovary, or it acts differently in the rat and the chick. It does not, however, compete with steroids for their receptors (25). Further study is required to distinguish between the alternatives. A polyphenol that has been named lithospermic acid has been isolated and chemically described (35). An oxidation product of lithospermic acid apparently is the active substance in plant extracts, but more work must be done on the structure of the biologically active form before a chemically pure substance will be available for pharmacologic studies.

Pineal peptides

Another substance that acts to suppress pituitary gonadotropin secretion was purified as a low molecular weight polypeptide from the pineal gland (51). At least two different peptides have been separated from melatonin and are capable of blocking the compensatory ovarian hypertrophy after hemiovariectomy. The preovulatory LH surge and ovulation can also be suppressed by these substances (52), and there is some evidence for postovulatory suppression of ovarian function as well. Perhaps a peptide substance that directly inhibits pituitary gonadotropin secretion rather than acting indirectly, as LRF does, could be identified with a minimum expenditure of time.

Inhibitors of ovarian steroid synthesis

Aminoglutethimide. The other types of compounds that act by interfering with progesterone secretion are those that inhibit steroidogenesis in the ovary and placenta. Aminoglutethimide is a compound that blocks the conversion of cholesterol to pregnenolone. Glasser and co-workers found that aminoglutethimide phosphate, when given to rats as a single intraperitoneal injection (150 mg/kg) after implantation, caused abortion in only 25% of the animals, although plasma progesterone was depressed by 80% within 30 minutes (28). Recovery of normal

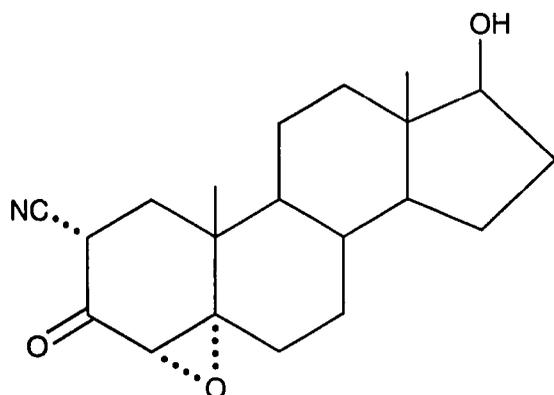


Figure 2. Trilostane

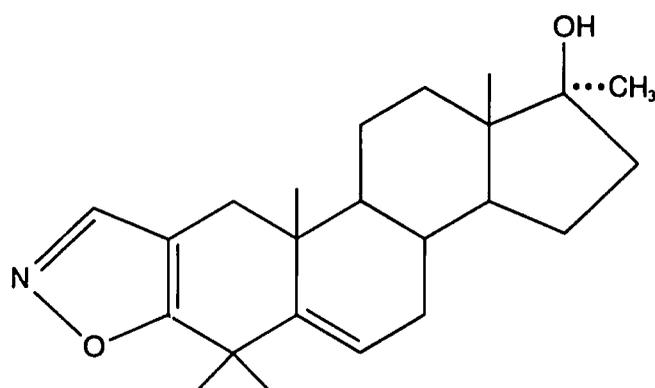


Figure 3. Azastene

plasma progesterone occurred within 48 hours. However, when three injections of the same dose were given, abortion occurred in all rats within 72 hours. This effect could be blocked by the administration of 5 mg of progesterone/rat/day, but LH, hCG, prolactin, and 20 α -dihydroprogesterone did not block the effect. The importance of both the degree and duration of progesterone depletion for interruption of pregnancy is well illustrated in this study.

In another study of aminoglutethimide in baboons, a similar effect was noted. The drug was given for 1 to 3 days to 6 baboons that were pregnant for 31 to 99 days. Serum progesterone was reduced to as little as 3.2% of the initial concentration in one animal, and to less than 20% of initial concentration in 4 of 5 of the remaining baboons, but pregnancy continued for at least 3 weeks. The fact that peripheral blood levels may not reflect the concentration at the uteroplacental junction was emphasized, particularly if the inhibitor is more effective in inhibiting ovarian than placental progesterone biosynthesis. Here, also, the duration of depletion must be considered as well.

Csapo and Erdos showed that after administration of anti-progesterone antiserum (APA) to rats, the effect could still be blocked if progesterone was given 3 hours later, but that the progesterone depletion induced irreversible changes in most animals by 6 hours, with the result that progesterone administration could not rescue the pregnancy (22). Unfortunately, the dose of aminoglutethimide could not be increased because of the CNS-depressing activity of the drug. Attempts to modify the structure to obtain greater specificity for inhibition of steroidogenesis have not been successful, but the congeners that have been tested by Glasser and colleagues are only those with modifications of the piperidine moiety (27). Aminoglutethimide at relatively low doses greatly enhanced the abortifacient activity of PGF_{2 α} in the rat, however (27), a finding that may be worthy of further investigation.

Oxymetholone. Oxymetholone was one of several compounds originally tested as substances that might increase progesterone clearance by increasing its metabolism (7).

The drug successfully shortened the luteal phase of the menstrual cycle, but this shortening apparently was achieved by an inhibition of progesterone biosynthesis. Oxymetholone has also been used as an anabolic steroid, and treatment of women after ovulation suppressed serum progesterone by 50% to 80%, and shortened the cycle by 6 to 8 days (19). The drug did not interfere with luteal function in women who also received hCG (4), nor did it terminate pregnancy when given for 7 to 10 days in cumulative doses of 350 to 3000 mg (9). This experience emphasizes the importance of testing contragestational drugs initially in the presence of hCG, if their mechanism is luteolysis, before testing their abortifacient activity in pregnant women.

Trilostane and azastene. Trilostane and azastene (Figures 2 and 3) are competitive inhibitors of 3β -hydroxysteroid dehydrogenase (HSD) (55). Inhibition of this enzyme presumably will block conversion of dehydroepiandrosterone to androstenedione as well as of pregnenolone to progesterone. Since conversion of pregnenolone to progesterone occurs in the adrenal as well as in the ovary and placenta, production of steroids, including cortisol and aldosterone, that succeed progesterone in the metabolic pathways of these organs, will be decreased. Some organ-specificity of these inhibitors, however, has been observed. Trilostane appears to be primarily a suppressant of adrenal steroidogenesis. Given orally to rats, it inhibits corticosterone and aldosterone production, and elevates circulating levels of pregnenolone at doses that are lower than those that produce adrenal hypertrophy or that inhibit gonadal steroidogenesis (57). In the monkey, also, serum cortisol is decreased at doses that are less than those necessary to terminate pregnancy.

Azastene appears to be equipotent in inhibiting the adrenal and ovary of the rat. However, Azastene produced a luteolytic effect and terminated pregnancy in the monkey at 500 to 1000 mg/day for 5 days, even though no effect on corticoid production was detectable (56).

Concurrent progesterone administration prevents the abortifacient action as expected. Schane and Creange

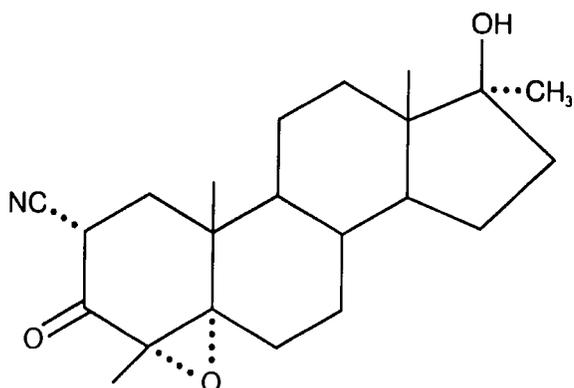


Figure 4. Win 32,729

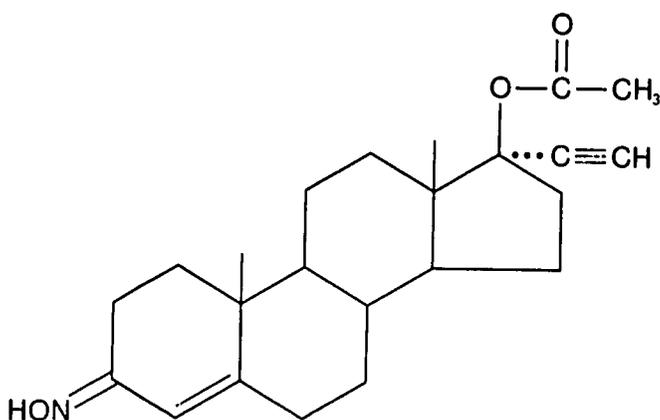


Figure 5. 17β-acetoxy-17α-ethinyl-4-androstene-3-one-(3-oxime) (ORF 9371)

used an interesting technique to distinguish between primary effects of this and other HSD inhibitors on progesterone secretion from secondary effects that decrease progesterone only as a consequence of disrupted placental circulation (55). They have administered a synthetic progestogen such as Provera (which can be distinguished from progesterone in the radioimmunoassay) along with an HSD inhibitor, to maintain pregnancy. Decreases in serum progesterone, other than those that can be attributed to Provera alone, must be due to the effect of the inhibitor on steroidogenesis. By this criterion, the HSD inhibitors are directly inhibitory to progesterone biosynthesis.

The undoing of Azastene, the recently most promising HSD inhibitor, is the by-now-familiar inability of the drug, in the presence of hCG, to induce luteolysis in women. The discrepancy between the effectiveness of Azastene in the pregnant monkey and in the human is puzzling. Perhaps the drug is metabolized differently. It may be inactivated more rapidly in the human, or an active metabolite may be produced more efficiently in the monkey.

Currently, investigators at Sterling-Winthrop have focused their attention on Win 32,729 (Figure 4), a related steroidal compound that is more potent than Azastene in the monkey by a factor of 10. Its interceptive activity is also prevented by progesterone, and cortisol is suppressed in the monkey when only 5 times the effective abortifacient dose is used.

Danazol. A compound that has found use in endometriosis, because of its activity in suppressing steroid-mediated actions on the uterus, is Danazol. This compound is related to ethinyl testosterone, by the addition of an isoxazole ring. It not only causes suppression of FSH and LH secretion, but it apparently also decreases progesterone secretion by a direct effect on the ovary. In addition, it binds to progesterone and androgen receptors, antagonizing the actions of these hormones. Postovulatory treatment causes a se-

vere depression in serum progesterone levels and shortens the luteal phase to 10 days; hCG treatment does not bring about recovery of luteal function (3). Thus, Danazol has real potential for occasional use, but the daily dose required for contraceptive protection is minimally 200 mg (17), a dose of steroid that would certainly burden liver detoxification ability.

Passive immunization against progesterone

The last of the progesterone-suppressing methods is one that we have been investigating at Northwestern University. This is still in the developmental stage, but in principle what we are attempting to do is to prepare a specific, high-affinity absorbent that will remove a sufficient amount of progesterone from the body to cause involution of the endometrium and promote contractility of the myometrium. To this end, we have produced a large volume of antiprogestone antiserum (APA) that is capable of inducing abortion in rats. This approach was reported by Csapo and associates (21) and Raziano, Ferin, and Vande Wiele (54) previously.

Although the concentrations of free progesterone measured in serum of these rats by the equilibrium dialysis method are not detectably different, progesterone is decreased in uterine tissue within 36 hours. In the interim, the APA injection causes a surge of LH and FSH release and a transient increase in concentrations of progesterone in the ovary, uterus, and other tissues (14).

Whether this burst of gonadotropin activity, presumably induced by an initial depletion of progesterone in the pituitary, is an obligatory component of the subsequent contragestational decline in progesterone is not known. In any event, the dose of APA which was sufficient to bind 6 μ g of progesterone was sufficient to bring about an eventual depletion of progesterone, and abortion.

The next step toward development of a practical application of this absorbent is to encapsulate APA in a manner that prevents its absorption into blood, but permits entry of progesterone into the microcapsules to bind to the entrapped APA. Ideally, such microcapsules would be effective

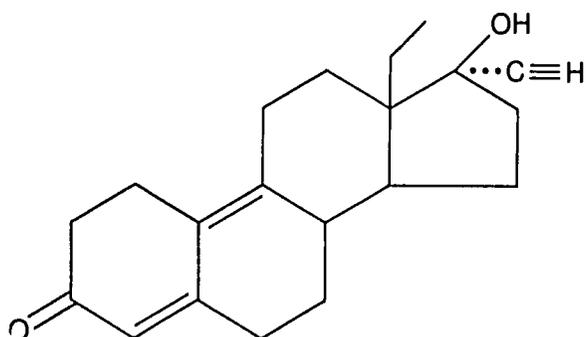


Figure 6. Norgestrienone (R2323)

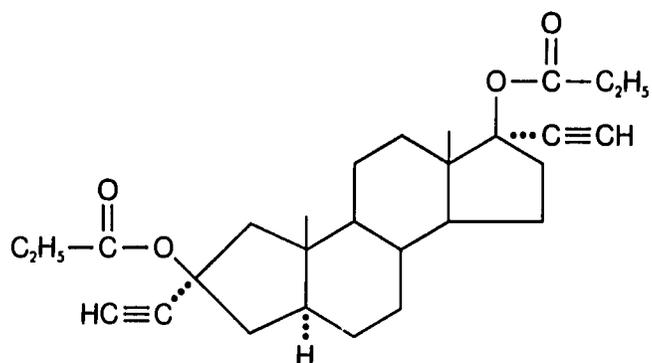


Figure 7. Anordrin

orally, absorbing progesterone that passes through the enterohepatic circulation or that diffuses into the gut.

Such an encapsulated preparation has been injected intraperitoneally, to compare the effect with that of the soluble antiserum injected into the same site. No detectable leakage of APA from the microcapsules was noted, as determined by the absence of antibody in blood. In contrast to a greater than 3-fold increase in serum progesterone in rats injected with soluble APA, a decline in serum progesterone occurred within 48 hours, falling to less than 4 ng/ml in rats receiving the encapsulated APA. Interestingly, a transient decrease in serum progesterone occurred in rats receiving the encapsulated polymer without APA, reflecting the relatively weak but abundant potential binding of progesterone to this material. This transient decrease was sufficient to reduce the number of viable fetuses by 50%. In this initial test, the polymer with APA was lethal to all rats, whereas all rats given the polymer alone survived the experiment. Further work is underway to study dose responses, to evaluate more hydrophilic polymers, and to investigate the oral route of administration.

PROGESTERONE ANTAGONISTS

Compounds included in this category are those that interact with progesterone competitively or noncompetitively for receptor binding, or that oppose an action of progesterone on the uterus. Only a few compounds have been found that act by competition for the progesterone receptor.

ORF 9371

One such compound is a steroidal antiprogestin from Ortho Pharmaceutical Co., ORF 9371, which has the structure 17 β -acetoxy-17 α -ethinyl-4-androstene-3-one-(3-oxime) (Figure 5). This compound is neither estrogenic nor antiestrogenic, and it has no inhibitory effect on gonadotropin secretion (31). It does inhibit uterine proliferation induced by progesterone in rabbits, and it prevents decidual development and implantation in rats. It does not bind to the estrogen receptor, although the

analog without the acetate group binds weakly, and it may be a metabolite *in vivo*.

R2323

A compound with similar properties is norgestrienone (R2323) (Figure 6). However, Mora and associates found no abortifacient activity of this compound in doses of 100 mg to 400 mg, when it was administered to 57 women shortly after missed menstrual periods (48). It does suppress serum progesterone in nonpregnant women, but hCG reverses this effect, which suggests that R2323 acts to suppress gonadotropin secretion.

Anordrin

Another compound that may act by antagonizing progesterone is Anordrin (Figure 7). This compound was considered an antiprogestin by Pincus and Banik as a result of their search for orally active contraceptive agents in the early 1960s (53). Recently, a report from China has disclosed extensive clinical investigations of Anordrin as a postcoital contraceptive: as the author noted, "The rate of protection against [conception] reached more than 99%..." (37). Clinical trials showed that women who received Anordrin did not have the excessive proliferation of the endometrium that is seen with postcoital estrogens. In most cases, suppression of the endometrial proliferation was seen, and some women had atrophic changes of the endometrium (37). Animal studies of the drug suggest that it has both luteolytic and estrogenic activity (20, 30), yet the great species differences and non-parallel dose-response curves require additional studies to adequately define the mode of action of Anordrin.

ORF 3858 and other estrogenic compounds

Other compounds, such as 2-methyl-3-ethyl-4-phenyl- Δ^1 -cyclohexene carboxylic acid (ORF 3858) (Figure 8), that have abortifacient activity, and are structurally related to diethylstilbestrol (DES) (Figure 9), have been found to be converted *in vivo* to products that have estrogenic properties. A deliberate effort has been made to prepare derivatives of DES and hexestrol that structurally resemble estriol, that is, that have hydroxyl groups on two adjacent carbon atoms in one ring, but not in both rings

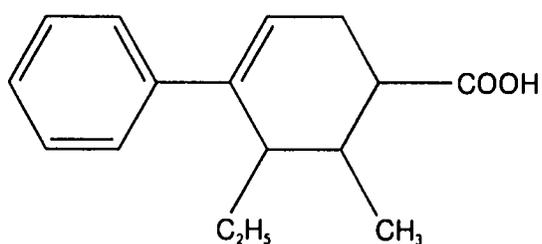


Figure 8. 2-methyl-3-ethyl-4-phenyl- Δ^1 -cyclohexene carboxylic acid (ORF 3858)

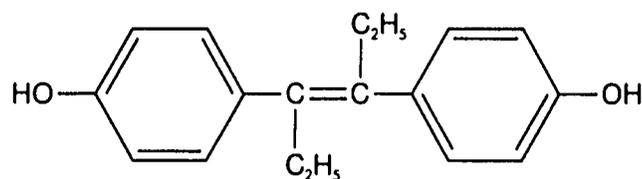


Figure 9. Diethylstilbestrol (DES)

(65). These compounds have reduced estrogenic activity in relation to their interceptive activity, but since they retain significant estrogenic activity, they have not been tested clinically.

Estrogens themselves, however, have been used as post-ovulatory interceptives, on the assumption that the infrequent use after unprotected coitus will not present the health hazard associated with long-term exposure to estrogens. In one study, pregnancy could be adequately prevented by giving women 50 mg of DES/day, 30 mg/day of conjugated equine estrogens, or 5 mg of ethinyl estradiol (EE)/day, for 5 consecutive days, if treatment was begun within 72 hours after unprotected coitus at midcycle (6). Nausea was experienced by about half of the patients, but without serious side-effects. In macaques given marginally abortifacient doses of estrogen, no fetal abnormalities were observed (49). Some improvement in this procedure is believed to accrue with the combined EE/dl-norgestrel treatment (60, 66). In the latter study, in which two tablets were taken immediately after unprotected intercourse, followed by two tablets within 12 hours (0.05 mg EE and 0.5 mg dl-norgestrel per tablet) no failures were observed among the two-thirds of patients who returned for follow-up. Still, about 12% experienced severe nausea and 8% reported vomiting. The mechanism for the estrogen effect presumably is in counteracting the progesterone action on the myometrium as well as the decidua; some lowering of plasma progesterone has been observed with DES, but only when treatment was begun on the day of the LH peak (40). The length of the luteal phase was unaltered, however, and an effect on secretion of progesterone by the intact corpus luteum seems unlikely. Progestins have also been administered without the estrogenic component for interceptive purposes. Norethindrone in particular has been well studied in this manner, but has proven ineffective (50).

Some evidence has been obtained for prostaglandin biosynthesis, as a mechanism by which the estrogens act to terminate pregnancy. Auletta and co-workers have shown that at least the luteolytic effect of estrogens in the rhesus monkey can be prevented by simultaneous administration of indomethacin (4). Administration of prostaglandins themselves in different forms and by different routes has proven to be an effective method of terminating early pregnancy, as discussed above and reviewed extensively elsewhere (33, 34). Most forms of prostaglandins act to

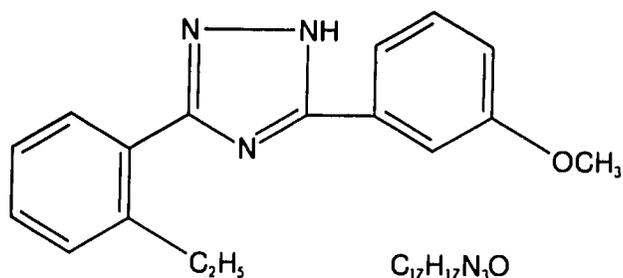


Figure 10. 3-(2-ethylphenyl)-5-(3-methoxyphenyl)-1H-1,2,4-triazole (dl-111-IT)

intercept pregnancy in the human at the uterine level, although some of the newer forms, particularly the 13-dehydro derivatives, may also have a luteolytic action that will contribute to their effectiveness in terminating pregnancy, as discussed above (47).

The triazole compounds

The difficult problem in applying prostaglandins to fertility regulation has been to limit the effects as much as possible to the reproductive organs.

One method of doing this may be to selectively promote synthesis or prevent metabolism of prostaglandins in organs of the reproductive tract. The triazole compounds being studied by Lerner and co-workers may have this potential, since they act to prevent metabolism of prostaglandins and thereby increase their availability to the organs in which they are produced, although presently available compounds do not have this degree of specificity (63).

Lerner has selected one triazole compound produced by Lepetit of Milan for further study. The compound is 3-(2-ethylphenyl)-5-(3-methoxyphenyl)-1H-1,2,4-triazole, and it has been assigned the symbol dl-111-IT (Figure 10). This compound is most effective in the monkey when injected intramuscularly between days 34 and 38 of gestation, at a dose of 10-25 mg/kg body weight. With a treatment on 5 successive days, 2 to 5 mg/kg/day was effective. In hamsters and rats the abortifacient dose remained effective in all animals when 4 mg/day of progesterone was given concomitantly. Thus, abortion does not depend on the luteolytic effect of the drug.

In this respect, and with regard to the side effects, dl-111-IT appears to act as a prostaglandin; metabolism of prostaglandins is inhibited in the reproductive tract, in the lung, and probably in other organs as well (42). The compound has no estrogenic, androgenic, or progestogenic activity, nor does it inhibit these activities of other compounds. It is relatively nontoxic, the LD_{50} being 300 times the ED_{50} in the hamster, but its greatest shortcoming, aside from its lack of specificity for the reproductive tract, may be its lack of activity by the oral route.

ORF 5513

Some other nonsteroidal compounds that have contragestational activity have been investigated. One relatively new compound is the salt of 3,5-bis-(dimethylamino)-1,2,4-dithiazolium chloride (ORF 5513) (31) (Figure 11). It is an unusual compound, in that it acts at several levels to interrupt the reproductive process; it inhibits ovulation, it inhibits implantation, and it is abortifacient. The compound lacks hormonal activity and has no apparent luteolytic effect. It is effective in preventing ovulation at doses of from 0.01 to 0.1 mg/kg body weight/day, but only if it is started 3 days or more before ovulation. Effective abortifacient doses in the rat were lowest between days 10 and 13 of pregnancy, when 5 mg/kg was effective in producing cellular changes in the chorionic villi and chorionic-fetal vessels.

Trichosanthin

Other interesting compounds under investigation are natural products that have been used for many centuries as aqueous extracts or "teas" to induce menstruation. Trichosanthin was isolated by Chinese scientists from the root of *Trichosanthis kirilowii*. It is a basic protein with a molecular weight of 18,000; it is said to induce abortion and to have an ameliorating effect on choriocarcinoma (13). Interestingly, it does not induce abortion in the two most commonly used laboratory species, the rat and the hamster, or in other species in early pregnancy. Hahn and associates have studied Trichosanthin in the guinea pig and the mouse (31). It has no effect on contractions of the nonpregnant guinea pig uterus, but it induces contractions in the pregnant animal when given intraperitoneally as a single injection of 200 μ g at the end of the first trimester (16-22 days). It has been postulated that Trichosanthin induces prostaglandin action within the uterus, and preliminary data show that indomethacin inhibits its effect. If this is an organ-specific induction of prostaglandin biosynthesis it would, of course, have substantial advantages over administration of prostaglandins for elective abortions.

Zoapatanol

Zoapatanol is another natural product that has been investigated recently by the group at Ortho. Teas made from the

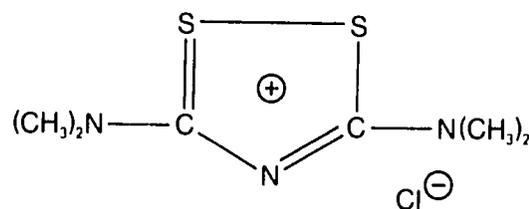


Figure 11. 3,5-bis-(dimethylamino)-1,2,4-dithiazolium chloride (ORF 5513)

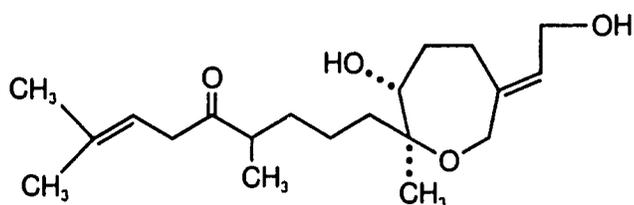


Figure 12. Zoapatanol

Montanoa tomentosa (zoapatle) plant have been used in Mexico for facilitation of childbirth, stimulation of menses, and termination of early pregnancy (39, 44). The diterpene structure containing an oxepane ring has been reported recently (Figure 12). In rats and hamsters, this compound inhibits implantation when given on days 1 through 6 of pregnancy. It also has an effect after implantation in the guinea pig; when given at the end of the first trimester, intrauterine death occurred. Landgren administered zoapatle orally to 6 women in early pregnancy (39). Administration resulted in menstrual-like cramps and a significant dilatation of the cervix in all subjects, but the zoapatle did not cause luteolysis, based on assays of plasma progesterone. No changes were detected in the cardiovascular system or in blood lipids, proteins, or electrolytes, and hematologic, liver, kidney, and thyroid function tests were all normal. Since definite uterotonic contractions are produced, this compound shows promise as a compound that may produce selective stimulation of prostaglandin secretion. Zoapatanol differs from Trichosanthin in that it is not a protein, and it acts earlier in pregnancy than does the Trichosanthin.

SUMMARY

Some new methods have been developed that act at each of the areas in which progesterone biosynthesis or action can be inhibited. Some of the new "super" agonists of LRF that may be absorbed intranasally interfere with gonadotropin-mediated ovarian secretions. If sufficient down-regulation of ovarian gonadotropin receptors can be achieved to prevent rescue of the corpus luteum by hCG, LRF agonists could prove to be an excellent once-a-month medication or menstrual inducer. The agonists are highly specific and free from unpleasant side-effects. Gonadotropins may be suppressed by pineal peptides as well, but a postovulatory application seems unlikely; perhaps these compounds, as well as LRF antagonists, could be used during the follicular phase of the cycle to suppress gonadotropins to the extent that only follicular luteinization occurs, without ovulation.

At the level of the ovary, hope has not completely faded for a luteolytic prostaglandin derivative, such as one of the 13-dehydro prostaglandins, that has only minor actions on smooth muscle. On the other hand, some possibility seems to exist of relatively specific actions on uterine musculature by the 16,16-dimethyl prostaglandins and other C-16 derivatives; these prostaglandins also have substantially reduced gastrointestinal effects. There is now evidence that the combining of an inhibitor of ovarian steroidogenesis with a prostaglandin may produce a synergistic interceptive action. Some inhibitors of steroidogenesis, such as Azastene, display a high degree of specificity for the ovary, and have minimal effects on the adrenal gland. Azastene itself has not proven effective in terminating pregnancy, but other similar compounds, which have a longer biological half-life and potentially greater activity in inhibiting placental steroidogenesis, are being developed. Other compounds, primarily natural products that have been used as "teas" for fertility control in different cultures around the world, also are being purified, synthesized, and investigated.

The target organs and sites of action of these compounds have not been well-characterized to date, but some, such as lithospermic acid, appear to suppress ovarian secretions, while others, such as zoapatanol, may stimulate endogenous production of prostaglandins. Endogenous prostaglandins may also be the active agent in the triazole compounds that were developed from psychoactive drugs; in this case, the drug causes a build-up of prostaglandins by decreasing their metabolism. The triazole compounds are active in primates, but they suffer somewhat from lack of specificity, causing gastrointestinal and respiratory side-effects.

Secreted progesterone may be inhibited in its actions by

increasing its clearance, by interfering with its binding to receptors, or by modifying the end-organs in such a way that the progesterone cannot exert its effects. Passive immunization to progesterone, while a useful tool for investigators, is limited because of immunological and other problems associated with repetitive injections of proteins.

Attempts are now being made to encapsulate antiprogesterone antibodies in a form that will allow the steroid to be bound, without allowing release of antibodies into the circulation. Steroid hormone analogs, such as norgestrienone, that bind to progesterone receptors, are capable of preventing the biologically active hormone from exerting its side-effects, but so far, the only drug that has been effective in the presence of hCG is Danazol; the main shortcoming of Danazol in this respect is the very large dose required and the attendant and potential additional

side-effects.

Other compounds that are competitive inhibitors may be nearing the time when clinical testing can be done. Substances interfering indirectly with the physiological function of progesterone, such as the estrogens, certainly also have a place in the treatment of unprotected midcycle coitus.

As many new compounds are discovered or rediscovered, and are investigated with the objective of promoting their optimal contragestational effect with a minimum of undesirable side-effects, more methods for regulation of fertility will become available. Methods more appropriate to the circumstances of gestational age and health needs of women of different cultures and convictions will increase the acceptability and use of contraception among couples interested in regulating their own fertility.

REFERENCES

- Agarwal MK: Evidence that natural vs synthetic steroid hormones bind to physicochemically distinct cellular receptors. *Biochem Biophys Res Commun* 73:767-772, 1976.
- Arrata WSM, Chatterton RT: Effect of prostaglandin $F_{2\alpha}$ on the luteal phase of the cycle in nonpregnant women. *Am J Obstet Gynecol* 120:954-959, 1974.
- Asch RH, Fernandez EO, Silerkhodr TM, Bartke A, Pauerstein CJ: Mechanism of induction of luteal phase defects by Danazol. *Am J Obstet Gynecol* 136:932-940, 1980.
- Auletta FJ, Caldwell BV, Speroff L: Estrogen-induced luteolysis in the rhesus monkey, reversal with indomethacin. *Prostaglandins* 11:745, 1976.
- Bergquist C, Nilius SJ, Wise L: Intranasal gonadotropin-releasing hormone agonist as a contraceptive agent. *Lancet* 2:215-217, 1979.
- Blye RP: The use of estrogens as post-coital contraceptive agents. *Am J Obstet Gynecol* 116:1044, 1973.
- Bolch OH, Warren JC: Induction of premature menstruation with catatoxic steroids. *Am J Obstet Gynecol* 111:1107, 1971.
- Breneman WR, Zeller RJ: *Lithospermum* inhibition of anterior pituitary hormones. *Biochem Biophys Res Commun* 65:1047-1053, 1975.
- Brenner PF, Mishell DR: A study of the abortifacient effect of oxymetholone in early gestation. *Contraception* 11:669, 1975.
- Bygdeman M: Menstrual regulation with prostaglandins. In Karim SMM (ed): *Practical Applications of Prostaglandins and their Synthesis Inhibitors*. Baltimore, University Park Press, 1979, pp 267-282.
- Casper RF, Sheehan K, Erickson G, Yen SSC: Neuropeptides and fertility control in the female. In Zatuchni GI, Labbok MH, Sciarra JJ (eds): *Research Frontiers in Fertility Regulation*. Hagerstown, Harper and Row, 1980.
- Casper RF, Yen SSC: Induction of luteolysis in the human with a long-acting analog of luteinizing hormone-releasing factor. *Science* 205:408-410, 1979.
- Chang MC, Saksens SK, Lau IF: Induction of mid-term abortion by trichosanthin in laboratory animals. *Contraception* 19(2):175, 1980.
- Chatterton RT, Cheesman KL, Mehta RR, Venton DL: Post ovulatory interception. In Zatuchni GI, Labbok MH, Sciarra JJ (eds): *Research Frontiers in Fertility Regulation*. Hagerstown, Harper and Row, 1980.
- Chen HC, Hodgen GD, Matsuura S, Lin LJ, Gross E, Reichert LE, Birken S, Canfield RE, Ross GT: Evidence for a gonadotropin from nonpregnant subjects that has physical, immunological and biological similarities to human chorionic gonadotropin. *Proc N Acad Sci* 73:2885-2889, 1976.
- Clayton RN, Harwood JP, Catt KJ: Gonadotropin-releasing hormone analogue binds to luteal cells and inhibits progesterone production. *Nature* 282:90-92, 1979.
- Colle ML, Greenblatt RB: Contraceptive properties of Danazol. *J Reprod Med* 17:98, 1976.
- Corbin A, Beattie CW, Tracy J, Jones R, Roell TJ, Yardley J, Rees RWA: The anti-reproductive pharmacology of LH-RH and agonistic analogues. *Int J Fertil* 23:81, 1978.
- Cox SW, Heinrichs WL, Paulsen CA, Conrad SH, Shiller HS, Henzl MR, Hermann WL: Perturbations of the human menstrual cycle by oxymetholone. *Am J Obstet Gynecol* 121:121, 1975.
- Crabbe P, Fillion H, Letourneaux Y, Diczfalusy E, Aedo A-R, Goldzieher JW, Shaikh AA, Castracane VD: Chemical synthesis and bioassay of anordrin and dinordrin I and II. *Steroids* 33:85-96, 1979.
- Csapo AI, Dray F, Erdos T: The biological effects of injected antibodies to estradiol-17 β and to progesterone in pregnant rats. *Endocrinology* 97:603, 1975.
- Csapo AI, Erdos T: The critical control of progesterone levels and pregnancy by antiprogesterone. *Am J Obstet Gynecol* 126:598-601, 1976.
- Das C, Talwar GP, Ramakrishnan S, Salahuddin M, Kumar S, Hinorani V, Coutinho E, Croxatto H, Hemmingson E, Johansson E, Luukkainen T, Shahani S, Sundaram K, Nash H, Segal S: Discriminatory effect of anti-Pr- β -hCG-TI antibodies on the neutralization of the biological activity of placental and pituitary gonadotropins. *Contraception* 18:35-50, 1978.
- Feil PD, Bardin CW: The use of medroxy-progesterone acetate to study progesterone receptors in immature, pregnant, and adult rabbit uterus. *Adv Exp Med Biol* 117:241-254, 1979.
- Findley WE, Jacobs BR: The antigonadotropic activity of *Lithospermum ruderale*. I. The lack of steroid-like activity at the receptor level. *Contraception* 21:199, 1980.
- Gassner FX, Hopwood ML, Jochle W, Johnson G, Sundercity SG: Antifertility activity of an oxidized polyphenolic acid from *Lithospermum ruderale*. *Proc Soc Exp Biol Med* 114:20-25, 1963.
- Glasser SR: Personal communication, 1980.
- Glasser SR, Northcutt RC, Chytil F, Strott CA: The influence of an antisteroidogenic drug (aminogluthethimide phosphate) on pregnancy maintenance. *Endocrinology* 90:1363, 1972.
- Goldberg E: Sperm specific antigens and immunological approaches for control of fertility. In Talwar P (ed): *Recent Advances in Reproduction and Regulation of Fertility*. Amsterdam, Elsevier/North Holland Biomedical Press, 1979, p 281.
- Gu Z, (Ku C-P), Chang MC: A-nor steroids as post-coital contraceptives in the hamster with special reference to the transport and degeneration of eggs. *Contraception* 20:549-557, 1979.
- Hahn DW, McGuire JL, Chang MC: Contraceptives. In Zatuchni GI, Labbok MH, Sciarra JJ (eds): *Research Frontiers in Fertility Regulation*. Hagerstown, Harper and Row, 1980.
- Henzl MR, Segre EJ, Nakamura RM: The influence of oxymetholone on the hCG stimulated corpus luteum. *Contraception* 8:515, 1973.
- Karim SMM (ed): *Obstetric and Gynaecological Uses of Prostaglandins*. Baltimore, University Park Press, 1976.
- Karim SMM (ed): *Practical Applications of Prostaglandins and their Synthesis Inhibitors*. Baltimore, University Park Press, 1979.
- Kelley CJ, Mahajan JR, Brooks LC, Neubert LA, Breneman WR, Carmack M: Polyphenolic acids of *Lithospermum ruderale*—Dougl. ex Lehm (Bonginaceae). 1. Isolation and structure determination of lithospermic acid. *J Org Chem* 40:1804-1815, 1975.
- Koch Y: Effects of antibodies against luteinizing hormone-releasing hormone on reproduction. In James VHT (ed): *Endocrinology*, Vol I. Amsterdam, Excerpta Medica, 1977, p 34.
- Ku C-P, Chu M-K, Chiang H-C, Chao S-H, Pany T-W, Tsou K: Pharmacological studies of a contraceptive drug-anordrin. *Chinese Med J* 2:177-184, 1976.
- Lan NC, Katzenellenbogen BS: Temporal relationships between hormone receptor binding and biological responses in the uterus: Studies with short and long-acting derivatives of estril. *Endocrinology* 98:220-227, 1976.
- Landgren BM, Aedo AR, Hagenfeldt K, Diczfalusy E: Clinical effects of orally administered extracts of *Montanoa tomentosa* in early human pregnancy. *Am J Obstet Gynecol* 135:480, 1979.
- Lehmann F, Just-Nastanski I, Böhrendt B, Czygan P-J, Bettendorf G: Effect of post-ovulatory administered oestrogens on corpus luteum function. *Acta Endocrinol* 79:329, 1975.
- Lemay A, Labrie F, Ferland L, Raynaud JP: Possible luteolytic effects of luteinizing-hormone releasing hormone in normal women. *Fertil Steril* 21:29-34, 1979.
- Lerner LJ, Carminati P: Effect of day of pregnancy and pregnancy terminating agents on prostaglandin synthesis and metabolism and histone metabolism in the rat utero-placental fetal complex and lung. *J Steroid Biochem* 8:395, 1977.
- Lerner LJ, Galliani G, Omodei-Sale A, Assandri A, Luzzani F, Gallico L, Grant AM: A new agent for the pharmacological control of pregnancy. In Zatuchni GI, Labbok MH, Sciarra JJ (eds): *Research Frontiers in Fertility Regulation*. Hagerstown, Harper and Row, 1980.
- Levine SD, Adams RE, Chen R, et al: Zoapatanol and montanol, novel oxepane diterpenoids, from the Mexican plant zoapatle (*Montanoa tomentosa*). *J Am Chem Soc*

- 101:3404, 1979.
45. MacDonald GJ, Beattie CW: Pregnancy failure in hypophysectomized rats following LHRH administration. *Life Sci* 24:1103-1110, 1979.
46. McCracken JA, Barcikowski B, Carlson JC, Green K, Samuelsson B: The physiological role of prostaglandin $F_{2\alpha}$ in corpus luteum regression. *Adv Biosci* 9:599-624, 1973.
47. McCracken JA, Eimer-Jensen N, Fried J: Prostaglandin $F_{2\alpha}$ and its 13-dehydro analogs: comparative luteolytic effects *in vivo*. In Channing CP, Marsh JM, Sadler WA (eds): *Ovarian Follicular and Corpus Luteum Function*. New York, Plenum Publishing Company, 1979, pp 577-601.
48. Mora G, Faundes A, Johansson EDB: Lack of clinical contraceptive efficacy of large doses of R2323 given before implantation or after a missed period. *Contraception* 12:211-220, 1975.
49. Morris JM, Van Wagenen G: Interception: the use of post-ovulatory estrogens to prevent implantation. *Am J Obstet Gynecol* 115:101, 1973.
50. Nygren K-G, Johansson EDB, Wide L: Post-ovulatory contraception in women with large doses of norethindrone. *Contraception* 5:445-456, 1972.
51. Orts RJ, Bensen G: Inhibitory effects on serum and pituitary LH by a melatonin-free extract of bovine pineal glands. *Life Sci* 12:513-519, 1973.
52. Orts RJ, Kocan KM, Johnson RP: Antifertility properties of bovine pineal extracts: reduction of ovulation and preovulatory luteinizing hormone in the rat. *Acta Endocrinol* 85:225-234, 1977.
53. Pincus B, Banik UK: Anti-progestins and implantation. *Excerpta Medica Int Congr Series* 72:558-562, 1963.
54. Raziano J, Ferin M, Vande Wiele RI: Effects of antibodies to estradiol-17 β and to progesterone on nidation and pregnancy in rats. *Endocrinology* 90:1133-1138, 1972.
55. Schane HP, Creange JE: An overview of luteal phase contraception. In Zatuchni GI, Lobbok MH, Sciarra JJ (eds): *Research Frontiers in Fertility Regulation*. Hagerstown, Harper and Row, 1980.
56. Schane HP, Creange JE, Anzalone AJ, Potts GO: Interceptive activity of Azastene in rhesus monkeys. *Fertil Steril* 30:343, 1978.
57. Schane HP, Potts GO, Creange JE: Inhibition of ovarian, placental and adrenal steroidogenesis in the rhesus monkey by tilostane. *Fertil Steril* 32:464, 1979.
58. Shrivvers CA: Antigens of the ovum as a potential basis for the development of contraceptive vaccine. In World Health Organization Symposium on Development of Vaccines for Fertility Regulation. Copenhagen, Scriptor, 1976, pp 81-91.
59. Smith MS, Neill JD: Termination at mid-pregnancy of the two daily surges of plasma prolactin initiated by mating in the rat. *Endocrinology* 98:696, 1976.
60. Smith RP, Ross A: Post-coital contraception using dl-norgestrel ethinyl estradiol combination. *Contraception* 17:247-252, 1978.
61. Stevens VC: Antifertility effects from immunization with intact, subunits, and fragments of hCG. In Edwards RG, Johnson MH (eds): *Physiological Effects of Immunity Against Reproductive Hormones*. Cambridge, Cambridge University Press, 1975, p 249.
62. Stevens VC: Anti-pregnancy immunization. In Zatuchni GI, Lobbok MH, Sciarra JJ (eds): *Research Frontiers in Fertility Regulation*. Hagerstown, Harper and Row, 1980.
63. Talwar GP: Anti hCG immunization. Introduction. *Contraception* 18:19, 1978.
64. Talwar GP: Immunology in reproduction. *J Reprod Med* 22:61, 1979.
65. Wotiz H: Personal communication, 1980.
66. Yuzpe AA, Lance WJ: Ethinyl estradiol and dl-norgestrel as a post-coital contraceptive. *Fertil Steril* 29:932, 1977.



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RESEARCH FRONTIERS IN FERTILITY REGULATION

GOSSYPOL: A POSSIBLE MALE ANTIFERTILITY AGENT REPORT OF A WORKSHOP

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In the early 1970s, reports began to appear in Chinese medical journals that gossypol, a yellowish substance occurring in certain species of cotton plant, was being investigated as a possible male antifertility agent. Much of the information about gossypol research was anecdotal in nature, however, and the published reports lacked complete information on controls, preliminary physical and biochemical studies of subjects, and follow-up evaluations.

Interest in the antifertility capability of gossypol spread westward, and numerous animal experiments were organized to confirm or refute the Chinese experience. These initial experiments demonstrated considerable variability in toxicity and utility of gossypol as a male contraceptive agent. Accordingly, the Program for Applied Research on Fertility Regulation (PARFR), as an organization providing scientific and technical assistance for research in the development of new or improved means of fertility control, served as the sponsor of a workshop bringing together a small group of scientific experts who have done various types of research with gossypol.

The major objective of the workshop, which was held in Chicago, Illinois in March, 1980, was to provide a free exchange of ideas concerning early and ongoing research on the use of gossypol, and to evaluate the potential of the compound as a method of fertility control in the male. The meeting was structured to review the initial interest in gossypol relative to animal and human nutrition, and to discuss recent and on-going studies on the toxicity and efficacy of gossypol as a male contraceptive.

The reports presented at the workshop, and some subsequent developments in the evaluation of gossypol, are summarized here.

HISTORY OF GOSSYPOL AS AN ANTIFERTILITY AGENT

The antifertility effects of gossypol were first suggested by the findings of epidemiologic studies done in the People's Republic of China which showed that in certain areas, there were more than the expected number of cases of infertility. Environmental factors were eventually discounted, and food poisoning was suspected; after some investigation, cottonseed oil was implicated as a possible source of the problem. A contributing factor may have been that some farmers had changed the oil-processing technology. For years, Chinese farmers had processed cottonseed oil for use in food preparation by first heating the cottonseed and then pressing the oil out. Then, during the 1950s, a new method of preparing the oil was adopted, and farmers took their cottonseed to a central location where it was pressed without heating (36). After exposure to this crude cottonseed oil for periods of a year or more, a number of people developed a condition characterized by fever and dyspepsia; women developed amenorrhea and men became infertile. When use of the oil was discontinued, the amenorrheic women resumed normal menstrual cycles; many of the exposed men did not immediately regain fertility, however. Gossypol was identified as an active ingredient in the cottonseed oil and was be-

lieved to be responsible for both the toxic effects and the infertility. Demographic investigations during the 1960s provided further evidence to implicate gossypol as the significant factor.

In 1971, Chinese investigators initiated experiments using purified gossypol in several species of animals, and in the following year, clinical studies of gossypol as a male contraceptive agent were begun. In 1972, a number of pharmaceutical chemists, pharmacologists, and physicians organized the National Coordinating Group on the Male Antifertility Agent, Gossypol, and clinical studies on the antifertility effect, the site of action, pharmacokinetics, and toxicity of gossypol were carried out. The findings were summarized in an article appearing in the Chinese Medical Journal in 1978, "A New Male Contraceptive Drug — Cotton Phenol (Gossypol)" (43).

According to this report, some 4,000 Chinese men had used a gossypol contraceptive pill for at least six months, and some for more than four years. The efficacy was said to be 99.89%. The men usually recovered fertility by three months after discontinuation of treatment, and several births of apparently healthy babies were observed among the wives of men who stopped using gossypol (41, 43).

This article and other reports from China caused considerable excitement among investigators in the field of population and family planning, for if the data and conclusions were correct — namely, that gossypol constituted a new non-steroidal method of fertility control for the male that could be highly effective and reversible, fully safe, and inexpensive — then possibly a simple answer to the world's population problem had been discovered. An additional attraction was that with an estimated world production of more than 40 million tons of cottonseed per year, well over 100,000 tons of gossypol would thereby be available, or at least 25 kg for every male in the world.

Another part of the cotton plant, the cotton root bark (*gossypium* species), has had a long history in various parts of the world as an abortifacient and menses inducer, and contains a high concentration of gossypol. With the growing interest in the male antifertility potential of gossypol, some scientists are taking a closer look at cotton root bark as well, for information about its safety, efficacy, and general utility. Slocumb and co-workers have been investigating its extensive folkloric use as a supposed abortifacient among women in the Southwest United States (52). The bark is stripped and boiled for two hours and the resulting supernatant is used as an active elixir; the elixir contains high concentrations of gossypol. It is sold at herbalist stores for about \$3 to \$4 for a 4-oz. fluid extract. Preliminary survey data suggest that cotton root bark ingestion is associated with the onset of menstrual-like cramps and bleeding in a high percentage of women within four to 72 hours. About three-fourths of the women report moderate gastrointestinal symptoms and headaches. Surveillance

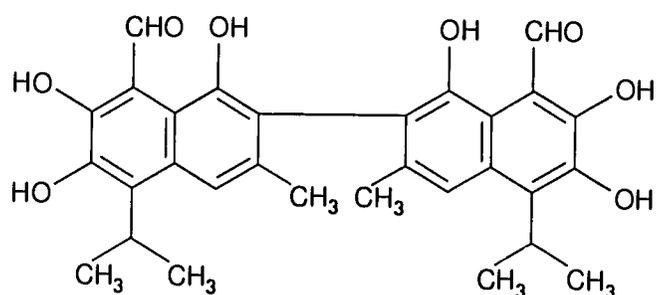


Figure 1. Gossypol.

and epidemiologic studies are underway to determine the efficacy and side-effects of self-administered cotton root bark as a contragestational agent or menses inducer.

CHEMICAL AND NUTRITIONAL HISTORY

Gossypol — (1,1',6,6',7,7'-hexahydroxy-5,5'-diisopropyl-3,3'-dimethyl[2,2'-binaphthalene]-8,8'-dicarboxaldehyde), molecular weight 518.54, empirical formula $C_{30}H_{30}O_8$ — is a yellowish pigment which occurs in certain species of cotton plant (Figure 1) (42). At least fifteen pigments have been isolated from the seeds, stem, and root of the cotton plant, but the predominant pigment is the yellow one, which is concentrated in the resin glands of the cotton seed (5). Gossypol was named by Marchlewski in 1899 (40); the chemical structure was identified in 1938 by Adams and associates (2) and confirmed with the total synthesis by Edwards in 1958 (25).

Gossypol occurs in three tautomeric forms: the aldehyde, the hemiacetal, and the phenolic quinoid; the major tautomer is the aldehyde form. Gossypol is markedly reactive and the phenol hydroxyls exhibit strongly acidic properties. Aldehyde-carbonyl groups can react with acids, bases, oxygen, and many other kinds of functional groups present in biochemical systems (5). Early investigators developed methods of isolating and extracting gossypol from cottonseed kernels, using petroleum and diethyl ethers, and called the ether-extractable gossypol "free" gossypol. The gossypol in the gossypol-protein complex formed by the reaction of gossypol with seed protein was called "bound" gossypol, because it could not be extracted by solvents (8, 9, 31).

The fate of ingested gossypol in various species was studied by the Chinese investigators (43). In rats, 19 days were required for the elimination of 97% of labeled gossypol, indicating that the gossypol remained in the body for a long time and might accumulate with chronic administration. In mice, rats, rabbits, dogs, and monkeys, the highest amounts of gossypol were found in the liver after oral administration. Large amounts were also found in muscle, kidney, and blood; no gossypol was detected in the brain. Most of the ingested gossypol was eliminated in the feces, with only small amounts eliminated in the urine

as a conjugate, or expired after decarbonylation. Although the peak concentration of gossypol in the testes was lower than that detected in other organs, at low doses the testicular tissue was highly sensitive to gossypol.

Recent investigations by Lee and Malling at the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina, suggest that gossypol works by inhibiting an enzyme that has a crucial role in the metabolism of sperm and sperm-generating cells (41). The investigators have provided some information as to the possible mechanism of action of gossypol, showing that its target enzyme is lactate dehydrogenase X. This finding indicates that gossypol does not affect either sex hormone levels or libido. It appears to inhibit to some extent each of several lactate dehydrogenases occurring throughout the body. Its greatest inhibitive effect, however, is on lactate dehydrogenase X, which is found only in sperm and testis cells. Gossypol appears to be a competitive inhibitor of a cofactor necessary for enzyme activity, thereby inhibiting sperm production. The agent also affects other enzymes. For example, in rodents, it can cause irreversible inactivation of malate dehydrogenase, but this effect has not been observed in human tissues. In rodents and humans, gossypol also inhibits glutathione S-transferase, an enzyme that participates in the detoxification of certain organic compounds, including potential carcinogens (41).

Gossypol in animal and human food

Although cottonseed is a by-product of cotton fiber production, processing the seeds is a major industry in the

cotton-producing areas of the world; oil obtained from cottonseed is useful in food preparation and cooking as salad oils, shortening, and margarine; cottonseed meal is used for animal feed and fertilizer; and high-protein cottonseed flour (e.g., Incaparina) is used to supplement protein-deficient diets in developing countries.

Gossypol is poisonous to nonruminant animals, including humans. This has inhibited the economic utilization of cottonseed products for nutrition. In 1915, Withers and Carruth established that gossypol was the factor responsible for the toxicity of cottonseed meal (61, 62). In order that the cottonseed oil and meal could be safely consumed by humans and domestic animals, extensive research was undertaken, focusing primarily on the removal or detoxification of gossypol. Two excellent recent reviews, one by Abou-Donia (1) and the other by Berardi and Goldblatt (5), document the laboratory animal and human research on gossypol that has been carried out toward this end.

Incaparina studies

In 1956, a research group at the Institute of Nutrition of Central America and Panama (INCAP) developed Incaparina, a high nutritive food intended for malnourished children, pregnant and lactating women, and adults suffering from protein/calorie malnutrition. Incaparina became commercially available in 1959 (6). Based on cottonseed protein, Incaparina contains cottonseed flour, corn flour, lysine, yeast, calcium carbonate, and vitamin and mineral supplements. In developing the flour, and determining its safety as food, the investigators studied the metabolic

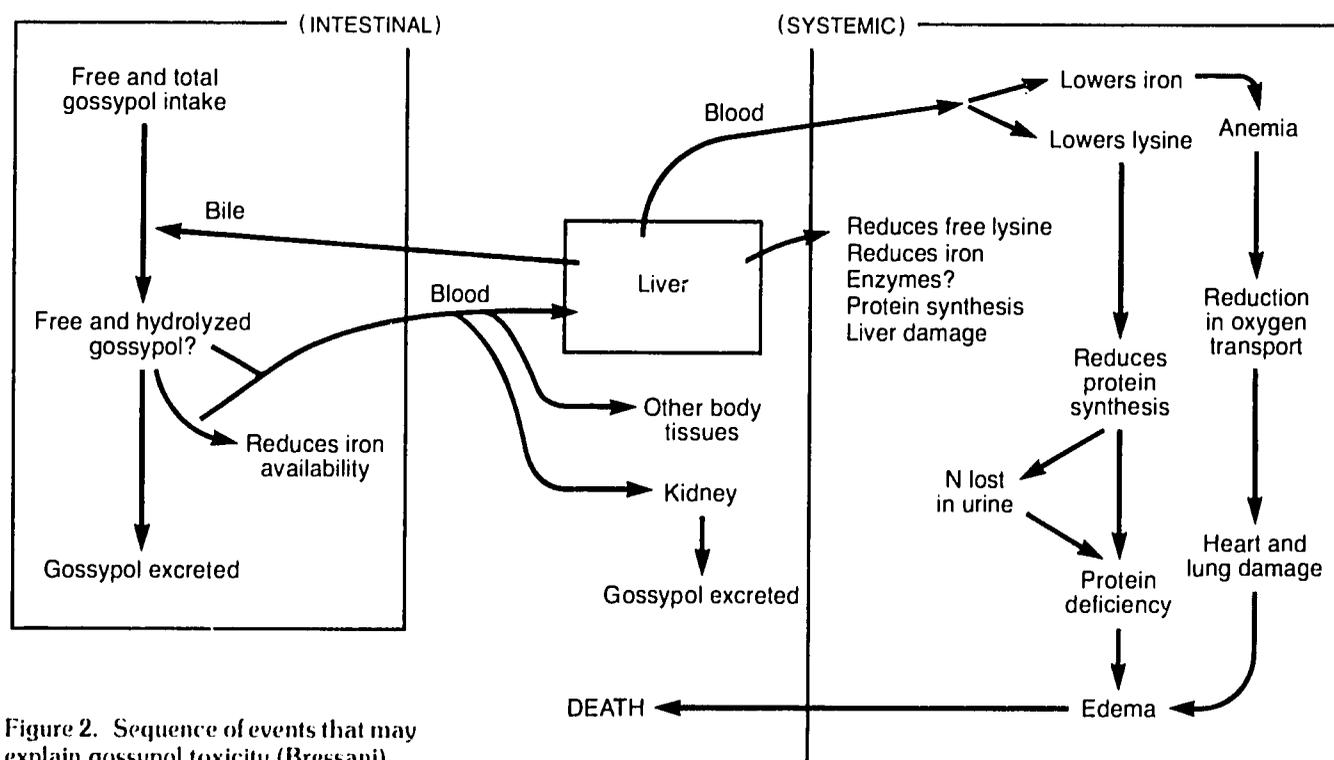


Figure 2. Sequence of events that may explain gossypol toxicity (Bressani).

activity of gossypol in experimental animals (swine, poultry, rats, and dogs) and in humans; the effects of cooking on the gossypol; and the long-range toxicity of gossypol.

In their early Incaparina investigations, Bressani and associates proposed that gossypol toxicity, or its antiphenologic effects, could be explained on the basis of its activity at the metabolic level. They developed a working scheme of gossypol toxicity action, as shown in *Figure 2* (6).

In 1959, the investigators ran long-term feeding tests to detect any possible harmful physiologic effects of gossypol, especially with regard to lactation and reproduction. The levels of gossypol used in these studies were very small, about 3.5 mg/rat/day. No negative effects on reproduction were seen: cottonseed flour-fed rats had relatively high fertility, possibly owing to the high level of protein fed, which may have introduced some protection against the toxic effects of gossypol; litters were of normal birth weight. At the end of the study, organ weights were normal, and no pathologic effects were detected. The investigators concluded that the flour was safe for human consumption.

With the growing interest in the antifertility effects of gossypol, some investigators are considering extension of the Incaparina research to include follow-up evaluations of the 3- to 6-year old children studied by Bressani's group in the

1950s to look at their present fertility levels, and epidemiologic-fecundity studies of the populations now depending mainly upon Incaparina for their nourishment.

TOXICITY

Extensive research has been performed to determine the toxic effects of gossypol in different species. Gossypol is often toxic to dogs, cats, swine, chickens, rats, mice, rabbits, guinea pigs, and other nonruminant animals (18, 26). The toxicity is greatly increased when gossypol is administered intravenously or intraperitoneally. In ruminant animals, oral gossypol is relatively non-toxic, probably because of bacterial metabolism in the rumen which results in the binding of gossypol to protein (1).

The mechanisms by which gossypol causes tissue damage are as yet poorly understood. Toxicity may be due to the action of gossypol on specific enzymes, or interference with amino acid, protein, or iron metabolism (5).

The pathologic symptoms of gossypol toxicity are many and varied, depending upon animal species. The common manifestations in a variety of laboratory and farm animals are depressed appetite, loss of body weight, and inefficient protein utilization (5). Cardiac irregularity is the most common acute toxic effect. In subacute reac-

SPECIES (REFERENCE)	SYMPTOMS	POSTMORTEM FINDINGS
RATS (12, 24, 28)	appetite loss; growth rate depression; diarrhea; anorexia; hair loss; anemia	intestinal dilation, impaction; hemorrhagic congestion of stomach, intestines; congestion in lungs, kidneys
CATS (49)	spastic paralysis, usually of hind legs; rapid pulse; dyspnea; cardiac irregularity	edema of lungs, heart; heart enlargement; degeneration of sciatic nerve
DOGS (22, 23, 59)	posterior incoordination; stupor; lethargy; diarrhea; anorexia; weight loss; vomiting	lung edema; hypertrophy and edema of heart; congestion, hemorrhages of liver, small intestine, stomach; fibrosis of spleen, gall bladder; congestion of splanchnic organs
RABBITS (34, 49)	stupor; lethargy; loss of appetite; diarrhea; spastic paralysis; decrease in litter weights	hemorrhages in small intestine, lungs, brain, leg bones; enlarged gallbladder; edema, impaction of large intestine
SWINE (14, 15, 30, 55)	"thumps" or labored breathing; dyspnea; weakness; emaciation	widespread congestion, edema of many organs; fluid in body cavities; edematous bladder, thyroid gland; flabby, dilated heart with microscopic lesions; renal lipidosis; atrophied spleens, myocardial injury

(Modified from Berardi L.C., Goldblatt L.A. Gossypol. In Liener H.E. [ed]. Toxic Constituents of Plant Foodstuffs. New York, Academic Press, 1969, p251)

Table 1. Symptoms and postmortem findings attributed to chronic toxicity of gossypol in cottonseed meals, selected nonruminants.

		REVERTANTS PER PLATE					
		TA 98	TA 100	TA 1535	TA 1537	TA 1538	
GOSSYPOL	(1.8 - 125 μ g per plate)	-S-9	16-29	78-114	7-10	3-6	22-23
		+S-9	26-45	101-117	8-12	6-9	29-30
NEGATIVE CONTROL	(solvent only)	-S-9	27	100	12	6	22
		+S-9	28	106	13	7	26

Positive controls used: 2-nitrofluorene — strains TA 98, TA 1538
 2-acetylaminofluorene, methyl methanesulfonate — TA 100, TA 1535
 9-aminoacridine — TA 1537

Doses of gossypol \geq 125 μ g/plate were toxic to these strains

Table 2. Gossypol acetic acid (Sigma Chemical Co., St. Louis, Mo) and gossypol formate (Shanghai Institute of Materia Medica) tested in the Ames *Salmonella* mutagen bioassay.

tions, pulmonary edema occurs, and in chronic reactions, malnutrition and growth retardation are seen. Table 1 indicates the toxic effects of chronic gossypol administration in cottonseed meal to selected nonruminant animals.

A variety of studies suggest that tolerance levels for gossypol are definitely associated with the species and even the strain of animal, the mode of administration, the mineral and protein content of the diet, the cumulative dose of free gossypol, and the type of gossypol administered. It is not certain whether the toxic metabolic effects of gossypol are related to its infertility effects. Most gossypol studies in animals have been done with cottonseed meal, rather than with pure gossypol. An intriguing finding is that more rigorous purification of the gossypol

seems to lead to loss in activity, suggesting that the antifertility effect might be associated with a highly potent trace constituent of cottonseed rather than with gossypol itself (21).

In studies with laboratory and farm species, the major dietary factors employed to modify gossypol toxicity expression have been iron and protein quantity and/or quality. In 1913, Withers and Brewster observed that iron salts alleviated cottonseed toxicity (60). In 1928, Clark proposed that gossypol reacted with the free amino groups of protein to form an insoluble complex (11). After a survey of the literature, Harper and co-workers concluded that the physiologic effects of ingested gossypol may be reduced or eliminated, within limits, by increasing the dietary level or quality of pro-

	DOSE (μ g per plate)	REVERTANTS PER PLATE			
		G 428		TR 2705	
		-S-9	+S-9	-S-9	+S-9
GOSSYPOL ACETIC ACID (Sigma)	2	34	58	22	37
	20	43	48	24	37
	200	39	59	26	33
GOSSYPOL FORMATE (Shanghai)	2	36	68	21	30
	20	45	91	30	25
	200	29	44	22	39
GOSSYPOL ACETATE (Peking)	2	42	66	31	58
	20	37	48	24	60
	200	40	50	34	82
SOLVENT ONLY (DMSO)		42-48		27-49	
STREPTONIGRIN	10	918	959	1017	703

Table 3. Gossypol tested in Ames *Salmonella* strains positive for streptonigrin.

tein, and that a major effect of protein is reduced gossypol absorption (32).

Most investigative studies with minerals have involved iron salts. Clawson and co-workers clarified the role of iron in preventing gossypol toxicity, and provided support for Clark's hypothesis that iron forms an insoluble complex with gossypol in the pig gut, since liver iron was inversely related to dietary gossypol, and dietary iron did not prevent injected gossypol toxicity (14, 15, 54). When high levels of iron (in 2:1 and 3:1 ratios of iron to gossypol) were added to the diet, pigs were able to survive, ingesting potentially lethal levels of gossypol, and gossypol accumulation in the tissues could be greatly reduced by dietary management (7).

Soluble iron salts added to a gossypol-containing diet fed to rats greatly improved survival rate and body weight gain, and the free and bound gossypol concentrations in the liver were reduced in direct relation to the amount of iron supplied. An inverse relationship was noted between the level of dietary protein and concentration of free and bound gossypol in the tissues of pigs, suggesting that gossypol apparently became bound to protein while in the digestive tract, and the bound form was not absorbed (50).

If the human reaction to gossypol is comparable to the reaction in test animals, a diet lacking adequate levels of protein, iron, or certain minerals could affect either the efficacy or the safety of its administration as an antifertility drug, and malnutrition could severely affect gossypol toxicity and its antifertility factors (32).

GENETIC TOXICITY OF GOSSYPOL

Using short-term mutagenicity screen tests, de Peyster has investigated the potential of gossypol to interfere with normal genetic replication processes. Results from these tests are frequently used to assist in predicting the potential teratogenic and carcinogenic hazard of a chemical. Gossypol acetic acid (Sigma Chemical Co.), gossypol formate (Shanghai Institute of Materia Medica), and gossypol acetate (Peking, Dr. Liu Kuo-chen), were evaluated in a small battery of preliminary *in vitro* and *in vivo* tests, selected for their ability to detect different types of damage to cellular DNA. The three *in vitro* tests were the Ames *Salmonella*/mammalian-microsome test (3), the *B. subtilis* multi-gene sporulation test (39), and the *S. cerevisiae* D3 mitotic recombination test (51). The *in vivo* mouse sperm head abnormality test was also performed (63), using intraperitoneal doses of 2, 4, 8, and 16 mg/kg/day for five consecutive days. This test was of particular interest because of the Chinese reports of "malformed spermatozoa" in the male volunteers (43).

Gossypol did not appear to be mutagenic in the *in vitro* tests (19, 20). The most extensive testing was done in

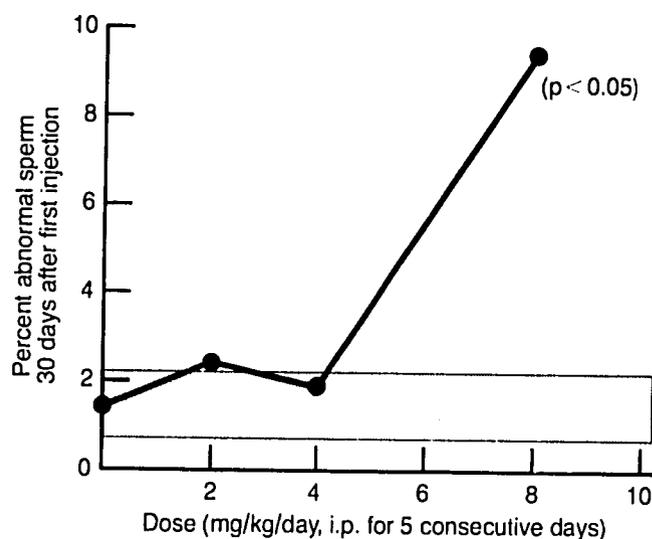


Figure 3. Induction of abnormal sperm head shape in B6C3 mice by gossypol acetic acid.

the standard test strains of *Salmonella* and in some newly developed *Salmonella* tester strains (Tables 2, 3). However, 8 mg/kg/day of gossypol acetic acid given to Charles River B6C3 mice did produce an increase in percentage of epididymal sperm with morphologically abnormal heads. At autopsy, an average of 9% abnormal shapes was seen in the caudae of treated mice, compared with 1.4% in corn oil-treated controls (Figure 3). Gossypol in doses of 16 mg/kg/day for five consecutive days was lethal to all mice in the group ($n = 5$). Using the same criteria for counting morphologically abnormal sperm, de Peyster found that methyl methanesulfonate, a potent mutagenic alkylating agent, given in daily doses of 80 mg/kg, produced an average of 20% abnormal sperm.

A wide variety of other chemicals with known mutagenic, carcinogenic, and teratogenic potential induce increased numbers of abnormal sperm (63), although the mechanisms by which abnormal shapes arise are not fully understood. Whether the effect of gossypol was due to direct action on DNA contained in the sperm head or to indirect biochemical or other interactions cannot be determined by this test alone. Regardless of the mechanism involved, de Peyster observes that the possible implications of increased numbers of abnormal sperm should be considered. An elevated proportion of abnormal sperm in the semen of fathers of spontaneous abortuses has been reported (27). Similarly, some investigators believe that structurally abnormal sperm are generally not viable and are associated with infertility, although this is not known for certain, and there is some experimental evidence to the contrary (53). Alternatively, abnormal sperm could also theoretically contain non-lethal mutations which end up in the gene pool of future live offspring. Observance of a high frequency of abnormal sperm heads in which damage may have

	DOSE	TIME PERIOD	EFFECT
MALE RATS	5 mg/kg/day	8 weeks	number of implantation sites in mated females not significantly decreased
	5-10 mg/kg/day	14 weeks	no toxicity; did not disturb sex drive or mating ability
	10 mg/kg/day	8 weeks	3 of 9 females mated to treated males not pregnant
	10 mg/kg/day	12 weeks	2 of 6 females mated to treated males not pregnant
	15 mg/kg/day	4 weeks	4 of 6 rats died
MALE HAMSTERS	5-15 mg/kg/day	6-14 weeks	no toxicity
	10 mg/kg/day	10 weeks	4 of 6 females mated to treated males not pregnant; in 2 pregnant hamsters, significantly reduced number of implantation sites compared to controls
MALE RABBITS	1.25-10 mg/kg/day	5-15 weeks	5 rabbits in good health, unchanged body weights; 1 rabbit died; effect on sperm production minimal or non-existent

Table 4. Results of oral administration of gossypol acetic acid in male rats, hamsters and rabbits; males were periodically mated with proestrous females that were subsequently killed and number of implantation sites recorded (10).

occurred through chemical interaction with DNA could also reflect concurrent DNA interaction in somatic cells, eventually leading to tumors or cell death.

Although these preliminary results and those of other investigators (16) would seem to indicate that gossypol does not have obvious mutagenic potential, de Peyster concludes that more extensive testing is warranted if safety with regard to genetic effects is to be assured.

ANTIFERTILITY STUDIES

Much remains to be learned about gossypol toxicity and efficacy, the reversibility of gossypol-induced infertility, and the mechanism of action of gossypol on spermatogenesis. To this end, a number of studies have been initiated using small animals and sub-human primates. Some of these studies are described below.

Animal studies

M. C. Chang, Gu, and Saksena studied the antifertility effects of orally administered gossypol acetic acid in male rats, hamsters, and rabbits (10). The summary of these studies is shown in *Table 4*. The male hamsters appeared to be more sensitive to the antifertility effects of gossypol and less sensitive to the toxicity effects than were male rats. In male rabbits, although sperm motility was disturbed in some cases, the number and fertilizing capacity of sperm

were not adversely disturbed. In some gossypol-treated rats, the numbers of sperm in the vas deferens or epididymis were decreased, but this was not true in the male hamsters. Also, the motility of sperm in the hamster appeared to be more affected by gossypol than was the case in the rat (10).

Waller and Zaneveld found that rabbits were very susceptible to toxic effects of gossypol acetate, and rats were resistant to its antifertility effects (57) (*Table 5*). They noted, however, that if the rats had been dosed for several additional weeks, an antifertility effect may have been achieved. In other rat studies, Bardin, Sundaram, and C. C. Chang, using gossypol acetic acid, found that the majority of treated animals became infertile; sperm concentration was significantly reduced, and increased numbers of nonmotile and abnormal sperm were seen in the cauda epididymidis (4) (*Table 5*). The mating performance of the rats was normal, and histologic examination of the organs of gossypol-treated animals showed no deviation from normal.

Hoffer and associates compared the effects of two different samples of gossypol (gossypol monoacetate from China* and a pure form of gossypol[†]), since at least some of the

* Provided by Dr. Sheldon Segal at the Rockefeller Foundation (Peking Batch #1).

† Obtained through Dr. Guy Jividen, with the United States cotton industry.

toxicity of gossypol may reside in contaminating compounds (33). The investigators looked for differences in purity, toxicity, or effect on the morphology of reproductive organs between these two compounds, when given to male rats at the lowest dose of gossypol (7.5 mg/kg) reported by the Chinese to be effective in producing infertility. No differences were seen in the morphologic effects of gossypol or gossypol monoacetate on the testis or epididymal sperm, at the doses and time intervals studied.

In another study, Hoffer studied the ultrastructural effects of higher doses of gossypol (20 and 30 mg/kg/day), fed by gavage to rats for seven weeks (Table 5). The animals were

sacrificed weekly and the testes and epididymides excised. Damage was seen in the seminiferous epithelium in the form of intercellular vacuoles, Sertoli cell vacuolization, and atrophic seminiferous tubules, but only in relatively few seminiferous tubules (Figure 4). By contrast, there was widespread damage to epididymal sperm, easily detectable by electron microscopy at week five (Figure 5). No morphologically demonstrable effects on the epididymal or vasal epithelium were observed. The discrepancy between the widespread damage to epididymal sperm and the more limited extent of testicular damage was intriguing to the investigators. Although some defective spermatids could be detected in the testis with the electron micro-

SPECIES (REFERENCE)	AMOUNT OF GOSSYPOL & DURATION OF TREATMENT	EFFECTS & MORPHOLOGICAL FINDINGS	CONCLUSIONS
RABBIT (57)	40 mg/kg/day 33 days	weight loss, death; epididymal sperm unchanged; severe liver and lung congestion, edema, intraperitoneal fluid	no antifertility effects, probably because toxic effects so severe
RAT (57)	40 mg/kg/day 28 days	normal health throughout; epididymal sperm appeared normal	no antifertility effects, but if study continued longer, antifertility effects might occur
RAT (4)	7.5 mg/kg/day 12 weeks	sperm concentration much reduced; nonmotile, abnormal sperm in cauda epididymides, sperm broken, sperm heads separated from tails, tails sharply bent; mating normal, serum LH, FSH, T normal	majority of rats infertile, return to fertility slow (12 wks post-treatment)
RAT (33)	20 and 30 mg/kg/day 7 weeks	damage to seminiferous epithelium; widespread damage to epididymal sperm by wk 5; no morphologically demonstrable effects on epididymal or vasal epithelium; no statistically significant changes in serum FSH, LH, T, or rates of fatty acid and cholesterol synthesis	total inhibition of sperm motility by 7 wks of treatment
ADULT RHESUS MONKEY (4)	0, 5, 20 mg/animal/day 3 months 80 mg/animal/day 7 weeks	no changes in blood chemistry values, CBC, or androgen, gonadotropin levels; serum potassium levels normal; no change in sperm count, although decapitated sperm frequent no effect on testes function; plasma LH and T normal; sperm count, motility, morphology normal	animals resistant to antifertility effects. 20 mg/animal dose, 5 × antifertility dose in humans, compared on body weight basis
STUMPTAIL MACAQUES (56)	10, 25, 50, 100 mg/ml gossypol/PVP co-precipitate	motility of sperm in vaginal fluid of mated females decreased with increasing concentrations of gossypol	80% + spermatazoa immotile at doses of 50 mg/ml co-precipitate

Table 5. Findings of selected gossypol studies in small animals and subhuman primates.

scope. deleterious changes were much more apparent in sperm which had already passed into the epididymis. The investigators theorized that the flagellar components in the testis might be destabilized by gossypol treatment, and that this instability manifests itself during epididymal transit (33).

In biochemical studies, Hoffer found no statistically significant changes either in serum FSH, LH, or testosterone in gossypol-treated rats, or in rates of testicular fatty acid and cholesterol synthesis. Sperm motility was examined at seven weeks, and total inhibition of sperm motility was noted. Bardin, Sundaram, and Chang (4) also examined effects of gossypol on serum levels of LH, FSH, and testosterone in rats and found that they were normal.

Hoffer is also looking at the antifertility properties and morphological effects of a number of analogs and deriva-

tives of gossypol including apogossypol hexacetate, which is reported to be less toxic than gossypol, with the idea that the antifertility action of gossypol could be separated from its toxicity by modifying its structure.

Sundaram and associates found the male rhesus monkey resistant to the toxicity and antifertility effects of gossypol (4) (Table 5). After administration of gossypol acetic acid to the monkeys for three months, no changes were seen in blood chemistry values, complete blood count, androgen or gonadotropin levels, or serum potassium levels. Sperm counts were normal, although decapitated sperm were frequent.

Hahn found that the hamster was much more sensitive to the antifertility effects of gossypol than rats or mice (29). High levels of gossypol administered to male mice caused toxic effects before any antifertility effect was observed



Figure 4. In a small proportion of seminiferous tubules of rats treated with gossypol, deleterious effects of gossypol treatment including the occurrence of atrophic seminiferous tubules and the presence of large intra- and intercellular vacuoles in the seminiferous epithelium can be observed. This is a light micrograph of an entirely atrophic seminiferous tubule from a rat treated with 7.5 mg/kg/day of gossypol for 4 weeks. Most of the cells seen here are Sertoli cells, and Sertoli cell nuclei can be recognized by their prominent nucleoli. (With permission of Anita P. Hoffer)

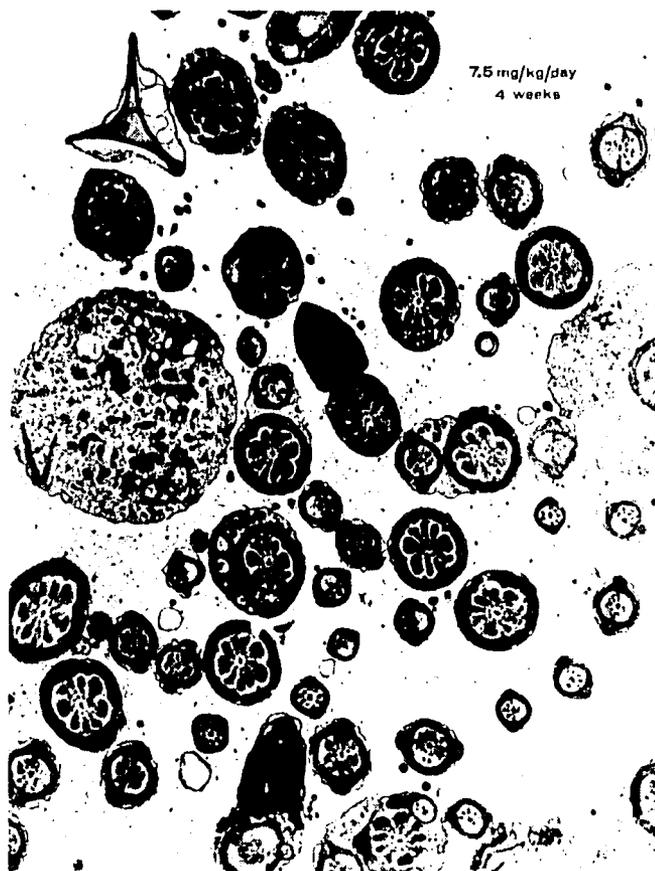


Figure 5. Electron micrograph of sperm in the lumen of the vas deferens of a gossypol-treated rat, showing sections through the sperm tail. This is from the vasa lumen after 4 weeks of 7.5 mg/kg/day of gossypol. In general, five different types of defect can be identified: Supernumerary or displaced outer dense fibers (ODFs), missing ODFs and/or doublets in principal piece, early signs of mitochondrial degeneration in midpiece, profiles consisting only of ODFs but devoid of mitochondria or fibrous sheath, and double tails. In the micrograph shown here, missing or displaced ODFs, double tails, vacuolated mitochondria and cytoplasmic droplets containing large numbers of ODFs can be observed. (With permission of Anita P. Hoffer)

SPECIES	AMOUNT OF GOSSYPOL & DURATION	EFFECTS
MALE MOUSE	40 mg/kg/day 5 wks	toxicity before antifertility effect achieved
	20 mg/kg/day 5 wks	no antifertility effect, little toxicity
	10 mg/kg/day 5 wks	no antifertility effect
MALE HAMSTER	10 mg/kg/day 5-6 wks	partial anti-fertility effect
	20 mg/kg/day 3 wks	total antifertility effect
FEMALE RAT	80 mg/kg/ on each of 3 days prior to expected ovulation	no inhibition of ovulation
FEMALE MOUSE	40 mg/kg on days 1-13 of pregnancy	26% of litter nonviable 4% of control nonviable
	80 mg/kg on days 1-13 of pregnancy	100% of litter nonviable

Table 6. Summary of findings by Hahn et al. with gossypol acetate in rats, mice, and hamsters (29).

(Table 6). At lower dose levels, there was less toxicity but no antifertility effect. In male hamsters, however, a partial antifertility effect was noted at five to six weeks, while at a higher dose level, a total antifertility effect was noted at three weeks.

In fertility studies of the female rat, a dose of gossypol on each of the three days prior to expected ovulation failed to inhibit ovulation (29). In the female mouse, administration of 40 to 80 mg/kg gossypol during days one to 13 of pregnancy resulted in nonviable offspring (26%-100% of the litters).

Waller, Cameron, and Zaneveld evaluated the vaginal spermicidal efficacy of a gossypol-polyvinylpyrrolidone (PVP) co-precipitate inserted into the vaginas of female *Macaca arctoides* (stumptail Macaques) (56). Immediately following insertion of the co-precipitate, the females were mated with males and a sample of vaginal fluid obtained. Spermatozoa were observed under a microscope for motility, and samples were tested with gossypol-PVP in concentrations of 10, 25, 50, and 100 mg/ml in a gelatin base. With increasing concentrations, a decrease in motility occurred. More than 80% of the spermatozoa were immotile at doses of 50 mg/ml or greater.

In vitro studies

Waller, Zaneveld, and Fong studied the *in vitro* spermicidal activity (determined according to a modified Sander/Cramer method) of gossypol, gossypol acetic acid, and polyvinylpyrrolidone (PVP) (58). No decrease in sperm

motility occurred at concentrations as high as 150, 150, and 200 mg/ml, respectively. On the other hand, a gossypol-PVP co-precipitate caused complete immobilization of all spermatozoa at 5 mg/ml within three minutes, and total immobilization in 20 seconds at 40 mg/ml (Table 7).

An *in vitro* study by Pösö and co-workers in Helsinki, using freshly obtained human spermatozoa, also showed that small concentrations of gossypol (25 to 100 μ moles/liter) inhibited sperm motility and interfered with glucose and fructose utilization by the spermatozoa (44). A study of gossypol effects on sperm velocity and percentage of rapidly moving sperm in a semen sample indicated that gossypol in doses as little as 1 ng/ml produced a 90% reduction of sperm motility (47).

HUMAN STUDIES

Thus far, over 10,000 healthy men in China have taken either gossypol acetic acid or gossypol formic acid as contraceptive pills for more than six months, and more than half of them have been clinically observed for two years (41). Subjects were initially treated with 20 mg daily for about two months. After either reduction of sperm count to below 4 million/ml or production of necrospermia, the subjects were shifted to a maintenance dose of 75 to 100 mg twice a month.

Examination of semen showed nonmotile, malformed, and dead sperm, as previously observed in the rat

	CONCENTRATION* (mg/ml)	20 SECONDS	3 MINUTES
PVP	30	+	+
	70	+	+
	200	+	+
GOSSYPOL (FREE)	20	+	+
	40	+	+
	80	+	+
	100	+	+
	150	+	+
GOSSYPOL ACETIC ACID	20	+	+
	40	+	+
	80	+	+
	100	+	+
	150	+	+
GOSSYPOL- PVP	1	+	+
	5	+	-
	10	+	-
	20	+	-
	40	-	-

* amount titrated per milliliter of saline
+ motile spermatozoa present
- no motile spermatozoa found

(Modified from Waller DP, Zaneveld LJD, Fong HHS: *In vitro* spermicidal activity of gossypol. *Contraception* 22(2):185, 1980)

Table 7. Antimotility effect of PVP, gossypol, and gossypol derivatives.

studies. Exfoliated abnormal spermatids and spermato-cytes were also present in the semen. Azoospermia was achieved as treatment continued.

Serum LH and testosterone levels remained within normal range. Some men developed elevated levels of pyruvate transaminase and mild changes in electrocardiographic patterns; others experienced lowered blood potassium levels, however these findings could not be linked conclusively to the use of gossypol.

Initially, some men experienced fatigue, increased or decreased appetite, gastrointestinal complaints, or decreased libido, but these symptoms gradually disappeared without discontinuation of pill use. The subjects usually recovered fertility after discontinuation of treatment for three months (41, 43).

Investigators at the Nanjing Institute of Materia Medica studied 148 men who had used gossypol as a contraceptive sometime between 1972 and 1977 (37, 45). They found that 4.7% suffered "apparent hypokalemic paralysis", a condition arising from a deficiency of potassium in the body. By comparison, only 0.1% of 8,482 married men of approximately the same ages and occupations, who had not used gossypol, experienced the deficiency disease during the same period. The incidence of the condition appeared to be regional, however; the greatest incidence was in Nanjing, while in many other districts, no cases were reported among gossypol users. A survey of the potassium content of princi-

pal foods in the Nanjing diet revealed an average potassium intake below the generally accepted nutritional requirement.

The investigators reported that when the diet of rats was modified to lower their potassium intake, gossypol appeared to affect their potassium metabolism (46). In human studies, the investigators compared gossypol-using patients with hypokalemia and normal controls who had never used gossypol, monitoring the amounts of dietary potassium that they excreted. They found that the total level of potassium in gossypol users' body tissues was lower than that of the controls, and that it remained lower even when the potassium in blood plasma and intercellular fluids returned to normal concentrations. Other experiments showed that gossypol was responsible for renal potassium loss, and that this mechanism was the cause of the onset of hypokalemic paralysis. When gossypol users in Nanjing who showed early warning symptoms of hypokalemia paralysis, such as fatigue and muscle weakness, took dietary supplements of potassium salt, they did not develop hypokalemia paralysis. The investigators concluded that increasing the level of potassium in users' diets would probably help to prevent gossypol-related hypokalemia (45).

Other than these Chinese studies, no human studies utilizing gossypol as a male contraceptive agent have been reported. Chinese investigators have started a new series

of human trials involving five clinical research centers. Approximately 1,000 men will have complete baseline studies performed, including blood counts, biochemistry, and semen analysis. Repeated studies will be done at regular intervals during gossypol initiation, and during the period of gossypol maintenance. Gossypol will be discontinued after varying months of use, following which semen analyses and other biologic parameters will be closely monitored to determine the time required for return to normal (reversibility).

CONCLUSION

There is no question that the oral administration of gossypol in appropriate doses causes severe oligospermia and azoospermia in certain susceptible species, including humans. Whether the original Chinese optimism regarding the potential of gossypol as a useful male contraceptive agent will prove correct will depend upon new research, in both animals and humans, that will address the significant issues of toxicity and reversibility. Laboratory investigations to determine the mechanism(s) of action of gossypol possibly could lead

to the development of synthetic compounds exhibiting the desired antifertility effect without the toxic effects so far noted in certain animals.

As it is obvious that no animal model can substitute effectively for the human, carefully designed clinical studies should be performed in settings that can provide additional information on dose-response, efficacy, side-effects, metabolic effects, and reversibility potential. Nutritional studies must be undertaken to determine the positive or negative effects on these parameters when gossypol is administered with supplements of iron, potassium, protein, or amino acids. The quality of diet is likely to be an important factor if gossypol is to be used as a male antifertility drug in developing countries.

Certainly, if developed into a practical contraceptive pill for men, gossypol will make a far-reaching contribution in fertility regulation, and it is likely to have an enormous impact on society and on the lives of individuals. The sources and supplies of gossypol from cotton and related plants are abundant. As a contraceptive drug, gossypol could be self-administered and convenient to use. If the safety of gossypol and the reversibility of its contraceptive action can be confirmed, the use of gossypol in fertility regulation will represent a great achievement in science, and will contribute to human welfare.

REFERENCES

1. Abou-Donia MB: Physiological effects and metabolism of gossypol. *Residue Reviews*. New York, Springer-Verlag, 1976, vol 61, pp 126-160.
2. Adams R, Geissman JA, Edwards JD: Gossypol, a pigment of cottonseed. *Chem Rev* 60:555-574, 1960.
3. Ames BN, McCann J, Yamasaki E: Methods for detection of carcinogens and mutagens with the *Salmonella/mammalian-microsome* mutagenicity test. *Mutat Res* 31:347-364, 1975.
4. Bardin CW, Sundaram KS, Chang CC: Toxicology, endocrine and histopathologic studies in small animals and Rhesus monkeys administered gossypol. Presented at PARFR Workshop on Gossypol. Program for Applied Research on Fertility Regulation, March 11, 1980, Chicago, Illinois.
5. Berardi LC, Goldblatt LA: Gossypol. In Liener IE (ed): *Toxic Constituents of Plant Foodstuffs*. New York, Academic Press, 1969, pp 211-266.
6. Bressani R: Human nutrition and gossypol. Presented at PARFR Workshop on Gossypol. Program for Applied Research on Fertility Regulation, March 11, 1980, Chicago, Illinois.
7. Buitrago JA, Clawson AJ, Smith FH: Effect of dietary iron on gossypol accumulation in an elimination from porcine liver. *J Animal Sci* 31:554-558, 1970.
8. Campbell KN, Morris RC, Adams R: The structure of gossypol. I. *J Am Chem Soc* 59: 1723, 1937.
9. Carruth FE: Contribution to the chemistry of gossypol, the toxic principle of cottonseed. *J Am Chem Soc* 40:647, 1918.
10. Chang MC, Zhiping Gu (Chi-ping Ku), Saksena SK: Effects of gossypol on the fertility of male rats, hamsters and rabbits. *Contraception* 21(5): 461-469, 1980.
11. Clark EP: Studies on gossypol. I The preparation, purification and some of the properties of gossypol, the toxic principle of cottonseed. *J Biol Chem* 75:725, 1927.
12. Clark EP: Studies on gossypol a progress report. *Oil Fat Ind* 6: 15-19, 1929.
13. Clawson AJ: Effects of gossypol on animal nutrition. Presented at PARFR Workshop on Gossypol. Program for Applied Research on Fertility Regulation, March 11, 1980, Chicago, Illinois.
14. Clawson AJ, Smith FH, Barrick ER: Accumulation of gossypol in the liver and factors influencing the toxicity of injected gossypol. *J Animal Sci* 21:911-915, 1962.
15. Clawson AJ, Smith FH, Osborne JC, Barrick ER: Effect of protein source, autoclaving and lysine supplementation on gossypol toxicity. *J Animal Sci* 20:547-552, 1961.
16. Colman N, Gardner A, Herbert V: Non-mutagenicity of gossypol in the *Salmonella/mammalian-microsome* plate assay. *Environ Mut* 1:315-320, 1979.
17. Dai R-X, Pang S-N, Lin X-K, Lui Z-L, Gong R-H: A study of antifertility effect of cottonseed. *Acta Biol Exp Sinica* 11:1-10, 1978.
18. Dai R-X, Pang S-N, Liu Z-L: Studies on the antifertility effect of gossypol. II. A morphological analysis of the antifertility effect of gossypol. *Acta Biol Exp Sinica* 11:27-30, 1978.
19. de Peyster A: Genetic toxicology and mutagenicity testing of gossypol. Presented at PARFR Workshop on Gossypol. Program for Applied Research on Fertility Regulation, March 11, 1980, Chicago, Illinois.
20. de Peyster A, Wang YY: Gossypol - proposed contraceptive for men passes the Ames test. *N Engl J Med* 301:275-276, 1979.
21. Djerassi C: The politics of contraception; the view from Beijing. *N Engl J Med* 303(6):334-336, 1980.
22. Eagle E: Chronic toxicity of gossypol. *Science* 109:361, 1949.
23. Eagle E: Effect of repeated doses of gossypol on the dog. *Arch Biochem Biophys* 26:68-71, 1950.
24. Eagle E, Bialek HF: Effect of single and repeated doses of gossypol on the rat. *Food Res* 15:232-236, 1950.
25. Edward JD Jr: Total synthesis of gossypol. *Am J Chem Soc* 80:3798-3799, 1958.
26. Fang VS: Personal communication, 1980.
27. Furujelm M, Jonson B, Lagergren C-G: The quality of human semen in spontaneous abortion. *Int J Fertil* 7(1):17-21, 1962.
28. Gallup WD: Further observations in eliminating the toxicity of cottonseed meal. *J Dairy Sci* 10:519-526, 1927.
29. Hahn DW, Rusticus C, Probst A, Homm R, Johnson N: Antifertility and endocrine activities of gossypol in rodents. Presented at PARFR Workshop on Gossypol. Program for Applied Research on Fertility Regulation, March 11, 1980, Chicago, Illinois.
30. Hale F, Lyman CM: Effect of protein level in the ration on gossypol tolerance in growing-fattening pigs. *J Animal Sci* 16:364-369, 1957.
31. Halverson JO, Smith FH: Estimation of gossypol in cottonseed meal — a modified method. *Ind Eng Chem* 5:29, 1933.
32. Harper GA, Phelps RA, Jones LA: Effects of diet and other factors upon the physiological effects of gossypol. Presented at PARFR Workshop on Gossypol. Program for Applied Research on Fertility Regulation, March 11, 1980, Chicago, Illinois.
33. Hoffer AP: Light and electron microscopic studies on the effects of gossypol in the male rat. Presented at PARFR Workshop on Gossypol. Program for Applied Research on Fertility Regulation, March 11, 1980, Chicago, Illinois.
34. Holley KT, Harms WS, Storherr RW, Gray SW: Cottonseed meal in swine and rabbit rations. *Georgia Agr Expt Sta Mimeo Ser* 12[NS], 1955, pp 1-27.
35. Hsueh S-P, Tsong S-T, Su S-Y, Wu Y-W, Liu Y, Chou T-H, Ma H-H: Cytological, radioautographic and ultrastructural observations on the antispermatogenesis action of gossypol in the rat. *Sci Sinica* 9:915-923, 1979.
36. Lobl TJ, Bardin CW, Chang CC: Pharmacologic agents producing infertility by direct action on the male reproductive tract. In Zatuchni GI, Labbok MH, Sciarra JJ (eds): *Research Frontiers in Fertility Regulation*. Hagerstown, Harper & Row, 1980, pp 146-168.
37. Low potassium levels from use of gossypol linked to paralysis. *Fam Plann Perspectives* 13(1):44-45, 1981.
38. Lu G-S: Purification of gossypol and preparation of derivatives. Presented at PARFR Workshop on Gossypol. Program for Applied Research on Fertility Regulation, March 11, 1980, Chicago, Illinois.
39. MacGregor JT, Sachs LE: The sporulation system of *Bacillus subtilis* as the basis of a multi-gene mutagen screening test. *Mutat Res* 38: 271-286, 1976.
40. Marchlewski L: Gossypol, ein Bestandteil der Baumwollsamensamen. *J Prakt Chem* 60:84, 1899.
41. Maugh TH II: Male "pill" blocks sperm enzyme. *Science* 212 (April 17): 314, 1981.
42. Merck Index, 8th Edition. Rahway, NJ, Merck & Co. 1968, p 505.
43. National Coordinating Group on Male Fertility: A new male contraceptive drug — cotton phenol (Gossypol). *Chinese Med J* 4:417-428, 1978.
44. Pösö H, Wichmann K, Jänne J, Luukkainen T: Gossypol, a powerful inhibitor of human spermatozoal metabolism. *Lancet* I (8173):885-886, 1980.
45. Qian S-Z, Jing G-W, Wu X-Y, Xu Y, Li Y-Q, Zhou Z-H: Gossypol related hypokalemia: Clinico-pharmacologic studies. *Chinese Med J* 93:477, 1980.
46. Qian S-Z, Xu Y, Chen C, Cao L-M, Sun S-G, Tang X-C, Wang Y-F, Shen L-Y, Zhu M-K: The influence of gossypol on the potassium metabolism of rats and the effect of some possible contributing factors (low-K and low-Mg intake). *Acta Pharm Sinica* 14:514, 1979.
47. Ridley A, Blasco L: Testosterone and gossypol effects on human sperm motility. Abstract. *Fertil Steril Abstr Suppl* 35(2):244, 1981.
48. Saksena SK, Salmons R, Lau IF, Chang MC: Gossypol, a male antifertility agent: its toxicological and endocrinological effects in male rabbits. *Contraception* (*in press*).
49. Schwartz EW, Alsborg CL: Pharmacol-

- ogy of gossypol. *J Agr Res* 28: 191-198, 1924.
50. Sharma MP, Smith FH, Clawson AJ: Effective levels of protein and gossypol and length of feeding period on the accumulation of gossypol in tissues of swine. *J Nutrition* 88:434-438, 1966.
51. Simmon VF: *In vitro* assays for recombinogenic activity of chemical carcinogens and related compounds with *Saccharomyces cerevisiae* D3. *J Natl Cancer Inst* 62(4):901-909, 1979.
52. Slocumb J: Medical and sociological aspects of *Gossypium* use among women in Southwest United States. Presented at PARFR Workshop on Gossypol. Program for Applied Research on Fertility Regulation, March 11, 1980, Chicago, Illinois.
53. Smith DM, Oura C, Zamboni L: Fertilizing ability of structurally abnormal spermatozoa. *Nature* 227:79-80, 1970.
54. Smith FH, Clawson AJ: Effect of diet on accumulation of gossypol in the organs of swine. *J Nutrition* 87:317-321, 1965.
55. Smith HA: The pathology of gossypol poisoning. *Am J Pathol* 33:353-365, 1957.
56. Waller DP, Cameron SM, Zaneveld LJD: Spermicidal effect of gossypol in an *in vitro* model for vaginal contraceptives. *J Andrology* 2:32, 1981.
57. Waller DP, Zaneveld LJD: *In vitro* and small animal studies on gossypol. Presented at PARFR Workshop on Gossypol. Program for Applied Research on Fertility Regulation, March 11, 1980, Chicago, Illinois.
58. Waller DP, Zaneveld LJD, Fong HHS: *In vitro* spermicidal activity of gossypol. *Contraception* 22(2):183-187, 1980.
59. West JL: Lesions of gossypol poisoning in the dog. *J Am Vet Med Assoc* 96:74-76, 1940.
60. Withers WA, Brewster FE: Studies on cottonseed meal toxicity. II. Iron as an antidote. *J Biol Chem* 15:161-166, 1913.
61. Withers WA, Carruth FE: Gossypol -- A toxic substance in cottonseed meal. A preliminary note. *Science* 41:324, 1915.
62. Withers WA, Carruth FE: Gossypol, the toxic substance in cottonseed meal. *J Agr Res* 7:261, 1915.
63. Wyrobek AJ, Bruce WR: The induction of sperm shape abnormalities in mice and humans. In Hollaender A, de Serres FJ (eds): *Chemical Mutagens*, vol 5. New York, Plenum Publishing Corporation, 1978.

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