

PDAA Q 589

37893

PROGRAM FOR APPLIED RESEARCH
ON FERTILITY REGULATION

S E M I - A N N U A L R E P O R T

July 1, 1984 - December 31, 1984

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
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In compliance with
Cooperative Agreement DPE-0546-A-00-1003-00

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July 30, 1984 and December 12, 1984	
<u>Research Frontiers in Fertility Regulation</u>	
Volume 3, Number 2, December, 1984	

Project Title and Contract Number:

Program for Applied Research on Fertility Regulation
 AID/csd-3608
 AID/DSPE-C-0035
 DPE-0546-A-00-1003-00

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
 July 1, 1981 - June 30, 1986 -- DPE-0546-A-00-1003-00

Reporting Period:

July 1, 1984 - December 31, 1984

Total Expenditures Through June 30, 1984:

AID/csd-3608	\$ 4,331,521.82
AID/DSPE-C-0035	3,370,727.26
DPE-0546-A-00-1003-00	<u>4,172,097.95</u>
TOTAL:	\$11,874,347.03

Total Expenditures July 1, 1984 Through December 31, 1984:

AID/csd-3608	\$ - 0 -
AID/DSPE-C-0035	- 0 -
DPE-0546-A-00-1003-00	<u>891,497.05</u>
TOTAL:	\$891,497.05

Commitments Through December 31, 1984: DPE-0546-A-00-1003-00 \$1,634,495.16

Total Funding Received 7/1/81-12/31/84: \$7,560,000

Total Budgeted 7/1/81-6/30/86: \$12,363,280

PROGRAM ACCOMPLISHMENTS

Scientific Summary

1. Meetings of the Scientific Advisory Committee (SAC) were held on July 30, 1984 and December 12, 1984. With PARFR staff, SAC reviewed extension, formal, and pilot study proposals received during the current period. Please refer to the SAC section (Program Accomplishments) and SAC Minutes (Appendix) for specific determinations.
2. Research progress was monitored by review of technical reports and site visits to projects. During this reporting period, the following site visit was made by PARFR staff:
 - a. 8/1-2/84 -- Gerald I. Zatuchni, M.D., M.Sc., Stolle Research and Development Corp., Cincinnati, Ohio. Dr. Zatuchni viewed the new research and manufacturing facilities for microcapsules.
3. The following meeting for the purpose of project development was attended by PARFR staff and consultants:
 - a. 10/9-10/84 -- Alfredo Goldsmith, M.D., M.P.H., Gerald I. Zatuchni, M.D., M.Sc., Lee R. Beck, Ph.D., Danny H. Lewis, Ph.D., and Al Seimens, Ph.D.; New York, New York (90-Day Microcapsule System).
4. Dr. Gerald Zatuchni presented two lectures on Contraceptive Development at the Canadian Fertility and Sterility Society on September 4-5, 1984 in Vancouver, British Columbia.
5. Drs. John Sciarra and Gerald Zatuchni represented PARFR at the European Congress of Fertility and Sterility held September 24-27, 1984 in Monaco. Dr. Zatuchni is also preparing a paper based on this meeting, to be titled: "Long-Acting Contraceptive Delivery Systems."
6. Drs. Alfredo Goldsmith and Gerald Zatuchni represented PARFR at an inter-agency meeting on Long-Acting Contraceptives held October 8, 1984 at The Population Council in New York, New York.
7. Drs. Alfredo Goldsmith, Ricardo Asch, and Kamran Moghissi attended the PARFR supported symposium held during the "IXth Latin American Congress of Obstetrics and Gynecology," October 20-26, 1984 in Caracas, Venezuela. All were speakers at the symposium. Dr. Goldsmith spoke on Vaginal Contraception and Long-Acting Methods of Contraception; Dr. Asch on LH-RH Peptides as Potential Contraceptives; and Dr. Moghissi on Detection of Ovulation and Implication for Natural Family Planing. Over 400 individuals attended the PARFR symposium.

Scientific Summary (cont'd)

8. Dr. Alfredo Goldsmith attended the Latin American Meeting on Human Reproduction held October 27-30, 1984 in Campinas, Brazil. Dr. Goldsmith delivered two lectures: Non-Surgical Female Sterilization and Biodegradable Pellets.
9. Dr. Gerald Zatuchni prepared a talk on Transcervical Sterilization that he delivered at the annual meeting of the American Association of Planned Parenthood Professionals held November 2-3, 1984 in San Antonio, Texas.
10. Dr. Gerald Zatuchni presented a paper entitled: "Contraception Update" at the annual Temple University post-graduate course on November 9, 1984 in Philadelphia, Pennsylvania.
11. Dr. Gerald Zatuchni attended the PARFR-supported NIH meeting on LH-RH held November 13-14, 1984 in Bethesda, Maryland.
12. Volume 3, Number 2 of PARFR's research technical information report was produced and distributed. The issue, "Long-Acting Injectable Norethisterone Contraceptive System: Review of Clinical Studies" was authored by Lee R. Beck, Ph.D.
13. Planning has begun for PARFR's 15th International Workshop, "Male Contraception: Advances and Future Prospects." The workshop will be held May 28-31, 1985 in Geneva, Switzerland.
14. Dr. Alfredo Goldsmith prepared the following two manuscripts based on PARFR-supported studies for publication with Biostatistical Assistance from Dr. David Edelman: Multicenter Clinical Trial of NET Pellets. Contraception, September, 1984. Vol. 30, No. 3, pp 239-252 and Tubal Occlusion by Quinacrine and Tetracycline in the Primate. Contraception, August, 1983. Vol. 30, No. 3, pp 161-167.

PROGRAM ACCOMPLISHMENTS

LDC Involvement

During this report period, the following subagreements in LDCs were executed:

1. PARFR-366 -- "Immunological Contraception - Study on the Time Course of Sperm Antibodies Production in Rabbits Following Intravasal Injection of BCG (Bacillus Calmette Guerin)"
Steven Y.W. Chan, Ph.D., University of Hong Kong, Hong Kong

2. PARFR-367 -- "Fertility Inhibition of In Vivo Immunization with Epididymal Proteins in Hamsters"
Jose A. Blaquier, M.D., Instituto de Biologia y Medicina Experimental, Buenos Aires, Argentina

The following subagreement terminated during this report period:

1. PARFR-305V -- "Radio-Opaque Methylcyanoacrylate (MCA) Delivered Through Single Application (FEMCEPT) Device"
Itic Zigelboim, M.D., Maternidad "Concepcion Palacios", Caracas, Venezuela

LDC Involvement (cont'd)LDC Research Funds

As of December 31, 1984, the following funds were budgeted or expended for research in LDCs:

<u>Country & PARFR #</u>	<u>Budget (Dollars)</u>	<u>Total Expenditures To Date</u>
<u>ARGENTINA</u>		
PARFR-367	\$ 9,900	\$ - 0 -
<u>BRASIL</u>		
PARFR-318B	14,982	14,701.49
PARFR-328B	<u>14,122</u>	<u>10,792.00</u>
TOTAL BRASIL:	\$29,104	\$ 25,493.49
<u>CHILE</u>		
PARFR-301C	31,476	31,476.00
PARFR-310C	8,000	8,000.00
PARFR-311C	9,000	9,000.00
PARFR-316C	27,000	27,000.00
PARFR-327C	20,880	20,520.00
PARFR-341C	<u>45,419</u>	<u>10,811.00</u>
TOTAL CHILE:	\$141,775	\$106,807.00
<u>EGYPT</u>		
PARFR-300E	11,930	11,930.00
PARFR-314E	<u>5,400</u>	<u>5,400.00</u>
TOTAL EGYPT:	\$17,330	\$17,330.00
<u>HONG KONG</u>		
PARFR-366	5,302	- 0 -
<u>MEXICO</u>		
PARFR-300M	23,056	23,056.00
PARFR-330M	28,710	24,572.00
PARFR-341M	<u>36,135</u>	<u>3,326.00</u>
TOTAL MEXICO:	\$87,901	\$ 50,954.00
<u>THAILAND</u>		
PARFR-354	9,800	3,775.44
<u>VENEZUELA</u>		
PARFR-305V	24,049	21,512.10
PARFR-322V	3,600	3,600.00
PARFR-327V	<u>19,535</u>	<u>17,043.23</u>
TOTAL VENEZUELA:	\$47,184	\$ 42,155.33
TOTAL LDC:	\$348,296	\$246,515.26

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. Monitoring Cooperative Agreement, DPE-0546-A-00-1003-00.

2. Coordinating and mailing the agendas for the July 30, 1984 and December 12, 1984 meetings of the Scientific Advisory Committee. The agenda for the July 30, 1984 meeting included 10 formal proposals, 2 extension proposals, 2 pilot study proposals and 15 technical reports. The agenda for the December 12, 1984 meeting included 12 formal proposals, 2 extension proposals, 1 pilot study proposal, and 27 technical reports.

3. Negotiating and executing:
 - 9 New Subagreements: 356a, 360, 361, 362, 363, 364, 365, 366, 367

 - 7 Additional Funding/Extension Amendments: 309, 315 (2), 337F, 338, 349, 361

 - 1 Additional Funding Amendment: 344

 - 1 No Cost Extension Amendment: 353

4. Mailing 4,500 copies of Vol. 3, Number 2 in the Research Frontiers in Fertility Regulation series.

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Subagreement Negotiations

PROJECT #	TITLE/INVESTIGATOR/INSTITUTION	ACTION	PERIOD	FUNDING
309	"Ovulation Inhibition by Anordrin" Robert T. Chatterton, Ph.D. Northwestern University Chicago, Illinois	Additional Funding/ Extension (Amendment #3)	1/1/82- 12/31/84	\$ 38,587 (\$187,575 total)
315	"Immunologic Suppression of Fertility by Synthetic Antigenic Determinants of LDH-C ₄ " Erwin Goldberg, Ph.D. Northwestern University Chicago, Illinois	Additional Funding/ Extension (Amendments #3 and #4)	3/1/82- 6/30/85	\$ 39,606 (#3 37,485 (#4 (\$199,184 total)
*337F	"Use-Effectiveness of a Levonorgestrel-Releasing Intracervical Device" Tapani Luukkainen, M.D., Ph.D. University of Helsinki Helsinki, Finland	Additional Funding/ Extension (Amendment #1)	5/1/83- 4/30/86	\$ 47,872 (\$97,537 total)
338	"Development of Sperm Enzyme Inhibitors as Vaginal Contraceptives" L.J.D. Zaneveld, D.V.M., Ph.D. Rush-Presbyterian-St. Luke's Medical Center Chicago, Illinois	Additional Funding/ Extension (Amendment #1)	7/1/83- 6/30/86	\$111,182 (\$160,950 total)
344	"Percutaneous Intra Vas Injection for Male Sterilization" Ralph M. Richart, M.D. Presbyterian Hospital Obstetric & Gynecological Services New York, New York	Additional Funding (Amendment #1)	9/1/83- 8/31/84	\$ 4,632 (\$49,668 total)
349	"Preparation of Fibrous Estradiol/ Progesterone IUDs for Phase I Clinical Trials, Continuation of PARFR-324" Richard L. Dunn, Ph.D. Southern Research Institute Birmingham, Alabama	Additional Funding/ Extension (Amendment #2)	11/1/83- 6/30/85	\$ 48,700 (\$98,694 total)

inadvertantly left off semi-annual report dated 1/1/84 - 6/30/84

7/1/84 - 12/31/84

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Subagreement Negotiations

PROJECT #	TITLE/INVESTIGATOR/INSTITUTION	ACTION	PERIOD	FUNDING
353	"Effect of Chronic Intrauterine Release of Estradiol and Progesterone on Uterine Histology in Intact Rabbits" Antonio Scomnegna, M.D. Michael Reese Hospital and Medical Center Chicago, Illinois	No-cost Extension (Amendment #1)	3/15/84- 12/31/84	
356a	"Development of an Immunocontraceptive Vaccine: Role of 23-Kd Antigen in Immunofertility and Fertility Regulation" Rajesh K. Naz, Ph.D. The George Washington University Washington, D.C.	New Subagreement (Replaces PARFR-356, PI changed institutions)	12/1/84- 8/31/85	\$ 59,593
360	"Inter- and Intra-Cycle Variation of Genital Peroxidases in Women" John C.M. Tsibris, Ph.D. University of Illinois at Chicago Chicago, Illinois	New Subagreement	7/1/84- 6/30/85	\$ 28,012
361	"Testosterone Microcapsule Formulation Study" Ricardo H. Asch, M.D. The University of Texas Health Science Center San Antonio, Texas	New Subagreement	7/1/84- 12/31/84	\$ 33,455
		Additional Funding/ Extension (Amendment #1)	7/1/84- 12/31/85	\$ 88,651 (\$122,106 total)
362	"Combination Injectable Steroidal Microsphere - Continuation of PARFR-332" Danny H. Lewis, Ph.D. Stolle Research and Development Corp. Birmingham, Alabama	New Subagreement	10/1/84- 5/31/85	\$ 67,195

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Subagreement Negotiations

PROJECT #	TITLE/INVESTIGATOR/INSTITUTION	ACTION	PERIOD	FUNDING
363	"Laboratory Studies on an Anti-spermatogenic Agent - THP for Control of Male Fertility" John P. Wiebe, Ph.D. University of Western Ontario London, Ontario, Canada	New Subagreement	10/1/84- 3/31/86	\$ 90,000
364	"Antifertility Effects of Microencapsulated LHRH Agonist" Francisco J. Rojas, Ph.D. The University of Texas Health Science Center San Antonio, Texas	New Subagreement	9/1/84- 12/31/85	\$63,723
		Additional Funding/ Extension (Amendment #1)	9/1/84- 6/30/86	\$ 495 (\$64,218 total)
365	"Optimization of Progesterone Microcapsule System" Thomas R. Tice, Ph.D. Southern Research Institute Birmingham, Alabama	New Subagreement	9/1/84- 10/31/84	\$ 7,998
		No-Cost Extension (Amendment #1)	9/1/84- 12/31/84	
366	"Immunological Contraception Study on the Time Course of Sperm Antibodies Production in Rabbits Following Intravasal Injection of BCG (Bacillus Calmette Guerin)" Steven Y.W. Chan, Ph.D. University of Hong Kong Hong Kong, Hong Kong	New Subagreement	10/1/84- 3/31/86	\$ 5,302
367	"Fertility Inhibition of <u>In Vivo</u> Immunization with Epididymal Proteins in Hamsters" Jose A. Blaquier, M.D. Instituto de Biologia y Medicina Experimental Buenos Aires, Argentina	New Subagreement	11/1/84- 10/31/85	\$ 9,900

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	0.6	\$ 3,266.52
Gerald I. Zatuchni, M.D., M.Sc. Director of Technical Assistance	5.1	27,450.66
Alfredo Goldsmith, M.D., M.P.H. Head, Research Project Development	5.7	31,030.48
Diane Krier-Morrow, M.B.A. Director of Administration	6.0	16,533.34
Susan Dewar Project Controller (Terminated 8/24/84)	1.8	3,390.86
Mary Nemeth Project Controller (Started 9/24/84)	3.3	4,604.18
Kelley Osborn Publications Coordinator	0.6	5,175.00
Ruvenia Thomas Secretary II	6.0	10,447.34
Asenath Williamson Secretary I	6.0	7,246.94
Josephine Harris Secretary I	6.0	7,620.44
<u>Fringe Benefits</u>		\$ 22,157.08
<u>Indirect Costs</u>		\$101,470.88

The membership of the Scientific Advisory Committee during this reporting period consisted of the following individuals:

John J. Sciarra, M.D., Ph.D., Chairman	Northwestern University
Andrzej Bartke, Ph.D.	Southern Illinois University
David A. Blake, Ph.D.	The Johns Hopkins University School of Medicine
William Droegemueller, M.D.	University of North Carolina
Ronald H. Gray, M.D.	The Johns Hopkins University School of Hygiene and Public Health
Gary D. Hodgen, Ph.D.	Eastern Virginia Medical School
Miriam H. Labbok, M.D., M.P.H. (Last meeting 12/13/84)	The Johns Hopkins University School of Hygiene and Public Health
Kamran S. Moghissi, M.D.	Wayne State University
Dean L. Moyer, M.D.	University of Southern California School of Medicine
Antonio Scomnegna, M.D.	Michael Reese Hospital and Medical Center
Rochelle N. Shain, Ph.D.	The University of Texas Health Science Center at San Antonio
Anne Colston Wentz, M.D.	Vanderbilt University

The Committee met twice during the current reporting period, on July 30, 1984, in Arlington, Virginia, and on December 12, 1984, in Chicago, Illinois.

At the July 30th meeting, the Committee reviewed 10 formal, 2 extension, and 2 pilot study proposals. Fifteen technical reports, including 2 final reports, were also reviewed.

Of the 10 formal proposals reviewed, 4 were approved by the Committee. Dr. John P. Wiebe's proposal, "Laboratory Studies of the Control of Male Fertility by a Non-Toxic, Non-Hormonal, Biological Antispermato-genic Agent" was approved with changes as indicated by SAC. Dr. Robert W. Rebar's proposal, "Clinical Pharmacokinetics/Pharmacodynamics of Controlled-Release Progesterone Microcapsules for the Regulation of Fertility" was approved in principal. Changes in the frequency of blood sampling, baseline data, and date of injection were made. A subagreement will not be written until the manufacturer is able to provide the progesterone microcapsules. Dr. Danny H. Lewis' proposal, "Development of a Three-Month Microsphere Contraceptive Formulation for the Combined Administration of Ethinyl Estradiol and Norethisterone" (continuation of PARFR-332) and Dr. Francisco J. Rojas' proposal, "Effects of the Controlled Release Microcapsule Formulation of the LH-RH Agonist D-Trp-6LH-RH on Suppression of Ovulation in Cynomolgus Monkeys" were both approved as presented.

One of the 2 extension proposals was approved with a reduction in funding suggested -- Dr. John W. Gibson's proposal, "Preparation of Fibrous Estradiol/Progesterone IUDs for Phase I Clinical Trials, Continuation of PARFR-324".

Dr. Steven Y.W. Chan's pilot study proposal, "Immunological Contraception - Study on the Time Course of Sperm Antibodies Production in Rabbits Following Intravasal Injection of BCG (Bacillus Calmette Guerin)" was approved with changes recommended by the Committee and Dr. Nancy Alexander, an independent reviewer.

At the December 12th meeting, 12 formal, 1 pilot study, and 2 extension proposals were reviewed. Twenty-seven technical reports (including 4 along with the proposals), including 1 final report, were also reviewed.

Of the 12 formal proposals reviewed, 6 were approved. Dr. Ricardo H. Asch's proposal, "NIH Androgen Release Study in Rhesus Monkeys", Dr. Lee R. Beck's proposal, "Baboon Endometrial Response to Long-Acting Progestin", and Dr. Robert T. Chatterton's proposal, "Anordrin: Pre-IND Study" were approved as presented. Dr. James R. Dingfelder's proposal, "Postcoital Tests Following Use of the Vaginal Spermicidal Barrier (VSB)" was approved with minor modifications in the protocol. Dr. Andrew V. Schally's proposal, "Development of Methods for Female and Male Contraception Based on LH-RH Antagonists" was approved; however, USAID technical staff would only approve studies needed for an FDA/IND Phase I clinical trial; therefore, Dr. Schally was not funded for this project. Dr. E.S. Nuwayser's proposal, "Development of Levonorgestrel Microcapsules" was approved with a recommendation to decrease the budget.

Minutes of both meetings are included in the Appendix.

CONSULTANTS

The following is a list of Program Consultants, indicating their areas of expertise, contributions to the program, and payment thereof. Included in this list of consultants are 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	Proposal Review 10/5/84		\$ 50
Andrzej Bartke, Ph.D. Obstetrics and Gynecology Andrology	SAC 7/29-30/84 SAC 12/11-12/84	2 days 2 days	420 420
Lee R. Beck, Ph.D.	RFFR: Vol. 3, No. 2		600
David A. Blake, Ph.D. Obstetrics and Gynecology Pharmacology	Proposal Review 9/11/84 Proposal and Tech. Reports Review 12/10/84	1 day	50 210
M. Yusoff Dawood Obstetrics and Gynecology	Proposal Review		50
William DroegemueLLer, M.D. Obstetrics and Gynecology	SAC 7/29-30/84 SAC 12/11-12/84	2 days 2 days	420 420
David A. Edelman, Ph.D. Biostatistician	Consultant Services 7/1-9/30/84	11 days	2,585
Ronald H. Gray, M.D. Epidemiology	SAC 12/11-12/84	2 days	420
Gary D. Hodgen, Ph.D. Reproductive Biology	SAC 12/11-12/84	2 days	420
Miriam H. Labbok, M.D., M.P.H. Epidemiology	SAC 7/29-30/84 SAC 12/11-12/84	2 days 2 days	420 420
Danny H. Lewis, Ph.D.	Preparation of IND 2/22-7/13/84		3,600
Kamran S. Moghissi, M.D. Reproductive Endocrinology	SAC 7/29-30/84 SAC 12/11-12/84	2 days 2 days	420 420
Dean L. Moyer, M.D. Experimental Pathology	SAC 7/29-30/84	2 days	420
Antonio Scommegna, M.D. Obstetrics and Gynecology Reproductive Endocrinology	SAC 7/29-30/84	2 days	420
Rochelle N. Shain, Ph.D. Social Anthropology	SAC 7/29-30/84 SAC 12/11-12/84	2 days 2 days	420 420

Consultants (cont'd)

Donald P. Waller, Ph.D. Pharmacology	Proposal Review 9/11/84		\$ 50
Anne Colston Wentz, M.D. Reproductive Endocrinology	SAC 7/29-30/84 SAC 12/11-12/84	2 days 2 days	420 420
		TOTAL	<hr/> \$13,915

SUMMARY FINANCIAL REPORTS

This section includes:

- A. Summary of Expenditures and Commitments under AID/csd-3608, AID/DSPE-C-0035, and AID/DPE-0546-A-00-1003-00
- B. Detail of Expenditures and Commitments under AID/DPE-0546-A-00-1003-00, effective 7/1/81-6/30/86
- C. Expenditures under AID/DPE-0546-A-00-1003-00 during the period 7/1/84-12/31/84

	<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>DPE-0546-A-00-1003-00</u> <u>(7/1/81-6/30/86)</u>
Expenditures 7/1/84-12/31/84	\$ - 0 -	\$ - 0 -	\$ 891,497.05
Expenditures through 6/30/84	<u>4,331,521.82</u>	<u>3,370,727.26</u>	<u>4,172,097.95</u>
Total Expenditures	\$4,331,521.82	\$3,370,727.26	\$5,063,595.00
Total Commitments @ 12/31/84	- 0 -	- 0 -	1,634,495.16
Uncommitted Balance	<u>180,990.68</u>	<u>39,272.74</u>	<u>861,909.84*</u>
Total Budget	<u>\$4,512,512.50</u>	<u>\$3,410,000.00</u>	<u>\$7,560,000.00</u>

* Additional Commitments not reflected in Financial Reports: \$1,331,239.

COOPERATIVE AGREEMENT: AID/DPE-0546-A-00-1003-00

EFFECTIVE DATES: 7/1/81-6/30/86

TOTAL AWARD: \$12,363,280

TOTAL AWARDED TO DATE: \$7,560,000

Category	Budget	%	7/1/81 - 12/31/84		
			Expenditures	Commitments	Total
<u>Research</u>	\$4,663,338	61.7	\$2,519,912.70	\$1,520,565.77	\$4,040,478.47
<u>Workshops and Publications</u>	451,374	6.0	333,072.81	34,000.00	367,072.81
<u>Consultants</u>	90,400	1.2	76,909.35	4,040.00	80,949.35
<u>Travel</u>	378,584	5.0	296,291.51	7,112.27	303,403.78
<u>Salaries and Fringe Benefits</u>	871,981	11.5	845,819.39	- 0 -	845,819.39
<u>Supplies, Communications and Rent</u>	471,694	6.2	399,729.03	9,824.40	409,553.43
<u>Equipment</u>	26,439	.4	12,511.35	- 0 -	12,511.35
<u>Indirect Costs</u>	606,190	8.0	579,348.86	58,952.72	638,301.58
	<u>\$7,560,000</u>		<u>\$5,063,595.00</u>	<u>\$1,634,495.16</u>	<u>\$6,698,090.16</u>

COOPERATIVE AGREEMENT: AID/DPE-0546-A-00-1003-00

EXPENDITURES FOR THE PERIOD: 7/1/84-12/31/84

<u>Category</u>	<u>Expended 7/1/81-6/30/84</u>	<u>Expended 7/1/84-12/31/84</u>	<u>Total Expended 7/1/81-12/31/84</u>
<u>Research</u>	\$2,052,769.19	\$467,143.51	\$2,519,912.70
<u>Workshops & Publications</u>	266,845.34	66,227.47	333,072.81
<u>Consultants</u>	63,459.35	13,450.00	76,909.35
<u>Travel</u>	266,102.11	30,189.40	296,291.51
<u>Salaries & Fringe Benefits</u>	706,296.55	139,522.84	845,819.39
<u>Supplies, Communications and Rent</u>	326,236.08	73,492.95	399,729.03
<u>Equipment</u>	12,511.35	- 0 -	12,511.35
<u>Indirect Costs</u>	477,877.98	101,470.88	579,348.86
TOTAL:	<u>\$4,172,097.95</u>	<u>\$891,497.05</u>	<u>\$5,063,595.00</u>

TECHNICAL REPORTS

The following technical reports were reviewed at the July 30, 1984 Scientific Advisory Committee Meeting:

<u>Project</u>	<u>Period Covered by Report</u>
PARFR-330 -- "A Clinical Evaluation of the Subdermal Norethindrone Pellet Implant (Phase II)"	11/16/83-6/15/84
PARFR-330T -- "A Clinical Evaluation of the Bioabsorbable Contraceptive Norethindrone Pellet Implant (Phase II)"	3/1/84-6/30/84
PARFR-332 -- "Development of an Injectable Long-Acting Estradiol Formulation"	7/12/83-6/1/84 (FINAL)
PARFR-334SRI -- "Development of Controlled-Release Progesterone Microcapsules for the Regulation of Fertility During Lactation"	3/1/83-6/15/84 (FINAL)
PARFR-337F -- "Use-Effectiveness of a Levonorgestrel-Releasing Intracervical Device"	2/1/84-5/31/84
PARFR-341 -- "Phase II Poly NET 90 Injectable Study"	Through 3/20/84
PARFR-341T -- "Phase II Poly NET 90 Injectable Study"	11/1/83-5/31/84
PARFR-343 -- "NIH/Biotek Levonorgestrel Microcapsules"	3/1/84-6/1/84
PARFR-348 -- "Development of Improved Methods and Materials for Injecting Microencapsulated Steroids"	
PARFR-350 -- "An Intra Tubal Device (ITD) for Female Sterilization"	Through May, 1984
PARFR-351 -- "Development of Methods for Female and Male Contraception Based on LH-RH Antagonists"	3/13/84-6/12/84
PARFR-352 -- "Baboon Testing of Duration of NET from Fused Pellets"	3/1/83-6/1/84
PARFR-353 -- "Effect of Chronic Intrauterine Release of Estradiol and Progesterone on Uterine Histology in Intact Rabbits"	Through June, 1984
PARFR-357 -- "Optimization of Release Profile of Norethisterone Injectable 90-Day Contraceptive"	5/1/84-6/30/84

<u>Project</u>	<u>Period Covered by Report</u>
PARFR-358 -- "Development of a 30-Day Injectable Contraceptive"	5/1/84-6/30/84

The following technical reports were reviewed at the December 12, 1984 Scientific Advisory Committee Meeting:

<u>Project</u>	<u>Period Covered by Report</u>
PARFR-315 -- "Immunologic Suppression of Fertility by Synthetic Antigenic Determinants of Lactate Dehydrogenase-C ₄ , Extension of PARFR-232"	June-November, 1984
PARFR-330 -- "A Clinical Evaluation of the Subdermal Norethindrone Pellet (Phase II)"	6/16/84-11/1/84
PARFR-330M -- "A Clinical Evaluation of the Subdermal Norethindrone Pellet (Phase II)"	11/1/83-7/31/84
PARFR-330T -- "A Clinical Evaluation of the Bioabsorbable Subdermal Contraceptive Norethindrone Pellet Implant (Phase II)"	6/30/84-11/15/84
PARFR-333 -- "Poly-gly NET 180 Microcapsule System - Phase I"	
PARFR-334UAB -- "Pharmacokinetic Studies in Baboons Relating to the Development of Controlled-Release Progesterone Microcapsule"	6/1/84-11/1/84
PARFR-337F -- "Use-Effectiveness of a Levonorgestrel-Releasing Intracervical Device"	6/1/84-9/30/84
PARFR-337T -- "Intracervical Device Acceptability Study"	6/1/83-2/1/84
PARFR-338 -- "Development of Sperm Enzyme Inhibitors as Vaginal Contraceptives"	7/1/84-11/1/84
PARFR-338UI -- "Toxicology Studies of Acrosin Inhibitors"	7/1/84-11/15/84
PARFR-339 -- "Efficacy Studies in Primates with the Shug in the Absence of a Tissue Wrap"	7/1/84-11/1/84
PARFR-339UI -- "Toxicology of Silicone Implanted (SHUGS) in the Vas Deferens"	7/1/84-11/15/84
PARFR-341 -- "Phase II Poly NET 90 Injectable Study"	12/1/83-10/30/84
PARFR-341C -- "Phase II Poly NET 90 Injectable Study"	Through 9/15/84

Technical Reports (continued)

<u>Project</u>	<u>Period Covered by Report</u>
PARFR-341T -- "Phase II Poly NET 90 Injectable Study"	11/1/83-10/26/84
PARFR-343 -- "NIH/Biotek Levonorgestrel Microcapsules"	6/1/84-11/1/84
PARFR-344 -- "Percutaneous Intra Vas Injection for Male Sterilization"	7/1/84-8/31/84 (FINAL)
PARFR-346 -- "Development of Controlled-Release Testosterone Microcapsules for Fertility Regulation of Males"	10/1/83-8/31/84 (FINAL)
PARFR-351 -- "Development of Methods for Female and Female Contraception Based on LH-RH Antagonist"	1/1/84-10/15/84
PARFR-352 -- "Baboon Testing of Duration of NET from Fused Pellets"	6/1/84-11/1/84
PARFR-355 -- "Enhancement of the Secretary Response to LDH-C ₄ "	7/1/84-9/30/84
PARFR-356a -- "Development of an Immunocontraceptive Vaccine: Role of 23-Kd Antigen in Immunoinfertility and Fertility Regulation"	5/1/84-8/7/84
PARFR-357 -- "Optimization of Release Profile of Norethisterone Injectable 90-Day Contraceptive"	6/30/84-11/1/84
PARFR-358 -- "Development of a 30-Day Injectable Contraceptive"	6/30/84-11/1/84
PARFR-359 -- "Active Immunization of Non-Human Primates and Rabbits with Zona Pellucida Proteins"	7/1/84-10/31/84
PARFR-360 -- "Inter- and Intra-Cycle Variation of Genital Peroxidases in Women"	7/1/84-11/1/84
PARFR-361 -- "Testosterone Microcapsule Formulation Study"	7/1/84-11/1/84

RESEARCH

PARFR SUBAGREEMENT EXPENSE SUMMARIES

This section summarizes the expenses of PARFR subagreements active during the period July 1, 1984 to December 31, 1984. Summaries are categorized according to the following AID Contraceptive Research Areas:

- | | |
|---|---|
| I. <u>FEMALE STERILIZATION</u> | VI. <u>NEUROPEPTIDES</u> |
| A. Surgical | A. Female |
| B. Transcervical | B. Male |
| C. Reversible | VII. <u>OTHER PHARMACEUTICAL AGENTS</u> |
| D. Other | A. Female |
| II. <u>MALE STERILIZATION</u> | B. Male |
| A. Reversible | VIII. <u>BARRIER CONTRACEPTION</u> |
| B. Non-Reversible | A. Female |
| C. Other | B. Male |
| III. <u>INTRAUTERINE CONTRACEPTION</u> | IX. <u>IMMUNOCONTRACEPTION</u> |
| IV. <u>STEROIDAL CONTRACEPTION - FEMALE</u> | A. Female |
| A. Injectable | B. Male |
| B. Implants | X. <u>MISCELLANEOUS</u> |
| C. Orals | |
| D. Other | |
| V. <u>STEROIDAL CONTRACEPTION - MALE</u> | |
| A. Injectable | |
| B. Implants | |
| C. Orals | |
| D. Other | |

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

I. FEMALE STERILIZATION

B. TRANSCERVICAL

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
327C	Instituto de Obstetricia y Ginecologia de Universidad Austral de Chile Valdivia, Chile Rene Guzman-Serani, M.D.	"Time Interval MCA/FEMCEPT Study"	12/1/82-11/30/84	\$ 20,880	\$ 2,650.00	\$20,520.00
327V	Maternidad "Concepcion Palacios" Caracas, Venezuela Itic Zighelboim, M.D. Wiktor Szczedrin, M.D.	"Time Interval MCA/FEMCEPT Study"	12/1/82-11/30/84	19,535	632.50	17,043.23

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

I. FEMALE STERILIZATION (continued)

C. REVERSIBLE

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
350	Tenon Hospital, University of Paris Paris, France Jacques Hamou, M.D.	"An Intra Tubal Device (ITD) for Female Sterilization"	1/1/84- 6/30/85	\$ 11,000	\$ 5,665.00	\$ 5,665.00

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

II. MALE STERILIZATION

A. REVERSIBLE

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
339	Rush-Presbyterian-St. Luke's Medical Center Chicago, Illinois Lourens J.D. Zaneveld, D.V.M., Ph.D.	"Efficacy of Studies in Primates with the Shug in the Absence of a Tissue Wrap"	7/1/83- 6/30/85	\$ 37,476	\$18,789.00	\$22,874.49
339UI	University of Illinois at Chicago Chicago, Illinois Donald P. Waller, Ph.D.	"Toxicology of Silicone Implanted (SHUGS) in the Vas Deferens"	7/1/84- 6/30/85	55,780	1,605.34	1,605.34

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

II. MALE STERILIZATION (continued)

B. NON-REVERSIBLE

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
344	Presbyterian Hospital Obstetric and Gynecological Services New York, New York Ralph M. Richart, M.D.	"Percutaneous Intra Vas Injection for Male Sterilization"	9/1/83- 8/31/84	\$ 54,300	\$21,984.71	\$54,300.00

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

II. MALE STERILIZATION (continued)

B. OTHER

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
363	The University of Western Ontario London, Ontario, Canada John P. Wiebe, Ph.D.	"Laboratory Studies on an Antispermatogetic Agent - THP for the Control of Male Fertility"	10/1/84- 3/31/86	\$90,000	\$ 5,491.41	\$ 5,491.41

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

III. INTRAUTERINE CONTRACEPTION

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
337F	University of Helsinki Helsinki, Finland Tapani Luukkainen, M.D., Ph.D.	"Use-Effectiveness of a Levonorgestrel-Releasing Intracervical Device"	5/1/83- 4/30/86	\$ 97,537	\$10,414.37	\$44,062.20
337T	The University of Texas Health Science Center San Antonio, Texas Rochelle N. Shain, Ph.D.	"Intracervical Device Acceptability Study"	6/1/83- 5/31/85	12,502	631.43	959.91
349	Southern Research Institute Birmingham, Alabama Richard L. Dunn, Ph.D.	"Preparation of Fibrous Estra- diol/Progesterone IUDs for Phase I Clinical Trials, Continuation of PARFR-324"	11/1/83- 6/30/85	98,694	10,799.43	51,510.08
353	Michael Reese Hospital and Medical Center Chicago, Illinois Antonio Scomegna, M.D.	"Effects of Chronic Intra- uterine Release of Estradiol and Progesterone on Uterine Histology in Intact Rabbits"	3/15/84- 12/31/84	7,895	- 0 -	- 0 -
D-52	Southern Research Institute Birmingham, Alabama	Preparation of an IND for the Fibrous E/P IUD Delivery System		5,000	- 0 -	- 0 -

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

IV. STEROIDAL CONTRACEPTION - FEMALE

A. INJECTABLE

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
309	Northwestern University Medical School Chicago, Illinois Robert T. Chatterton, Ph.D.	"Ovulation Inhibition by Anordrin"	1/1/82- 12/31/84	\$187,575	\$15,687.93	\$133,277.26
334SRI	Southern Research Institute Birmingham, Alabama Thomas R. Tice, Ph.D.	"Development of Controlled-Release Progesterone Microcapsule"	3/1/83- 4/30/84	49,500	193.65	49,500.00
334UAB	The University of Alabama at Birmingham Birmingham, Alabama Lee R. Beck, Ph.D.	"Pharmacokinetics Studies in Baboons Relating to PARFR-334SRI"	3/1/83- 7/31/84	16,741	7,759.93	16,734.75
341	The University of Alabama at Birmingham Charles E. Flowers, Jr., M.D. and Lee R. Beck, Ph.D.	"Phase II Poly NET 90 Injectable Study"	12/1/83- 11/30/85	79,264	19,773.87	36,008.46
341A	Emory University Atlanta, Georgia Howard J. Tatum, M.D.	"Phase II Poly NET 90 Injectable Study"	1/1/84- 12/31/85	32,905	1,971.63	1,971.63
341C	Centro Nacional de la Familia Santiago, Chile Horacio B. Croxatto, M.D. and Soledad Diaz, M.D.	"Phase II Poly NET 90 Injectable Study"	1/1/84- 12/31/85	45,419	10,811.00	10,811.00

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

IV. STEROIDAL CONTRACEPTION - FEMALE (continued)

A. INJECTABLE (continued)

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
341I	Associazione per Studio della Riproduzione Umana Roma, Italy Giuseppe Benagiano, M.D.	"Phase II Poly NET 90 Injectable Study"	1/1/84- 12/31/85	\$ 39,655	\$ - 0 -	\$ 2,803.35
341M	Instituto de Investigacion Cientifica, University of Durango Durango, Mexico Roberto Rivera, M.D.	"Phase II Poly NET 90 Injectable Study"	1/1/84- 12/31/85	36,135	- 0 -	3,326.00
341T	The University of Texas Health Science Center San Antonio, Texas Jose P. Balmaceda, M.D. and Ricardo H. Asch, M.D.	"Phase II Poly NET 90 Injectable Study"	1/1/84- 12/31/85	82,487	12,133.31	18,876.08
343	The University of Alabama at Birmingham Birmingham, Alabama Lee R. Beck, Ph.D.	"NIH/Biotek Levonorgestrel Microcapsules"	11/1/83- 10/31/84	46,040	31,608.06	41,149.86
348	Stolle Research and Development Corporation Birmingham, Alabama Danny H. Lewis, Ph.D.	"Development of Improved Methods and Materials for Injecting Microencapsulated Steroids"	11/1/83- 11/30/84	49,555	5,753.00	49,555.00
357	Stolle Research and Development Corp. Birmingham, Alabama Danny H. Lewis, Ph.D.	"Optimization of Release Profile of Norethisterone Injectable 90-Day Contraceptive"	5/1/84- 10/31/84	49,119	49,119.00	49,119.00

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

IV. STEROIDAL CONTRACEPTION - FEMALE (continued)

A. INJECTABLE (continued)

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
358	Stolle Research and Development Corp. Birmingham, Alabama Danny H. Lewis, Ph.D.	"Development of a 30-Day Injectable Contraceptive"	5/1/84- 1/31/85	\$ 11,800	\$ 6,744.00	\$ 6,744.00
362	Stolle Research and Development Corp. Birmingham, Alabama Danny H. Lewis, Ph.D.	"Combination Injectable Steroidal Microsphere - Continuation of PARFR-332"	10/1/84- 5/31/85	67,195	- 0 -	- 0 -
365	Southern Research Institute Birmingham, Alabama Thomas R. Tice, Ph.D.	"Optimization of Progesterone Microcapsule System"	9/1/84- 12/31/84	7,998	- 0 -	- 0 -
D-41	The University of Alabama at Birmingham Birmingham, Alabama	RIA analysis for Poly NET Studies - PARFR-300E, 300I, 300M, 300T			2,070.00	11,853.00
D-44	Northwestern University Chicago, Illinois	Animal Purchase and Care - 12 Cynomologous Monkeys for Anordrin Study		4,620	801.66	4,161.11
D-51	Reproductive Endocrinology Laboratory Chicago, Illinois	Laboratory Tests and Analysis (Ovulation Inhibition by Anordrin)		3,228	3,296.00	3,296.00
D-55	Stolle Research and Development Corp. Birmingham, Alabama	Preparation of 194 syringes loaded with Poly NET 180 System for Phase II clinical studies		29,488	- 0 -	- 0 -

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

IV. STEROIDAL CONTRACEPTION - FEMALE (continued)

A. INJECTABLE (continued)

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
D-64	The University of Alabama at Birmingham Birmingham, Alabama	Baboon Testing of Progesterone Microcapsules			\$12,544.00	\$12,544.00

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

IV. STEROIDAL CONTRACEPTION - FEMALE (continued)

B. IMPLANTS

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
330	Cornell University Medical College New York, New York Brij B. Saxena, Ph.D., D.Sc. and Gopi N. Gupta, Ph.D.	"A Clinical Evaluation of the Subdermal Norethindrone Pellet (Phase II)"	2/1/83- 6/30/84	\$ 49,995	\$ 7,357.15	\$48,291.34
330M	Instituto de Investiga- cion Cientifica Durango, Mexico Roberto Rivera, M.D.	"A Clinical Evaluation of the Subdermal Contracep- tive Norethindrone Pellet (Phase II)"	4/1/83- 9/30/84	28,710	12,648.00	24,572.00
330T	The University of Texas Health Science Center San Antonio, Texas Ricardo H. Asch, M.D.	"A Clinical Evaluation of the Bioabsorbable Subder- mal Contraceptive Norethin- dron Pellet Implant (Phase II)"	3/1/83- 2/28/85	48,139	8,029.87	27,353.58
352	The University of Alabama at Birmingham Birmingham, Alabama Lee R. Beck, Ph.D.	"Baboon Testing of Duration of NET from Fused Pellets"	12/1/83- 11/30/84	29,420	17,383.64	19,892.68
D-62	Dynatech R/D Company Cambridge, Massachusetts	Levonorgestrel Rods Drug Release Study Relating to PARFR-320			4,415.50	4,415.50

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

V. STEROIDAL CONTRACEPTION - MALE

A. INJECTABLE

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
346	Southern Research Institute Birmingham, Alabama Thomas R. Tice, Ph.D.	"Development of Controlled-Release Testosterone Microcapsules for Fertility Regulation of Males"	10/1/83-8/31/84	\$ 49,641	\$35,124.58	\$49,641.00
361	The University of Texas Health Science Center San Antonio, Texas Ricardo H. Asch, M.D.	"Testosterone Microcapsule Formulation Study"	7/1/84-12/31/85	122,106	- 0 -	- 0 -

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

VI. NEUROPEPTIDES

A. FEMALE

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
347	The University of Texas Health Science Center San Antonio, Texas Ricardo H. Asch, M.D.	"Studies on the Anovulatory Potency and Side Effects on an Inhibitory Analog of LH-RH in Cynomologous Monkeys"	2/1/84- 1/31/86	\$145,501	\$16,343.76	\$24,746.33
364	The University of Texas Health Science Center San Antonio, Texas Francisco J. Rojas, Ph.D. and Ricardo H. Asch, M.D.	"Antifertility Effects of Microencapsulated LHRH Agonist"	9/1/84- 6/30/86	64,218	- 0 -	- 0 -

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

VIII. BARRIER CONTRACEPTION

A. FEMALE

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
338	Rush-Presbyterian-St. Luke's Medical Center Chicago, Illinois Lourens J.D. Zaneveld, D.V.M., Ph.D.	"Development of Sperm Enzyme Inhibitors as Vaginal Contraceptives"	7/1/83- 6/30/86	\$160,950	\$27,401.30	\$58,121.88
338UI	The University of Illinois at Chicago Chicago, Illinois Donald P. Waller, Ph.D.	"Toxicology Studies of Acrosin Inhibitors"	7/1/84- 6/30/86	84,866	1,255.92	1,255.92
345	Professional Staff Assn., University of Southern California Medical Ctr. Los Angeles, California Gerald S. Bernstein, M.D., Ph.D.	"Effect of the Vaginal Spermicidal Barrier Contraceptive on Sperm Transport in the Human"	10/1/83- 3/31/84	6,375	3,471.85	3,471.85

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

IX. IMMUNOCONTRACEPTION

A. FEMALE

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
315	Northwestern University Evanston, Illinois Erwin Goldberg, Ph.D.	"Immunologic Suppression of Fertility by Synthetic Antigenic Determinants of Dehydrogenase-C ₄ - Extension of PARFR-232"	3/1/82- 6/30/85	\$199,184	\$10,038.68	\$121,914.36
351	The Tulane University School of Medicine New Orleans, Louisiana Andrew V. Schally, Ph.D.	"Development of Methods for Female and Male Contraception Based on LH-RH Antagonist"	1/1/84- 12/31/84	65,153	29,972.15	41,596.13
355	Medical Research Founda- tion of Oregon Beaverton, Oregon Nancy J. Alexander, Ph.D.	"Enhancement of the Secretary Immune Response to LDH-C ₄ "	4/15/84- 4/14/85	47,335	14,357.78	22,259.39
356	Medical Research Founda- tion of Oregon Beaverton, Oregon Rajesh K. Naz, Ph.D. and Nancy J. Alexander, Ph.D.	"Development of an Immunocon- traceptive Vaccine: Role of 23-Kd Antigen in Immunoinfer- tility and Fertility Regulation"	5/1/84- 4/30/85	66,686	10,402.21	13,992.14 Terminated
356a	The George Washington University Washington, D.C. Rajesh K. Naz, Ph.D.	"Development of an Immunocon- traceptive Vaccine: Role of 23-Kd Antigen in Immunoinfer- tility and Fertility Regulation"	12/1/84- 8/31/85	59,593	- 0 -	- 0 -
359	Baylor College of Medicine Houston, Texas Bonnie S. Dunbar, Ph.D.	"Active Immunization of Non- Human Primates and Rabbits with Zona Pellucida Proteins"	6/1/84- 5/31/85	77,741	27,498.93	27,498.93

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

IX. IMMUNOCONTRACEPTION (continued)

A. FEMALE (continued)

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
D-32	Biologic Resources Laboratory, University of Illinois at Chicago Chicago, Illinois	Animal maintenance, papio baboons for PARFR-315, and rhesus monkeys for PARFR-317			\$12,193.16	\$ 84,989.45
D-57	Northwestern University Evanston, Illinois	Chemicals and radioimmunoassays - PARFR-355		\$ 25,000	7,000.00	20,050.00
D-63	Ohio State University Development Fund Columbus, Ohio	Immunogenicity of Pig Zona in Baboons			24,655.00	24,655.00

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

IX. IMMUNOCONTRACEPTION (continued)

B. MALE

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
329	Northwestern University Evanston, Illinois Erwin Goldberg, Ph.D.	"Targeting Liposomes to the Male Reproductive Tract with Antibody LDH-C ₄ "	12/1/82- 11/30/83	\$ 10,000	\$ 812.83	\$ 10,000.00
351	The Tulane University School of Medicine New Orleans, Louisiana Andrew V. Schally, Ph.D.	"Development of Methods for Female and <u>Male</u> Contraception Based on LH-RH Antagonist"	1/1/84- 12/31/84	65,153	29,972.15	41,596.13
366	University of Hong Kong Hong Kong, Hong Kong Steven Y.W. Chan, Ph.D.	"Immunological Contraception - Study on the Time Course of Sperm Antibodies Production in Rabbits Following Intra- vasal Injection of BCG (Bacillus Calmette Guerin)"	10/1/84- 3/31/86	5,302	- 0 -	- 0 -
367	Instituto de Biologia y Medicina Experimental Buenos Aires, Argentina Jorge A. Blaquier, M.D.	"Fertility Inhibition of <u>In</u> Vivo Immunization with <u>Epididymal</u> Proteins in Hamsters"	11/1/84- 10/31/85	9,900	- 0 -	- 0 -

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 7/1/84-12/31/84

X. MISCELLANEOUS

<u>PARFR #</u>	<u>INSTITUTION & INVESTIGATOR(S)</u>	<u>TITLE</u>	<u>DATES</u>	<u>BUDGET</u>	<u>EXPENDITURES THIS PERIOD</u>	<u>TOTAL EXPENDITURES</u>
354	Mahidol University Bangkok, Thailand Montri Chulavatnatol, Ph.D.	"Screening of Thai Plants for Proteins (or Lectins) as Potential Vaginal Contraceptives"	4/1/84- 3/31/85	\$ 9,800	\$ 3,775.44	\$ 3,775.44
360	University of Illinois at Chicago Chicago, Illinois John C.M. Tsibris, Ph.D.	"Inter- and Intra-Cycle Variation of Genital Peroxidases in Women"	7/1/84- 6/30/85	28,127	1,898.13	1,898.13
D-60	Reproductive Endo- crinology Laboratory Chicago, Illinois	Measurement of LH and Preg- nenediol Glucuronide relating to PARFR-360		7,200	2,680.00	2,680.00

FOLLOWING ARE SIX MONTH TECHNICAL REPORT SUMMARIES
OF ALL PROJECTS DURING THIS PERIOD
7/1/84 - 12/31/84

Projects are listed by PARFR number and not by
"Contraceptive Research Area."

PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 309

TITLE: "Ovulation Inhibition by Anordrin"

INSTITUTION: Northwestern University Medical School

DEC 28 1984

PRINCIPAL INVESTIGATOR: Robert T. Chatterton, Ph.D.

FUNDING PERIOD: 1/1/82-12/31/84

AMOUNT FUNDED: \$187,575

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

The objective of the study was to test the efficacy of anordrin to inhibit ovulation in the monkey.

The dose response studies, and studies of the critical time of the menstrual cycle for effect and the carry over effects of anordrin on luteal activity have now been completed. As described in the previous report there was an approximately linear increase in the length of the follicular phase of the menstrual cycle with increasing doses of anordrin. There was also a linear decrease in the production of pregnanediol during the luteal phase of menstrual cycles with increasing doses of anordrin, but there was no significant decrease in pregnanediol production in menstrual cycles immediately following treatment cycles in which as much as 0.4 mg anordrin/kg body weight was given.

With regard to the time of the menstrual cycle in which anordrin must be given to inhibit ovulation, it is now clear that administration of anordrin on day 6 fails to produce an effect in approximately 50% of animals. It is evident that anordrin must be given within the first four days of the menstrual cycle to consistently inhibit ovulation.

Some studies of the effect of anordrin on gonadotropin secretion have also been completed. Within 3 days after the injection of anordrin serum LH rose to a concentration which is approximately half of the midcycle preovulatory surge. However, this increase in LH was not associated with an increase in steroid biosynthesis by the ovary. During the monthly injections of anordrin there were periodic elevations of urinary LH comparable to those of the midcycle surges of LH in control cycles. Here also there is no evidence for a steroidogenic response by the ovary. It is evident that anordrin treatment makes the ovary unresponsive to LH.

The responses to 5 monthly injections of anordrin have been largely, but not completely documented at this time. Ovulation was suppressed in all monkeys for 6 months or more as evidenced by weekly serum estradiol and progesterone measurements and urinary pregnanediol excretion. At the present time, 3 months after the last injection, luteal activity and some vaginal bleeding has occurred in 5 of the 6 treated monkeys. Two of the six monkeys had a single incidence of spotting 2 weeks after the second injection. Vaginal cornification characteristic of that observed during mid-luteal phase of control cycles was observed throughout the 6 month period of time. Uterine biopsies which have been obtained in some of the monkeys indicate suppression of endometrial development. It seems at this time that the estrogenic and antiestrogenic actions of anordrin are expressed differently in different organs and tissues. The study of the occurrence of ovulation by biopsy of the luteal tissue in anordrin-treated monkeys is currently under way and we have no results to report at this time.


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12/21/84
DATE

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 315

TITLE: "Immunologic Suppression of Fertility by Synthetic Antigenic Determinants of Lactate Dehydrogenase-C₄, Extension of PARFR-232"

INSTITUTION: Northwestern University

PRINCIPAL INVESTIGATOR: Erwin Goldberg, Ph.D.

FUNDING PERIOD: 3/1/82-11/30/84

AMOUNT FUNDED: \$199,184

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

The objective of this project is to develop a contraceptive vaccine based on synthetic peptides containing antigenic determinants of sperm-specific LDH-C₄. Female baboons have been immunized with MC5-15, one such peptide, conjugated to diphtheria toxoid (DT, the carrier protein). Immunosuppression of fertility and its reversibility are being examined.

Fertility studies were begun on 2-28-84. Female baboons received i.m. inoculations of 5 mg PT-MC5-15 in CGP 11,637 adjuvant, 7-14 days before ovulation. The animals were mated after each of four immunizations or until conception occurred. Antibody levels were monitored weekly and at the time of mating. Of the fourteen immunized animals, only three conceived (21%). By comparison, 10 out of 14 (71%) of the control animals conceived (71%). This represents a reduction in fertility of 71%, which is significant by chi square analysis at a p .05. The mean circulating antibody levels of the non-pregnant animals at the time of the first through the fourth matings were 43.6, 56.4, 63.2, and 52.9 ng LDH-C₄ bound/ml of serum, respectively. The mean antibody titer for the three animals that became pregnant was 40 ng bound/ml.

Following the fourth mating, immunizations were discontinued. The baboons are now being mated to determine if fertility suppression is reversible. Thus far, two animals have been mated once and six animals have been mated twice. The mean antibody levels for the first two matings declined to 27 and 15 ng LDH-C₄ bound/ml serum respectively. Two animals have conceived. Their antibody titers were 7 and 20 ng LDH-C₄ bound/ml. These preliminary results suggest that fertility suppression is reversible. Since the ratio of circulating antibody to antibody in the reproductive tract may vary with the individual, the critical immunosuppressive serum antibody level may, likewise, be individually variable.


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1/9/85
DATE

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION
SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 327C

TITLE: "Time Interval MCA/FEMCEPT Study"

INSTITUTION: Instituto de Obstetricia y Ginecologia de Universidad Austral

PRINCIPAL INVESTIGATOR: Rene Guzman-Serani, M.D.

FUNDING PERIOD: 12/1/82-11/30/84

AMOUNT FUNDED: \$20,880

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

The 60 women that belong to this study were treated with two applications of MCA.

In order to compare three different manners of application, women were divided in three groups and treated with two dosis of MCA following three different protocols: second dosis two, three and four months after the first one. This part of the research was done between February and August 1983 and all the patients fulfilled with all the requirements of the protocol.

During the period elapsed between the 1 of July and the 31 of December 1984, we performed follow-up visits to 54 of the 60 patients treated.

In all cases we found total normality in the genital tract; no menstrual disorders and no pregnancies.

With these data we can conclude that MCA has been a safe and effective method of female non surgical sterilization between women treated in our center, up to date.

It is necessary a long-term follow-up study in order to know the real effectiveness of MCA/Femcept System and this is what we are doing.

René Guzmán Serani, M.D.

January 11, 1985

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R. Guzman

11 Jan. 1985

PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION
SIX MONTH TECHNICAL REPORT SUMMARY

JAN 2 1985

PARFR- 327 V

TITLE: TIME INTERVAL MCA/FEMCEPT STUDY

INSTITUTION: Maternidad "Concepción Palacios"

PRINCIPAL INVESTIGATOR: Itic Zigelboim, M.D.

FUNDING PERIOD: 12/1/82 - 1/1-84

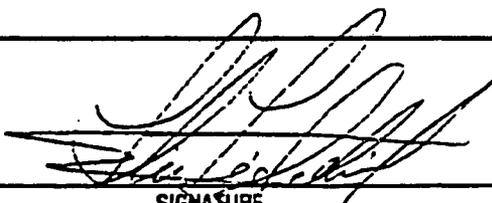
AMOUNT FUNDED: 19,535 U.S.\$

Below is a project summary for the July 1, 1984 - December 31, 1984

period.

During the above mentioned period the following was accomplished:

1. H.S.G. was performed on two patients.
2. In one patient reinjection was performed ,due to patency of one of the falopian tubes.
3. Followups were done on 11 patients,after H.S.G. showed bilateral occlusion
4. All the protocols and the H.S.G's were mailed to BioNexus.



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January 4, 1985

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 330

TITLE: "A Clinical Evaluation of the Subdermal Norethindrone Pellet (Phase II)"

INSTITUTION: Cornell University Medical College

PRINCIPAL INVESTIGATOR: Brij B. Saxena, Ph.D., D.Sc.

FUNDING PERIOD: 2/1/83-12/31/84

AMOUNT FUNDED: 49,995

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

Forty-two women have completed the study satisfactorily for 12 month period at New York. The pellets have been removed and the volunteers have been discharged from the study in good physical and mental condition. A full report has been submitted to PARFR, FDA and FHI. The Phase II study with the NET pellets is summarized as follows. The average release rates of NET in women in New York, San Antonio and Mexico was respectively, 150.3 ± 7.2 , 208.2 ± 20 , 265.3 ± 53.4 μg NET/day with 3 pellets and 212.5 ± 8.6 , 341.71 ± 48.95 , 342.33 ± 34.6 μg NET/day with 4 pellets. The serum NET levels with 3 and 4 pellets were sustained. No initial 'burst effect' was observed. During initial 6 months, the serum NET levels were 0.4 - 0.6 ng/ml with 3 pellets and 0.6 - 0.7 ng/ml with 4 pellets. After 6 months the serum NET levels were 0.4 - 0.6 ng/ml with both 3 and 4 pellets. The serum samples from Mexico and San Antonio have already been analyzed for NET concentrations and the data has been forwarded to the respective centers and FHI. At New York a total of 275 cycles with 3 pellets and 175 cycles with 4 pellets were evaluated. With 3 and 4 pellets, respectively, 15% and 8% of menstrual cycles were ovulatory, 23% and 14% of the cycles were amenorrhic, 7% and 22% of the volunteers had >10 days of bleeding whereas, 70% and 64% had <10 days of bleeding. With 3 pellets two cycles were fertilized, there was no pregnancy with 4 pellets. Overall evaluation of NET pellets as long-term contraception suggested the following: The NET fused pellets can be easily manufactured, sterilized and stored in preloaded disposable trocars. The size and shape of the pellets render subcutaneous implantation and removal as an easy out-patient procedure. The pellets can be retrieved easily and thus the contraception is reversible at will. Lack of any serious side effects and convenience of use rendered these pellets as highly acceptable contraceptive by the women. The advantages of this method of contraception outweigh the menstrual irregularity and minor transitory side effects. It should, however, be pointed out that although these pellets are biodegradable, they induce the formation of a fibrous capsule around them during the implant period. The drug is constantly released from the pellet, but is trapped in the fibrous capsule which acts as a barrier and thus impedes the bioavailability of the drug in the serum. Modification of these pellets which may retard the formation of fibrous capsule around the pellets could provide a longer contraception without increasing the dose of the NET. The manuscript for publication of the results of Phase II clinical trial at New York, as well as, the comprehensive report of Phase II study at Cornell (NY), Durango (Mexico) and San Antonio (TX) are in preparation. In order to establish the extent of biodegradability of NET-pellets a study in five baboons in collaboration with Dr. Lee Beck in Alabama is in progress.

Brij B. Saxena

12/27/84

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

JAN 2 1985

PARFR- 33QM

TITLE: "A Clinical Evaluation of the Subdermal Contraceptive Norethindrone Pellet (Phase II)"

INSTITUTION: Instituto de Investigacion Cientifica, Durango, Mexico

PRINCIPAL INVESTIGATOR: Roberto Rivera, M.D.

FUNDING PERIOD: 4/1/83-9/30/84

AMOUNT FUNDED: \$ 28,710

Below is a project summary for the July 1, 1984 through December 31, 1984

period.

Nineteen of the 20 subjects have terminated their participation in the study. The remaining subject will terminate on March, 1985. The insertion of the pellets was conducted without any problem in all the subjects. There was not any local side-effect throughout the observation period. The only complaints by the subjects were related to menstrual effects. Eight subjects presented different degrees of alterations of their menstrual patterns mostly in the form of intermenstrual bleeding or spotting in the first two or three cycles after insertion; only two of these subjects presented prolonged bleeding or spotting throughout the study period. Interestingly in the 6 cases where weekly hormonal determinations allow some evaluation of the ovarian function, the two ovulatory subjects showed normal menstrual patterns, while the 4 subjects with anovulatory cycles showed various alterations of the menstrual pattern. In the same 6 subjects, in two cases the progesterone values suggested the presence of ovulation in all the cycles, while other two cases showed inhibition of ovulation in all the cycles, the other two subjects showed progesterone values suggestive of ovulation in only one and two of the observed cycles, respectively. All these 6 subjects ovulated in the cycle following the removal of the implant. With the limitations of a monthly determination of progesterone in the other 14 cases, 4 of them ovulated in at least one or two of their cycles. One pregnancy, terminating in a spontaneous abortion in approximately the 23rd week of gestation, occurred in approximately the 17th week after insertion. This subject had already ovulated prior to the pregnancy.


ROBERTO RIVERA, M.D.

January 7, 1985

DATE

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 330T

TITLE: "A Clinical Evaluation of the Bioabsorbable Subdermal
Contraceptive Norethindrone Pellet Implant (Phase II)"

INSTITUTION: The University of Texas Health Science Center at San Antonio

PRINCIPAL INVESTIGATOR: Ricardo H. Asch, M.D.

FUNDING PERIOD: 3/1/83-2/28/85

AMOUNT FUNDED: \$48,139

Below is a project summary for the 7/1/84 through 12/21/84 period.

We were contracted to compare the effects of subdermal implants of bioabsorbable pellets of Norethindrone (NET) in order to identify the lowest dose and duration that is contraceptively effective, safe and acceptable by users. A total of 19 subjects were recruited and randomly received implants of 3 (n=11) or 4 (n=8) pellets of 35 mg each in the forearm without difficulty under local anesthesia. Data was collected regarding cycle length, blood loss, ovulation, steroid levels, lipoprotein profiles (HDL, LDL and VLDL cholesterol) and blood chemistries (SMAC 24) on all subjects. Pellets were removed after 6 months from 15 subjects, the remaining 4 subjects continued in the study for a total period of 1 year.

To date, pellets have been removed from all subjects without complications or breakage. The pellets have been mailed to Dr. B. Saxena to determine residual NET. The tissue surrounding the pellets was fixed in formaldehyde and will be examined histologically by an experienced pathologist at Cornell University for presence of fibrosis, inflammation or neoplastic-type changes.

No clinical nor chemical pregnancies occurred in either group. Periodic urine pregnancy tests were negative on all subjects throughout the study.

Blood samples collected during the study showed no significant changes in SMAC or lipoprotein profiles. Absence of ovulation was evidenced in most subjects as determined by serial progesterone levels.

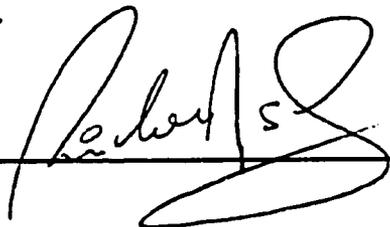
Serum samples have been shipped to Dr. Saxena for determination of serum NET values.

Serious side effects were observed in only one subject, consisting of nausea and vomiting and membranous dysmenorrhea with passage of an endometrial cast one month after implant. Removal of the pellets produced almost immediate disappearance of these symptoms.

Bleeding calendars were collected from all subjects. Cycle length and blood loss varied greatly among individuals in both groups, with one subject who received 4 pellets being amenorrheic for the duration of the study.

Patient acceptability was excellent. No local effects due to pellet implantation or removal were observed in any subject.

All data obtained has been submitted to IFRP for statistical analysis. A final technical report will be submitted to PARFR when the data analysis is completed. An abstract submitted to the Pacific Coast Fertility Society has been accepted for the Annual Meeting next April 24-28, 1985 in Las Vegas, Nevada.



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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

DEC 2 1984

PARFR- 333T

TITLE: "Poly-gly NET 190 Microcapsule System" (Phase I)

INSTITUTION: The University of Texas Health Science Center at San Antonio

PRINCIPAL INVESTIGATOR: Jose P. Balmaceda, M.D.

FUNDING PERIOD: 3/1/83-2/29/84

AMOUNT FUNDED: \$40,249

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

This report represents the final one on the study of Poly-gly NET microcapsule system PARFR 333T contract. We tested safety and effectiveness of a system of biodegradable microcapsules containing Norethisterone in 10 women previously sterilized. During the period of time included by this report we have completed blood sampling and menstrual charts for all the volunteers. Blood samples were done at weekly intervals and serum separated to determine levels of NET, estradiol and progesterone by radioimmunoassay.

Lipoproteins and hepatic function tests were measured monthly.

Biodegradable microcapsules contained approximately 20% of NET weight were supplied by Dr. Lee R. Beck, Southern Research Institute and University of Alabama. Five patients received injection containing 100 ug of NET and five received injections containing 200 ug of NET. After injection syringes were returned to Dr. Beck's laboratories for the measurement of residual NET and determination of efficiency.

NET SERUM LEVELS

A rapid rise of serum NET occurred immediately following the injection. After that levels slowly diminished, until a second rise occurred between days 90 and 120. Actual dosages received, or efficiency of the injection was never reported to our center.

SERUM ESTRADIOL AND PROGESTERONE

Serum estradiol levels varied widely during the study and in some patients levels normally observed in the late follicular phase, suggesting that ovarian activity was not completely suppressed. However, progesterone serum levels remained under 3 ng/ml in all patients indicating absence of ovulation or corpus luteum activity. Using the same criteria all 10 patients were ovulatory during the control cycle.

MENSTRUAL BLEEDING PATTERN

If we compared mean values, there was a significant increase in number of days of bleeding. During the first two 30 days periods following the injection as compared with the control cycles. After that the difference is not significant. Individual variation though is very notorious and some patients had marked oligomenorrhea, while others bled continuously for 25 days.



SIGNATURE

12/18/84

DATE

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 334UAB

TITLE: "Pharmacokinetic Studies in Baboons Relating to PARFR-334SRI"

INSTITUTION: The University of Alabama in Birmingham

(Progesterone
microcapsules)

PRINCIPAL INVESTIGATOR: Lee R. Beck, Ph.D.

FUNDING PERIOD: 3/1/83-7/31/84

AMOUNT FUNDED: \$16,741

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

6-month report for PARFR 334UAB

Progesterone (P4)-releasing microspheres are being evaluated for release duration and ovarian suppression in baboons. To date, four formulations have been tested in 10 baboons. The most recent group of three baboons was injected with 63-125 um diameter microspheres containing 59.8% by weight P4, for a total dose of 250 to 265 mg progesterone.

Serum progesterone levels were sufficient to inhibit perineal cyclicity for at least 60 days. Two baboons had apparently normal cycles starting at 60 days posttreatment, and the third baboon returned to normal cyclicity 120 days posttreatment.

Four additional batches are being scheduled for treatment during the next 2 months.



SIGNATURE

January 2, 1985
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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION
SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 337F

TITLE: "Use Effectiveness of a Levonorgestrel-Releasing
Intracervical Device"

INSTITUTION: University of Helsinki

PRINCIPAL INVESTIGATOR: Tapani Luukkainen, M.D., Ph.D.

FUNDING PERIOD: 5/1/83-4/30/86

AMOUNT FUNDED: 97,537

Below is a project summary for the July 1, 1984 through December 31, 1984

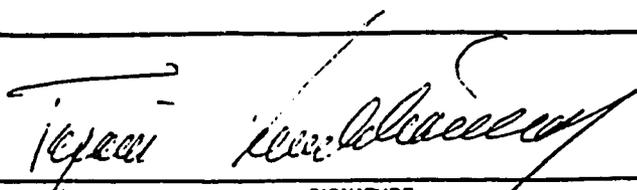
period.

This project aims to the evaluation of clinical performance, efficacy, acceptability and endocrine as well as histological effects of an intracervical contraceptive device releasing levonorgestrel.

To date one hundred and forty-two women have had an ICD inserted. We intend to enroll altogether 200 women for the study on the clinical performance of the device, to be followed-up five years. One accidental pregnancy has occurred by the end of the year 1985. Total number of woman-months gained is 1585, thus giving the Pearl index of 0.76. In eleven cases the device has expelled and in 26 cases the device had to be removed. The most frequent reason for removal was bleeding or spotting, claimed by eight patients. Infection was the reason for removal in three patients. Thirty-nine percent of patients did not complain about any side-effects, and the most common side-effects reported were lower abdominal pain and bleeding disturbances (16 and 14 %, respectively). The acceptance study will be reported by Dr. Shain and the results of the endocrine and histological studies will be ready for report later.

The current reporting period has gained us more clinical data, while still continuing the enrollment of study patients. The first pregnancy occurred in an epileptic patient after 7 months of use. The patient had been treated with anti-epileptic drugs, which are known to induce an increased metabolism of steroids at least in liver. Plasma LNG concentrations will be determined.

The progress of the study indicates that the aims of this clinical trial will be reached within the time-table. The occurrence of the first pregnancy seems to indicate that the lowering of the release rate of LNG from the device may not be aimable. The trial has demonstrated, that the present device has higher rate of expulsions than was found with the prototype. The modification of the present device before larger trials seems to be justified.



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January 25, 1985

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 337T

TITLE: "Intracervical Device Acceptability Study"

INSTITUTION: The University of Texas Health Science Center at San Antonio

PRINCIPAL INVESTIGATOR: Rochelle N. Shain, Ph.D.

FUNDING PERIOD: 6/1/83-5/31/85

AMOUNT FUNDED: \$12,502

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

To date a total of 369 questionnaires have been received from Finland. These include 185 initial interviews (110-ICD, 45-LNG IUD, and 30-Nova T); 137 3-month follow-up interviews (95-ICD, 22-LNG IUD, and 20-Nova T); and 47 12-month interviews from ICD subjects. With the exception of 23 questionnaires that have been returned to Finland for clarification, all instruments have been coded and the vast majority of these have been entered into the computer and are awaiting analyses. In this report some preliminary data from the 3-month follow-up questionnaire (87-ICD, 21-LNG IUD, and 20-Nova T) are presented. The preliminary nature of these findings must be stressed: very few control group questionnaires have been included and computer programs are in the process of being written - thus errors still exist.

Preliminary Findings	ICD Users (N=87)	LNG-IUD Users (N=21)	NOVA T Users (N=20)
Cannot feel device in general	87.4%	85.7%	85.0%
Husbands can feel device (as reported by subject)	20.7%	14.3%	20.0%
Change in desire for intercourse since device inserted			
additional	7.0%	9.5%	0.0%
less	7.0%	9.5%	0.0%
no difference	81.4%	81.0%	100.0%
unsure	4.7%	0.0%	0.0%
Presence of side effects in general	44.8%	33.3%	35.0%
Presence of especially bothersome side effects	5.7%	9.5%	5.0%
Have good or mostly good feelings about device	91.9%	95.2%	90.0%
Dissatisfied with device	6.9%	4.8%	0.0%
Would recommend to friends	71.3%	76.2%	65.0%
if effects improved	16.1%	14.3%	25.0%
Would continue using if not in study	87.2%	90.5%	95.0%
if improvements made	9.3%	4.8%	5.0%
More satisfied with current device than previous IUD	(N=72) 86.1%	(N=15) 60.0%	(N=18) 33.3%
equally satisfied	1.4%	26.7%	50.0%
Discontinued between 1-3 months	5.7%	0.0%	0.0%

In summary, although the ICD is associated with numerous side effects, relatively few are especially bothersome, at least at the 3-month follow-up. Moreover, the overwhelming majority of ICD users have used previous IUDs (primarily the Nova-T and other copper IUDs) and find the ICD more acceptable. This will be explored in detail in future analyses.

Rochelle Shain

SIGNATURE

1/15/85

DATE

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 338

TITLE: "Development of Sperm Enzyme Inhibitors as Vaginal Contraceptives"

INSTITUTION: Rush-Presbyterian-St. Luke's Medical Center

PRINCIPAL INVESTIGATOR: Lourens J.D. Zaneveld, D.V.M., Ph.D.

FUNDING PERIOD: 7/1/83-6/30/86

AMOUNT FUNDED: \$160,950

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

Through animal studies, aryl guanidinobenzoates (AG) (inhibitors of the sperm enzyme acrosin) were shown to be much more potent vaginal contraceptives than nonoxynol-9 (N-9) and also to be effective antifertility agents towards human spermatozoa in vitro. Additionally, acute and chronic toxicity studies have shown that a number of the AG's are less toxic than N-9. The present objectives are to perform all the experiments required for FDA approval of a Phase I Clinical Trial which include: 1) vaginal irritation and absorption studies, and chronic toxicity studies (performed by Dr. D.P. Waller at the University of Illinois); and 2) the development of tests to determine if the fertilizing capacity of the spermatozoa has been impeded (motility measurements will not suffice). A simple, clinical test was developed that evaluates the activity of acrosin on as few as 10^6 human spermatozoa. Experiments are presently in progress to determine the concentration and time required for the AG's to inhibit acrosin when added to spermatozoa. The experiments with one of the inhibitors (4-carboethoxyphenyl 4-guanidinobenzoate) have been completed. At as low a concentration as 10^{-4} M, 83% of the acrosin is inhibited on the spermatozoa, even when they are mixed with the inhibitor for less than two min. At that time period, 65% and 50% inhibition is seen at 10^{-5} and 10^{-6} M, respectively. At longer incubation periods (e.g., 5 min.) inhibition becomes 90% or more at both 10^{-4} and 10^{-5} M. Thus, the inhibitor interacts very quickly with the spermatozoa to inhibit most of the acrosin, even at very low concentrations. Collaborative efforts are in progress with the VLI in order to develop the sponge as a delivery system for the AG's. It was shown that the enzyme inhibitory activity of the aryl guanidinobenzoates is not altered by mixing with N-9. Additionally, the spermicidal activity of N-9 is not decreased by the aryl guanidinobenzoates. By contrast, the AG's were found to be rather potent spermicides themselves so that the mixture of N-9 and AG was more spermicidal than that of N-9 alone. The mutagenic potential of the AG's was investigated using the Ames test. None of the compounds demonstrated significant mutagenic activity. A mixture of N-9 and one of the AG's was also not mutagenic. The outcome of this work should be an improved vaginal contraceptive.



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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 338UI

TITLE: "Toxicology Studies of Acrosin Inhibitors"

INSTITUTION: The University of Illinois at Chicago

PRINCIPAL INVESTIGATOR: Donald P. Waller, Ph.D.

FUNDING PERIOD: 7/1/84-6/30/86

AMOUNT FUNDED: \$84,866

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

This study will provide toxicology information to support the submission of an IND for a Phase I Clinical Trial of an aryl guanidinobenzoate as a new and effective vaginal contraceptive. The protocol for the evaluation of vaginal irritation in the rabbit was written and four potential compounds were tested. One of the compounds had little or no effect on the vagina, two compounds were mildly irritating and one was somewhat irritating. Studies are also in progress to develop HPLC methods for the determination of the aryl guanidinobenzoates in blood following vaginal administration. This information will be utilized to determine which aryl guanidinobenzoate should be used in the development of a formulation for a Phase I Clinical Trial.

Donald P. Waller

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11 Jan 1985

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 339

TITLE: "Efficacy of Studies in Primates with the Shug in the
Absence of a Tissue Wrap"

INSTITUTION: Rush-Presbyterian-St. Luke's Medical Center

PRINCIPAL INVESTIGATOR: Lourens J.D. Zaneveld, D.V.M., Ph.D.

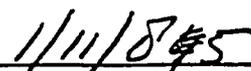
FUNDING PERIOD: 7/1/83-6/30/85

AMOUNT FUNDED: \$37,476

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

A vas deferens blocking device has been developed, called the Shug, that was shown to reversibly prevent sperm passage through the vas deferens by two different primate studies. A protocol was submitted to the FDA to initiate a Phase I Clinical Trial. The trial will involve 30 patients who wish to undergo a vasectomy. Half of these will be used as control and will undergo a standard vasectomy. A Shug will be implanted in the other 15 men. For a 6 month period, the ejaculates of the men will be obtained and semen analyses performed. Subsequently, the Shugs and the vasa will be removed for study. The FDA had some questions in regard to the protocol and an Amendment was submitted. However, several more questions were posed by the FDA. The agency was visited and an agreement was reached. Presently, another Amendment is being prepared for which an extensive literature review is required. Additionally, a two year rat study has been initiated in collaboration with Dr. D.P. Waller at the University of Illinois to satisfy FDA requirements. Silicone devices for implantation (scaled down to the size of the rat) have been prepared, the implantation technique has been developed in the rat, and trial implants have been performed. In the near future, all the rats will be implanted with the devices. The outcome of this work should be a reversible male contraceptive technique.


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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION
SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 339UI

TITLE: "Toxicology of Silicone Implanted (SHUGS) in the Vas Deferens"

INSTITUTION: University of Illinois at Chicago

PRINCIPAL INVESTIGATOR: Donald P. Waller, Ph.D.

FUNDING PERIOD: 7/1/84-6/30/85

AMOUNT FUNDED: \$55,780

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

This study will provide toxicology information to support an IND application for the SHUG (See PARFR-339). The FDA has requested that the tissue biocompatibility of the silicone material to be used in the manufacture of the SHUG be tested at the site of implantation. Preliminary experiments were performed to determine the size and amount of material required for the implantation of the silicone in the vas deferens of the rat. Samples of silicone thread were manufactured by the Bivona Surgical Supply Company from the same material to be used in the manufacture of SHUG's for subsequent clinical trials. Silicone thread with a diameter of 0.7 mm was identified as the appropriate size material for the study and surgical procedures developed for the implantation of the silicone material. Arrangements have been made for the production and packaging of the silicone thread to be used in the implantation. The implantations will begin upon receipt of the silicone thread in the near future. Six months, one year and two years after implantation, the vas deferens will be removed from groups of animals and examined histologically for signs of pathology. This study will demonstrate the biocompatibility of silicone in the vas deferens of the rat and will support the development of the male contraceptive device known as the SHUG.



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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

JAN 7 1985

PARFR- 341

TITLE: "Phase II Poly NET 90 Injectable Study"

INSTITUTION: The University of Alabama in Birmingham

PRINCIPAL INVESTIGATOR: Lee R. Beck, Ph.D.

FUNDING PERIOD: 3/1/83-11/30/85

AMOUNT FUNDED: \$79,264

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

PARFR 341

A Phase II study on the injectable 3-month norethisterone (NET) copolymer (poly d,l-lactide-co-glycolide) microsphere contraceptive system was started in a total of 17 women at two centers. Fabrication and formulation modifications had been effected to reduce the free drug retained in the microspheres, and to improve the manufacture process. The clinical trials were discontinued, however, when it was determined that the initial NET release rates were slower than expected, resulting in inadequate serum NET levels for ovulation inhibition in the early posttreatment interval. The release profiles were similar in all subjects: serum NET levels rose above 1 ng/ml from approximately days 60 through 120 posttreatment, then rapidly returned to baseline levels. Parellel studies in baboons using the same NET dose (75 mg) - therefore approximately a four-fold greater dose on a per weight basis - verified that NET was being released during the first 2 months posttreatment. A separate study has been initiated to further refine the system pharmacokinetics before resuming the Phase II clinical trials. An additional dose-response Phase I study will be included on the final formulation to ensure that an appropriate dose is used in the Phase II investigations.



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January 2, 1985

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION
SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 341A

TITLE: "Phase II Poly NET 90 Injectable Study"

JAN 9 1985

INSTITUTION: Emory University

PRINCIPAL INVESTIGATOR: Howard J. Tatum, M. D.

FUNDING PERIOD: 1/1/84-12/31/85

AMOUNT FUNDED: \$32,905

Below is a project summary for the July 1, 1984 through December 31, 1984

period.

There has been no activity since April 30, 1984 when the program was placed on temporary hold by PARFR Administration.

Total disbursements of \$1,485.43 had been made prior to the April 30th.


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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 341C

TITLE: "Phase II Poly NET 90 Injectable Study"

INSTITUTION: Centro Nacional de la Familia

PRINCIPAL INVESTIGATOR: Horacio B. Croxatto, M.D.

FUNDING PERIOD: 1/1/84-12/31/85

AMOUNT FUNDED: \$45,419

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

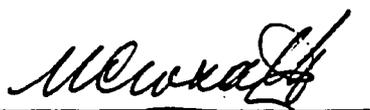
This study was undertaken to assess the safety, contraceptive effectiveness and effect on ovarian function of the 75 mg NET poly (DL-lactide-co-glicolide) microsphere injectable formulation.

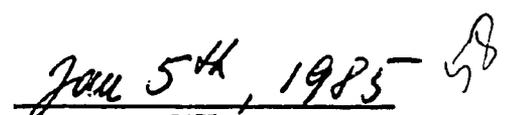
Each of four women received a single injection of the NET injectable formulation. Blood samples were drawn during one pretreatment cycle in 2 of these women to determine estrogen and progesterone levels and assess the occurrence of ovulation. After drug administration, clinical follow up and blood sampling were continued in all until one or two normal cycles were detected. During treatment, blood samples were obtained once or twice a week in 2 women during month 1, in one during month 2, in all women during months 3 to 6 and in 2 women during month 7. An aliquot of each serum sample was lyophilized and sent to Dr. Lee Beck in Alabama for NET determination. The rest of each sample was frozen for measuring estradiol and progesterone. Inhibition of ovulation was observed on month 4 of treatment in all cases but plasma progesterone levels compatible with ovulation were observed at earlier and later intervals. Bleeding irregularities were observed in the 4 women and no other side effects were detected.

Due to an unexpected problem with the release rate of this batch of microspheres the subjects were protected with an IUD or spermicides and the study was temporarily discontinued until a new batch is provided.

This report covers the period July 1, 1984 through December 31, 1984.

Reinitiation of the study is expected to take place during 1985.


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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION
SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 341I

TITLE: "Phase II Poly NET 90 Injectable Study"

INSTITUTION: Associazione per lo Studio della Riproduzione Umana

PRINCIPAL INVESTIGATOR: Giuseppe BENAGIANO M.D.

FUNDING PERIOD: 1/1/84 - 12/31/85

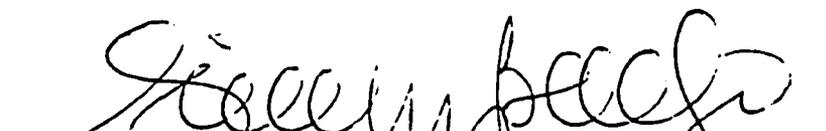
AMOUNT FUNDED: \$ 39,655

Below is a project summary for the july 1st, 1984 - december 31st 1984 period.

As indicated in the previous report, on 21 March 1984 we received a telex from PARFR informing us that the study would have to be disconnected because the release rates of the NET-90 injectable formulations received were too low to insure contraceptive efficacy.

For this reason no activity was carried out during the present semester and no funds were received.

Our group is ready to reinstate the study as soon as we receive the new batch of NET-90 systems from PARFR.


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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION
SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 341M

TITLE: "Phase II Poly NET 90 Injectable Study"

INSTITUTION: Instituto de Investigacion Cientifica, Juarez University
of Durango

PRINCIPAL INVESTIGATOR: Roberto Rivera, M.D.

FUNDING PERIOD: 1/1/84-12/31/85

AMOUNT FUNDED: \$36,135

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

The study was terminated on April 20, 1984, due to indications that the releaserates of the NET 90 injectable formulation -- were too low to insure contraceptive efficacy.


ROBERTO RIVERA, M.D.

SIGNATURE

January 7, 1985

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

DEC 2 1984

PARFR- 341T

TITLE: "Phase II Poly NET 90 Injectable Study"

INSTITUTION: The University of Texas Health Science Center at San Antonio

PRINCIPAL INVESTIGATOR: Jose P. Balmaceda, M.D.

FUNDING PERIOD: 1/1/84-12/31/85

AMOUNT FUNDED: \$82,487

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

We were contracted to test the safety, contraceptive effectiveness and effect on ovarian function of the 75 mg injectable NET poly (DL-lactide-co-glycolide) microsphere on up to 50 subjects. Recruitment of healthy, regularly cycling females satisfying the protocol criteria, who consented to use the injectable microsphere as their sole means of contraception, began in November 1983 with the first subject receiving the injection 1-3-84. The subjects were followed for a control cycle prior to receiving the injection during which time baseline lab data was collected and monthly bleeding records were initiated. The subjects were then scheduled for clinic visits for blood sampling for P, E and NET levels per the protocol and were to receive repeat injections at 90, 180 and 270 days.

After 15 subjects had been injected we were notified by Dr. Lee Beck, University of Alabama, that serum NET levels following injection were lower than had been expected when compared to Phase I and were advised to have the subjects continue to use a barrier contraceptive for the month following injection. In the interim one of our subjects became pregnant. Because of these events we temporarily discontinued the study. No new subjects were recruited and the subjects already injected were advised to use another form of contraception. Nine subjects who decided to use a barrier form of contraception were asked to continue having weekly blood sampling to determine P, E & NET serum levels for 150 days following injection. All of the subjects have completed their sampling, termination exams have been performed and menstrual charts have been collected.

Serum NET levels did not rise until nine weeks post injection, peaking around 12 weeks and then declining sharply over the next 3 weeks. These results are in contradiction to Phase I where NET levels rose immediately after injection and gradually declined until a second rise was evident between days 90-120.

Eight of the thirteen subjects, that were followed after injection, have serum progesterone levels suggestive of ovulation during the first 30 days after injection. Furthermore, of the nine subjects that completed more than 90 days of follow-up after injection, 7 had evidence of ovulation in that period. However, ovulation was suppressed in all subjects during the weeks correlating with the higher NET serum levels.

Mean values in total number of bleeding days show insignificant changes following injection. Individual variation, though, is notorious with some subjects having marked oligomenorrhea and amenorrhea while other bled for 30 consecutive days.


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12/18/84
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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION
SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 343

TITLE: "NIH/Biotech Levonorgestrel Microcapsules"

INSTITUTION: The University of Alabama in Birmingham

PRINCIPAL INVESTIGATOR: Lee R. Beck, Ph.D.

FUNDING PERIOD: 11/1/83-~~10/31/84~~^{4/30/85}

AMOUNT FUNDED: \$46,040

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

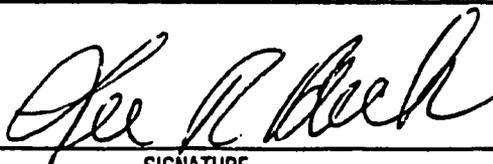
6 month report for PARFR 343 (UAB AC #107A and B) - NIH/BIOTEK levonorgestrel microcapsules -12/25/85:

Two groups of five baboons each were injected intramuscularly with doses of Biotek microcapsules containing 10 or 20 mg levonorgestrel (LN). The study has been underway for one year, with the high dose (Group B -20 mg LN) effectively inhibiting ovulation for the entire treatment interval in the five baboons. Baboons receiving the low dose (Group A - 10 mg LN) ovulated at least one to five times in the treatment interval, following serum LN levels between approximately 0.4 and 1.0 ng/ml.

Peak serum LN levels of 2.91 to 6.36 ng/ml were reached in the first 3 days posttreatment in Group A, while most values were less than 2.0 ng/ml after the first 4 weeks posttreatment. Average serum LN values for each baboon from 2 weeks through 300 days posttreatment ranged from 0.64 to 1.23 ng/ml. Release rates were very stable over the treatment interval, although most serum LN levels were less than 1.0 ng/ml on days 300 to 350 posttreatment in this group.

Initial peak levels of up to 12 ng LN/ml were reached in the first 3 weeks posttreatment in the high dose group (Group B), with near zero order release occurring in the subsequent 9 months. From 3 weeks through 300 days posttreatment, average serum LN levels for each baboon in Group B ranged from 2.14 to 5.57 ng/ml. These serum LN averages declined only slightly from days 300 to 350 posttreatment (range = 1.63 to 5.44 ng LN/ml).

Weekly serum sampling will be continued until LN values reach and remain at baseline levels.


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January 2, 1985
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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 344

JAN 2 1985

TITLE: "Percutaneous Intra Vas Injection for Male Sterilization"

INSTITUTION: Presbyterian Hospital, Obstetrics and Gynecology Services

PRINCIPAL INVESTIGATOR: Ralph M. Richart, M.D.

FUNDING PERIOD: 9/1/83-8/31/84

AMOUNT FUNDED: \$54,300

Below is a project summary for the July 1, 1984 through December 31, 1984

period.

A new iodide-containing compound was formulated for closure of the vas deferens. This material is viscous but flows readily under pressure through a fine needle. The compound was placed in the vas deferens of mongrel dogs, first under direct vision and then using a percutaneous technique in which the vas is isolated under the scrotal skin between the thumb and forefingers and a sharp needle is passed vertically through the vasal wall until it just penetrates the vas lumen. The needle is then withdrawn, and a thin blunt cannula passed through the same needle track until it too penetrates the vasal lumen. At this point it is rotated 90° and slid into the vas. In these experiments, the iodide-containing formulation was compared with methylcyanoacrylate to study the efficacy of closing the vas. After the vasa had been injected, an x-ray was taken of the scrotum to study the distribution of the radio-opaque materials. The animals were then serially sacrificed at intervals, and those vasa examined histologically for closure. These vasa from animals sacrificed at 30 days had necrotic epithelium with necrotic debris in the lumen. Three of 8 vasa treated with MCA were closed as were 3 of 8 vasa treated with the iodide compound. At 60 days, 5 out of 7 vasa treated with MCA were closed, and 9 out of 9 vasa treated with the iodide compound were closed. In a separate series, 14 of 16 vasa treated with MCA containing trifluoroacetic acid were closed between 45 and 60 days. There were no histological changes in the epididymis or testes, and no side effects were noted. It is clear that it is possible to close the vasa with a high degree of success using an injected chemical compound without significant side effects. This technique should be applicable on a percutaneous basis to humans.

Ralph M. Richart

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Dec 21, 1984

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION
SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 345

TITLE: "Effect of the Vaginal Spermicidal Barrier Contraceptive
on Sperm Transport in the Human"

INSTITUTION: University of Southern California Medical Center

PRINCIPAL INVESTIGATOR: Gerald S. Bernstein, M.D., Ph.D.

FUNDING PERIOD: 10/1/83-3/31/84

AMOUNT FUNDED: \$6,375

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

*Dr. Bernstein Again neglected to
submit a report*

PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 346

TITLE: "Development of Controlled-Released Testosterone Microcapsule
for Fertility Regulation of Males"

INSTITUTION: Southern Research Institute

PRINCIPAL INVESTIGATOR: Thomas R. Tice, Ph.D.

FUNDING PERIOD: 10/1/83-8/31/84

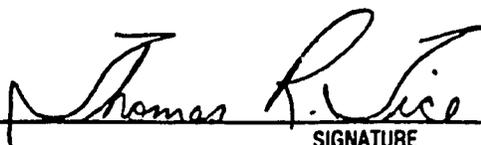
AMOUNT FUNDED: \$49,641

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

The objective of this research program is to develop a controlled-release testosterone microcapsule formulation that is both injectable and biodegradable. With a single administration, the ideal formulation should deliver about 2 to 6 mg of drug per day to maintain a serum testosterone level of about 2 to 4 ng/mL for a duration of 90 days. This testosterone microcapsule formulation should be useful for the suppression of gonadotropins for male contraception or as a supplemental testosterone treatment used in conjunction with a male contraceptive based on luteinizing hormone/releasing hormone.

Microcapsules containing 44 wt % testosterone and 56 wt % 85:15 poly(DL-lactide-co-glycolide) were tested in castrated rhesus monkeys. The results of this pharmacokinetics study indicated that testosterone was released from the microcapsules for a duration of at least 90 days. The rate of release of testosterone, however, was not as constant as desired. The rate of testosterone release during the first 50 days of treatment was nearly three times the rate during the period from Day 50 to 90.

More recently, the testosterone microcapsule formulation has been optimized to even out the release of testosterone from the microcapsules by slowing down the initial release. More specifically, three different microcapsule formulations (about 40% loaded) were prepared for testing in a second pharmacokinetics study. Two of the formulations (having microcapsules ranging from 45 to 90 μ m in diameter) were exposed to 0.5 Mrad of gamma radiation. The third formulation contained 90- to 125- μ m microcapsules and was exposed to 2.0 Mrad of gamma radiation. These formulations are currently being tested in castrated rhesus monkeys.


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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION
SIX MONTH TECHNICAL REPORT SUMMARY

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PARFR- 347

TITLE: "Studies on the Anovulatory Potency and Side Effects of an
Inhibitory Analog of LHR in Cynomologous Monkeys"

INSTITUTION: The University of Texas Health Science Center at San Antonio

PRINCIPAL INVESTIGATOR: Ricardo H. Asch, M.D.

FUNDING PERIOD: 2/1/84-1/31/86

AMOUNT FUNDED: 146,501

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 348

TITLE: "Development of Improved Methods and Materials for Injecting
Microencapsulated Steroids"

INSTITUTION: Stolle Research and Development Corporation

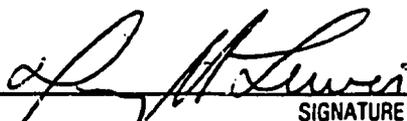
PRINCIPAL INVESTIGATOR: Danny H. Lewis, Ph.D.

FUNDING PERIOD: 11/1/83-11/30/84

AMOUNT FUNDED \$49,555

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

The objective of this work is to develop improved techniques and materials for injecting steroid-loaded biodegradable microspheres into human patients. The research program has been directed to the following tasks: (1) preparation of representative microspheres; (2) physiochemical characterization of the microspheres; (3) lyophilization studies; and (4) evaluation of the physical properties of the administration system. Co-investigators at the Universities of Iowa and Tennessee have assisted in laboratory studies in these areas. The work conducted at the University of Tennessee has been relatively basic in nature and has resulted in a reliable particle counting procedure useful in assessing the quantity of microspheres remaining in a syringe. Four candidate vehicles were evaluated by the Tennessee group and one was rated superior to the vehicle used in previous clinical trials. Studies at Iowa were more applied in nature and involved extensive formulation work as well as investigation of lyophilization as an alternative approach. Several vehicle formulations were recommended by the Iowa group as improvements over the previous system. Preliminary results indicate that the microspheres could be pretreated with the surfactant and/or thickening agent, lyophilized, and reconstituted in water or saline. We have utilized the findings at Tennessee and Iowa to guide further development effort in collaboration with Ortho Pharmaceutical Corporation. An improved injection vehicle is now being evaluated at Ortho and will be available for the upcoming clinical trials with the various steroids. All results clearly indicate that the higher loaded (50%) microspheres will be much easier to administer than were the 25%-loaded norethisterone formulations.


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SIX MONTH TECHNICAL REPORT SUMMARY

PARFR-349

TITLE: "Preparation of Fibrous Estradiol/Progesterone IUDs for Phase I
Clinical Trials, Continuation of PARFR-324"

INSTITUTION: Southern Research Institute

PRINCIPAL INVESTIGATOR: Richard L. Dunn, Ph.D.

FUNDING PERIOD: 11/1/83-^{6/30/85}~~10/31/84~~

AMOUNT FUNDED: \$98,694

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

The objective of this research is to develop an IUD delivery system for the combined administration of estradiol and progesterone. The system is based on a conventional T-shaped IUD wrapped with coaxial fibers containing either estradiol or progesterone. During previous reporting periods, we developed coaxial fiber systems for both estradiol and progesterone. However, we have not yet identified sheath polymers that exhibit optimum rates of release and mechanical properties.

Our effort during this reporting period has still been directed toward identifying an alternative sheath polymer for the coaxial fibers. As described in our last Six Month Technical Report Summary (5428-II, SoRI-EAS-84-668) on Project 5428 (PARFR-349), we identified five candidate materials, prepared progesterone- and estradiol-loaded coaxial fibers with each sheath material except for Chemplex 1017X, and evaluated the in vitro release of the steroids from individual fibers and fiber-wrapped IUDs. Based on the results from the release studies, we prepared additional progesterone-loaded coaxial fibers with a thicker sheath of polyethylene (PE) LL 6101 (Exxon Chemicals, Houston, TX) and estradiol-loaded coaxial fibers with a sheath of Ultrathene (UE) 635 (ethylene-vinyl acetate [EVA] copolymer, 9% VA, US Industrial Chemicals [USI], Charlotte, NC).

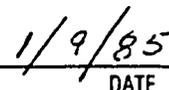
No in vitro release studies have been conducted on the progesterone-loaded fibers with the thicker sheath, but we expect the rate of release of progesterone from these fibers to be close to the target value of 1.0 to 1.5 $\mu\text{g}/\text{cm}/\text{day}$. In vitro release studies were conducted to determine the rate of release of estradiol from the coaxial fibers having a sheath of UE 635. The in vitro release from fiber-wrapped IUDs was determined also.

These data show that the permeability of estradiol in UE 635 is suitable for this application and the rate of release (0.39 to 0.46 $\mu\text{g}/\text{cm}/\text{day}$) is close to the target value of 0.5 $\mu\text{g}/\text{cm}/\text{day}$. Also, these results demonstrate that fibers prepared from an elastomeric sheath material are ideal for this application because approximately the same rate of release is obtained from fiber-wrapped IUDs as for individual fibers.

These results are encouraging. However, USI has expressed some reluctance in allowing the use of their materials for any IUD application. Consequently, four candidate materials were selected in addition to the materials described in our last Six Month Technical Report Summary. These include two ethylene



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SIX MONTH TECHNICAL REPORT SUMMARY

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PARFR- 350

TITLE: "An Intra Tubal Device (ITD) for Female Sterilization"

INSTITUTION: Tenon Hospital, University of Paris

PRINCIPAL INVESTIGATOR: Jacques Hamou, M.D.

FUNDING PERIOD: 1/1/84-6/30/85

AMOUNT FUNDED: \$11,000

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

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SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 351

TITLE: "Development of Methods for Female and Male Contraception
Based on LHRH Antagonist"

INSTITUTION: The Tulane University School of Medicine

PRINCIPAL INVESTIGATOR: Dr. Andrew V. Schally

FUNDING PERIOD: 1/1/84-12/31/84

AMOUNT FUNDED: \$65,153

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

The objective of the project was to investigate the contraceptive effects of antagonistic analog (N-Ac-D-p-Cl-Phe^{1,2}, D-Trp³, D-Arg⁶, D-Ala¹⁰)-LH-RH in male and female rats. Fertility of the animals, genetic abnormalities in the offspring and effects on blood pressure in rats were also tested.

Male rats were treated with ORG 30276 at doses of 10µg/kg, 100µg/kg or 1000 µg/kg per day for 60 days. The control rats were injected with the vehicle only. The treatment with the highest dose of the antagonist brought about a significant decrease in the weights of the anterior pituitaries, testes, seminal vesicles and ventral prostates and reduced serum and pituitary LH levels. The intermediate dose of the antagonist only affected seminal vesicle weights. The histology of the testes from rats treated with the highest dose showed spermatogenesis markedly depressed, not beyond the stage of spermatocytes I; the interstitium showed cells with fibroblastic appearance. The testes of the rats injected with 10µg/kg and 100µg/kg of the analog were similar to the control rats. Twenty days after stopping treatment with the analog there was a marked recovery of the weight of the testes, seminal vesicles and ventral prostates. However, the animals were still infertile when caged with female rats. Sixty days after treatment the animals had recovered testicular function and fertility. The offspring were normal, with no evidence of genetic abnormalities.

Female rats were treated with ORG 30276 at doses of 10µg/kg, 100µg/kg or 1000 µg/kg per day for 15 days. Control rats were injected with the vehicle only. The treatment with ORG 30276 did not modify body weight. Anterior pituitary and uterine weights were significantly decreased in the group of rats treated with the highest dose of the antagonist. Ovarian weights also were decreased significantly, showing a dose-response relationship. The animals treated with the highest dose of ORG 30276 had significantly lower serum LH and FSH. All the rats treated with 1000µg/kg of ORG 30276 had diestrous vaginal smears indicating a blockade of ovulation while 50% of the rats given 100µg/kg also had diestrous. Fertility was checked every 15 days after stopping the treatment with ORG 30276. At 15 and 30 days after the last injection of ORG 30276, most of the rats were fertile when caged with male rats. Blood pressure was not modified by ORG 30276.

The results obtained show that the treatment with ORG 30276 suppresses gonadal function and that the effects are reversible. Once the ovaries and the testes recover their function after the withdrawal of the treatment, the rats, males or females, recover their fertility. No apparent abnormalities were seen in the offspring. The analog does not seem to have any teratologic effect on the offspring. This investigation shows that LH-RH antagonists can be used for the development of a new birth control method.


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DATE

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 352

TITLE: "Baboon Testing of Duration of NET from Fused Pellets"

INSTITUTION: The Board of Trustees of the University of Alabama for the
University of Alabama in Birmingham

PRINCIPAL INVESTIGATOR: Lee R. Beck, Ph.D.

FUNDING PERIOD: 12/1/83-11/30/84

AMOUNT FUNDED: \$29,420

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

6 month report for PARFR 352 - 12/26/84

Cholesterol-fused norethisterone (NET) pellets were implanted subcutaneously in five baboons. One baboon received two, two received three, and two received four pellets. Weekly blood samples are being analyzed for NET quantity by radioimmunoassay. Serum NET levels ranged from <0.125 to 1.05 ng/ml (two pellets), 0.41 to 1.67 ng/ml (three pellets), and 0.43 to 2.66 ng/ml (four pellets) over the treatment interval. Average NET values during the treatment interval were approximately 0.5, 0.91 and 1.36 ng/ml for baboons receiving two, three and four pellets, respectively.

The pellets have been in place for 1 year. The baboons with three or four pellets have had two of 20 values <0.5 ng NET/ml in the last 5 weeks (days 323 to 351 posttreatment). Average serum NET values for the last 5 weeks are reduced 11 to 49% from the averages for each baboon during the first 300 days posttreatment.

Ovarian cyclicity has been suppressed for at least 300 days in baboons treated with three or four pellets. The baboon with two pellets has received supplemental estrogen, precluding an evaluation of ovarian function.



SIGNATURE

January 2, 1985

DATE

SIX MONTH TECHNICAL REPORT SUMMARY

JAN 1 1985

PARFR- 353

TITLE: "Effect of Chronic Intrauterine Release of Estradiol and Progesterone on Uterine Histology in Intact Rabbits"

INSTITUTION: Michael Reese Hospital and Medical Center

PRINCIPAL INVESTIGATOR: Antonio Scommegna, M.D.

FUNDING PERIOD: 3/15/84-12/31/84

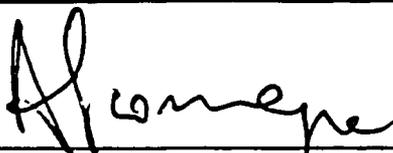
AMOUNT FUNDED: \$7,895

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

Estradiol and progesterone in doses of 2 μ g and 6 μ g per day respectively were chronically released in the uterine lumen of rabbits through separate delivery systems made up of hormone loaded polyethylene fibers.

At the end of three months, segmental histologic changes were noted limited to the section of the horn in contact with the fibers. Thus in uterine horns containing both estrogen and progesterone releasing fibers the endometrial changes characteristic of each hormone were noted in the region of the horn adjacent to the respective fiber. Changes attributable to the effect of both however were noted only in the middle of the horn in the region immediately adjacent to both hormone releasing fibers.

It is concluded that to obtain a uniform effect delivery system releasing both hormones must be constructed in such a fashion so that the release of both hormones occurs in a uniform manner throughout the whole length of the uterine horn.



SIGNATURE

1-7-85

DATE

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 354

TITLE: "Screening of Thai Plants for Proteins (or Lectins) as Potential Vaginal Contraceptives"

INSTITUTION: Faculty of Science, Mahidol University

PRINCIPAL INVESTIGATOR: Montri Chulavatnatol, Ph.D.

FUNDING PERIOD: 4/1/84-3/31/85

AMOUNT FUNDED: \$9,800

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

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SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 355

TITLE: "Enhancement of the Secretary Response to LDH-C₄"

INSTITUTION: Medical Research Foundation of Oregon

PRINCIPAL INVESTIGATOR: Nancy J. Alexander, Ph.D.

FUNDING PERIOD: 4/15/84-4/14/85

AMOUNT FUNDED: \$47,335

Below is a project summary for the 7/1/84 through 12/31/84

period.

The objective of this study was to evaluate whether activation of the secretory immune system to a sperm-specific antigen, LDH-C₄, results in reduced fertility. Sixteen rhesus macaques received primary (1°) and secondary (2°) immunizations of LDH-C₄ and vaginal implants of the antigen and concanavalin A. The 2° immunization was accomplished via the bronchiole-associated lymphoid tissue (BALT) or gut-associated lymphoid tissue (GALT) route. Blood, oral lavage, and vaginal lavage samples were taken at various intervals through day 42 after the 2° immunization. Three months after the 1° immunization, an implant containing 2.5 mg of LDH-C₄ and 0.25 µg of concanavalin A in a gel of 1% agarose was placed in the vagina to determine whether a booster effect would follow local stimulation. Blood, oral lavage, and vaginal lavage samples were taken at the time of implantation, and 3 and 7 days after implantation. The anti-LDH-C₄ IgG and IgA were assessed by radioimmunoassay. Both serum IgG and IgA levels were higher in the GALT monkeys than in the BALT group, although the differences were not significant. The rise was maximal 14 days after 2° immunization. A local booster on day 85 did not result in a difference 3 days later. Vaginal IgG and IgA levels significantly rose after systemic 1° immunization. The IgA levels were boosted 3 days after local stimulation on day 88 (p < 0.057). Vaginal IgA levels were not a transudation from serum. Vaginal fluid IgG values were highest on day 21 post 2° immunization (p < 0.03). Some animals seem to be better responders than others.

Oviductal fluid was collected by laparotomy from two females. No measurable levels of antibodies to LDH-C₄ were found. Because of this finding, future laparotomies are not planned.

We do not know what levels of antibodies are necessary to prevent pregnancy. To enhance the immune response, a second immunization will be given. Since the response to BALT and GALT stimulation was similar and since GALT stimulation is easier and possibly more effective, we plan to give 8 of the females (4 from the initial GALT and 4 from the initial BALT group; we ranked the animals according to initial responsiveness and then divided into equivalent groups) a second GALT immunization. This approach will allow us to compare the efficacy of a second immunization and compare those stimulated by GALT with those by BALT. This step will provide further information of levels of antibody necessary to prevent fertility.



SIGNATURE

12-20-84

DATE

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 356a

TITLE: "Development of an Immunocontraceptive Vaccine: Role of 23-Kd Antigen in Immunoifertility & Fertility Regulation"

INSTITUTION: George Washington University

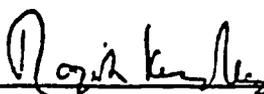
PRINCIPAL INVESTIGATOR: Rajesh K. Naz. Ph.D.

FUNDING PERIOD: 1/1/84-11/30/85

AMOUNT FUNDED: \$59,593

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

The objective of this project is to investigate the use of the 23-Kd glycoprotein (FA-1), isolated by using monoclonal antisperm antibody MA-24, as an effective immunocontraceptive. MA-24 developed against a human sperm membrane glycoprotein belongs to the IgG_{2a} subclass and is germ-cell specific. It cross-reacts with mouse, rabbit, rhesus, and human sperm. It blocks human sperm penetration of zona-free hamster ova and also inhibits in vitro fertilization of mouse ova by murine sperm by mechanisms(s) other than agglutination and immobilization of sperm. This monoclonal antibody is against a membrane glycoprotein of 23-Kd (FA-1) which is localized on the postacrosome, midpiece, and tail of sperm. FA-1 has been isolated from human sperm and testis by using an MA-24-IgG-Sepharose-4B immunoaffinity column and shows a single band on SDS-polyacrylamide gel electrophoresis (PAGE). This purified testicular glycoprotein shows a significant reaction with sera from immuno-infertile couples in an enzyme-linked immunosorbent assay (ELISA) (Science, 1984). The antigen isolated from murine germ cells again shows a single band on SDS-PAGE even with an ultrasensitive silver stain and occurs mainly as a dimer of 46-Kd molecular mass. Presently we are engaged in producing large amounts of ascites to construct more immunoaffinity columns for isolation of FA-1 in sufficient quantity required for active immunization studies. We are checking the effect of MA-24 on the fertilization and fertility in vivo. Recently we artificially inseminated female rabbits with sperm treated with IgG purified from MA-24 ascites. Preliminary results show an inhibition of fertility at 9 days post insemination as expressed by percentage of implants vs corpora lutea ratio. These experiments show that these antibodies are effective in reducing fertility in in vivo conditions. These data will also indicate the amounts of antibody required in local secretions for inhibition vs complete block of fertilization and fertility. This antigen appears to be immunogenic in mice and we are characterizing the murine polyclonal antiserum raised against FA-1.



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10 January, 1985

DATE

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 357

TITLE: "Optimization of Release Profile of Norethisterone Injectable
90-Day Contraceptive"

INSTITUTION: Stolle Research and Development Corporation

PRINCIPAL INVESTIGATOR: Danny H. Lewis, Ph.D.

FUNDING PERIOD: 5/1/84-10/31/84

AMOUNT FUNDED: \$49,119

Below is a project summary for the

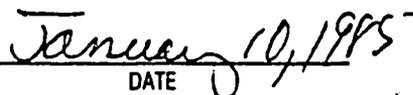
period.

In a recent Phase II clinical trial with the 90-day NET microsphere formulations serum NET did not reach efficacious levels until several weeks posttreatment in that study. This was primarily due to an improvement in the microsphere quality after we switched to an improved micro-encapsulation process. We have now demonstrated that faster releasing formulations can be achieved by increasing the NET content of the microspheres. An obvious advantage also gained is the reduced total mass of material to be administered to the patient. In vitro release profiles and preliminary data from baboon evaluations indicate that we have made substantial progress in optimizing the NET release profile. During this reporting period, we found that microspheres loaded with 40 to 50% by weight of NET appear to be the most promising. We observed that when we attempted to load higher amounts (65%) into the polymeric excipient, the quality of the formulations was compromised.

Photomicrographs taken by scanning electron microscopy (SEM) show no or very little evidence of unencapsulated NET at loadings of 40 to 50%. The samples look very much like the 25%-loaded formulations tested in the Phase II trial. In vitro data clearly show that we have significantly increased the rate of NET release. We now have a complete data base of in vitro-in vivo correlations to guide our selections; therefore, we have a high level of confidence that the higher loaded microspheres will be useful as a 90-day injectable. Baboon data are available on a prototype formulation. We expect to prepare during January 1985, a large master batch of NET microspheres in the Stolle GMP facility for use in Phase I and II clinical trials during 1985.



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SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 358

TITLE: "Development of a 30-Day Injectable Contraceptive"

INSTITUTION: Stolle Research and Development Corporation

PRINCIPAL INVESTIGATOR: Danny H. Lewis, Ph.D.

FUNDING PERIOD: 5/1/84-1/31/85

AMOUNT FUNDED: \$11,800

Below is a project summary for the July 1, 1984 through December 31, 1984

period.

The objective of this project is to develop a one-month (30 day) injectable Norethisterone (NET) microsphere contraceptive formulation. This project involves (1) production of candidate NET microspheres by the patented Stolle process; and (2) evaluation of the most promising systems in the baboon. During this reporting period, we initiated and completed evaluations of prototype formulations in the baboon model. In earlier work, we prepared controlled release microspheres from NET and various lactide-glycolide copolymers. The microspheres were fabricated by means of the Stolle patented microencapsulation procedure previously described. The candidate polymers were selected to afford relatively short in vivo degradation times. We were successful in loading the microspheres with approximately 50% of NET by weight. The primate studies indicate that a 30-day formulation can readily be achieved with a 50:50 lactide:glycolide copolymer and microspheres 25-45 microns in diameter. Studies were also favorable with a 70:30 copolymer, although those results were not as close to the desired performance as were the data on the 50:50 polymer. We expect to evaluate one or two additional samples in baboons to confirm our present findings. At that point, an IND could be submitted for Phase I clinical testing of the 30-day system.


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SIX MONTH TECHNICAL REPORT SUMMARY

JAN 20 1985

PARFR- 359

TITLE: "Active Immunization of Non-Human Primates and Rabbits
with Zona Pellucida Proteins"

INSTITUTION: Baylor College of Medicine

PRINCIPAL INVESTIGATOR: Bonnie S. Dunbar, Ph.D.

FUNDING PERIOD: 6/1/84-5/31/85

AMOUNT FUNDED: \$77,741

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

The objective of this project is to determine if antibodies to zona pellucida (ZP) antigens can be developed in primates which will reduce fertility. To date, we have isolated ZP and have electrophoretically purified two ZP proteins which we have sent to India (for Dr. Sehgal and Dr. Talwar) and to Dr. Vern Stevens at Ohio State University. We have received 10 bleedings from baboons immunized with one purified antigen in Dr. Steven's lab and have assayed these using both RIA and ELISA methods. All five animals have high titers of antibodies. They are now being studied for effects of immunization on ovarian function and hormone levels. Dr. Sehgal visited our laboratory this period and learned to isolate ZP proteins and carry out assays. On January 5, a research associate from Dr. Sehgal's laboratory arrived to work in my laboratory for 9 months. We anticipate that we will have fertility and ovarian function data in baboons within the next 6 month period.



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1-7-84

DATE

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR-

TITLE: "Effects of Immunization with Zona Pellucida Antigens on Ovarian Function in Baboons"

INSTITUTION: Ohio State University

PRINCIPAL INVESTIGATOR: Vernon C. Stevens

FUNDING PERIOD:

AMOUNT FUNDED:

Below is a project summary for the

July 1, 1984 - December 31, 1984

period.

The purpose of the study was to ascertain whether either of two purified pig zona pellucida preparations will elicit immune responses in female baboons that result in alteration of ovarian function. A research plan involving monitoring menstrual cycles (including assessment of serum ovarian steroid levels) for three cycles, immunizing 5 animals with each of the two preparations, measuring antibody levels to the antigens and monitoring post-immunization cycles cases initiated in July, 1984. To date, the preimmunization cycles have been completed and immunizations performed. Post immunization evaluations have been conducted for three months with one zona preparation but the second zona preparation was delayed in arriving and the immunization with it are now in progress. Hormone levels have been completed on all control cycles but none on post immunization cycles.

Up to this time, no external parameter of cycle events has been altered by the immunizations. Should no effects on hormone function be found, a decision will be made in mid-1985 whether to mate the females with fertile males. Should significant affects on ovarian steroid levels be found, levels of FSH and LH in collected sera will be measured.


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SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 360

TITLE: "Inter-and Intra-Cycle Variation of Genital Peroxidases in Women"

INSTITUTION: University of Illinois at Chicago

PRINCIPAL INVESTIGATOR: John C.M. Tsibris, Ph.D.

FUNDING PERIOD: 7/1/85-6/30/85

AMOUNT FUNDED: \$28,127

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

The levels of Guaiacol Peroxidase (GP), a Ca^{++} -extracted enzyme from cervical mucus or vaginal fluids (sampled near the posterior fornix), can define the fertile period in women and other mammals. GP concentration decreases rapidly 4-5 days before ovulation (the LH + 1 day) and rises again 1-2 days after ovulation. GP levels are measured by a simple colorimetric assay (guaiacol + H_2O_2) and are expressed as activity units/g wet sample; one GP unit increases by one the 470 nm absorbance (A) of the reaction mixture per min. In the luteal phase there is a strong positive correlation between GP and serum progesterone, therefore, GP was also proven useful in detecting, a) low progesterone levels, suggestive of a luteal phase defect, and b) early pregnancy.

The objective of this project is to test the reproducibility of the cervical mucus GP patterns in ten volunteers, each tested for six menstrual cycles. Daily samples of cervical mucus are collected with a fertility cannula at the external os, following the insertion of a speculum, and GP activity is measured spectrophotometrically. First-morning urine is also collected for the determination of LH and pregnanediol (done by RIA in Dr. R.T. Chatterton's laboratory) to define the time and verify the occurrence of ovulation, respectively.

In the first six months of the project we have trained a new medical technologist (MT) and another assistant who is alternating with the MT on weekends. Twenty-one of the 60 cycles have been completed (GP, BBT and urine pregnanediol data); the urine LH assays will be completed within 2-3 weeks. The results look very encouraging because the GP patterns seem reproducible and the midcycle "dip" is sharp. For example, in the six cycles of one volunteer the midfollicular and midluteal GP concentrations ranged between 100-300 U/g, fell below 20 U/g for 4-6 days at midcycle with a nadir of 0-10 U/g. Assuming we obtain an average 25 mg of cervical mucus, the drop from at least 100 U/g to 20 U/g would represent a drop from 2.5 A units/min to 0.5 A units/min; we expect that such a preovulatory drop (or postovulatory rise) in the intensity of the copper-red color of oxidized guaiacol should be easily perceived with the naked eye. As expected, the BBT rise is not distinct enough to define the ovulation time. It should be noted that similar GP patterns have been observed in the previous PARFR-sponsored study of vaginal fluid GP. One of our volunteers became pregnant during her first test cycle and as expected her postovulatory GP levels rose and remained high alerting us, within 11-13 days from ovulation, to perform a beta-HCG test which was positive.

We expect that the remaining studies will confirm that the GP method can, 1) define the fertile period, and 2) be useful in alerting the user of certain "abnormalities" e.g. low progesterone production, occurrence of certain infections and as an early indicator of pregnancy.

John C.M. Tsibris
SIGNATURE

JANUARY 11, 1985
DATE

SIX MONTH TECHNICAL REPORT SUMMARY

JAN 11 1985

PARFR- 361

TITLE: "Testosterone Microcapsule Formulation Study"

INSTITUTION: The University of Texas Health Science Center at San Antonio

PRINCIPAL INVESTIGATOR: Ricardo H. Asch, M.D.

FUNDING PERIOD: 7/1/84-12/31/85

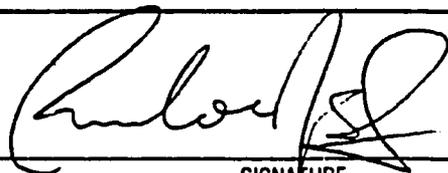
AMOUNT FUNDED: \$122,106

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

Twelve adult male rhesus monkeys were purchased and placed under quarantine for 45 days at the Laboratory Animal facilities of the UTHSCSA. After the quarantine baseline levels of the hormones T, DHT, FSH and LH were established. Animals were then bilaterally castrated with the simultaneous removal of the epididymis. After castration, blood samples were collected daily for 1 week to determine acute changes in hormone values induced by castration. The following 3 weeks post castration hormone levels were determined periodically. One month after castration the animals were divided into 3 groups of 4 animals each. Different dosages of testosterone microcapsules were given to each group. Hormone levels have been closely monitored following the microcapsule injection.

The testes were sent to Dr. Swerdloff for LH-RH activity analysis. Dr. Alexander has received the epididymis for studies on specific protein synthesis and the molecular mechanisms that control them. A small section of each testis and epididymis was saved for histological analysis.

Precastration transiliac biopsies have been performed and sent to Dr. Lindsay for analysis. Precastration and postcastration serum and urine samples were also sent to Dr. Lindsay for bone metabolism studies. Various blood parameters, blood chemistries, CBC and lipoprotein profiles (HDL, LDL, VLDL, cholesterol) have been determined before and after castration, and at one month intervals following the microcapsule injection. Analysis of all results are in progress now. The initial part of the study is projected to end by mid February, 1985.



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1-9-85

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SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 362

TITLE: "Combination Injectable Steroidal Microsphere - Continuation of
PARFR-332"

INSTITUTION: Stolle Research and Development Corporation

PRINCIPAL INVESTIGATOR: Danny H. Lewis, Ph.D.

FUNDING PERIOD: 10/1/84-5/31/85

AMOUNT FUNDED: \$67,195

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

The objective of this project is to develop and evaluate a long-acting injectable microsphere formulation for the combined administration of ethinyl estradiol (EE) and norethisterone (NET). This subagreement is a continuation of PARFR-332 which was to determine the feasibility of producing biodegradable microspheres containing estrogen. During this initial reporting period, we have produced EE microspheres by means of the solvent-evaporation microencapsulation process patented by Stolle Research and Development. We utilized a poly(lactide-co-glycolide) with a lactide:glycolide ratio of 85:15 for the initial development effort. Current work is aimed at initiating a study in baboons with a prototype formulation prepared in the Stolle GMP microencapsulation facility. Baboons will be treated with a formulation comprising 40% by weight of EE in an 85:15 lactide:glycolide copolymer. The microspheres are 25-90 microns in diameter. This preliminary study will be conducted early in January 1985. The primary baboon evaluations will involve treatment of animals with a combination of NET and EE. Those trials will be initiated prior to completion of the preliminary study. This program is expected to result in a novel combination contraceptive designed to minimize bleeding problems and provide efficacious NET serum levels over a three-month period.


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SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 363

JAN 16 1985

TITLE: "Laboratory Studies on an Antispermatogetic Agent -
THP for Control of Male Fertility"
INSTITUTION: The University of Western Ontario

PRINCIPAL INVESTIGATOR: John P. Wiebe, Ph.D.

FUNDING PERIOD: 10/1/84-3/31/86

AMOUNT FUNDED: \$90,000

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

The funding for this project began October, 1984, and consequently the current reporting period comprises only the first 3 months of this investigation. The general objective of the project is to determine the antifertility effects of intratesticular injection of THP (1,2,3-trihydroxypropane) in small animals and subhuman primates. We had already shown that in the laboratory rat, a single injection results in cessation of spermatogenesis (99.99% reduction in sperm) and consequent infertility for at least 6 months, without reduction in libido, secondary sex characters or alteration in hormone levels and hormone receptors. The proposed investigations are to determine if the sterility is permanent or reversible, if the THP treatment is effective in rabbits and monkeys, what the tissue distribution and early cytological and biochemical changes of tissues and cells exposed to THP may be. Two experiments on rats have been completed which show that between 1 and 8 days after THP injection, the serum LH and FSH levels are higher while the LH and FSH binding to receptors is lower than in corresponding controls; from 15 days until the end of the experiments (32-54 days) the hormone and receptor values for the THP treated rats are similar to those of the controls. In the absence of mating, a reduction in epididymal sperm number is observed by 4 days after treatment; by 8 days the sperm number is 80% lower and by 51 days it is 90-95% lower than in controls. Light microscopical observations of the testicular tissues from these experiments are in progress. An experiment has been completed to determine the tissue distribution of ^{14}C -THP at 5, 15, 30, 45, 60, 120, 180, 240 min, 24 h, and 7 days after intratesticular injection and the results are being analyzed. An experiment on rabbits (n=7) is in progress and indicates no change in ejaculate volume, a 90% reduction in sperm number and a significant reduction in sperm motility and viability following THP treatment. An experiment on monkeys (n=4) has been begun. We have tested an electroejaculation probe and generator which we specifically designed for the monkey work. The parameters for spectrophotometric measurements of sperm numbers and motility have been established and we will use these procedures in the future. It is anticipated that we will be able to provide results of experiments currently in progress in the next Report.



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SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 364

TITLE: "Antifertility Effects of Microencapsulated LHRH Agonist"

INSTITUTION: The University of Texas Health Science Center at San Antonio

PRINCIPAL INVESTIGATOR: Francisco J. Rojas, Ph.D.

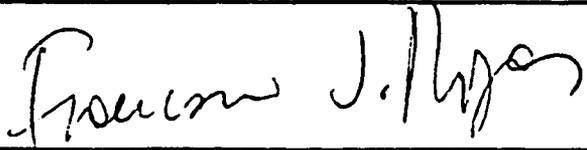
FUNDING PERIOD: 9/1/84-12/31/85

AMOUNT FUNDED: \$63,723

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

In the initiation of the project, we confronted two unexpected situations: 1) a delay in obtaining the cynomolgus monkeys and, 2) a new regulation in our Institution stating that quarantine must be extended to 60 days instead of 45 days as estimated originally in the research proposal. Due to this delay (animals were indeed received by November 15) PARFR kindly granted an extension without additional cost, and provided extra funding to cover the entire period of quarantine. During this initial stage of the project, therefore, concentration was placed on organization and delineation of the research protocols that are being utilized in the data collection and follow-up phases of the study. In this period of times, we have also received the first shipment of D-Trp-6-LH- RH microcapsules from Dr. Schally; we hope to obtain all the amount of microcapsules needed within two months.

Since PARFR funding allowed the hiring of a Research Assistant, we have been training this person in the quantitative determination of D-Trp-6-LH-RH in serum by Radioimmunoassay, iodination of the LH-RH analog, collection of samples, and performing laparoscopies and vaginal smears for the estimation of menstrual regularity. Presently, we are in the process of completing the study on the regularity of the menstrual cycles and we expect to start analysing the first samples in the next weeks.



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11/11/85

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SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 365

TITLE: "Optimization of Progesterone Microcapsule System"

INSTITUTION: Southern Research Institute

PRINCIPAL INVESTIGATOR: Thomas R. Tice, Ph.D.

FUNDING PERIOD: 9/1/84-10/31/84

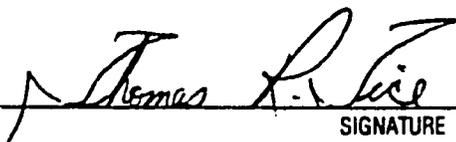
AMOUNT FUNDED: \$7,998

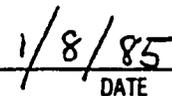
Below is a project summary for the July 1, 1984 through December 31, 1984 period.

The objective of this research program is to optimize further an injectable, biodegradable progesterone microcapsule formulation developed by Southern Research Institute. The microcapsule formulation is designed to deliver about 3 to 5 mg of progesterone per day for 90 days, giving contraceptive protection with a natural steroid for lactating mothers.

Initially, a highly loaded progesterone microcapsule formulation was fabricated by using a solvent-evaporation microencapsulation process. The microcapsules consisted of 65 wt % progesterone and 35 wt % 85:15 poly(DL-lactide-co-glycolide), a biocompatible polyester that biodegrades to lactic acid and glycolic acid. Three doses of this progesterone microcapsule formulation were tested in baboons. Two of the baboons treated showed high levels of progesterone for the first four weeks after the microcapsules were injected. The progesterone serum levels for these baboons then dropped off during the last eight weeks of the study. The third baboon had more uniform progesterone levels (in the desired range of about 3 to 5 ng/mL) throughout the study.

During this reporting period, we optimized the progesterone microcapsule formulation to improve the in vivo release kinetics of the microcapsules, i.e., to decrease the initial release of progesterone and even out the release of progesterone from the microcapsules throughout the desired 90-day period. More specifically, three different microcapsule formulations (about 50% loaded) were prepared for testing in baboons. Two of these formulations (containing microcapsules ranging from 45 to 125 or 63 to 125 μ m in diameter) were sterilized by exposing them to 1.0 Mrad of gamma radiation. The third formulation contained 63- to 125- μ m microcapsules and was exposed to 2.5 Mrad of gamma radiation. The three different optimized microcapsule formulations are currently being tested in baboons. The results of these studies should identify a formulation that will efficaciously deliver progesterone at a controlled rate for a period of three months.


SIGNATURE


DATE

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 366

TITLE: "Immunological Contraception-Study on the Time Course of Sperm
Antibodies Production in Rabbits Following Intravasal Injection
of BCG (Bacillus Calmette Guerin)"
INSTITUTION: University of Hong Kong

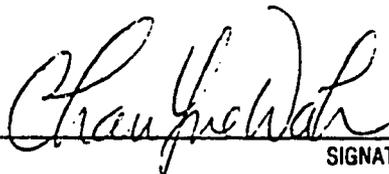
PRINCIPAL INVESTIGATOR: Steven Y. W. Chan, Ph.D.

FUNDING PERIOD: 10/1/84-3/31/86

AMOUNT FUNDED: \$5,302

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

The objective of the project is to study the time course of development of serum and seminal plasma sperm - reactive antibodies in adult male rabbits following intravasal injection of BCG (Bacillus Calmette Guerin). The project was recently approved by PARFR and the effective date of the project was October 1, 1984. During the funding period of October 1 - December 31, 1984, orders for experimental rabbits from the University of Hong Kong Laboratory Animal Unit and essential chemicals from overseas companies were sent out through the Finance Office of the University. It is anticipated that the animals and chemicals will soon be available by the early beginning of 1985 for the initiation of the planned study.



SIGNATURE

December 27, 1984.

DATE

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 367

TITLE: "Fertility Inhibition by In Vivo Immunization with Epididymal Proteins in Hmasters"

INSTITUTION: Instituto de Biología y Medicina Experimental

PRINCIPAL INVESTIGATOR: Jorge A. Blaquier, M.D.

FUNDING PERIOD: 11/1/84-10/31/85

AMOUNT FUNDED: \$9,900

Below is a project summary for the July 1, 1984 through December 31, 1984 period.

Evidence gathered in our laboratory, and by others aswell, suggests that androgen-dependent secretory epididymal proteins may play a key role in the development of fertilizing capacity that occurs during epididymal transit in mammals. Reports also indicate that "in vitro" exposure of rat and hamster mature spermatozoa to antibodies raised against these proteins interferes with fertility.

The objective of our project is to use a purified preparation of two hamster epididymal proteins that associate with spermatozoa (EP2-EP3) as autoantigens to study sperm function, fertility and the entry of immunoglobulins into the lumen of the epididymis in immunized animals.

To achieve these goals we must prepare the antigen in sufficient amounts and good purity, immunize adult male and female hamsters and then test their fertility, sperm functions and investigate the presence of immunoglobulins in association with spermatozoa.

In the two months elapsed since the initiation of this project we obtained antigen to begin immunizations. Through two steps of purification of crude epididymal cytosol, ion exchange chromatography and gel filtration, we obtained a preparation in which EP2-EP3 represent approximately 70% of total protein. This preparation was used to begin immunization of 5 males and 4 females. Two injections of 150 ug protein, 24 days apart, were given to each animal. In addition, a group of 5 males was injected with the same amount of Freund's adjuvant but without antigen to serve as control.

We also had to develop a technique allowing for the repeated bleeding of the animals to test for circulating antibodies. This was achieved through puncture of the suborbital sinus under ether anesthesia. So far none of the animals has developed titers of circulating antibodies measurable by immunodifusion.

The expected results of this project are: 1) demonstration of the autoantigenicity of epididymal proteins EP2-EP3 in hamsters; 2) Blockade of fertility in immunized males and females; 3) determination of the mode of action of immunoglobulins on sperm (immobilization, agglutination, interference with zona pellucida binding or vitelline membrane fusion), and 4) determination of the entry of immunoglobulins into the epididymis.

Jorge Blaquier

SIGNATURE

Dec. 27/1984

DATE

PARFR SCIENTIFIC ADVISORY COMMITTEE

MEETING XXXXV

Monday, July 30, 1984

HYATT ARLINGTON AT KEY BRIDGE
1325 Wilson Boulevard
Arlington, Virginia 22209
(703) 841-9595

MINUTES

VOTING SAC MEMBERS PRESENT

John J. Sciarra, M.D., Ph.D.
Andrzej Bartke, Ph.D.
William Droegemueller, M.D.
Miriam H. Labbok, M.D., M.P.H.
Kamran S. Moghissi, M.D.
Dean L. Moyer, M.D.
Antonio Scommegna, M.D.
Rochelle N. Shain, Ph.D.
Anne Colston Wentz, M.D.

VOTING SAC MEMBER ABSENT

David A. Blake, Ph.D.

PARFR STAFF PRESENT

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

USAID STAFF PRESENT

Laneta Dorflinger, Ph.D.
James D. Shelton, M.D., M.P.H.
Jeffrey M. Spieler, M.Sc.
Russel J. Thomsen, M.D.

I. ANNOUNCEMENTS

- A. We had a moment of silence for the sudden death of Dr. Uwe Goebelsmann.
- B. Dr. Anne Wentz was introduced to the Committee. Her C.V. was shared with members of the Committee.
- C. Dr. Andrzej Bartke assumed the position of Chairman, Department of Physiology, Southern Illinois University, Carbondale.
- D. The following SAC meetings were scheduled for Chicago:
 Wednesday, December 12, 1984
 Friday, April 12, 1985
- E. PARFR's International Workshop on Intrauterine Contraception held at the Sheraton Plaza Hotel in Chicago, May 29-June 1, 1984 was a huge success. Ninety participants attended from 22 countries.

II. NEW BUSINESS

A. FORMAL PROPOSALS

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"
Funding Requested: \$21,540 Length of Project: One Year

The Committee reviewed the material provided and requested a detailed formal proposal for a Phase I clinical trial to be conducted in Denver only.

Wung-Wai Tso, Ph.D., The Chinese University of Hong Kong, Shatin
"To Characterize the Antifertility Efficacy of a Stable Aqueous
Gossypol Preparation"
Funding Requested: \$13,800 Length of Project: One Year

The proposal was reviewed and an independent review by Drs. Blake and Waller was requested. Depending on the outcome of those reviews, the proposal will be implemented.

John P. Wiebe, Ph.D., University of Western Ontario, London, Ontario,
Canada
"Laboratory Studies of the Control of Male Fertility by a Non-Toxic,
Non-Hormonal, Biological Antispermato-genic Agent"
Funding Requested: \$59,500 -- 1st Yr. Length of Project: Three Years
\$61,610 -- 2nd Yr.
\$64,250 -- 3rd Yr.

The Committee approved the proposal and recommended that the following experiments should be conducted first:

1. To determine whether rats treated with intratesticular THP are permanently sterilized (long-term studies).
2. If fertility returns after any dose, examine sperm morphology and motility, conception rate and development of the offspring (fetal and postnatal) during the recovery phase.
3. To determine the effectiveness of THP in non-rodent species, as proposed.
4. To examine early responses, including tissue distribution of labelled compound and histological changes in the testes, again as proposed.
5. To initiate morphological and biochemical assessment of organs which may be exposed to significant concentrations of THP after intratesticular administration of effective doses.

A. FORMAL PROPOSALS: (continued)

Duane L. Venton, Ph.D., The University of Illinois at Chicago
"Inhibition of Ovulation by Specific Antagonists of Prostaglandin F_{2a}"
Funding Requested: \$29,400 -- U of I Length of Project: One Year
\$43,991 -- NU

The Committee tabled the proposal until more data is provided in relation to the specificity of the compounds for the ovarian receptors. Additionally, a major change was suggested for the evaluation of ovulation inhibition, mainly serial laparoscopy or ultrasound. PARFR staff will see if Northwestern University's animal facility can conduct such experiments. If not, another animal facility will be approached.

Robert W. Rebar, M.D., Northwestern University Medical School, Chicago
"Clinical Pharmacokinetics/Pharmacodynamics of Controlled-Release Progesterone Microcapsules for the Regulation of Fertility"
Funding Requested: \$76,036 Length of Project: Nine Months

The proposal was approved in principal. Changes in the frequency of blood sampling, baseline data, and date of injection were made.

Danny H. Lewis, Ph.D., Stolle Research and Development Corporation,
Birmingham, Alabama
"Development of a Three-Month Microsphere Contraceptive Formulation for the Combined Administration of Ethinyl Estradiol and Norethisterone"
(Continuation of PARFR-332 - Refer to Technical Report)
Funding Requested: \$67,195 Length of Project: One Year

The Committee approved the proposal as presented.

Francisco J. Rojas, M.D., Ph.D., The University of Texas Health Science Center at San Antonio
"Effects of the Controlled Release Microcapsule Formulation of the LH-RH Agonist D-Trp-⁶LH-RH on Suppression of Ovulation in Cynomolgus Monkeys"
Funding Requested: \$65,494 Length of Project: One Year

The Committee approved the proposal as presented.

Mohamed I. Abdalla, M.D., Cairo University, Cairo, Egypt
"Natural Family Planning Salivary Estradiol as a Marker for Prediction of Ovulation"
Funding Requested: \$51,600 Length of Project: Nine Months

The proposal was tabled until further review of the literature is conducted by PARFR staff.

A. FORMAL PROPOSALS (continued)

John W. Gibson, M.S., Southern Research Institute, Birmingham, Alabama
"Development of a Vaginal Delivery System for Sodium Tetradecyl
Sulfate, an Acrosin Inhibitor"
Funding Requested: \$75,693 Length of Project: One Year

The proposal was not approved at this time. PARFR staff will explore mechanisms to have Dr. Zaneveld work with SRI on a sperm acrosin - sponge delivery system, if the need arises.

C. Irving Meeker, M.D., Maine Medical Center, Portland, Maine
"A Tubal Plug and Clip Method for Female Sterilization"
Funding Requested: \$5,200 Length of Project: One Year

The committee maintains their decision of funding a Phase I clinical trial for the tubal plug and clip method for female sterilization. Depending on the outcome of FDA discussion, PARFR will consider for approval a proposal to perform all necessary studies for IDE approval.

B. PILOT STUDY PROPOSALS

Steven Y.W. Chan, Ph.D., University of Hong Kong, Queen Mary Hospital,
Hong Kong
"Immunological Contraception - Study on the Time Course of Sperm
Antibodies Production in Rabbits Following Intravasal Injection of
BCG (Bacillus Calmette Guerin)"
Funding Requested: \$4,900 Length of Project: One Year

The Committee agreed with all the recommendations made by Dr. Nancy Alexander (independent reviewer) and the proposal, with these changes incorporated, was approved.

Jorge A. Blaquier, Instituto de Biologia y Medicina Experimental,
Buenos Aires, Argentina
"Effects of In Vivo Immunization with Specific Epididymal Proteins
Upon Fertility in Male Hamsters"
Funding Requested: \$10,000 Length of Project: One Year

The Committee agreed with all the recommendations made by Dr. Nancy Alexander (independent reviewer) and the proposal, with these changes incorporated, was approved.

C. EXTENSION PROPOSALS

Ralph M. Richart, M.D., Columbia University, New York, New York
"Methylcyanoacrylate as a Female Sterilization Agent"

The letter proposal was tabled until data on the FEMTEST is available and longer follow-up data on patients enrolled in the 2-shot protocols is provided.

PARFR-349 -- John W. Gibson, M.S., Southern Research Institute, Birmingham, Alabama

"Preparation of Fibrous Estradiol/Progesterone IUDs for Phase I Clinical Trials, Continuation of PARFR-324"

Funding Requested: \$48,700 Length of Project: Six Months

The extension proposal was approved with reduction in funding suggested.

E. TECHNICAL REPORT REVIEW

The following technical reports were reviewed in detail:

1. POLY NET 90

- a. PARFR-341 -- Charles E. Flowers, Jr., M.D. and Lee R. Beck, Ph.D.,
The University of Alabama in Birmingham
"Phase II Poly NET 90 Injectable Study"
- b. PARFR-341T -- Jose P. Balmaceda, M.D. and Ricardo H. Asch, M.D.,
The University of Texas Health Science Center at San Antonio
"Phase II Poly NET 90 Injectable Study"

2. FUSED PELLETT

- a. PARFR-330 -- Brij B. Saxena, Ph.D., D.Sc., Cornell University
Medical College
"A Clinical Evaluation of the Subdermal Norethindrone Pellet Implant (Phase II)"
- b. PARFR-330T -- Ricardo H. Asch, M.D., The University of Texas
Health Science Center at San Antonio
"A Clinical Evaluation of the Bioabsorbable Contraceptive Norethindrone Pellet Implant (Phase II)"

3. PARFR-332 (FINAL) -- Danny H. Lewis, Ph.D., Stolle Research and
Development Corporation, Birmingham, Alabama
"Development of an Injectable Long-Acting Estradiol Formulation"

4. PARFR-334SRI (FINAL) -- Thomas R. Tice, Ph.D., Southern Research
Institute, Birmingham, Alabama
"Development of Controlled-Release Progesterone Microcapsule"

E. TECHNICAL REPORTS REVIEW (continued)

5. PARFR-337F -- Tapani Luukkainen, M.D., Ph.D., University of Helsinki, Finland
"Use Effectiveness of a Levonorgestrel-Releasing Intracervical Device"
6. PARFR-343 -- Lee R. Beck, Ph.D., The University of Alabama in Birmingham
"NIH/Biotech Levonorgestrel Microcapsules"
7. PARFR-348 -- Danny H. Lewis, Ph.D., Stolle Research and Development Corporation, Birmingham, Alabama
"Development of Improved Methods and Materials for Injecting Microencapsulated Steroids"
8. PARFR-350 -- Jacques Hamou, M.D., Tenon Hospital, Paris, France
"An Intra Tubal Device (ITD) for Female Sterilization"
9. PARFR-351 -- Andrew V. Schally, Ph.D., Tulane University, New Orleans, Louisiana
"Development of Methods for Female and Male Contraception Based on LH-RH Antagonists"
10. PARFR-352 -- Lee R. Beck, Ph.D., The University of Alabama in Birmingham
"Baboon Testing of Duration of NET Release from Fused Pellets"
11. PARFR-353 -- Antonio Scomegna, M.D., Michael Reese Hospital and Medical Center, Chicago
"Effect of Chronic Intrauterine Release of Estradiol and Progesterone on Uterine Histology in Intact Rabbits"
12. PARFR-357 -- Danny H. Lewis, Ph.D., Stolle Research and Development Corporation, Birmingham, Alabama
"Optimization of Release Profile of Norethisterone Injectable 90-Day Contraceptive"
13. PARFR-358 -- Danny H. Lewis, Ph.D., Stolle Research and Development Corporation, Birmingham, Alabama
"Development of a 30-Day Injectable Contraceptive"

III. MISCELLANEOUS

- A. The following subagreements were executed on projects reviewed and approved at the April 11, 1984 SAC Meeting:

1. PARFR-359 -- Bonnie S. Dunbar, Ph.D., Baylor College of Medicine, Houston, Texas
"Active Immunization of Non-Human Primates and Rabbits with Zona Pellucida Proteins"
Funding Period: 6/1/84-5/31/85 Amount Funded: \$77,741

III. MISCELLANEOUS (continued)

2. PARFR-360 -- John C.M. Tsibris, Ph.D., University of Illinois at Chicago, Illinois
"Inter- and Intra-Cycle Variation of Genital Peroxidase in Women"
Funding Period: 7/1/84-6/30/85 Amount Funded: \$28,012
3. PARFR-361 -- Ricardo H. Asch, M.D., The University of Texas Health Science Center at San Antonio
"Testosterone Microcapsule Formulation Study"
Funding Period: 7/1/84-12/31/84 Amount Funded: \$33,455

B. Amendments to subagreements for projects reviewed and approved at the April 11, 1984 SAC Meeting:

1. Amendment #3 to PARFR-309 -- Robert T. Chatterton, Ph.D., Northwestern University Medical School
"Ovulation Inhibition by Anordrin"
Total Period: 1/1/82-6/30/84 Total Funded: \$148,988
2. Amendment #1 to PARFR-338 -- Lourens J.D. Zaneveld, D.V.M., Ph.D., Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois
"Development of Sperm Enzyme Inhibitors as Vaginal Contraceptives"
Total Period: 7/1/83-6/30/86 Total Funded: \$111,182
3. Amendment #1 to PARFR-339 -- Lourens J.D. Zaneveld, D.V.M., Ph.D., Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois
"Efficacy of Studies in Primates with the Shug in the Absence of a Tissue Wrap"
Total Period: 7/1/83-6/30/85 Total Funded: \$37,476

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

PARFR SCIENTIFIC ADVISORY COMMITTEE
MEETING XXXXVI

Wednesday, December 12, 1984
HYATT REGENCY O'HARE
9300 West Bryn Mawr Avenue
Rosemont, Illinois 60018
(312) 696-1234

MINUTES

VOTING SAC MEMBERS PRESENT

John J. Sciarra, M.D., Ph.D.
Andrzej Bartke, Ph.D.
William Droegemueller, M.D.
Ronald H. Gray, M.D.
Gary D. Hodgen, Ph.D.
Miriam H. Lobbok, M.D., M.P.H.
Kamran S. Moghissi, M.D.
Rochelle N. Shain, Ph.D.
Anne Colston Wentz, M.D.

VOTING SAC MEMBERS ABSENT

David A. Blake, Ph.D.
Dean L. Moyer, M.D.
Antonio Scornegna, M.D.

PARFR STAFF PRESENT

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

USAID STAFF PRESENT

Laneta Dorflinger, Ph.D.
Jeffrey M. Spieler, M.Sc.

I. ANNOUNCEMENTS

- A. Drs. Ronald H. Gray and Gary D. Hodgen were introduced to the Committee. SAC procedures were explained by Dr. Sciarra.
- B. The following SAC meetings were scheduled for 1985:
 - Friday, April 12, 1985 -- Chicago at Hyatt Regency O'Hare
 - July, 1985 -- Chicago
 - December, 1985 -- Washington, D.C.

II. NEW BUSINESS

A. PROPOSALS

Kenneth G. Gould, Ph.D., Emory University, Atlanta, Georgia
"Modification of Cervical Mucus for Fertility Control"
Funding Requested: \$124,364 (1st Yr.) Length of Project: Two Years

The Committee reviewed the material provided and voted not to approve the proposal.

as

A. PROPOSALS (continued)

Paul Primakoff, Ph.D., The University of Connecticut Health Center,
Farmington

"Purification of Guinea Pig Sperm Surface Antigens and
Investigation of Their Use as Contraceptive Vaccines"

Funding Requested: \$52,369 Length of Project: One Year

The Committee felt that the proposal was well written; however, it is "too basic" for PARFR funding. The Committee requested that the PI prepare a proposal in keeping with the applied research objectives of PARFR.

Andrew V. Schally, Ph.D., Tulane University School of Medicine, New
Orleans, Louisiana

"Development of Methods for Female and Male Contraception Based
on LH-RH Antagonists"

(Includes Technical Report, PARFR-351)

Funding Requested: \$69,798 Length of Project: One Year

The Committee approved the proposal as presented; however, USAID technical staff will only approve studies needed for an FDA/IND Phase I clinical trial.

Extension to PARFR-309 -- Robert T. Chatterton, Ph.D., Northwestern
University Medical School, Chicago, Illinois

"Ovulation Inhibition by Anordrin"

Funding Requested: \$70,349 Length of Project: One Year

Robert T. Chatterton, Ph.D., Northwestern University Medical School,
Chicago, Illinois

"Anordrin: Pre-IND Studies"

Funding Requested: \$150,000 Length of Project:

Due to the impossibility of implementing a Phase I clinical trial in Europe, the Committee again approved the implementation of Pre-IND studies. A project development team consisting of Drs. Blake and Hodgen will be convened in Chicago on January 16, 1985.

Thomas R. Tice, Ph.D., Southern Research Institute, Birmingham, Alabama

"Evaluation of the Tissue Compatibility of Progesterone Microcapsules"

Funding Requested: \$30,004 Length of Project: One Year

The Committee did not approve the proposal; however, if the Chilean IRB still requires the data, a study not to exceed \$5,000 is approved for implementation in Chile.

A. PROPOSALS (continued)

E.S. Nuwayser, Ph.D., Biotek, Inc., Woburn, Massachusetts

"Development of Levonorgestrel Microcapsules"

(Includes Technical Report, PARFR-343, Lee R. Beck, Ph.D., University of Alabama in Birmingham, "NIH/Biotek Levonorgestrel Microcapsules")

Funding Requested: \$99,820

Length of Project: One Year

The Committee approved the proposal with a recommendation to decrease the budget.

Extension to PARFR-346 -- Thomas R. Tice, Ph.D., Southern Research Institute, Birmingham, Alabama

"Development of Controlled-Release Testosterone Microcapsules for Fertility Regulation of Males"

(Includes Final Technical Report of PARFR-346)

Funding Requested: \$49,987

Length of Project: One Year

The Committee tabled this proposal until Dr. Asch provides animal release data for his PARFR-361 project which recently started. If the animal data are available, this proposal will be considered again at the April 12, 1985 SAC meeting.

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

"NIH Androgen Release Study in Rhesus Monkeys"

(Includes Technical Report, PARFR-361, R. Asch, M.D., UTHSCSA,

"Testosterone Microcapsule Formulation Study")

Funding Requested: \$38,071

Length of Project: One Year

The Committee approved the proposal as presented. Initiation of the project depends on availability of the compound from NIH.

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

"Baboon Endometrial Response to Long-Acting Progestin"

Funding Requested: \$78,800

Length of Project: One Year

The Committee approved the proposal. The Statement of Work will be reviewed by NIH and initiation depends on the availability of both compounds from NIH.

B. TECHNICAL REPORT REVIEW

The following technical reports were reviewed in detail:

PARFR-315 -- Erwin Goldberg, Ph.D., Northwestern University, Evanston, Illinois

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

B. TECHNICAL REPORT REVIEW (continued)

PARFR-355 -- Nancy J. Alexander, Ph.D., Oregon Regional Primate Research Center, Beaverton, Oregon
"Enhancement of the Secretary Response to LDH-C₄"

PARFR-356a -- Rajesh K. Naz, Ph.D., The George Washington University Medical Center, Washington, D.C.
"Development of an Immunocontraceptive Vaccine: Role of 23-Kd Antigen in Immunoinfertility and Fertility Regulation"

PARFR-359 -- Bonnie S. Dunbar, Ph.D., Baylor College of Medicine, Houston, Texas
"Active Immunization of Non-Human Primates and Rabbits with Zona Pellucida Proteins"

PARFR-330 -- Brij B. Saxena, Ph.D., D.Sc., Cornell University Medical College, New York, New York
"A Clinical Evaluation of the Subdermal Norethindrone Pellet (Phase II)"

PARFR-330M -- Roberto Rivera, M.D., Instituto de Investigacion Cientifica, Durango, Mexico
"A Clinical Evaluation of the Subdermal Norethindrone Pellet (Phase II)"

PARFR-330T -- Ricardo H. Asch, M.D., The University of Texas Health Science Center at San Antonio
"A Clinical Evaluation of the Bioabsorbable Subdermal Contraceptive Norethindrone Pellet Implant (Phase II)"

PARFR-352 -- Lee R. Beck, Ph.D., The University of Alabama in Birmingham
"Baboon Testing of Duration of NET from Fused Pellets"

PARFR-333 -- Charles E. Flowers, Jr., M.D. and Lee R. Beck, Ph.D., The University of Alabama in Birmingham
"Poly-gly NET 180 Microcapsule System, Phase I"

PARFR-341 -- Charles E. Flowers, Jr., M.D. and Lee R. Beck, Ph.D., The University of Alabama in Birmingham
"Phase II Poly NET 90 Injectable Study"

PARFR-341C -- Horacio B. Croxatto, M.D. and Soledad Diaz, M.D., Centro Nacional de la Familia, Santiago, Chile
"Phase II Poly NET 90 Injectable Study"

PARFR-341T -- Jose P. Balmaceda, M.D. and Ricardo H. Asch, M.D., The University of Texas Health Science Center at San Antonio
"Phase II Poly NET 90 Injectable Study"

PARFR-357 -- Danny H. Lewis, Ph.D., Stolle Research and Development Corporation, Birmingham, Alabama
"Optimization of Release Profile of Norethisterone Injectable 90-Day Contraceptive"

B. TECHNICAL REPORT REVIEW (continued)

PARFR-358 -- Danny H. Lewis, Ph.D., Stolle Research and Development Corporation, Birmingham, Alabama
"Development of a 30-Day Injectable Contraceptive"

PARFR-334UAB -- Lee R. Beck, Ph.D., The University of Alabama in Birmingham
"Pharmacokinetic Studies in Baboons Relating to The Development of Controlled-Release Progesterone Microcapsule"

PARFR-337F -- Tapani Luukkainen, M.D., Ph.D., University of Helsinki, Finland
"Use Effectiveness of a Levonorgestrel-Releasing Intracervical Device"

PARFR-337T -- Rochelle N. Shain, Ph.D., The University of Texas Health Science Center at San Antonio
"Intracervical Device Acceptability Study"

PARFR-338 -- Lourens J.D. Zaneveld, D.V.M., Ph.D., Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois
"Development of Sperm Enzyme Inhibitors as Vaginal Contraceptives"

PARFR-338UI -- Donald P. Waller, Ph.D., University of Illinois at Chicago
"Toxicology Studies of Acrosin Inhibitors"

PARFR-339 -- Lourens J.D. Zaneveld, D.V.M., Ph.D., Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois
"Efficacy of Studies in Primates with the Shug in the Absence of a Tissue Wrap"

PARFR-339UI -- Donald P. Waller, Ph.D., University of Illinois at Chicago
"Toxicology of Silicone Implanted (SHUGS) in the Vas Deferens"

PARFR-344 (FINAL) -- Ralph M. Richart, M.D., Columbia University, New York, New York
"Percutaneous Intra Vas Injection for Male Sterilization"

PARFR-360 -- John C.M. Tsibris, Ph.D., University of Illinois at Chicago
"Inter- and Intra-Cycle Variation of Genital Peroxidases in Women"

III. MISCELLANEOUS

A. The following subagreements were executed on projects reviewed and approved at the July 30, 1984 SAC Meeting:

1. PARFR-362 -- Danny H. Lewis, Ph.D., Stolle Research and Development Corporation, Birmingham, Alabama
"Combination Injectable Steroidal Microsphere - Continuation of PARFR-332"

Funding Period: 10/1/84-5/31/85

Amount Funded: \$67,195

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III. MISCELLANEOUS (continued)

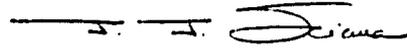
2. PARFR-363 -- John P. Wiebe, Ph.D., The University of Western Ontario, London, Ontario, Canada
"Laboratory Studies on an Antispermato-genic Agent - THP for Control of Male Fertility"
Funding Period: 10/1/84-3/31/86 Amount Funded: \$90,000
 3. PARFR-364 -- Francisco J. Rojas, Ph.D. and Ricardo H. Asch, M.D., The University of Texas Health Science Center at San Antonio
"Antifertility Effects of Microencapsulated LHRH Agonist"
Funding Period: 9/1/84-6/30/86 Amount Funded: \$64,218
 4. PARFR-366 -- Steven Y.W. Chan, Ph.D., University of Hong Kong, Hong Kong
"Immunological Contraception - Study on the Time Course of Sperm Antibodies Production in Rabbits Following Intravasal Injection of BCG (Bacillus Calmette Guerin)"
Funding Period: 10/1/84-3/31/86 Amount Funded: \$5,302
 5. PARFR-367 -- Jorge A. Blaquier, M.D., Instituto de Biologia y Medicina Experimental, Buenos Aires, Argentina
"Fertility Inhibition of In Vivo Immunization with Epididymal Proteins in Hamsters"
Funding Period: 11/1/84-10/31/85 Amount Funded: \$9,900
 6. Dr. Rebar's proposal will be funded once Stolle is able to provide the progesterone microcapsules.
- B. Amendments to subagreements for projects reviewed and approved at the July 30, 1984 SAC Meeting:
1. Amendment #1 to PARFR-349 -- Richard L. Dunn, Ph.D., Southern Research Institute, Birmingham, Alabama
"Preparation of Fibrous Estradiol/Progesterone IUDs for Phase I Clinical Trials, Continuation of PARFR-324"
Total Period: 11/1/83-6/30/85 Total Funded: \$98,694
- C. Dr. Miriam Labbok is thanked for her many years of service to PARFR as our USAID Project Monitor from 1978 to 1981 and as a member of our Scientific Advisory Committee from October, 1981 through December, 1984.
- D. A listing of all topics covered in our Research Frontiers in Fertility Regulation series was distributed. SAC was asked to communicate suggested topics for future issues to the program staff.
- E. The Ob-Gyn Department Annual Report will be sent to all SAC members. Section VIII lists PARFR's active projects.

III. MISCELLANEOUS (continued)

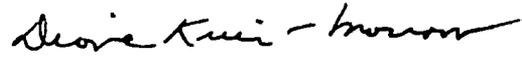
- F. SAC was asked to submit suggestions for topics for PARFR's 1986 workshop.

here 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.
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RESEARCH FRONTIERS IN FERTILITY REGULATION

LONG-ACTING INJECTABLE NORETHISTERONE CONTRACEPTIVE SYSTEM: REVIEW OF CLINICAL STUDIES

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Synthetic steroid hormones are generally accepted as a safe and efficacious means of fertility control. However, the formulations currently available fall short of ideal with regard to ease of administration and lack of side effects. There are questions regarding safety following long-term use of formulations containing estrogen, and efficacy may be compromised due to failure of user compliance.

To overcome these disadvantages, delivery systems are being developed to improve the benefit-to-risk ratio by providing continuous administration of low levels of contraceptive steroids for up to several years following a single administration.

The rationale and the advantages and disadvantages of long-acting controlled release steroidal contraceptive systems have been previously reviewed (1, 6, 11, 12, 14). The most advanced systems include depot steroid formulations, biodegradable and non-biodegradable implants, medicated intrauterine and intravaginal devices, and injectable small particulate systems.

This report provides an up-to-date summary of the research supported by the Program for Applied Research on Fertility Regulation (PARFR) to develop a long-acting, injectable, biodegradable microsphere delivery system for the contraceptive steroid, norethisterone (NET). We will trace the development of the microsphere delivery system from the initial prototype formulations to the present, describing the capabilities of the delivery system for controlling both the rate and duration of NET release, in light of the results obtained from the clinical testing program, including both pharmacokinetic and pharmacodynamic studies.

NET MICROSPHERE DELIVERY SYSTEM

The NET microsphere delivery system consists of microspheres composed of a biodegradable polymer and NET. The microspheres are prepared using a solvent evaporation process that has undergone substantial modification and improvement during the course of this program. Microspheres with diameters ranging from 10 μm to 240 μm have been used in studies of rate and duration of NET release, injection efficiency, and biodegradation.

Initially, formulations capable of releasing NET at a near zero order rate were developed and tested in baboons. This prototype system was evaluated in clinical trials, and the results gave rise to an improved second generation formulation, which has been tested in multicenter clinical trials. Based on the results of these studies, further improvements in the delivery system have been made, and the final version is currently being evaluated in a Phase II clinical study.

The microsphere formulation has been varied during the development phase of the research to optimize the NET release rates, biodegradation kinetics, and ease of administration. Details regarding the manufacture of the NET microspheres and the improvements made in the microencapsulation process have been published (7, 9, 10) and will not be reviewed here, except to emphasize where appropriate the biological considerations that necessitated improvements in the delivery system design.

PROTOTYPE SYSTEM

The polymer first evaluated as excipient for making NET microspheres was dl-poly(lactic acid) (PLA). PLA had previously been proven safe for human use in absorbable suture material, and long-term toxicity had been thoroughly evaluated. Early results showed that microspheres made from PLA using a solvent evaporation process had no adverse effects in rats, thus confirming the histocompatibility of the polymer and removal of potentially irritating solvents and dispersing agents used in the manufacturing process.

Prior to animal testing, microspheres made of PLA containing NET were evaluated *in vitro*, in an attempt to define parameters that might be predictive of their performance *in vivo*. Scanning electron microscopy was used to monitor the spherical integrity and surface characteristics of the microspheres. The rate of NET release from each batch of microspheres was tested *in vitro*. These quality control procedures have been repeated with each formulation and batch of the microspheres that has been subjected to *in vivo* evaluation. Additionally, following the *in vitro* quality control analysis, each new formulation has been tested in baboons to evaluate safety and pharmacokinetics. Figure 1 shows the *in vitro* NET release profile from a representative microsphere formulation and Figure 2 shows a typical scanning electron micrograph of the microspheres.

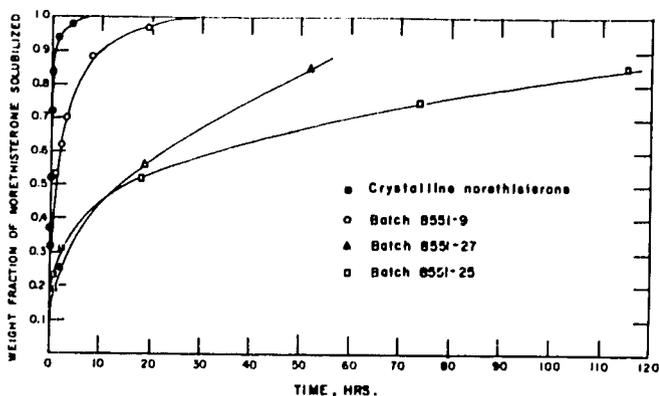


Figure 1. Norethisterone release *in vitro* from microspheres of varying diameter ranges. (Source: Beck LR, Tice TR: Poly (lactic acid) and poly (lactic acid co-glycolic acid) contraceptive delivery systems. In Mishell DR Jr (ed): Long-Acting Steroid Contraception, pp175-199. New York, Raven Press, 1983.

Pharmacokinetic studies in baboons were used to demonstrate the dose response capabilities of the prototype system (2, 3). Microspheres 10 μm to 240 μm in diameter containing 25% by weight NET were injected into baboons and serum estradiol (E2), progesterone (P4), and NET concentrations were determined by radioimmunoassay (RIA). The slopes of the NET release curves

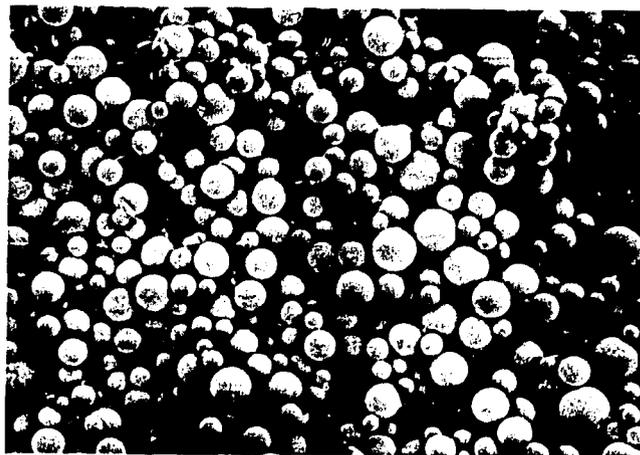


Figure 2. Scanning electron micrograph of norethisterone microspheres (x 450).

using different doses of the same batch were not significantly different from each other, and there was no difference in the duration of NET release. The differentiating feature among the different doses was the higher serum NET levels achieved with the higher doses. Two of the doses tested, 75 mg and 50 mg NET, were sufficient to inhibit ovarian cyclicity and ovulation in the baboons over a 6-month interval. Parallel studies in rats demonstrated that release was occurring primarily by diffusion of the hormone from the microspheres. On the basis of these preclinical animal studies, this prototype formulation was judged safe for use in Phase I clinical trials.

PHASE I CLINICAL TRIALS

Sixty-three women at three centers were treated with the prototype NET-PLA microsphere formulation (Table 1). In the first study (Group A; Table 1) 24 women were treated with 50 mg to 100 mg of microencapsulated NET using PLA microspheres that ranged in diameter from 60 μm to 240 μm (8). Poor injection efficiencies experienced by untrained practitioners with saline-suspended microspheres resulted in actual doses ranging from 7 mg to 95 mg of NET, expanding the dose-range of the study. Doses of microencapsulated NET ranging from 0.132 mg to 0.267 mg per kilogram body weight had no effect on ovarian function over the 6-month treatment interval, whereas higher doses caused complete or partial suppression of ovarian function for varying periods after treatment.

Figure 3 shows the mean serum levels of NET for seven subjects who received doses of microencapsulated NET ranging from 1.22 mg to 2.30 mg NET per kilogram body weight. Ovulation was inhibited for 3 to 6 months in this group of subjects.

Group	Months*	No.	Dose (mg)	P/C†	% Load	µm Diameter
A	6	14	100	P	25	60-240
		10	50	P	25	60-240
B	6	19	200	P	24	90-212
C	6	20	150	P	24	90-212
D	3	5	75	C	20-21	63-90
		5	100	C	20-21	63-90
E	3	5	75	C	20-21	63-90
		3	100	C	20-21	63-90
F	3	5	75	C	20-21	63-90
		5	100	C	20-21	63-90
G	3	5	75	C	20-21	63-90
		5	100	C	20-21	63-90
H	3	5	75	C	20-21	90-106
		5	100	C	20-21	90-106
I	6	5	75	C	20-21	125-212
		5	150	C	20-21	125-212
J	6	5	75	C	20-21	125-212
		5	150	C	20-21	125-212
K	3	14	75	C	23.6	45-90

* Expected release duration

† P = PLA, C = PLGA (copolymer) formulation

Table 1. Clinical Trials with Norethisterone Microspheres

Menstrual abnormalities are the most common side effect of long-acting steroidal contraceptives. Although this sample size was too small to establish a meaningful correlation between microsphere dose and the amount of menstrual bleeding, the higher doses caused a reduction in the quantity of blood lost in each episode and an increase in the interval between episodes in some subjects.

This preliminary trial reinforced the results of the animal pharmacodynamic and pharmacokinetic studies and demonstrated that higher doses would be necessary to achieve ovulation suppression in women for a 6-month period using this formulation.

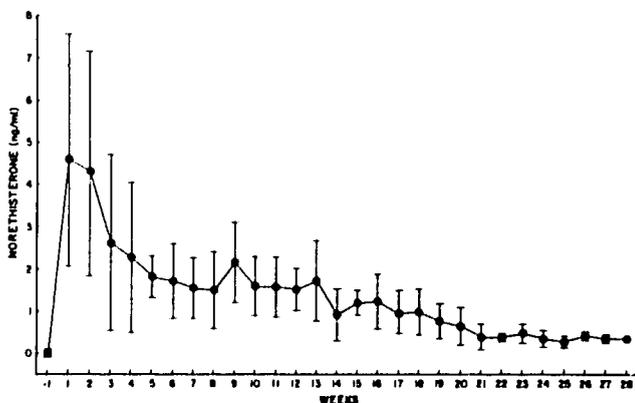


Figure 3. Mean serum levels of immune-reactive NET in 7 human subjects following IM injection of 1.50 ± 0.37 mg NET/kg body weight. (Source: Beck LR, Ramos RA, Flowers CE Jr, Lopez GZ, Lewis DH, Cowsar DR: Clinical evaluation of injectable biodegradable contraceptive system. *Am J Obstet Gynecol* 140:799, 1981.

The next studies, therefore, used theoretical doses of 150 mg and 200 mg NET in 25.6% loaded microspheres with diameters ranging from 90 µm to 212 µm (Groups B and C; Table 1). This size range was prepared as a composite by mixing equal masses of the following specific size fractions: 90 to 106, 106 to 125, 125 to 150, 150 to 180, and 180 to 212 µm. This ensured even distribution of microsphere diameters over the final size range. The vehicle was changed in an attempt to improve injection efficiency to 2% carboxymethylcellulose, 1% tween-20, and 93% water.

Twenty patients were treated with microspheres containing 150 mg of NET (Group C; Table 1). The actual doses ranged from 22 mg to 144 mg NET (104 ± 37). Twelve subjects received doses greater than 138 mg. The serum NET profile was characterized by an initial slight burst (less than 4.0 ng NET/ml) followed by a gradual decline (Figure 4). The duration of NET release was approximately 6 months. The serum NET profiles in the subjects in this study and those in the former group who received a wider size range of microspheres (60-240 µm) differed in that the smaller microspheres produced higher serum NET levels during the first week and lower levels during the last month post-treatment. These differences can be explained on the basis that the smaller microspheres used in the first study had faster release rates.

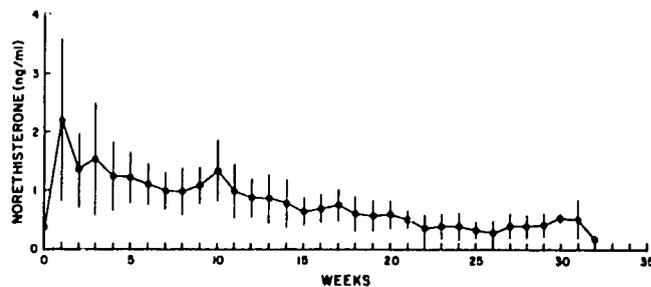


Figure 4. Mean serum levels of immune-reactive NET in 13 women following IM injection of 2.45 ± 0.44 mg NET/kg body weight. (Source: Beck LR, Flowers CE Jr, Pope VZ, Tice TR, Dunn RL, Gilley RM: Poly (d,l-lactide-co-glycolide)/norethisterone microcapsules: clinical study. In Zatuchni GI, Goldsmith A, Shelton JD, Sciarra JJ (eds): *Long-Acting Contraceptive Delivery Systems*, pp 407-417. Philadelphia, Harper & Row, 1984.

Nineteen patients were treated at a second center (13) with the same formulation and size range using an even higher dose, 200 mg NET (Group B; Table 1). Injection efficiencies were excellent in this study, averaging $92 \pm 3\%$. Ovulation was inhibited for at least 24 weeks in 16 of 18 subjects. The serum NET levels were higher and serum NET curves parallel to those in subjects who

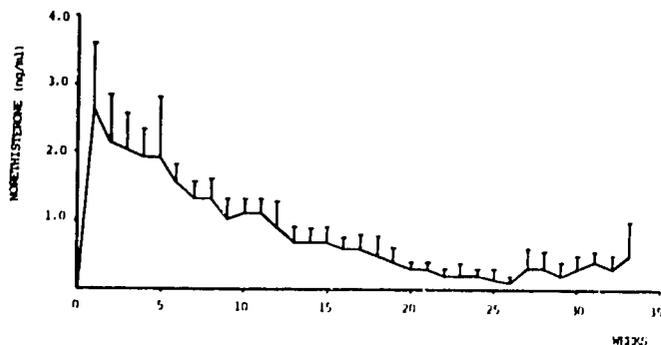


Figure 5. Mean serum levels of immune-reactive NET in women following IM injection of PLA microspheres containing 200 mg NET. (Source: Rivera R, Flores C, Aldaba S, Hernandez A: Norethisterone Microspheres 6-month System: Clinical Results. In Zatuchni GI, Goldsmith A, Shelton JD, Sciarra JJ (eds): Long-Acting Contraceptive Delivery Systems, pp 418-424. Philadelphia, Harper & Row, 1984.

received the lower dose (Figure 5). One subject resumed ovulatory cycles 16 weeks post-treatment, after NET levels had dropped below 2 ng/ml. Two subjects had single progesterone values suggestive of ovulation during the first 7 weeks post-treatment. These elevated progesterone values, however, were found to be inconsistent with the other weekly samples, preventing definitive diagnosis of ovulation. In most subjects, serum NET levels fell below 1.0 ng/ml between the 10th and 22nd weeks post-treatment, and were below 0.5 ng/ml usually by week 25.

Bleeding patterns were altered in these subjects, with a range of 1 to 10 bleeding episodes per subject over the 239-day reference period. Total spotting days per subject ranged from 1 to 85, and total bleeding days from 3 to 58. Bleeding episodes were an average of 6.6 days, ranging from 3 to 16 days in length. The longest nonbleeding interval was 166 days. In general, the average number of bleeding and spotting days per 30-day reference period decreased with increasing time from injection, with a maximum of 9.68 in the second 30 days to a low of 3.21 per subject 241 to 270 days post-treatment.

We concluded from these dose response clinical studies that PLA microspheres are capable of delivering NET continuously for approximately 6 months, and that the duration of ovarian suppression is dose-dependent within a given microsphere formulation and size limit. The shape of the particular release curve within a given formulation is dependent upon microsphere size distribution and dose of NET contained in the microspheres.

Comparison of the serum NET profiles attained using different doses at three centers shows the influence of microsphere size on NET release rates. The size distribution of microspheres in the first study was 60 μm to

240 μm , whereas the size distribution used at the other two centers was 90 μm to 212 μm . Smaller microspheres provided more rapid release and higher initial serum NET levels, with a resulting steeper slope of the curve and shorter duration of action. A narrower size range results in flatter release curves more nearly approaching zero order release (Figures 4 and 5). These curves, however, are characterized by a gradual decline in serum NET levels over the treatment period.

The early animal and human studies demonstrated the good potential of the microsphere system; however, it was determined from biodegradation studies that up to 12 months were required for the PLA microspheres to completely biodegrade. Altering the molecular weight of the polymer and reducing the diameter of the microspheres did not significantly change the biodegradation interval.

We became concerned, further, that repeated injections of PLA microspheres at 6-month intervals might allow an undesirable build up of PLA in the muscle tissues at the injection site. Additionally, small amounts of hormone associated with this residual polymer might be released at a later time. We concluded that a PLA excipient that has a 12-month biodegradation time is not optimal for systems designed to provide steroid treatment for 6 months or less. We therefore centered our research efforts on developing a polymer formulation that provides better synchronization between duration of NET release and biodegradation of the polymer.

SECOND GENERATION NET MICROSPHERE FORMULATION

To achieve faster biodegradation, polyglycolic acid (PGA) was incorporated into the polymer. We found that when molar ratios of lactide:glycolide were decreased in step-wise fashion, biodegradation time was reduced proportionately (7, 9). NET microspheres made with the more rapidly biodegrading copolymers were evaluated in baboons to determine the pharmacokinetics of specific copolymer formulations (7). From these studies we selected a copolymer with a lactide:glycolide molar ratio (85:15) that biodegrades in 6 months.

Pharmacokinetic studies in baboons using NET microspheres made from the copolymer poly lactide-co-glycolide (PLGA) resulted in release profiles uniquely characteristic of this formulation. The copolymer formulation produces a biphasic release curve (Figure 6). A diffusional release pattern characterized by decreasing NET levels with time, similar to those previously described for the PLA systems, occurs during the first 10 weeks post-treatment. The duration of this diffusional release phase is variable, depending on formulation. A secondary rise in the serum NET level occurs later during the

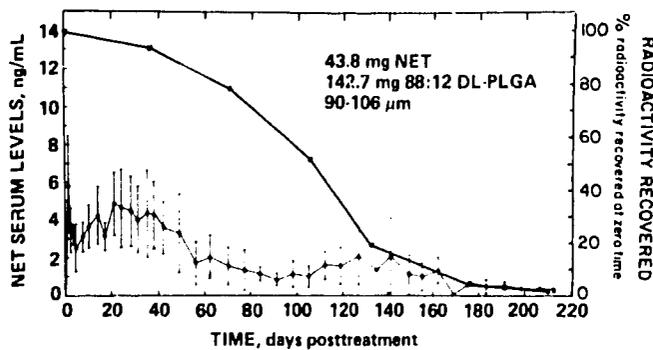


Figure 6. Biodegradation curve of copolymer superimposed on mean serum levels of NET in baboons treated with the copolymer formulation. (Source: Beck LR, Pope VZ, Flowers CE, Cowsar DR, Tice TR, Lewis DH, Dunn RL, Moore AB, Gilley RM: Poly (d,l-lactide-co-glycolide)/norethisterone microcapsules: an injectable biodegradable contraceptive. *Biol Reprod* 28:186, 1983).

treatment interval. This secondary phase corresponds with the period of rapid polymer biodegradation (Figure 6).

We concluded, from the pharmacokinetic studies in baboons, that NET release from copolymer-fabricated microspheres occurs via both diffusion and bioerosion. We anticipated that this dual release mechanism could be exploited to develop formulations having more discrete release intervals, uniform steroid levels, and less “tailing off” of NET release than occur with the PLA formulation.

Following further baboon studies, a master batch of microspheres comprising 22% NET in a copolymer excipient containing 86% to 88% PLA and 14% to 12% PGA respectively was made for use in clinical trials. Five centers participated in a study to evaluate this PLGA-NET microsphere formulation with appropriate characteristics to provide 3 months of continuous NET release. Two microsphere diameter ranges, 63 μm to 90 μm and 90 μm to 106 μm , were evaluated at doses of either 75 mg or 100 mg NET.

The smaller microspheres (63-90 μm) released NET for approximately 20 weeks in ten women treated with two different doses, 75 mg and 100 mg (Group D; Table 1). The release profiles in both groups of women were biphasic (Figure 7). After an initial post-injection peak, serum NET levels gradually declined until about 8 weeks after treatment, when a secondary rise and fall in NET levels occurred between 8 and 20 weeks post-treatment. Ovarian function was suppressed for 3 to 4 months in all subjects who received the full dose of either 75 mg or 100 mg of NET (4, 5).

The serum NET curves of the subjects receiving the two doses were parallel during the initial diffusional release phase, with the 100 mg dose producing proportionately higher serum NET levels. During the biodegradation

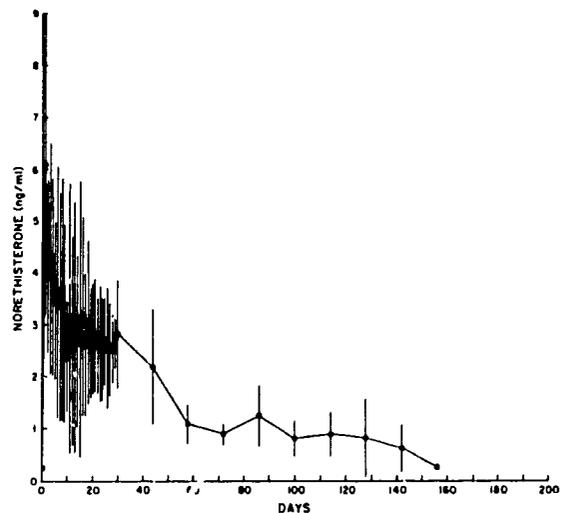


Figure 7. Serum levels of immune-reactive NET in Group D women following IM injection with 75 or 100 mg NET in PLGA microspheres. (Source: Beck LR, Flowers CE Jr, Pope VZ, Tice TR, Dunn RL, Gilley RM: Poly (d,l-lactide-co-glycolide)/norethisterone microcapsules: clinical study. In Zatuchni GI, Goldsmith A, Shelton JD, Sciarra JJ (eds): *Long-Acting Contraceptive Delivery Systems*, pp 407-417. Philadelphia, Harper & Row, 1983).

phase, the curves remained parallel, although the serum NET levels in the subjects receiving the higher dose were only slightly greater (Figure 7).

There were no significant dose-related effects on bleeding patterns in these two groups of women, although the low dose group appeared to have less spotting during the 120- to 140-day interval post-treatment.

Two post-treatment uterine biopsy specimens were obtained from each of these subjects and were evaluated for progestin effects by light microscopy. Small glands, slightly hypertrophic stromal cells, and limited pre-decidual reaction about the arterioles, characteristic progestin responses, were evident in these biopsies. Glands with classical secretory exhaustion, a characteristic response to oral contraceptives, were uncommon. Breakthrough bleeding was attributed to disruption of the integrity of the surface epithelium, which allowed blood to escape into the uterine cavity. Tissue degeneration with leukocytic infiltration was also present. These endometrial changes are typical responses to norethisterone.

The injection efficiencies in this study averaged 90%, reflecting the benefit of careful instruction of the practitioners by technicians experienced in the procedure for injecting the microsphere suspensions, and use of the improved injection vehicle.

Five subjects received the 75 mg NET dose and three received 100 mg NET at a second center participating in

the 3-month Phase I clinical trial of the copolymer formulation (Group E; Table 1). Three subjects were dropped from this study because of difficulty with the injection.

The 100 mg group had only slightly higher serum NET levels than the 75 mg group (Figure 8). No ovulatory progesterone levels (≥ 3 ng/ml) were reported in the 74 to 108 days post-treatment during which blood samples were obtained.

A third center (Group H; Table 1) tested equivalent doses, but used microspheres ranging in diameter from 90 μm to 106 μm . This center had participated in one of the earlier studies, and the experience that had been acquired with the injection protocol was reflected by injection efficiencies ranging from 90% to 99% in all subjects. Ovarian cyclicity was suppressed for an average of 22 weeks following treatment, with the earliest occurrence of ovulatory progesterone levels at 14 weeks post-treatment, and the longest suppression exceeding 26 weeks.

Menstrual alterations were the only side effects reported in this study. Six subjects experienced non-bleeding intervals of greater than 90 days' duration; four of these had over 150 days between bleeding episodes. Three subjects had over 50 days of spotting and/or bleeding in the 189 to 210 day reference period, with a mean of 36 for all subjects. Although bleeding episodes were 5 days or less in half the subjects, four subjects had bleeding episodes exceeding 10 days in length. There appeared to be no relationship between dose and bleeding patterns in these two groups.

Serum NET levels were consistently higher in the subjects who received 100 mg NET (Figure 9) during both release phases, similar to release profiles in subjects at the first two centers. Increasing the diameter of the microspheres

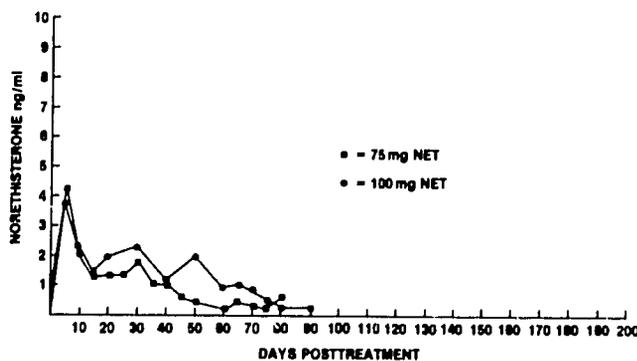


Figure 8. Serum levels of immune-reactive NET in Group E women following IM injection with 75 or 100 mg NET in PLGA microspheres.

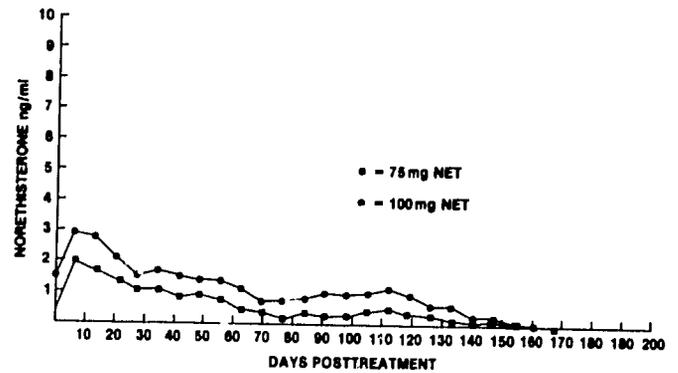


Figure 9. Serum levels of immune-reactive NET in Group H women following IM injection with 75 or 100 mg NET in PLGA microspheres.

did not significantly affect the release profiles, when compared to the subjects who received the 63 μm to 90 μm microspheres.

Composite NET release curves for each dose from the subjects at these three centers (75 mg: n = 14; 100 mg: n = 13) are similar to those found at the individual centers, with the increased number of subjects appearing to minimize peaks and valleys (Figure 10). These release profiles demonstrate the capability of the copolymer system reliably to provide continuous controlled release of contraceptive quantities of NET. This particular formulation consistently released NET for approximately 4 months in women subjects.

The fourth center (Group F; Table 1) experienced poor injection efficiencies resulting from the use of needles having improper bore size for microsphere injection. This

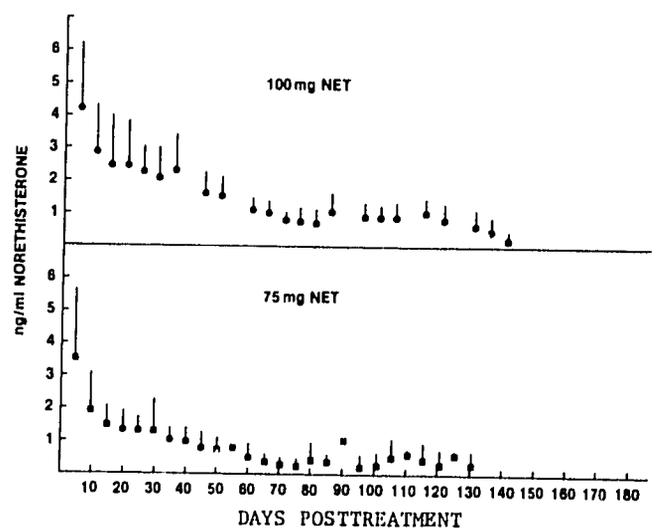


Figure 10. Serum levels of immune-reactive NET in Group D, E and H women following IM injection with 75 or 100 mg NET in PLGA microspheres.

center tested 63 μm to 90 μm diameter microspheres at 75 mg and 100 mg doses. Seven injections were attempted using needles with a bore size smaller than 18-gauge. Three subjects had normal ovulatory cycles following treatment, and two had prolonged first cycles before resuming normal cyclicity. One subject had ovulatory progesterone levels throughout, but lower than normal estradiol peaks and scanty blood flow; and another resumed ovulation the second month post-treatment. Injection efficiencies ranged from 5.7% to 16.5% in these subjects. We concluded from this that minimum needle bore size needed for this formulation was 18-gauge. The remaining three subjects were treated using an 18-gauge needle for injection, and ovulatory progesterone levels were not encountered until 93, 109 and 112 days post-treatment. These three subjects, therefore, had treatment effects similar to those seen following successful injections at the other three centers.

Problems with injection also occurred at the fifth center (Group G; Table 1). The practitioners subjectively estimated that injection efficiency, based on material remaining in the syringes, was between 90% and 100%; but actual doses, determined by measuring residual NET in the syringes, ranged from 31.8% to 95.7% ($n = 8$) of intended doses. Because of the multiple doses resulting from variable injection efficiencies, no attempt was made to group these 10 subjects according to dose. Nine of 10 subjects had ovulatory serum progesterone levels within 102 ± 5 days post-treatment, regardless of dose.

Serum HDL and cholesterol were quantitated before and at the end of the treatment interval in the subjects at four centers ($n = 40$). No significant effects on serum lipid levels were observed following continuous administration of NET for 3 months.

A second clinical study at two centers (Groups I and J; Table 1) was undertaken to further evaluate the effect of microsphere size on pharmacokinetics. For this study, the size range of the microspheres was increased to 125 μm to 212 μm . Two doses were evaluated in 10 subjects at each center. Five subjects at each center received a 75 mg NET dose and five received a 150 mg dose. Nine subjects in Group I were anovulatory for the first 5 months post-treatment. Three subjects who received the 75 mg dose and one who received the 150 mg dose ovulated between the 5th and 6th month post-treatment.

Serum NET profiles in these subjects were biphasic (Figure 11). Increasing the diameter range from 63 μm to 90 μm up to 125 μm to 212 μm shifted the biodegradation phase to the right, effectively extending the duration of action. Serum NET levels gradually declined during the first 10 weeks post-treatment, with the biodegradation phase providing increased NET levels during the 13th through 20th weeks post-treatment.

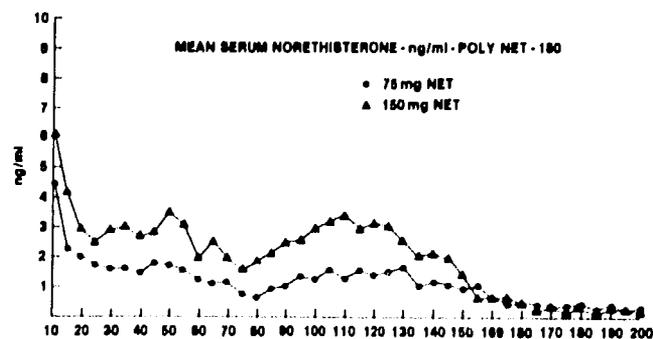


Figure 11. Serum levels of immune-reactive NET in Group I women following IM injection with 75 or 150 mg NET in PLGA microspheres 125-212 μm in diameter.

The total spotting and bleeding days per 30-day period post-treatment ranged from 0 to 29 per patient. Fifteen of 71 periods were amenorrheic, and 19 30-day intervals contained greater than 7 days of spotting and bleeding. Eleven 30-day periods with greater than 7 bleeding or spotting days occurred in the first 3 months post-treatment, three of which were single periods in the 2nd or 3rd months in three patients receiving the 150 mg dose. Eight periods with greater than 7 bleeding or spotting days occurred in the second 90 days post-treatment, three in the low dose group and five in the high dose group. The amenorrheic periods were distributed fairly evenly between the two groups, with one patient in each dose group experiencing 120 days without bleeding, and the other amenorrheic periods randomly distributed among the other subjects.

At the second center (Group J; Table 1), one subject in each group had ovulatory progesterone levels 160 days post-treatment, and the other eight subjects had no progesterone value over 3 ng/ml during the 160- to 175-day sampling interval. Serum NET levels were generally lower than those in subjects at the first center, and a dose-related difference in release profiles was not evident (Figure 12). The reason for this discrepancy between the two centers is most likely due to different injection

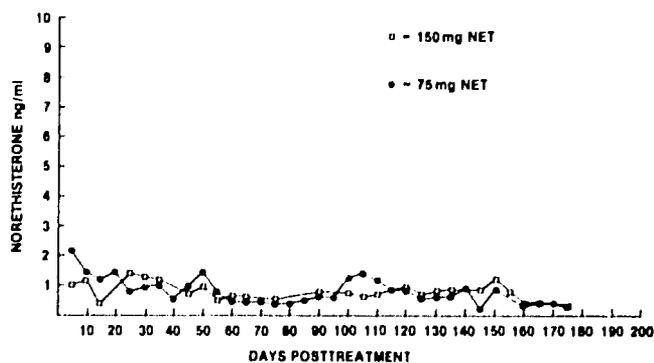


Figure 12. Serum levels of immune-reactive NET in Group J women following IM injection with 75 or 150 mg NET in PLGA microspheres 125-212 μm in diameter.

efficiencies. This has not been confirmed, however, because injection efficiencies were not established at the second center.

As with the 3-month study, serum lipoproteins were unaffected in the women receiving the 6-month NET doses at both centers.

PHASE II STUDIES

We decided, on the basis of the results of the multicenter Phase I clinical study, to initiate a Phase II study (Group K, Table 1) to evaluate the contraceptive efficacy of the copolymer microsphere formulation using a 75 mg dose of microencapsulated NET. Based on past experience, we thought microspheres made of 85% polylactide and 15% polyglycolide, ranging in diameter from 45 μm to 90 μm and containing 20% by weight norethisterone, should provide 3 months of contraceptive protection in women.

A batch of microspheres was prepared according to these specifications using an improved process that results in high quality microspheres. A comparison of the quality of microspheres produced by this process to the earlier process has been previously published (10). Although the microspheres produced by the new process contained the identical polymer and norethisterone concentration, the *in vitro* rate of norethisterone was slower.

Parallel *in vivo* studies in baboons and women demonstrate that the quality of the microspheres significantly affects pharmacokinetics. The serum norethisterone profiles in 14 human subjects treated with microspheres produced by the improved process are shown in Figure 13. Unlike earlier formulations, the serum levels of norethisterone gradually increased for 30 days to 40 days post-treatment. Early fast release, or burst effect, as it is commonly termed, does not occur. One of the subjects in this study became pregnant during the first month

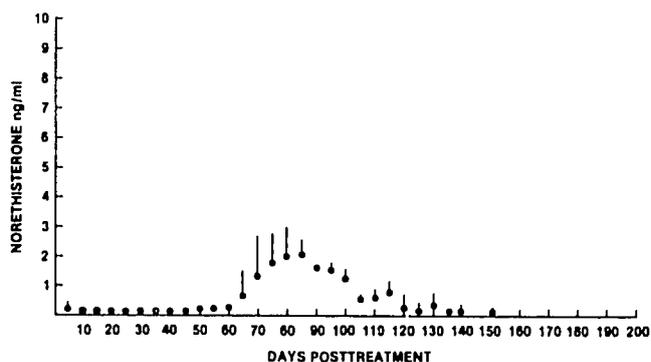


Figure 13. Serum levels of immune-reactive NET in Group K women following IM injection with 75 mg NET.

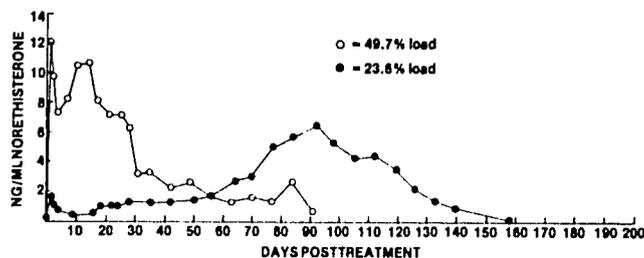


Figure 14. Serum levels of immune-reactive NET in baboons following IM injection with 75 mg NET in 24% loaded or 50% loaded PLGA microspheres.

post-treatment because of the lower than expected serum norethisterone levels. We decided, therefore, to discontinue further studies using this dose and batch of microspheres.

Based on the pharmacokinetic studies in women and baboons, and the results from additional animal experiments, we concluded that the change in the serum norethisterone release was due to better encapsulation of norethisterone in the polymer matrix.

Improvement in the microencapsulation process has reduced the amount of free or unencapsulated norethisterone in a formulation, which in turn reduces the early burst effect characteristic of all the earlier formulations. Better-quality microspheres produced by the improved process provide more precise control of norethisterone release. Although the higher quality microspheres are superior from a controlled release standpoint, they were not suitable for use in the Phase II clinical trial because the initial release rates were too low.

Additional experiments were performed to determine the best way to achieve faster release rates without compromising the improvement that had been gained in the quality of the microspheres. We found that the norethisterone release rate during the first 30 days post-treatment could be significantly accelerated by increasing the concentration of norethisterone in the microspheres.

Figure 14 compares serum norethisterone profiles in baboons treated with the same dose of microencapsulated NET, 75 mg. Formulation A contains 24% by weight norethisterone and formulation B 50%. Both microsphere formulations were prepared by the improved process, yields high quality microspheres.

This experiment clearly demonstrates that the higher norethisterone-loaded microspheres produced substantially faster release rates during the first 30 days post-treatment. Comparative scanning electron micrographic studies show that the two formulations are of equal quality.

We also learned from these experiments that increasing the concentration of norethisterone in the microspheres to 50% substantially improves the injectability of the formulation. This improvement results from a reduction in total mass of the particles to be injected. For example, the weight of microspheres necessary to achieve a 75 mg dose of norethisterone from formulation A is 341 mg, whereas with formulation B only 150 mg is required. We know from the results of the multicenter Phase I study that injectability is a serious problem. The use of more heavily loaded microspheres should solve the injection problem. In addition, we have initiated studies at two different centers to develop an improved injection vehicle and to determine the optimum needle size and syringe design.

Although these studies are still in progress, substantial improvements have been reported, and we feel confident that the injectability problems will be solved prior to initiation of the Phase III studies.

CONCLUSIONS

Evaluation of the course of this research program reveals a number of problems and the importance of well-coordinated pharmacokinetic studies in both animals and human volunteers. The latest norethisterone microsphere formulation being used in expanded Phase II efficacy studies differs substantially from the original prototype system. Improvements have been made in the manufacturing process, pharmacokinetics of the norethisterone microspheres, biodegradation kinetics of the polymer, and the injectability of the formulation.

We have attempted to make improvements in response to the problems as they surfaced during the animal or human studies. This continuum of improvement over a number of years demonstrates the inherent flexibility of this delivery system. The ability to make changes in the performance of the delivery system in response to safety and physiological considerations is highly advantageous.

The applicability of this delivery system for human use was realized by undertaking a number of Phase I studies in which minor changes were made in the dose and composition of the microsphere formulations. Our purpose is to perfect a delivery system for application in women. Although we found the baboon to be an extremely useful and predictive animal model, final evaluation and fine-tuning of the delivery system has been based on the results of the actual clinical trials. As a result, we now have an improved process for the

formulation of norethisterone microspheres that provides a more precise control of release; we have improved the pharmacokinetics of the delivery system by optimizing the drug loading and size distribution of the microspheres, and we have optimized the biodegradation of the delivery system by changing the molar ratios of polylactic and polyglycolic acid.

Finally, we have substantially improved the injectability by improving the vehicle for preparing microsphere suspensions and by increasing the concentration of norethisterone in the microspheres, thereby minimizing the mass of particles to be injected. These improvements bring us to the present state of the art and a formulation that we feel is suitable for use in expanded Phase II studies.

This research program is still in progress, and although we feel we have reached a new point on the continuum of improvements, need for further modifications and improvements may become apparent during the course of the Phase II and III clinical trials.

Looking backward, we see a foundation of polymer and microencapsulation technology developed during this research that supports not only this contraceptive application but a number of other controlled release drug formulations.

Looking forward, we see few remaining obstacles to the eventual approval and wide-scale use of this injectable contraceptive system in both developing and developed countries. We anticipate that additional improvements will come through the use of alternative steroids and/or combinations of different steroids. This will provide better bleeding control, which remains the single most objectionable feature of this long-acting injectable contraceptive. Studies are currently underway to improve the bleeding control by the use of alternative progestogens and/or combinations of estrogens and progestogens.

In presenting this review, we have emphasized the problems we have encountered during the course of this research, because these problems established the need for improvement and the justification for the research. In continuing this research, we expect additional problems and anticipate further improvements.

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