

PDAAT-932
46236

PROGRAM FOR APPLIED RESEARCH
ON FERTILITY REGULATION

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

January 1, 1986 - June 30, 1986

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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REPORT SUMMARY

Project Title and Contract Number:

Program for Applied Research on Fertility Regulation
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
633 Clark Street, Room 1-203
Evanston, Illinois 60201

Contract Period: July 1, 1981 - June 30, 1987

Reporting Period: January 1, 1986 - June 30, 1986

Total Expenditures Through December 31, 1985: \$7,536,176.10

Total Expenditures January 1, 1986 Through June 30, 1986: \$1,136,803.88

Total Expenditures Through December 31, 1985
Immunology Agreement: \$3,285.19

Total Expenditures January 1, 1986 Through June 30, 1986
Immunology Agreement: \$162,214.42

Commitments Through June 30, 1986: \$1,440,665.63

Commitments Through June 30, 1986 Immunology Agreement: \$234,103.95

Total Appropriation 7/1/81-6/30/87: \$10,460,000

Total Appropriation 9/1/85-6/30/87 Immunology Agreement: \$450,000

Total Award 7/1/81-6/30/87: \$12,363,280

PROGRAM ACCOMPLISHMENTS

Scientific Summary

1. Research progress was monitored by review of technical reports and site visits. During this reporting period, the following visits were made by PARFR staff:
 - a. 2/3/86 -- Diane Krier-Morrow, M.B.A.; University Hospital of Jacksonville, Florida (PARFR-386J -- Andrew M. Kaunitz, M.D., Principal Investigator).
 - b. 2/5/86 -- Diane Krier-Morrow, M.B.A.; Mount Sinai Medical Center, Miami Beach, Florida (PARFR-386F -- Jerome J. Hoffman, M.D., Principal Investigator).
 - c. 3/6/86 -- Alfredo Goldsmith, M.D., M.P.H., Diane Krier-Morrow, M.B.A.; University of Texas Health Science Center, San Antonio, Texas (PARFR-337T, 347, 361, 364, 387T -- Ricardo H. Asch, M.D.).
 - d. 3/10/86 -- Alfredo Goldsmith, M.D., M.P.H.; Cornell University, New York, New York (PARFR-387N -- Mukul Singh, M.D., Clinical Investigator).
 - e. 3/17/86 -- Dr. Alfredo Goldsmith met with Lynda Cole and Al Siemens at Family Health International in Research Triangle Park, North Carolina on the Poly NET 90 Studies.
 - f. 3/18/86 -- Alfredo Goldsmith, M.D., M.P.H., Dr. Ramirez; Mount Sinai Medical Center, Miami Beach, Florida (PARFR-386F -- Jerome J. Hoffman, M.D., Principal Investigator).
 - g. 3/18/86 -- Alfredo Goldsmith, M.D., M.P.H.; University Hospital of Jacksonville, Florida (PARFR-386J -- Andrew M. Kaunitz, M.D.).
 - h. 4/2-3/86 -- Alfredo Goldsmith, M.D., M.P.H.; Mexico (PARFR-336M and 388M -- Roberto Rivera, M.D., Principal Investigator).
 - i. 4/6-9/86 -- Alfredo Goldsmith, M.D., M.P.H.; Associazione per Studio della Riproduzione Umana, Rome, Italy (PARFR-386I -- Giuseppe Benagiano, M.D., Principal Investigator).
 - j. 4/22/86 -- Alfredo Goldsmith, M.D., M.P.H.; Instituto Chileno de Medicina Reproductiva, Santiago, Chile (PARFR-386C -- Horacio B. Croxatto, M.D., Principal Investigator).
2. Drs. J.J. Sciarra, Alfredo Goldsmith, and Gerald Zatuchni and Diane Krier-Morrow had an AID debriefing of the November, 1985 AID Evaluation of PARFR (site visit) by Linda E. Atkinson, Ph.D. and Duff Gillespie, Ph.D., Deputy Director, AID Research Division, Office of Population, at the PARFR Office on January 13, 1986.
3. Dr. Alfredo Goldsmith and Diane Krier-Morrow attended a meeting at Family Health International in Research Triangle Park, North Carolina on January 20, 1986 regarding the Poly NET 90 Study.

Scientific Summary (cont'd)

4. Dr. Gerald Zatuchni and Diane Krier-Morrow attended an AID Cooperating Agency Meeting in Washington, D.C. on January 16, 1986.
5. Dr. Gerald Zatuchni taught a post-graduate course at the University of New Mexico in Albuquerque, New Mexico on February 17, 1986.
6. Drs. J.J. Sciarra and Gerald Zatuchni represented PARFR at a WHO Meeting (immunocontraception) in Washington, D.C. on March 2-4, 1986.
7. Diane Krier-Morrow and Dr. Gerald Zatuchni participated in a meeting of the committee regarding the Contraceptive Development - Reproductive Immunology Program in Washington, D.C. on March 3, 1986.
8. Dr. Gerald Zatuchni taught a post-graduate course in Albuquerque, New Mexico on April 2-4, 1986.
9. Drs. Alfredo Goldsmith, Erwin Goldberg and Jose Balmaceda represented PARFR at an ALIRH meeting in Vina Del Mar, Chile on April 27 - May 1, 1986 and presented several papers.
10. Drs. Alfredo Goldsmith, L.J.D. Zaneveld and Donald P. Waller represented PARFR at a meeting with FDA officials in Maryland on May 12, 1986 regarding the Sperm Acrosin IND and Shug IDE status.
11. Dr. Alfredo Goldsmith met with Dr. James Shelton and Jeffrey Spieler at AID/Washington on June 12, 1986 to discuss progress of Poly NET 90 Studies and prepare Agenda for the September 8, 1986 Meeting.

PROGRAM ACCOMPLISHMENTS

LDC Involvement

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

1. PARFR-386C -- "Phase II Poly NET 90 Injectable Study"
Horacio B. Croxatto, M.D., Instituto Chileno de Medicina Reproductiva,
Santiago, Chile
2. PARFR-386M -- "Phase II Poly NET 90 Injectable Study"
Roberto Rivera, M.D., Instituto de Investigacion Cientifica,
Durango, Mexico
3. PARFR-388M -- "Phase I Poly NET 30 Injectable Study"
Roberto Rivera, M.D., Instituto de Investigacion Cientifica,
Durango, Mexico
4. PARFR-389 -- "Insertion Technique of a Reversible Vas Deferens Occlusive Device"
Marcos Paulo P. de Castro, M.D., PROPATER: Promocao da Paternidade Responsavel",
Sao Paulo, Brazil

Additional funding and an extension for the following subagreement was executed:

1. PARFR-388M -- "Phase I Poly NET 30 Injectable Study"
Roberto Rivera, M.D., Instituto de Investigacion Cientifica,
Durango, Mexico

The following subagreement terminated during this reporting period:

1. PARFR-389 -- "Insertion Technique of a Reversible Vas Deferens Occlusive Device"
Marcos Paulo P. de Castro, M.D., PROPATER: Promocao da Paternidade Responsavel",
Sao Paulo, Brazil

LDC Research Funds

As of June 30, 1986, 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	\$ 9,900.00
<u>BRASIL</u>		
PARFR-318B	14,982	14,701.49
PARFR-328B	14,122	10,792.00
PARFR-389	<u>1,795</u>	<u>1,795.00</u>
TOTAL BRASIL:	\$ 30,899	\$ 27,288.49
<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	20,880.00
PARFR-341C	45,419	10,811.00
PARFR-386C	<u>25,036</u>	<u>4,030.00</u>
TOTAL CHILE:	\$166,811	\$111,197.00
<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	2,564.20
<u>MEXICO</u>		
PARFR-300M	23,056	23,056.00
PARFR-330M	28,710	28,410.00
PARFR-341M	36,135	3,326.00
PARFR-386M	25,762	3,507.00
PARFR-388M	<u>53,064</u>	<u>- 0 -</u>
TOTAL MEXICO:	\$166,727	\$ 58,299.00
<u>THAILAND</u>		
PARFR-354	9,800	9,633.61
<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:	\$453,953	\$278,367.63

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. Administering the Contraceptive Development - Reproductive Immunology Program with the National Institute of Immunology, New Delhi, India.
3. Negotiating and executing:
 - 16 New Subagreements: 385, 386C, 386I, 386J, 386M, 387P, 387T, 388M, 389, 391, CD-RI-005, CD-RI-006, CD-RI-007, CD-RI-008a, CD-RI-008b, CD-RI-008c
 - 5 No-Cost Extension Amendments: 378, 382, 383, 388M, CD-RI-005
 - 11 Additional Funding/Extension Amendments: 309, 309a, 315, 338, 339, 339UI, 363, 375, 385, CD-RI-001, CD-RI-002
 - 2 Additional Funding Amendments: 360, 388M

1/1/86 - 6/30/86

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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	Extension/ Additional Funding (Amendment #7)	1/1/82- 6/30/86	\$ 37,419 (\$300,112 total)
309a	"Toxicity Studies of Anordrin" Donald P. Waller, Ph.D. The University of Illinois at Chicago Chicago, Illinois	Extension/ Additional Funding (Amendment #1)	7/1/85- 6/30/86	\$ 5,437 (\$93,313 total)
315	"Immunologic Suppression of Fertility by Synthetic Antigenic Determinants of LDH-C4" Erwin Goldberg, Ph.D. Northwestern University Evanston, Illinois	Extension/ Additional Funding (Amendment #6)	3/1/82- 9/30/86	\$ 36,017 (\$446,995 total)
338	"Development of Sperm Enzyme Inhibitors as Vaginal Contraceptives" Lourens J.D. Zaneveld, D.V.M., Ph.D. Rush-Presbyterian-St. Luke's Medical Center Chicago, Illinois	Extension/ Additional Funding (Amendment #2)	7/1/83- 6/30/87	\$ 38,981 (\$199,931 total)
339	"SHUG Device Studies" Lourens J.D. Zaneveld, D.V.M., Ph.D. Rush-Presbyterian-St. Luke's Medical Center Chicago, Illinois	Extension/ Additional Funding (Amendment #3)	7/1/83- 6/30/87	\$ 15,087 (\$71,073 total)
339UI	"Toxicology of Silicone Implanted (SHUG) in the Vas Deferens" Donald P. Waller, Ph.D. The University of Illinois at Chicago Chicago, Illinois	Extension/ Additional Funding (Amendment #2)	7/1/84- 6/30/86	\$ 35,943 (\$91,723 total)

1/1/86 - 6/30/86

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Subagreement Negotiations

PROJECT #	TITLE/INVESTIGATOR/INSTITUTION	ACTION	PERIOD	FUNDING
355	"Enhancement of the Secretary Immune Response to LDH-C ₄ " Nancy J. Alexander, Ph.D. Medical Research Foundation of Oregon Portland, Oregon	No-cost Extension (Amendment #3)	4/15/84- 12/31/86	
360	"Inter- and Intra-Cycle Variation of Genital Peroxidases in Women" John C.M. Tsibris, Ph.D. The University of Illinois at Chicago Chicago, Illinois	Additional Funding (Amendment #2)	7/1/84- 6/30/86	\$ 5,750 (\$86,823 total)
363	"Laboratory Studies on an Antispermatogenic Agent - THP for Control of Male Fertility" John P. Wiebe, Ph.D. University of Western Ontario London, Ontario, Canada	Extension/ Additional Funding (Amendment #1)	10/1/84 12/31/86	\$ 6,500 (\$96,500 total)
375	"Baboon Immunologic Evaluation with LDH-C ₄ and <u>In Vitro</u> Fertilization Studies in Rodents" Kenneth S.K. Tung, M.D. University of New Mexico Albuquerque, New Mexico	Extension/ Additional Funding (Amendment #2)	5/1/85- 6/30/86	\$ 28,653 (\$46,588 total)
378	"Preparation of Testosterone Microspheres" Danny H. Lewis, Ph.D. Stolle Research & Development Corp. Lebanon, Ohio	No-cost Extension (Amendment #1)	7/1/85 6/30/86	
382	"Postcoital Effectiveness of the Vaginal Spermicidal Barrier" Gerald S. Bernstein, Ph.D., M.D. Professional Staff Association, Los Angeles County, University of Southern California Medical Center Los Angeles, California	No-cost Extension (Amendment #1)	12/1/85- 6/30/86	

1/1/86 - 6/30/86

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Subagreement Negotiations

PROJECT #	TITLE/INVESTIGATOR/INSTITUTION	ACTION	PERIOD	FUNDING
383	"Postcoital Tests: Disposable Minidiaphragm" Milos Chvapil, M.D., Ph.D., D.Sc. Bio-Products, Inc. Tucson, Arizona	No-cost Extension (Amendment #1)	10/1/85- 11/30/86	
385	"Toxicity Study of an Iodine Transcervical Sterilization Medium" Donald P. Waller, P.D. The Board of Trustess of The University of Illinois Chicago, Illinois	New Subagreement ----- Extension/ Additional Funding (Amendment #1)	11/1/85- 3/31/86 11/1/85- 6/30/86	\$ 46,577 \$ 978 (\$47,555 total)
386C	"Phase II Poly NET 90 Injectable Study" Horacio B. Croxatto, M.D. Instituto Chileno de Medicina Reproductiva Santiago, Chile	New Subagreement	12/1/85- 5/31/87	\$ 25,036
386I	"Phase II Poly NET 90 Injectable Study" Giuseppe Benagiano, M.D. Associazione per Studio della Riproduzione Umana Rome, Italy	New Subagreement	12/1/85- 5/31/87	\$ 25,190
386J	"Phase II Poly NET 90 Injectable Study" Andrew M. Kaunitz, M.D. University Hospital of Jacksonville Jacksonville, Florida	New Subagreement	12/1/85- 5/31/87	\$ 34,822
386M	"Phase II Poly NET 90 Injectable Study" Roberto Rivera, M.D. Instituto de Investigacion Cientifica Durango, Durango, Mexico	New Subagreement	12/1/85- 5/31/87	\$ 25,762

1/1/86 - 6/30/86

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Subagreement Negotiations

PROJECT #	TITLE/INVESTIGATOR/INSTITUTION	ACTION	PERIOD	FUNDING
387P	"Phase II Poly NET 90 Injectable Study - Pharmacokinetics" David Archer, M.D. Magee Women's Hospital Pittsburgh, Pennsylvania	New Subagreement	12/1/85- 11/30/86	\$ 95,951
387T	"Phase I Poly NET 90 Injectable Study - Pharmacokinetics" Jose P. Balmaceda, M.D. The University of Texas Health Science Center San Antonio, Texas	New Subagreement	12/1/85- 11/30/86	\$ 99,241
388M	"Phase I Poly NET 30 Injectable Study" Roberto Rivera, M.D. Instituto de Investigacion Cientifica Durango, Durango, Mexico	New Subagreement ----- No-cost Extension (Amendment #1) ----- Additional Funding (Amendment #2)	1/1/86- 10/31/86 3/1/86- 12/31/86	\$ 46,464 \$ 6,600 (\$53,064 total)
389	"Insertion Technique of a Reversible Vas Deferens Occlusive Device" Marcos Paulo P. de Castro, M.D. PROPATER: "Promocao da Paternidade Responsavel Sao Paulo, Brazil	New Subagreement	1/18/86- 1/28/86	\$ 1,760
391	"Phase I Progesterone Microcapsules" Robert W. Rebar, M.D. Northwestern University Chicago, Illinois	New Subagreement	1/1/86- 12/31/86	\$ 69,352 (\$35,000 approved through 6/30/86)
CD-RI-001	"Training and Collaboration in Molecular Biology" William W. Chin, M.D. Joslin Diabetes Center Boston, Massachusetts	Extension/ Additional Funding (Amendment #1)	10/1/85- 6/30/86	\$ 13,257 (\$37,611 total)

1/1/86 - 6/30/86

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Subagreement Negotiations

PROJECT #	TITLE/INVESTIGATOR/INSTITUTION	ACTION	PERIOD	FUNDING
CD-RI-002	"Training and Collaboration in Bovine and Murine <u>In Vitro</u> Fertilization and Gamete Culture" Neal L. First, Ph.D. University of Wisconsin - Madison Madison, Wisconsin	Extension/ Additional Funding (Amendment #1)	10/21/85- 3/31/86	\$ 559 (\$7,292 total)
CD-RI-005	"Training and Collaboration in Immunocontraception" Deborah Anderson, Ph.D. Brigham and Women's Hospital Boston, Massachusetts	New Subagreement ----- No-cost Extension (Amendment #1)	3/10/86- 5/9/86 4/27/86- 6/30/86	\$ 7,884
CD-RI-006	"Training and Collaboration in Immunocontraception" Anthony G. Sacco, Ph.D. Wayne State University Detroit, Michigan	New Subagreement	7/1/86- 11/30/86	\$ 15,713
CD-RI-007	"Training and Collaboration in Immunocontraception" Erwin Goldberg, Ph.D. Northwestern University Evanston, Illinois	New Subagreement	7/14/86- 9/13/86	\$ 17,927
CD-RI-008a	"Equipment for India Project" G.P. Talwar National Institute of Immunology New Delhi, India	Purchase Order		\$ 22,737.90
CD-RI-008b	"Equipment for India Project" G.P. Talwar National Institute of Immunology New Delhi, India	Purchase Order		\$ 15,976.57
CD-RI-008c	"Equipment for India Project" G.P. Talwar National Institute of Immunology New Delhi, India	Purchase Order		\$ 13,912.38

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	\$ 3,397.02
Gerald I. Zatuchni, M.D., M.Sc. Director of Technical Assistance	5.1	28,844.52
Alfredo Goldsmith, M.D., M.P.H. Head, Research Project Development	5.7	32,241.48
Diane Krier-Morrow, M.B.A. Director of Administration	6.0	18,073.02
Mary Nemeth Project Controller	6.0	8,925.00
Kelley Osborn Publications Coordinator	0.6	1,695.00
Ruvenia Thomas Secretary II	6.0	12,286.68
Asenath Williamson Secretary I	6.0	8,473.67
Josephine Harris Secretary I	6.0	8,478.45
<u>Fringe Benefits</u>		\$ 24,388.64
<u>Indirect Costs</u>		\$108,364.09

CONSULTANTS

The following is a list of Program Consultants, indicating their areas of expertise, contributions to the program, and payment thereof.

<u>Consultant</u>	<u>Purpose</u>	<u>Effort</u>	<u>Fee</u>
David A. Edelman, Ph.D. Biostatistician	Consultant Services 10/3-12/23/85	13 days	\$ 3,055.00
	Consultant Services 1/28-3/29/86	8.5 days	1,997.50
Forrest C. Greenslade, Ph.D.	Consultant Services 1/27-2/20/86	3 days	753.81
	Consultant Services 3/1-31/86	1 day	251.27
Alan E.C. Holden	Consultant Services 8/3/85-3/1/86	7 days	700.00
Danny H. Lewis, Ph.D.	IND Preparation Nov.-Dec., 1985	19 days	3,800.00
	IND Preparation Jan.-March, 1986	21 days	4,200.00
Patricia A. O'Hern	Consultant Services 5/5-7/86	3 days	330.00
Timothy Parmley, Ph.D.	Consultant Services 1/26-30/86	5 days	1,306.50
Denise T. Resnik	Consultant Services 1/27-2/20/86	4.5 days	1,012.50
	Consultant Services 3/1-31/86	6 days	1,350.00
John F. Williford Product Development Specialist	Consultant Services 5/5-7/86	3 days	649.65
Lourens J.D. Zaneveld, D.V.M., Ph.D.	Consultant Services 8/18/85-4/29/86	28 days	5,600.00
		TOTAL	<u>\$25,006.23</u>

EXPENDITURES UNDER AID/DPE-0546-A-00-1003-00
DURING THE PERIOD 1/1/86-6/30/86

<u>Category</u>	<u>Expended 7/1/81-12/31/85</u>	<u>Expended 1/1/86-6/30/86</u>	<u>Total Expended 7/1/81-6/30/86</u>
<u>Research</u>	\$4,124,486.83	\$ 668,315.01	\$4,792,801.84
<u>Workshops & Publications</u>	396,569.47	54,885.06	451,454.53
<u>Consultants</u>	117,040.85	28,235.04	145,275.89
<u>Travel</u>	426,038.55	38,740.36	464,778.91
<u>Salaries & Fringe Benefits</u>	1,132,105.30	148,814.68	1,280,919.98
<u>Supplies, Communications and Rent</u>	535,641.22	89,449.64	625,090.86
<u>Equipment</u>	12,511.35	- 0 -	12,511.35
<u>Indirect Costs</u>	791,782.53	108,364.09	900,146.62
TOTAL:	<u>\$7,536,176.10</u>	<u>\$1,136,803.88</u>	<u>\$8,672,979.98</u>

DETAIL OF EXPENDITURES AND COMMITMENTS UNDER AID/DPE-0546-A-00-1003-00,
EFFECTIVE 7/1/81-6/30/87

TOTAL AWARD: \$12,363,280

TOTAL APPROPRIATION TO DATE: \$10,460,000

Category	Budget Appropriation	%	7/1/81 - 6/30/86		
			Expenditures	Commitments	Total
<u>Research</u>	\$ 6,458,803	61.8	\$4,792,801.84	\$1,391,523.99	\$ 6,184,325.83
<u>Workshops and Publications</u>	451,456	4.3	451,454.53	- 0 -	451,454.53
<u>Consultants</u>	146,109	1.4	145,275.89	- 0 -	145,275.89
<u>Travel</u>	475,584	4.6	464,778.91	296.09	465,075.00
<u>Salaries and Fringe Benefits</u>	1,278,443	12.2	1,280,919.98	- 0 -	1,280,919.98
<u>Supplies, Communi- cations and Rent</u>	684,163	6.5	625,090.86	11,362.05	636,452.91
<u>Equipment</u>	12,512	.1	12,511.35	- 0 -	12,511.35
<u>Indirect Costs</u>	952,930	9.1	900,146.62	37,483.50	937,630.12
	<u>\$10,460,000</u>		<u>\$8,672,979.98</u>	<u>\$1,440,665.63*</u>	<u>\$10,113,645.61</u>

* This figure includes known commitments as of 6/30/86. In addition, anticipated commitments to 6/30/87 for Research and Administrative Costs are estimated at \$641,127.14.

EXPENDITURES UNDER THE PARFR INDO-US IMMUNOLOGY AGREEMENT
 DURING THE PERIOD 1/1/86-6/30/86
 AID/DPE-0546-A-00-1003-00

<u>Category</u>	Expended <u>9/1/85-12/31/85</u>	Expended <u>1/1/86-6/30/86</u>	Total Expended <u>9/1/85-6/30/86</u>
<u>Indirect Costs</u>	\$ 657.04	\$ 9,594.72	\$ 10,251.76
<u>Supplies</u>	2,400.00	13,392.27	15,792.27
<u>Equipment</u>	- 0 -	97,637.49	97,637.49
<u>Travel</u>	228.15	12,491.86	12,720.01
<u>Subagreements</u>	- 0 -	29,098.08	29,098.08
TOTAL:	<u>\$3,285.19</u>	<u>\$162,214.42</u>	<u>\$165,499.61</u>

DETAIL OF EXPENDITURES AND COMMITMENTS UNDER THE PARFR INDO-US IMMUNOLOGY AGREEMENT
 AID/DPE-0546-A-00-1003-00
 EFFECTIVE 9/1/85-6/30/87

TOTAL AWARD: \$450,000

TOTAL APPROPRIATION TO DATE: \$450,000

Category	Budget Appropriation	%	9/1/85 - 6/30/86		
			Expenditures	Commitments	Total
<u>Indirect Costs</u>	\$ 31,200	7.0	\$ 10,251.76	\$ 12,460.79	\$ 22,712.55
<u>Supplies</u>	60,000	13.3	15,792.27	31,592.69	47,384.96
<u>Equipment</u>	232,800	51.7	97,637.49	125,629.55	223,267.04
<u>Travel</u>	26,000	5.8	12,720.01	7,092.00	19,812.01
<u>Subagreements</u>	100,000	22.2	29,098.08	57,328.92	86,427.00
TOTAL:	<u>\$450,000</u>		<u>\$165,499.61</u>	<u>\$234,103.95</u>	<u>\$399,603.56</u>

RESEARCH

PARFR SUBAGREEMENT EXPENSE SUMMARIES

This section summarizes the expenses of PARFR subagreements active during the period January 1, 1986 to June 30, 1986. Summaries are categorized according to the following AID Contraceptive Research Areas:

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

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

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>
385	University of Illinois Chicago, Illinois Donald P. Waller, Ph.D.	"Toxicity Study of an Iodine Transcervical Sterilization Medium"	11/1/85- 6/30/86	\$ 47,555	\$ - 0 -	\$ - 0 -
D-72	BioNexus, Inc. Raleigh, North Carolina	Supplies for Iodine Toxicology Study (PARFR-385)		\$ 3,000	3,011.00	3,011.00

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

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>
376	Maine Medical Center Portland, Maine C. Irving Meeker, M.D.	"Pre-IDE Studies - Tubal Clip"	5/1/85- 4/30/86	\$ 29,774	\$ 20,533.42	\$ 29,774.00

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

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.	"SHUG Device Studies"	7/1/83- 6/30/87	\$ 71,073	\$ 8,137.51	\$46,005.00
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- 6/30/86	91,723	64,860.78	72,657.95
389	PROPATER: "Promocao da Paternidade Responsavel" Sao Paulo, Brazil Marcos Paulo P. de Castro, M.D.	"Insertion Technique of a Reversible Vas Deferens Occlusive Device"	1/18/86- 1/28/86	1,795	1,795.00	1,795.00

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

II. MALE STERILIZATION (continued)

C. 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	\$18,277.04	\$88,718.30
380	Rush-Presbyterian-St. Luke's Medical Center Chicago, Illinois Lourens J.D. Zaneveld D.V.M., Ph.D.	"Preliminary Evaluation of 3-M Impression Material as an Injectable Vas Occlusive Device"	8/1/85- 4/30/86	10,832	6,936.86	9,357.44

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

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>
337T	The University of Texas Health Science Center San Antonio, Texas Rochelle N. Shain, Ph.D.	"Intracervical Device Acceptability Study"	6/1/83- 6/30/86	\$ 12,502	\$ 686.81	\$10,009.17

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

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- 6/30/86	\$300,112	\$ 49,418.03	\$216,580.17
309b	Hazleton Laboratories America, Inc. Vienna, Virginia Sandra L. Morseth, Ph.D.	"Teratology of Anordrin"	1/1/86- 6/30/86	52,400	(14,000.00)	- 0 -
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	- 0 -	43,972.33
368	Biotek, Inc. Woburn, Massachusetts E.S. Nuwayser, Ph.D.	"NIH/Biotek Levonorgestrel Microcapsules"	2/1/85- 1/31/86	80,496.56	14,221.52	80,496.56
373	Stolle Research and Development Corporation Cincinnati, Ohio Danny H. Lewis, Ph.D.	"90-Day Levonorgestrel Microspheres"	4/1/85- 3/31/86	67,404	11,234.00	56,170.00
386A	Emory University Atlanta, Georgia Howard J. Tatum, M.D.	"Phase II Poly NET 90 Injectable Study"	12/1/85- 5/31/87	49,542	2,657.16	2,657.16

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

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>
386C	Instituto Chileno de Medicina Reproductiva Santiago, Chile Horacio B. Croxatto, M.D.	"Phase II Poly NET 90 Injectable Study"	12/1/85- 5/31/87	25,036	4,030.00	4,030.00
386F	Mount Sinai Medical Center of Greater Miami Miami Beach, Florida Jerome J. Hoffman, M.D.	"Phase II Poly NET 90 Injectable Study"	12/1/85- 5/31/87	\$ 52,549	\$ 10,271.82	\$ 10,271.82
386I	Associazione per Studio della Riproduzione Umana Rome, Italy Giuseppe Benagiano, M.D.	"Phase II Poly NET 90 Injectable Study"	12/1/85- 5/31/87	25,190	3,335.00	3,335.00
386J	University Hospital of Jacksonville Jacksonville, Florida Andrew M. Kaunitz, M.D.	"Phase II Poly NET 90 Injectable Study"	12/1/85- 5/31/87	34,822	5,249.67	5,249.67
386M	Instituto de Investigacion Cientifica Durango, Durango, Mexico Roberto Rivera, M.D.	"Phase II Poly NET 90 Injectable Study"	12/1/85- 5/31/87	25,762	3,507.00	3,507.00
387N	Cornell University Medical College New York, New York Brij B. Saxena, Ph.D., D.Sc.	"Phase II Poly NET 90 Injectable Study - Pharmacokinetics"	12/1/85- 11/30/86	99,532	13,578.54	13,578.54

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

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>
387P	Magee Women's Hospital Pittsburgh, Pennsylvania David Archer, M.D.	"Phase II Poly NET 90 Injectable Study - Pharmacokinetics"	12/1/85- 11/30/86	95,951	15,755.63	15,755.63
387T	University of Texas Health Science Center San Antonio, Texas Jose P. Balmaceda, M.D.	"Phase I Poly NET 90 Study - Pharmacokinetics"	12/1/85- 11/30/86	\$ 99,241	\$ - 0 -	\$ - 0 -
388	Stolle Research and Development Corp. Cincinnati, Ohio Danny H. Lewis, Ph.D.	"Preparation and Characteri- zation of Poly NET 30 Microcapsules for Phase I Clinical Study"	11/1/85- 3/31/86	29,307	17,583.00	17,583.00
388M	Instituto de Investigacion Cientifica Durango, Durango, Mexico Roberto Rivera, M.D.	"Phase I Poly NET 30 Injectable Study - Pharmacokinetics"	3/1/86- 12/31/86	53,064	- 0 -	- 0 -
391	Northwestern University Chicago, Illinois Robert W. Rebar, M.D.	"Phase I Progesterone Microcapsule Clinical Trial"	1/1/86- 12/31/86	69,352	- 0 -	- 0 -
D-69	American Scientific Products McGaw Park, Illinois Sarstedt, Inc. Princeton, New Jersey	Plastic containers and stoppers and serum separating tubes for use in the Poly NET 90 studies		1,370.28	91.40	1,370.28

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

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-70	Serono Diagnostic, Inc. Braintree, Massachusetts Vira Chemicals, Inc. Miami, Florida	Estradiol Direct and Progesterone Direct RIA Kits for use in the Poly NET 90 studies		22,005.50	8,563.40	19,883.90
D-71	Scientific Supply Co. Schiller Park, Illinois	Pregnancy tests and vial viewers for use in the Poly NET 90 studies		\$ 2,415.65	\$ 1,779.95	\$ 2,415.65
D-74	Stolle Research and Development Corp. Lebanon, Ohio	3200 Assays relating to the Poly NET 90 Studies		32,000	670.00	670.00
D-75	University of South Alabama Mobile, Alabama	Analysis of Endometrial Biopsies via LM, TEM and SEM relating to the Poly NET 90 Studies		46,800	22,620.00	22,620.00

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

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>
309a	The University of Illinois at Chicago Chicago, Illinois Donald P. Waller, Ph.D.	"Toxicity Studies of Anordrin"	7/1/85- 6/30/86	\$ 93,313	\$ 50,346.21	\$ 50,346.21
361	The University of Texas Health Science Center San Antonio, Texas Ricardo H. Asch, M.D.	"Testosterone Microcapsule Formulation Study"	7/1/84- 6/30/86	122,106	- 0 -	106,839.85
378	Stolle Research and Development Corp. Cincinnati, Ohio Danny H. Lewis, Ph.D.	"Preparation of Testosterone Microspheres"	7/1/85- 6/30/86	39,233	- 0 -	32,694.15

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

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	\$ 6,393.90	\$ 86,706.69
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 -	30,496.64

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

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- 6/30/87	\$199,931	\$ 22,356.80	\$122,294.11
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	- 0 -	55,512.11
371	Eastowne Ob-Gyn and Infertility Chapel Hill, North Carolina James R. Dingfelder, M.D.	"Vaginal Spermicidal Barrier (VSB) Postcoital Tests"	4/1/85- 6/30/86	15,598	2,227.50	2,227.50
382	Professional Staff Association Los Angeles, California Gerald S. Bernstein, Ph.D., M.D.	"Postcoital Effectiveness of the Vaginal Spermicidal Barrier"	10/1/85- 5/31/86	5,984	852.87	852.87
383	Bio-Products, Inc. Tucson, Arizona Milos Chvapil, M.D., Ph.D., D.Sc.	"Postcoital Test: Disposable Minidiaphragm"	10/1/85- 5/31/86	12,512	- 0 -	- 0 -

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

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- 9/30/86	\$446,995	\$121,253.64	\$363,542.07
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- 6/30/86	99,794	27,121.08	86,844.70
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- 6/30/86	99,931	34,012.76	87,157.28
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- 5/31/86	144,256	11,467.93	97,548.56
375	University of New Mexico Albuquerque, New Mexico Kenneth S.K. Tung, M.D.	"Baboon Immunologic Evaluation with LDH-C ₄ and <i>In Vitro</i> Fertilization Studies in Rodents"	5/1/85- 6/30/86	46,588	13,941.72	21,640.59
379	Duke University Medical Center Durham, North Carolina Christopher P. Carron, Ph.D.	"Idiotope Vaccine for Sperm- Targeted Immunocontraception"	8/1/85- 6/30/86	58,391	29,302.72	40,282.28

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

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>
384	The Ohio State University Research Foundation Columbus, Ohio Vernon C. Stevens, Ph.D.	"Effects of Immunization of Female Baboons with Zona Pellucida Antigens on Ovarian Functions"	7/1/85- 4/30/86	\$ 27,080	\$ 11,313.57	\$ 11,313.57

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

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>
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- vascular Injection of BCG (Bacillus Calmette Guerin)"	10/1/84- 3/31/86	\$ 5,302	\$ 788.16	\$ 2,564.20

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

IX. IMMUNOCONTRACEPTION (continued)

C. 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>
CD-RI-001	Joslin Diabetes Center Boston, Massachusetts William W. Chin, M.D.	"Training and Collaboration in Molecular Biology"	10/1/85- 6/30/86	\$ 37,611	\$ 23,809.08	\$ 26,968.08
CD-RI-002	University of Wisconsin - Madison Madison, Wisconsin Neal L. First, Ph.D.	"Training and Collaboration in Bovine and Murine <u>In Vitro</u> Fertilization and Gamete Culture"	10/21/85- 3/31/86	7,292	2,130.00	2,130.00
CD-RI-004a	C. Reichert Optische Werks c/o Toshniwal Brothers (Delhi) Private, Ltd. New Delhi, India G.P. Talwar	"Equipment for India Project"		18,971.83	- 0 -	- 0 -
CD-RI-004b	General Electric Company Milwaukee, Wisconsin G.P. Talwar	"Equipment for India Project"		50,150	50,150.00	50,150.00
CD-RI-004c	Jeol Ltd. c/o Toshniwal Brothers (Delhi) Private, Ltd. New Delhi, India G.P. Talwar	"Equipment for India Project"		72,679.36	- 0 -	- 0 -
CD-RI-005	Brigham and Women's Hosp. Boston, Massachusetts Deborah J. Anderson, Ph.D.	"Training and Collaboration in Immunocontraception"	4/27/86 6/30/86	7,884	- 0 -	- 0 -

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

IX. IMMUNOCONTRACEPTION (continued)

C. OTHER (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>
CD-RI-006	Wayne State University Detroit, Michigan Anthony G. Sacco, Ph.D.	"Training and Collaboration in Immunocontraception"	7/1/86- 11/30/86	\$ 15,713	\$ - 0 -	\$ - 0 -
CD-RI-007	Northwestern University Evanston, Illinois Erwin Goldberg, Ph.D.	"Training and Collaboration in Immunocontraception"	7/14/86- 9/13/86	17,927	- 0 -	- 0 -
CD-RI-008a	Polysciences, Inc. Warrington, Pennsylvania G.P. Talwar	"Equipment for India Project"		22,737.90	- 0 -	- 0 -
CD-RI-008b	Bio-Rad Watford Hertfordshire, England G.P. Talwar	"Equipment for India Project"		15,976.57	- 0 -	- 0 -
CD-RI-008c	Reichert Jung Heidelberger, West Germany G.P. Talwar	"Equipment for India Project"		13,912.38	- 0 -	- 0 -

RESEARCH PROJECTS BY AID CONTRACEPTIVE RESEARCH AREA
 UNDER COOPERATIVE AGREEMENT AID/DPE-0546-A-00-1003-00
 1/1/86-6/30/86

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>
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- 6/30/86	\$ 86,823	\$ 38,218.83	\$ 68,041.65

FOLLOWING ARE SIX MONTH TECHNICAL REPORT SUMMARIES
OF ALL PROJECTS DURING THIS PERIOD
1/1/86 - 6/30/86

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

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

FUNDING PERIOD: 1/1/82-6/30/86

AMOUNT FUNDED: \$330,112

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

The objective of the research during the last six months has been to determine the pharmacokinetics and metabolism of anordrin and to conduct tests of its toxicity in preparation for Phase I clinical trials. ¹⁴C-Anordrin was prepared commercially by the Amersham Company under contract with PARFR. This was found to be radiochemically identical to authentic anordrin supplied by Dr. G. Chettur of the IITRI, Chicago. Four monkeys were given intravenous doses of ¹⁴C-anordrin in propylene glycol on the first day of the menstrual cycle, and after they had menstruated were given the same dose (0.2 mg/kg) intramuscularly in sesame oil. Another three monkeys were given a dose of 1.0 mg/kg i.m. The average duration of amenorrhea after 0.2 mg/kg i.v. was 49 days, after 0.2 mg/kg i.m. was 60 days, and after 1.0 mg/kg i.m. was 71 days. Serum, urine and feces were collected until the radioactivity had decreased to less than 100 cpm/0.25 ml in any sample. Generally, menstruation occurred at about the time that this concentration was reached in serum. Serum was assayed for bound and free anordrin, anordiol (the de-esterified metabolite) and two other metabolites, III and IV. The bound/free (B/F) ratios of anordrin in serum averaged 3.7; anordiol and compound III had B/F ratio of only about 0.2. Despite the strong binding of anordrin to a plasma protein, the long duration of effect of anordrin is not attributable to the unmetabolized compound since the serum half-life is < 2 min. The mathematical analysis of the kinetic data is not complete at the present time, but anordiol appears to have a long half-life of approximately 70 min or more. Compounds III and IV have much longer half-lives, but have not been determined yet. Toxicity has been evaluated by Dr. D. Waller and his associates at the University of Illinois in Chicago. Monkeys, dogs, and rats received anordrin intramuscularly in sesame oil in schedules recommended by the FDA. The pathology report should be made available shortly. We have measured cholesterol, HDL, prolactin, estradiol, testosterone, progesterone, cortisol, and thyroxine in these monkeys. The only significant differences found were in HDL and cortisol; HDL in vehicle-treated and 50 times the MED were 79 + 9 and 58 + 9 (SD) mg/dl, respectively (P<0.02). The respective values for cortisol were 282 + 125 (SD) and 535 + 132 ng/ml (P<0.05). Progesterone fluctuated between 1 and 7 ng/ml in the control group, but remained at 3 ng/ml or less after treatment had begun in groups receiving anordrin. The other hormones remained within the normal range during treatment. The results support our interest in conducting Phase I clinical trials.



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

PARFR- 309a

TITLE: "Toxicity Studies of Anordrin"

INSTITUTION: The University of Illinois at Chicago

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

FUNDING PERIOD: 7/1/85-6/30/86

AMOUNT FUNDED: \$93,313

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

Anordrin Toxicity Testing

The primary goal of this project was to assess the toxicity of anordrin administered to rats, dogs and subhuman primates for a 90 day period.

No toxicity was evident during the dosing period. All groups of animals have been autopsied and the tissues sent out for histopathological examination. The histopathology report should be completed shortly.



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14 June 86

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

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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: 3/1/82-9/30/86

AMOUNT FUNDED: \$446,995

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

The general objective of this project is to develop a contraceptive vaccine. The experimental strategy is to utilize one or more synthetic antigenic peptides of the sperm specific LDH-C₄ isozyme to elicit an immune response to the intact molecule. Fertility suppression in female baboons immunized with MC5-15 peptide conjugated to Diphtheria Toxoid (DT) was demonstrated previously. During this project period peptide synthesis has proceeded on schedule and essentially according to plan. Modifications in sequence and number of peptides were introduced on the basis of structural information that became available during this time period. This involved computer graphics modeling (supported by NIH) of the LDH-C monomeric and tetrameric structures from X-ray crystallographic data refinement (Hogrefe *et al.*, in preparation). From the model it is clear that peptide 221-230 is unlikely to be accessible as an antibody binding site and therefore its synthesis has been abandoned. On the other hand, the sequence of a topographic determinant was deduced from the model. This peptide would consist of a combination of residues from peptides 5-15 and 211-226 appropriately spaced to simulate their relative positions on the surface of LDH-C₄. Two sequences are proposed for synthesis. These are:

I. 1S-G*⁻5E-6Q-G*⁻216A-G*⁻219T-G*⁻222D-223K-224E
 II. 216A-G*⁻219T-G*⁻222D-223K-224E-G*⁻1S-G*⁻5E-6Q
 S=Serine; G*⁻=Glycine spacer; E=Glutamic Acid; Q=Glutamine; A=Alanine; T=Threonine; N=Asparagine; K=Lysine

Another and unplanned aspect of this study was the isolation of the human *Ldh-c* gene. This was an unexpected accomplishment that represents a breakthrough permitting us to deduce the amino acid sequence of human LDH-C₄. Thus we can compare MC5-15 with HC5-15. The sequence substitutions are boxed:

MC	E	Q	L	I	Q	N	L	V	P	E	D	K
HC	E	Q	L	I	E	K	L	L	L	D	D	G

The differences are sufficient to warrant synthesis of HC5-15 for further analysis. This peptide determinant should provoke antibodies of greater specificity and higher affinity to human LDH-C₄ and therefore may prove more effective than MC5-15 as an immunocontraceptive. We expect to be able to test this hypothesis.

Erwin Goldberg
 SIGNATURE

June 26, 1986
 DATE

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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: 6/1/83-6/30/86

AMOUNT FUNDED: \$12,502

Below is a project summary for the January 1, 1986 - June 30, 1986

period.

To date a total of 820 questionnaires have been received from Finland. These include 295 initial interviews (110-ICD, 100-LNG IUD, and 85-Nova T); 285 3-month follow-up interviews (106-ICD, 98-LNG IUD, and 81 Nova T); and 243 12-month interviews (92-ICD, 86-LNG IUD, and 65-Nova T). A total of 799 instruments have been coded and their data analyzed. Preliminary results from the 12-month follow-up data indicate that both the ICD and LNG IUD devices were associated with lighter and shorter menses, more irregular cycles, more spotting, less cramping and some amenorrhea. The Nova T was associated with heavier and longer menses, more cramping, more spotting and more irregular cycling. On many 12-month follow-up measures (cannot feel the device, husbands cannot feel the device, change in desire for intercourse, have good or mostly good feelings about the device, dissatisfied with device, would recommend to friends), there were no significant differences between groups. However, at 12-months, 15% of ICD users, compared to only 6% of LNG IUD and 5% of Nova T users ($p=.04$), perceived especially bothersome side effects. Moreover, by the 12-month interval 24% of ICD users, compared to 8% of LNG IUD users and 9% of Nova T users ($p<0.001$), had discontinued their device and 8%, 1%, and 1% of ICD, LNG and Nova T users, respectively, had expelled their device.

Although the ICD sample had experienced significantly more discontinuations than the two control groups, ICD users in general were significantly more satisfied than the controls with their current device compared to their previously used IUDs. This seeming discrepancy is explained by group differences in prior contraceptive behavior patterns. Significantly more ICD users than members of the other two control groups volunteered for the present study because they disliked all other methods, were dissatisfied with the last method they used, were dissatisfied with their prior IUD, experienced unacceptable side effects from their prior IUD, and were dissatisfied with prior mechanical methods. Additionally, this group discontinued significantly more contraceptive methods because of dissatisfaction. As noted in previous reports, the ICD group as a whole appeared to be considerably more particular about contraceptive methods in general and/or sensitive to side effects. This finding was confirmed by Tapani Luukkainen, M.D.

After all remaining interviews are received from Finland, multivariate regression analysis and analyses of covariance will be performed to determine the extent to which prior contraceptive behavior has influenced the higher discontinuation rates shown by ICD sample members and whether controlling for this behavior eliminates group differences in discontinuation.



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July 29, 1986

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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.

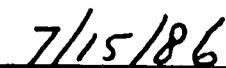
FUNDING PERIOD: 7/1/83-6/30/87

AMOUNT FUNDED: \$199,931

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

The overall objective of this research is to develop a vaginal contraceptive method that is more effective and less toxic than nonoxynol-9 (N-9). Our efforts have focused on the synthesis and evaluation of 4-aryl guanidinobenzoates, inhibitors of the sperm enzyme acrosin. Some of these compounds were shown: 1) to possess much higher vaginal contraceptive activity in rabbits than N-9; 2) to prevent penetration of human sperm into zona-free hamster oocytes; and 3) to be less irritating to the rabbit vagina than N-9. Based on efficacy and toxicity studies, acetaminophen 4-guanidinobenzoate (AGB) was selected for clinical trials using the "Today sponge" (VLI) for delivery. Initial sponges were unsatisfactory but clinically applicable sponges have now been constructed. The in vitro release rate of AGB from sponges containing different amounts of the inhibitor (in the absence and presence of N-9) was tested under various conditions. It was determined that the sponges containing 350 mg AGB (maximum amount) would most likely be optimal for clinical evaluation considering that it is probably desirable to deliver a dose of about 100 mg over a one day period. At pH 4.0 (the approximate pH of vaginal fluid), 75 mg of AGB was released from these sponges over a one day period in the absence of N-9, decreasing thereafter. In the presence of N-9, the release rate was higher: 120 mg for the first day. Vaginal irritation studies with this sponge in rabbits proved unsuccessful because the rabbits would eject the sponges from their vaginas within 24-48 hours. A meeting was organized with the FDA and all our results with AGB were submitted in summary form. It was agreed that a Phase I Clinical Trial could be performed when a 30 day subchronic toxicity test under GLP conditions has been completed and a satisfactory IND has been submitted. Rabbit vaginal irritation studies with the sponge containing AGB will not be required in view of the nonirritating properties of AGB when applied to the vagina in formulation.


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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 January 1, 1986 - June 30, 1986 period.

Acrosin Inhibitors

This project is to complete preclinical toxicity testing for an acrosin inhibitor. Previous vaginal irritation and toxicity screening was utilized to determine the best agent from several synthesized acrosin inhibitors.

Rabbit vaginal irritation testing was completed for the compound selected as the agent of choice. Histopathological examination demonstrated the non-toxic nature of the compound as a gum acacia suspension. Final vaginal irritation studies were to have been performed but difficulty was encountered due to the choice of the sponge as the mode of administration. Following the development of an inserter to administer the test material deep into the vagina, the ability of the rabbit vagina to expell the sponge within 24-48 hours after insertion was noted. Several methods were assessed in an effort to find an animal model to retain the sponge and be able to replace it on a daily basis during vaginal irritation testing. The methods included creating a stricture in the vagina by partially tying off the vagina with umbilical tape. Rats were also found to expell small pieces of the sponge placed in the vagina.

Discussions with the FDA following these experiments have resulted in a possible use of the gum acacia data to demonstrate the lack of vaginal irritation of the selected acrosin inhibitor. They also have agreed to use the gum acacia suspension as the formulation to be administered vaginally in subchronic toxicity testing. Subchronic testing of the acrosin inhibitor can now be performed.

Radiolabelled Acrosin inhibitor has also been obtained and the pharmacokinetic studies will be completed shortly.



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

PARFR- 339

TITLE: "Shug Device Studies"

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

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

FUNDING PERIOD: 7/1/83-6/30/87

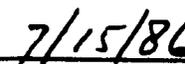
AMOUNT FUNDED: \$71,073

Below is a project summary for the January 1, 1986 - June 30, 1986

period.

The objective of this research is to develop a reversible male sterilization technique by obstructing the vas deferens. A device (the Shug) has been constructed consisting of two silicone plugs, held together by a nylon thread, that completely occluded the vas over a 7 month period in two separate primate trials. All animals ejaculated normal amounts of spermatozoa when the device was removed. Histopathological studies with silicone in the rat vas are in progress and no toxicity has been found in the 6 month implants. Techniques were developed to allow easy implantation of the Shug into the human vas and were evaluated in ten patients at Propater, Sao Paolo, Brasil. One of the methods caused minimal tissue damage and allowed Shug implantation within about 5 min per side. This technique will be used for the clinical trials. The 1 mm diameter Shug fits snugly but not tightly in the human vas lumen and appears optimal for clinical evaluation. A meeting was held with the FDA to discuss any further requirements for a limited clinical trial. A 3-month study will be allowed if the following conditions are met: 1) submission of the histopathology report covering the 6 month rat toxicity study; 2) performance of an experiment to evaluate if the Shug causes any changes in the motility and morphology of ejaculated human sperm in vitro; 3) presentation of the composition of the nylon thread; and 4) preparation of an updated clinical protocol for 40 test patients and 40 controls. Experiments are presently in progress to complete the in vitro evaluation of the Shug effect on spermatozoa. The company (Ethicon) that produces the thread was contacted but was not willing to give the composition of the nylon. However, it has supplied us with the NDA number (80-950). The clinical protocol is being prepared. The one year rat toxicity study is being completed and, if satisfactory, the clinical study can be expanded to allow implantation for at least 4 months. Since life time toxicity studies in a second animal species will be required before the second phase of clinical trials will be approved by the FDA, studies are in progress to determine if a silicone plug can be implanted in a mouse vas deferens.


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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: The University of Illinois at Chicago

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

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

AMOUNT FUNDED: 91,723

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

Shug

The primary purpose of this study is to evaluate the effects of silicone implants in the vas deferens of the rat. Small threads of silicone were implanted in two hundred rats and two hundred additional rats underwent sham surgery. Autopsies were scheduled for six months, one year and two years after implantation.

The six month autopsies have been completed. Histopathological examination revealed only moderate tissue responses to the presence of the silicone thread. The report has been sent to the FDA to be included in the IND file for the SHUG device.

A group of fifty animals underwent a vasectomy in which the vas deferens was tied off to simulate the blockage of the vas deferens in the animals with silicone thread. This group is a control to determine if the rat testes will demonstrate any adverse effects due to a blockage of the vas deferens. In the weeks following the implantation of the silicone thread a significant number of implanted rats had swollen testes which has subsequently resolved in most animals. This same effect was observed in the vasectomized rats. This group of animals was recently sacrificed six months after their vasectomy and tissues sent for histopathological examination.

The one year exposure group and controls will be autopsied during June and will be sent for histopathological examination at that time.

No gross toxicity has been observed in the long term exposure animals after one year of exposure.



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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 347

TITLE: "Studies on the Anovulatory Potency and Side Effects of an
Inhibitory Analog of LH-RH 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: \$145,501

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

No response.

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

PARFR- 355

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

INSTITUTION: Medical Research Foundation of Oregon

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

FUNDING PERIOD: 4/15/84-12/31/86

AMOUNT FUNDED: \$99,794

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

We investigated whether cholera toxin B (CTB) and muramyl dipeptide (MDP) enhances the production of IgA to lactate dehydrogenase C₄ (LDH-C₄). It is critical to establish an immunization procedure that will result in a maximal IgA response.

Because of our difficulty in stimulating measurable LDH-C₄-specific antibody levels in our past experiment, we injected 115 CD-1 female mice with 100 µg LDH-C₄ in Complete Freund's Adjuvant (CFA) one week before use. Groups of five mice received surgical implants of uterine agarose plugs containing LDH-C₄ (100 µg) and/or CTB (10 µg) and/or MDP (10 µg) into the right uterine horn. Both uterine horns were ligated at the cervical end. At weekly intervals thereafter, serum samples, intestinal lavage, and uterine wash samples were collected. Serum samples were obtained from posterior retro-orbital plexus blood collections. Intestinal lavage samples were induced by intragastric administration of a lavage solution followed by intraperitoneal injection of a 0.1 mg pilocarpine solution. The samples were collected in a solution containing soybean trypsin protease inhibitor and EDTA to prevent antibody degradation. Afterwards, the mice were sacrificed by cervical dislocation. Intrauterine fluid was collected from both the right and left side. All samples were stored at -20°C.

Dr. Goldberg performed enzyme-linked immunosorption assays (ELISAs) to determine IgA and IgG levels specific for LDH-C₄. Our results indicate that LDH-C₄ plus both of the adjuvants, MDP and CTB, stimulate the highest and most prolonged response. This combination is being used in the present study.

Now that the components for maximal uterine stimulation have been identified, we are establishing the most efficient route of immunization. Various immunizations are being compared in terms of longevity and strength of response. As before, groups of five CD-1 females were primed, although LDH-C₄ and adjuvants were injected i.m. without CFA. One group, however, received LDH-C₄ in CFA as before in order to provide a positive control. The protocol outlined in our original application is being followed. Serum, lavage, and uterine wash samples will be taken at weekly intervals and analyzed as previously described. This information should indicate an effective means of inducing a high IgA intrauterine response.

N. J. Alexander
SIGNATURE

June 27, 1986
DATE

PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 36a

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

INSTITUTION: The George Washington University

PRINCIPAL INVESTIGATOR: Rajesh K. Naz, Ph.D

FUNDING PERIOD: 12/1/84-6/30/86

AMOUNT FUNDED: \$99,931

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

We have purified FA-1 from either deoxycholate (DOC) - or lithium diiodosalicylate (LIS) - solubilized murine testes by immunaffinity chromatography using monoclonal antibody MA-24 which inhibited penetration of zona-free hamster ova by human sperm and *in vitro* fertilization in mice (Science, 225:342, 1984). The FA-1 thus isolated is homogeneous and shows a single band of 47 kilodaltons (kDa) when analyzed by slab SDS-PAGE and silver staining. Following removal of the detergent and extensive dialysis or treatment with 0.15M NaCl, PAGE analysis shows a 23 kDa band. Two-dimensional (2D) PAGE of the eluted FA-1 shows 4-5 polypeptides in the 47 kDa or 23 kDa range. The dialyzed FA-1 contains a major 23 kDa and a minor 48 kDa band when separated on both sucrose and cesium chloride gradients. High performance size exclusion chromatography shows a major peak at 23 kDa and a minor peak at 50 kDa. Further analysis of the 23 kDa peak by reverse-phase chromatography resolves the antigen into 3 peaks, which gave similar 2D patterns. The FA-1 reveals a positive reaction with periodic-Schiff reagent and contained glucose and mannose, which together constituted 18.8% of the total antigen mass. Amino acid analysis shows a high percentage of aspartic and glutamic acid, while the N-terminal analysis shows serine and aspartic acid (Naz et al; Proc. Natl. Acad. Sci., USA. Aug, 1986 issue). Female rabbits were actively immunized against the fertilization antigen (FA-1) isolated from lithium diiodosalicylate (LIS)-solubilized murine testis. Three trials were performed in order to check the effect of immunization on fertility. In all of these trials, there was a significant ($P < .001$) reduction of fertility as determined by the percentage of 3-day implants/corpora lutea ratio (FA-1, 0-26.3%; adjuvant control, 79.4-100%). A complete block was observed in animals which received intravenous immunization with the antigen. Antisera collected from FA-1-immunized rabbits were negative in the agglutination and the immobilization techniques, and demonstrated modal titers of $\geq 1:2560$ in the enzyme linked immunosorbent assay (ELISA) using FA-1. Antisera were tissue-specific and showed binding to the specific protein bands of 47,000 and 23,000 Mr, dimeric and monomeric forms of FA-1, respectively, in the Western blot procedure. Ova collected from rabbits inseminated with sperm which had been treated with antiserum for immunized rabbits showed reduced fertilization rates (anti-FA-1, 3.9-27.7%; control rabbit serum, 87.8%). It is concluded that active immunization with FA-1 resulted in a tissue-specific immune response which caused a reduction of fertility in rabbits, by a mechanism(s) involving an inhibition of the fertilization process. Presently, we are trying to isolate and characterize the antigenic determinants of FA-1 for large scale practical use to test in sub-humans and primates.

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

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: 6/1/84-5/31/86

AMOUNT FUNDED: \$144,256

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

The objectives of this proposed project is to determine if immunization with zona pellucida (ZP) antigens can effectively reduce fertility without altering ovarian function. Dr. Dunbar visited Dr. Shoba Sehgal's laboratory in Chandigarh, India to discuss the ongoing studies in which rhesus monkeys have been immunized with total heat-solubilized ZP. These animals have maintained high serum titers of antibodies for 17 months even though they have not been boosted for over 12 months. The ovarian function of these animals was found to be altered after 9 months. Ovaries obtained from baboons immunized with a purified partially deglycosylated purified ZP protein (I) using MDP as adjuvant also showed a complete reduction of maturing ovarian follicles, although this was not observed in two other ovaries. Immunoblot analysis of antibodies in sera from the baboons demonstrate that antibodies against the ZP protein (I) are present in animals with altered ovarian function. It will be necessary to test the two other more minor ZP proteins which are now known to be substrates for the sperm enzyme acrosin to determine if immunization with these will result in infertility without altering ovarian function.


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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

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

AMOUNT FUNDED: 86,823

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

Since February 1986 we have made good progress in meeting the objectives of this grant and we expect that within the 3-month extension (until September 30, 1986) we will complete the data collection and analysis and prepare 2 manuscripts for publication.

The objectives of the project were to:

1) Study twenty patients diagnosed with a common vaginal infection and observe the cervical mucus Guaiacol Peroxidase (GP) levels for a week while they underwent their prescribed treatment. So far we have studied 7 women. Due to the lower socioeconomic status of these patients we had some delays with recruitment and compliance with appointments but we expect to complete the study by September.

2) Study twenty women who would self-sample their cervical mucus and compare their GP levels with those collected at the cervical os by a technician. We have completed 19 of these cycles. The remaining cycle will provide GP samples needed for biochemical studies (see below).

3) Study ten women and develop a colorimetric GP test. We have set up 5 color-hue levels to which the technician-collected anterior fornix GP levels are compared. Seven cycles have been completed.

4) Carry out a biochemical characterization of GP to determine the size and charge of GP isoenzymes during the menstrual cycle and in the presence of common vaginal infections. We have succeeded in performing one- and two-dimensional SDS-PAGE studies and identified in infected mucus a new group of acidic proteins (pI ca.5, molecular mass in the 70-90 kDa range). The GP staining of the gels is under study due to the putative removal of the heme group and/or calcium from GP during electrophoresis under the required denaturing-reducing conditions. We found that our analysis of the GP-iodinated cervical mucus proteins is facilitated by performing a protein cross-linking step (using disuccinimidyl suberate, DSS) either before iodination of native mucus or after the iodinated proteins are extracted from mucus with 0.5 M calcium chloride. Such DSS studies will reveal the presence of other proteins (such as proteoliasin) which may bind and regulate the GP activity.

5) Study the effect of the ejaculate (15 volunteers) on the cervical mucus GP and identify the cause(s) of the GP inhibition by the ejaculate. This in vitro study is now under way.

The results of this research will allow us to make some important decisions about sampling and assay conditions in preparation for entering clinical trials.

John C.M. Tsibris

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

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

AMOUNT FUNDED: \$122,106

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

No response.

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

PARFR- 363

TITLE: "Laboratory Studies on an Antispermatogetic Agency - 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 January 1, 1986 - June 30, 1986 period.

Telex sent July 26, 1986. No response.

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION
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: 9/1/84-6/30/86

AMOUNT FUNDED: \$64,218

Below is a project summary for the January 1, 1986 - June 30, 1986

period.

The objective of this project is to determine whether single injections of microcapsules releasing D-Trp-6-LH-RH (at a rate of 20 μ g/day, for 30 days) every month can suppress LH levels and consistently inhibit ovulation in the regularly cycling cynomolgus monkey (*Macaca fascicularis*).

According to the proposed experimental protocol, we initiated the following different treatments. This design consisted of four groups of monkeys (5 animals/group).

Group 1 received a single s.c. injection of microcapsules releasing D-Trp-6-LH-RH (at a rate of 20 μ g/day, for 30 days) every 30 days.

Group 2 received, in addition to the microcapsules as in Group 1, a progesterone challenge (50 mg, i.m.) on day 25 of each cycle.

Group 3 and 4 represented the corresponding controls for the experimental groups and therefore, they received oil vehicle or placebo microcapsules.

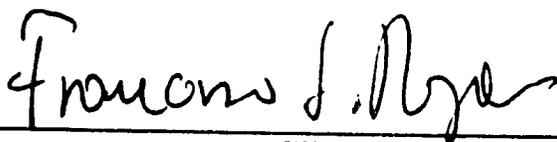
The degree of folliculogenesis and ovulation date for each month was determined by laparoscopies performed at periodic intervals. In addition, blood was drawn every week to determine serum concentrations of LH, FSH, estradiol, progesterone and prolactin by radioimmunoassay. Concentrations of D-Trp-6-LH-RH in peripheral plasma were also monitored throughout the study in the monkeys receiving microcapsules.

At present, our data indicate that a single injection of D-Trp-6-LH-RH microcapsules every 30 days provided a sustained concentration of immunoreactive D-Trp-6-LH-RH in the serum for 8 consecutive months.

Also, we found that all monkeys remained anovulatory during treatment with D-Trp-6-LH-RH microcapsules, while the controls presented monthly ovulatory cycles. Furthermore, treated animals were amenorrheic and serum LH, FSH, progesterone and estradiol concentrations were significantly reduced during treatment.

Finally, we have found that all treated animals returned to normal menstrual cyclicity within three months after discontinuation of D-Trp-6-LH-RH microcapsules.

These data provide strong support to the concept that treatment with D-Trp-6-LH-RH microcapsules may be a novel approach for a monthly hormonal contraceptive in primates.



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7/15/86

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION
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 January 1, 1986 - June 30, 1986 period.

Telex sent July 26, 1986. No response.

SIGNATURE

DATE

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

PARFR- 371

TITLE: "Vaginal Spermicidal Barrier (VSB) Postcoital Tests"

INSTITUTION: Eastowne Ob-Gyn and Infertility

PRINCIPAL INVESTIGATOR: James R. Dingfelder, M.D.

FUNDING PERIOD: 7/1/85-6/30/86

AMOUNT FUNDED: \$15,598

Below is a project summary for the January 1, 1986 and June 30, 1986 period.

No response.

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

PARFR- 372

TITLE: "Progestational Agents Effects on Baboon Endometrium"

INSTITUTION: Stolle Research and Development Corporation

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

FUNDING PERIOD: 3/1/85-4/30/86

AMOUNT FUNDED: \$76,120

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

Normally cycling female baboons were treated with one of three long-acting progestational contraceptives to determine endometrial response following exposure to these synthetic steroids. Six groups of five baboons each were injected intramuscularly with Depo-Provera (2 mg/kg or 0.5 mg/kg), a levonorgestrel (LN) oxime (6 mg/kg or 3 mg/kg), or a LN ester (0.5 mg/kg or 1 mg/kg). A second injection was given after 60 (LN oxime) or 90 (LN ester, Depo-Provera) days. An endometrial biopsy procedure was performed at a selected interval following each injection. The endometrial samples obtained are being evaluated by light and electron microscopy by Dr. Walter Wilborn at the University of South Alabama. Blood samples are being obtained at least once weekly for determination of exogenous and endogenous steroids by Mason Laboratories. Perineal sex skin changes are being evaluated daily to supplement determination of ovarian cyclicity derived from evaluation of steroid data. During the 180 day treatment interval, a total of two sex skin cycles occurred in the five baboons treated with 2 mg/kg Depo-Provera; while each baboon treated with the low dose had at least one sex skin cycle following each injection. The low dose LN oxime was not very effective at cycle cycle inhibition, and the high dose did not completely suppress the sex skin swelling. Perineal turgescence resumed 35 to 45 days following treatment with the low dose LN ester, and 47 to 60 days after treatment with the 1 mg/kg dose.


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7/12/86
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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION
SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 373

TITLE: "90-Day Levonorgestrel Microspheres"

INSTITUTION: Stolle Research and Development Corporation

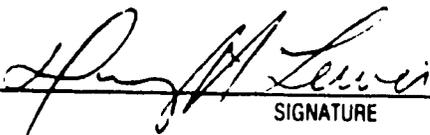
PRINCIPAL INVESTIGATOR: Danny H. Lewis, Ph.D.

FUNDING PERIOD: 4/1/85-3/31/86

AMOUNT FUNDED: \$67,404

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

The objective of this program is to develop a 90-day injectable levonorgestrel formulation. This product would be similar to the 90-day norethisterone system currently being evaluated by PARFR in Phase II trials. The availability of such a formulation would allow a direct comparison of the norethisterone, norgestimate, and levonorgestrel systems in humans. A prototype formulation has been developed and evaluated in the baboon model. Three doses were tested in three baboons each 12, 25, and 50 mg of levonorgestrel. The study was completed; however, the serum samples have not yet been analyzed due to relocation of the Stolle RIA laboratory. Visual observations of the baboon sex skin indicated that an acceptable 90-day formulation had been achieved. Therefore, if the serum drug values are satisfactory, it is anticipated that a Phase I trial can be initiated.


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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 375

TITLE: "Baboon Immunologic Evaluation with LDH-C₄ and In Vitro
Fertilization Studies in Rodents"

INSTITUTION: University of New Mexico

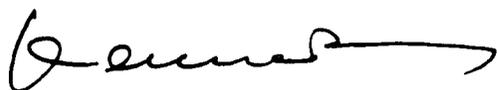
PRINCIPAL INVESTIGATOR: Kenneth S.K. Tung, M.D.

FUNDING PERIOD: 5/1/85-6/30/86

AMOUNT FUNDED: \$46,588

Below is a project summary for the January, 1986 - June 30, 1986 period.

During the past 6 months, we have carried out a number of studies on the LDH-X molecule in the fertilization process. We have studied the effect of rabbit or mouse antisera to mouse LDH-X or its antigenic peptides, monoclonal antibodies to mouse LDH-X (ascites or purified IgG) on mouse fertilization in vitro (IVF). Of over 20 reagents examined, only 2 monoclonal antibodies were found to reproducibly inhibit IVF. More significantly, rabbit anti-LDH-X antiserum IgG known to react strongly with mouse LDH-X had no effect on IVF. The overall impression we gained is that anti-LDH-X antibody does not inhibit fertility by inhibiting the fertilization process. We next studied the effect of monoclonal anti-LDH-X antibody on fertility in vivo by passive transfer of antiserum into mice that were subsequently induced to ovulate and mated. The result was negative. In fact, transfer of antiserum to mouse sperm, known to inhibit IVF strongly, had no effect in vivo. These findings seriously question the validity of the mouse model in fertility assessment. This may in turn be due to the fact that insemination in mice is intra-uterine, which does not allow time for the antibody to block sperm transit. In addition, we have completed the study on the immunopathology of baboons immunized with LDH-X peptides. The major finding has been elevated LDH, alkaline phosphatase and hypergammaglobulinemia. However, these changes were found in both experimental and control baboons, and the elevated levels were computed on normal human standards. Also, all baboons had anti-smooth muscle antibodies. We suggest the possibility that the liver function of baboons injected with adjuvants may be abnormal.



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7/22/86

DATE

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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION

SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 376
TITLE: "PRE IDE Studies - Tubal Clip"
INSTITUTION: Maine Medical Center
PRINCIPAL INVESTIGATOR: C. Irving Meeker, M.D.
FUNDING PERIOD: 5/1/85-4/30/86 AMOUNT FUNDED: \$29,774
Below is a project summary for the January 1, 1986 through
June 30, 1986 period.

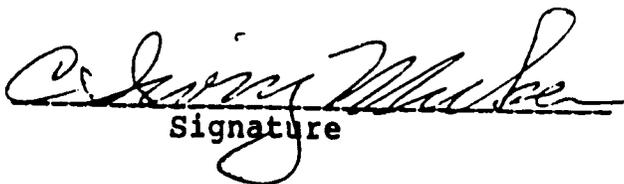
The objective of this project is to answer the remaining questions in order to receive approval of an IDE. The basic issues remain those of toxicity, carcinogenicity, and possible toxicological effects of Teflon in the reproductive tract.

During this six months, 50 of the mice with Teflon plugs and clips in the uterus were sacrificed and examined. All animals had devices in place for more than six months. Necropsy, including microscopic sections of the uterine horn showed no malignant change in any animal and minimal foreign body reaction in the uterine horn of most.

In a separate study, 8 of 10 rabbits conceived with a Teflon plug and clip in place in one fallopian tube. Thirty-six fetuses were delivered. One had a hypoplastic kidney, one had a hypoplastic sternum, and two (from the same mother) were hydrocephalic. There were no other anomalies noted. All three of these anomalies are reported infrequently but at least occasionally in control groups of rabbits. A total of 20 hydrocephalic fetuses were reported among 674 control animals in three different studies in the literature. In addition, with any degree of vitamin A deficiency, from 58 to 100% of the offspring are hydrocephalic. It was concluded that the two fetuses in the present study could not be used to either rule in or rule out the presence of teratologic anomalies secondary to the use of Teflon.

On June 27, 1986, a meeting was held with representatives of the FDA, Dr. Meeker, and James D. Shelton, M.D., M.P.H., Chief, Office of Population for the Agency for International Development, to review this data. Subsequent to that meeting, verbal agreement was reached with the FDA to allow the initial five patients to be started this Fall while we await the results of the remaining mice in the toxicity and carcinogenicity experiment.

It is expected that the revised Consent Form and Protocol will receive formal approval in the next several weeks so that these initial human studies may be undertaken.


Signature


Date

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

PARFR-378

TITLE: "Preparation of Testosterone Microspheres"

INSTITUTION: Stolle Research and Development Corporation

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

FUNDING PERIOD: 7/1/85-6/30/86

AMOUNT FUNDED: \$39,233

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

The objective of this project is to prepare a 90-day testosterone system for evaluation in rhesus monkeys and for testing in a Phase I human trial. A candidate formulation was prepared, fully characterized in vitro, and tested in the monkey by Dr. Ricardo Asch at the University of Texas in San Antonio. Two doses 50 mg of T and 25 mg of T were administered to 4 animals each. The test animals also received 200 ug of LHRH antagonist daily. Both doses resulted in normal testosterone levels over a period of 90 days in the monkey. Based on these encouraging results, clinical materials were then prepared in the Stolle Parenteral Drug Facility. The materials have been fully characterized in vitro and are available for Phase I testing in humans. The clinical protocol is not yet finalized and the project is delayed at the present. All tasks required by Stolle have been completed except final packaging and sterilization of the clinical material.


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

PARFR- 379

TITLE: "Idiotope Vaccine for Sperm-Targeted Immunocontraception"

INSTITUTION: Duke University Medical Center

PRINCIPAL INVESTIGATOR: Christopher P. Carron, Ph.D.

FUNDING PERIOD: 8/1/85-6/30/86

AMOUNT FUNDED: \$58,391

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

Immunological response to a foreign antigen elicits the formation of antibodies against the antigen and a second group of antibodies directed against the first, termed anti-idiotypic antibodies, some of which carry the internal image of the original antigen. Anti-idiotypic antibodies carrying the image of the antigen may behave immunologically like the antigen itself. The overall objective of this project is to determine the feasibility of generating sperm-targeted immunocontraception by active immunization with anti-idiotypic antibodies (Ab2) made against murine monoclonal anti-sperm antibodies (Ab1).

Monoclonal anti-sperm antibodies (mAb) M29, M2, M41 and M42 have been produced using syngeneic mouse testis as immunogen. M29 and M42 inhibit mouse fertilization *in vivo* and *in vitro*, whereas M2 and M41 have no effect. Sera from rabbits inoculated with purified mAbs were absorbed with normal mouse and isotype-specific immunoglobulin (Ig) and the anti-idiotypic Ig fraction (Ab2) isolated by Protein A-chromatography. Binding specificity of Ab2 for mAb was confirmed by measuring the reactivity of Ab2 with homologous and heterologous mAbs in an ELISA. Competitive inhibition studies were performed to demonstrate that purified rabbit anti-Id mAb contain antibodies directed against the antigen-binding site of the mAb. Ab2 competitively inhibited ¹²⁵I-labeled mAb binding to mouse sperm suggesting that the Ab2 possessed subpopulations directed against sites similar or adjacent to the antigen-binding site of the mAb. These results are supported by recent studies showing that antigen-containing extracts of mouse sperm inhibit anti-Id mAb binding to mAb. Ab2 reactive with the antigen-combining site of mAb may contain subpopulations which bear the internal image of the sperm antigen recognized by the mAb. Immunization with Ab2 may induce antibodies which react with native sperm antigen.

Induction of Ab-1 like Ab3 in mice immunized with Ab2 was tested by measuring the inhibition of ¹²⁵I-labeled mAb binding to immobilized anti-Id mAb by Ab3. Female mice immunized with Ab2 develop Ab3 which competitively inhibit Ab1 binding to anti-Id mAb. Moreover, preliminary results show that these Ab3 sera inhibit homologous mAb binding to mouse sperm. Together, these results suggest that the Ab3 share idiotypes with Ab1 and exhibit identical binding specificity.

Thus far we have shown that immunization of mice with Ab2 results in the elevation of circulating antibodies to specific sperm antigens. Attempts to determine whether this humoral response is accompanied by the induction of infertility have been hampered by technical problems related to the mating of immune animals. We expect that we will overcome these difficulties and that we will then be able to test the immunocontraceptive effect of immunization with Ab2.



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7/14/86

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

PARFR- 380

TITLE: "Preliminary Evaluation of 3-M Impression Material as an Injectal
Vas Occlusive Device"

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

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

FUNDING PERIOD: 8/1/85 - 4/30/86

AMOUNT FUNDED: \$10,832

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

This project has been completed although the histopathology studies are still in progress. The objective of the work was to perform preliminary experiments in dogs to determine if the injection of 3-M Impression Material (vinyl polysiloxane impression material, light body-regular set, type 1, low viscosity; Dental Products, 3M, St. Paul, MN) into the vas deferens results in the obstruction of sperm transport. A technique was developed for the injection of the material into the vas. About 2-3 cm of vas lumen was implanted. Four dogs were implanted. After recovery from the surgery, the dogs were ejaculated approximately every two weeks for a 3 month period and the semen analyses compared to those of ejaculates obtained before implant. One of the dogs refused to produce ejaculates after implantation. The other three dogs became essentially azoospermic although occasionally a few, immotile, mostly decapitated sperm could be found in the ejaculates. After the 3 month period, the vasa were excised, fixed and sent to Dr. Ralph Richards for study. Sections were also taken of the testis and epididymis and sent for analysis. No gross pathological lesions were notable in any of these tissues or in any of the abdominal and thoracic organs observed.


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7/15/86
DATE

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

PARFR- 382

TITLE: "Postcoital Effectiveness of the Vaginal Spermicidal Barrier"

INSTITUTION: Professional Staff Association, Los Angeles County -
University of Southern California Medical Center

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

FUNDING PERIOD: 10/1/85 - 6/30/86

AMOUNT FUNDED: \$5,984

Below is a project summary for the January 1, 1986 - June 30, 1986

period.

This study was designed to determine whether the VSB inhibits sperm transport in women. The results of post-coital tests done with the VSB in place are compared to control tests in which intercourse takes place at mid-cycle without use of a vaginal contraceptive: To date eight women have successfully completed both the control test and the test with the VSB. Of the VSB tests, five women had no sperm in the post-coital cervical mucus, one had no sperm with progressive motility, and two others had mean values of 0.2 and 1.7 sperm with progressive motility per HPF, respectively (normal: 5 sperm with progressive motility per HPF). Most of the above tests were done in the current reporting period. So far the VSB has effectively inhibited sperm transport in all the subjects studied. If there are similar findings in the two remaining subjects, these studies suggest that the device warrants further study for tolerance to wear and clinical effectiveness in preventing pregnancy.


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7-25-86
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PROGRAM FOR APPLIED RESEARCH ON FERTILITY REGULATION
SIX MONTH TECHNICAL REPORT SUMMARY

PARFR- 383

TITLE: "Postcoital Test: Disposable Minidiaphragm"

INSTITUTION: Bio-Products, Inc.

PRINCIPAL INVESTIGATOR: Milos Chvapil, M.D., Ph.D., D.Sc.

FUNDING PERIOD: 10/1/85-11/30/86

AMOUNT FUNDED: \$12,512

Below is a project summary for the January 1, 1986 - June 30, 1986

period.

To this date, the study on postcoital testing as outlined has not yet started. The preliminary study in the acceptance of disposable minidiaphragms in ten volunteers (not part of PARFR protocol) indicated a need for improvement of the self-adhesion (was only eight hours) and better cohesion of the minidiaphragm as the intravaginally inserted cups became too fragile with 24 hours wear.

We expect to resolve the polymer-science related problems with the manufacturing of the devices within one month.

Milos Chvapil MD

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6-18-86

DATE

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

JUN 23 1986

PARFR- 384

TITLE: "Effects of Immunization of Female Baboons with Zona
Pellucida Antigens on Ovarian Functions"

INSTITUTION: The Ohio State University Research Foundation

PRINCIPAL INVESTIGATOR: Vernon C. Stevens, Ph.D.

FUNDING PERIOD: 7/1/85-4/30/86

AMOUNT FUNDED: \$27,080

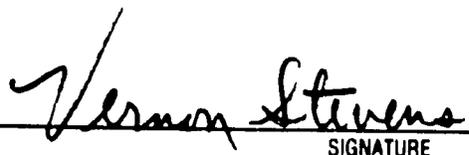
Below is a project summary for the January 1, 1986 - June 30, 1986 period.

The objective of this project was to ascertain whether immunization of female baboons with either of two porcine zona pellucida antigens (ZP-1 and ZP-3) caused any alteration in ovarian function. The parameters assessed in the study were 1) cycle length, 2) serum levels of estradiol and progesterone and ovarian histology. Five females were immunized with each of the antigens following a control period of at least three menstrual cycles. In one control and in one post-immunization cycle, frequent serum samples were collected for ovarian steroid determinations. Other serum samples were collected following immunizations for antibody level measurements and progesterone concentrations as indices of ovulation. Ovaries of all females were surgically excised on all animals after nine menstrual cycles from the last booster immunization were completed.

All animals exhibited typical menstrual cycle events and hormone profiles during the control cycles. Immunizations with the ZP-1 antigen resulted in menstrual cycle disruptions in three of the five females. Two of these became amenorrhic near the end of the study. The hormonal profiles of ZP-1 immunized females showed a marked reduction in estradiol levels soon after immunization with little change in progesterone levels. It was concluded that ZP-1 immunizations clearly effected ovarian function in baboons.

Few effects of immunizations of baboons with porcine ZP-3 were detected in this study. In approximately 18 months of study, only two cycles in each of two animals and one in another were anovulatory. Cycle lengths were not altered. The only alteration in hormone profiles was an anovulatory pattern of progesterone in one female.

Results of assays of antibody levels and histological examination of excised ovaries were not available for correlation with the above findings.


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June 17, 1986

DATE

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

PARFR- 385

TITLE: "Toxicity Study of an Iodine Transcervical Sterilization Medium"

INSTITUTION: The Board of Trustees of the University of Illinois

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

FUNDING PERIOD: 11/1/85-6/30/86

AMOUNT FUNDED: \$47,555

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

Transcervical Administration Of An Iodine Containing Medium

The primary purpose of this study was to assess the toxicity of transcervical administration of an iodine containing medium to be used as sclerosing agent in fallopian tubes.

The test substance and vehicle were administered to cynomolgus monkeys using both the transcervical and intraperitoneal routes of administration. Forty five days after the administration of the iodine containing preparation the animals were autopsied and tissues sent out for histopathological examination. No gross toxicity was noted. The histopathology report did not indicate any signs of toxicity.


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

PARFR- 386A

TITLE: "Phase II Poly NET 90 Injectable Study"

INSTITUTION: Emory University

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

FUNDING PERIOD: 12/1/85-5/31/87

AMOUNT FUNDED: \$49,542

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

OBJECTIVE OF THE PROJECT:

To evaluate the safety and contraceptive effectiveness of 65mg and 100mg injectable NET formulations.

SUMMARY OF PROJECT TO DATE:

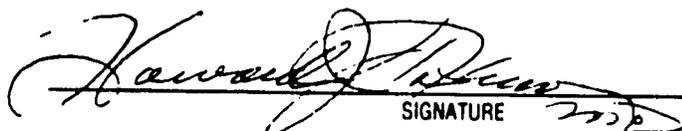
Recruitment of participants for the study was initiated January 8, 1986, but was stopped temporarily due to administrative delays. These problems were resolved and participant recruitment was resumed on May 19, 1986.

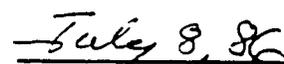
Because a large number of women were being excluded from the study for being overweight, Dr. Alfredo Goldsmith granted permission on May 30, 1986 for the revised Metropolitan Life Insurance Company Table to be substituted for the original height-weight table provided by PARFR. Although the Metropolitan Table revises upward the "ideal weights", numerous women have needed to be excluded from the study for being overweight.

Eleven patients have been preadmitted to the study as of July 8, 1986 and three additional patients have appointments. On the average, two patients have been preadmitted per week. One patient has been admitted to the study and was given her first injection June 5, 1986.

EXPECTED OUTCOME:

Completion of volunteer enrollment and continuation of the study on safety and contraceptive effectiveness of injectable NET formulations.


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

PARFR- 386C

TITLE: "Phase II Poly NET 90 Injectable Study"

INSTITUTION: Instituto Chileno de Medicina Reproductiva

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

FUNDING PERIOD: 12/1/85-5/31/87

AMOUNT FUNDED: \$25,036

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

The objective of this study is to evaluate the safety and contraceptive effectiveness of 2 injectable formulations of microencapsulated NET (65 mg and 100 mg). The study is designed to assess: the frequency of pregnancy, side effects and adverse reactions, bleeding pattern and NET plasma levels through one year during which each women will receive injections at 90 day intervals.

Twenty healthy women were enrolled, ten in each dose group. The first subject received the first injection on January 6 and the last one on June 12. The second injection has been administered to four subjects. No pregnancies have occurred and no major problems have been reported. No subject has been terminated.

The bleeding pattern is well tolerated and amenorrhea or hypomenorrhea are the predominant feature.

Blood samples for NET determination have been drawn according to the protocol and submitted for analysis.

The injection procedure is not difficult but air bubbles frequently stick to the injection syringe and complicate the procedure.

The trial is ongoing according to the protocol and the results are encouraging.



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July 1, 86

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

PARFR- 386F

TITLE: "Phase II Poly NET 90 Injectable Study"

INSTITUTION: Mount Sinai Medical Center of Greater Miami

PRINCIPAL INVESTIGATOR: Jerome J. Hoffman, M.D.

FUNDING PERIOD: 12/1/85-5/31/86

AMOUNT FUNDED: \$52,549

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

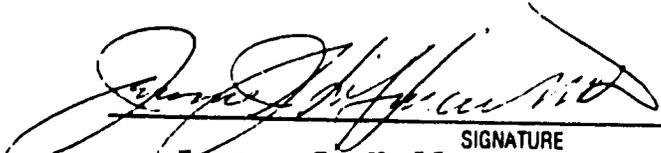
This is a Phase II study the objective of which is to evaluate the safety and contraceptive effectiveness of formulations of 65 mg and 100 mgm of norethindrone contained in absorbable microspheres. It is a single blind study involving 20 patients, followed for one year, and receiving four deep intramuscular injections at three month intervals.

To date we have seen 24 patients (including rejectees) for 86 visits. 17 patients have been injected, six of whom have been injected for a second time. Four more patients have been screened and are awaiting their menses before reporting in for their first injection. One patient who has been injected once is moving to Tampa and will have to drop out. We are awaiting a decision from PARFR Northwestern as to whether we should replace her. This is why we have screened four more patients instead of the requisite three.

We have encountered no pregnancies nor any major problems. Six patients have been observed to have long periods of amenorrhea. Two had episodes of prolonged and heavier menses. One patient was observed to have had some intermenstrual staining. In general, complaints have been few and menstrual aberrations were reported when solicited but not, for the most part, offered as a complaint.

At this juncture, though early, it appears that NET in both dosages functions as an effective means of conception control. While, in most instances, the menses are affected in a number of ways, none of these were severe enough to elicit expressions of patient discontent.

July 3, 1986


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Jerome J. Hoffman, M.D., F.A.C.S.

DATE

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

PARFR- 386 I

TITLE: "Phase II Poly NET 90 Injectable Study"

INSTITUTION: Associazione per Studio della Riproduzione Umana

PRINCIPAL INVESTIGATOR: Giuseppe Benagiano, M.D.

FUNDING PERIOD: 12/1/85-5/31/87

AMOUNT FUNDED: \$25,190

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

During this period the study has moved from the preparative stage into the actual clinical phase.

Thirteen subjects have been screened among volunteers recruited through the field clinic of the Association for Contraceptive Education and the Family Planning Unit of the First Department of Obstetrics and Gynecology of the University of Rome la Sapienza.

On 30 June 1986, ~~13~~ 8 volunteers have been injected and it is expected that at least ten more could be injected by the end of the next month when some ten to fifteen more volunteers will be interviewed.

A major problem encountered in recruiting and selecting subjects is the poor cycle control achieved in the first 5 subjects: although all five accepted to continue in the study, they all complained of serious menstrual disturbance following the first injection.

It must be understood that the average Italian woman does not tolerate any disturbance related to menstruation, as this scares them, beside the obvious interference with sexual activity.

Since in the field clinic the Lady in charge of logistics talks freely to possible volunteers and encourages them to accept to participate, we have a relatively high number of women who show up to discuss participation. However, they have all been warned by the Lady in question that this "medicine" causes menstrual disorders and - since we cannot deny it, we find it increasingly difficult to convince women to volunteer.

No other side effect of any importance has been found so far and women in the study are frank to admit that, if cycle control were better, they would unhesitatingly choose this injection.

Scarelli

18/7/1986

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

JUL 7 1986

PARFR- 386J

TITLE: "Phase II Poly NET 90 Injectable Study"

INSTITUTION: University Hospital of Jacksonville

PRINCIPAL INVESTIGATOR: Andrew M. Kaunitz, M.D.

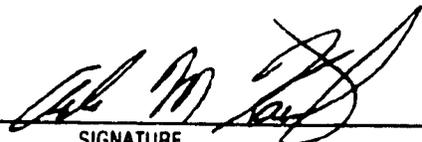
FUNDING PERIOD: 12/1/85-5/31/87

AMOUNT FUNDED: \$34,822

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

The purpose of this investigation is to evaluate clinical efficacy, menstrual effects and possible adverse effects of the injectable Poly NET 90 contraceptive. During the period 1-1-86 through 6-30-86:

- Patients #1 through #20 were enrolled.
- Ten patients were discontinued 90 days after their first injection due to protocol problems. All of these patients used the NET injection as their sole contraception for their 90 day participation. No pregnancies or significant adverse effects occurred in this cohort.
- Four other patients will receive no additional injection:
 - Two women were not compliant with follow-up study procedures
 - One woman has headaches
 - One woman developed a rash approximately one week after her NET injection
- The 6 women continuing in the study are overall very pleased with the study preparation. No pregnancies have occurred, and the bleeding patterns have in general been quite agreeable to the study participants, all of whom hope to continue this contraceptive method for the duration of the study.


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

PARFR- 386M

TITLE: "Phase II Poly NET 90 Injectable Study"

INSTITUTION: Instituto de Investigacion Cientifica

PRINCIPAL INVESTIGATOR: Roberto Rivera, M.D.

FUNDING PERIOD: 12/1/85 -5/31/87

AMOUNT FUNDED: \$25,762

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

Telex sent July 26, 1986. No response.

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DATE

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

PARFR- 387N

TITLE: "Phase II Poly NET 90 Injectable Study - Pharmacokinetics"

INSTITUTION: Cornell University Medical College

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

FUNDING PERIOD: 12/1/85-11/30/86

AMOUNT FUNDED: \$99,532

Below is a project summary for the **JANUARY 1986 through JULY 11, 1986** period.

A total of 50 volunteers have been interviewed to participate in the Phase II polynet microsphere contraceptive efficacy study. Primary clinical evaluation has been done to select potential volunteers who may meet the criteria of enrollment in the study. Twenty-six volunteers have actually entered into full evaluation of the control cycle. A total of seven volunteers did not qualify for the study. Currently a total of nine volunteers are undergoing evaluation of the control cycle. Eleven volunteers have already received their first injections, out of which four volunteers have also received their second injection. There are five volunteers in the orange group, i.e. injected with 100 mg NET and six in green group, i.e. injected with 65 mg NET. The cumulative observations are as follows: (1) Ovulation: There is total suppression of ovulation in all of the volunteers starting from the first month of injections in both the groups. (2) Bleeding Patterns: Three volunteers in the 65 mg NET group (Green) showed prolonged episodes of bleeding and/or spotting, without excessive bleeding. One volunteer remained in total amenorrhea. One volunteer in the 100 mg NET group (orange) showed total amenorrhea and one volunteer showed occasional intermenstrual spotting. However, bleeding and/or spotting episodes have not been a major complaint by the volunteers in either 65 mg (green) or 100 mg (orange) NET groups. (3) Contraceptive Efficacy: There has not been any incidence of pregnancy in either group. (4) Side Effects: There is no evidence of weight gain, water retention, breast discomfort or uterine cramps, so far, in any of the volunteers who have received polynet injections. There has been no reaction, pain or discomfort in ten volunteers at the site of injection, however one volunteer developed pain in the same buttock 16 days after the injection. (5) There has been no change in serum LDL/HDL ratio from pre to post injection cycles in all the volunteers. (6) There is no significant change in serum SMAC from pre to post injection cycles in all the volunteers. The pap smear urinalysis, haemoglobin levels did not change from the pre to post injection cycle in all the volunteers. All the NET samples and used injection syringes have been sent to Stroll Research and Development Corporation. The serum sample for SMBG analysis have been sent to Population Council. Comments: At this stage of the study it appears that polynet microspheres injection as delivery system for contraception is highly acceptable by the volunteers and there have been no pregnancies so far. This method of contraception has potential of a safe and acceptable method of fertility control.

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

PARFR- 387P

TITLE: "Phase II Poly NET 90 Injectable Study - Pharmacokinetics"

INSTITUTION: Magee-Women's Hospital

PRINCIPAL INVESTIGATOR: David Archer, M.D.

FUNDING PERIOD: 12/1/85 - 11/30/86

AMOUNT FUNDED: \$95,951

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

The objectives of this study are to evaluate the safety, contraceptive effectiveness, and effect on ovarian function of 65 and 100 mg doses of the injectable NET formulation. Pharmacokinetics of each dose will also be studied.

Our first patient was injected February 1986, and through July 11, 1986, 17 women have received their first injections. Additionally, five women have received their second injection. Out of 18 screening endometrial biopsies, 4 were anovulatory and were repeated before injections were given.

Estrogen and progesterone serum levels following NET injections have been compatible with inhibition of ovarian function in the six women's blood analyzed to date.

The only unusual symptoms noted by any of the patients have been a facial rash in one patient, hives on legs in another, acne in a third, and a hemoglobin of 10.6 gm in a fourth. No treatment was required except for the recommendation of an iron supplement for the low hemoglobin. The patient who noted hives on her legs was given injections of depo medrol on two occasions and is currently under treatment by an allergist for symptoms thought to be related to an allergy to dusts and molds.

Bleeding patterns have been light in 4 patients, regular in 4, and lasting over 10 days per month in 4 patients, although not heavy flow. The women experiencing more days of bleeding have indicated that this would not hinder them from continuing the drug.

It is anticipated that another initial injection will be given by July 18, 1986. Our final two volunteers are scheduled for evaluation in July, and should therefore receive the first injection by August 30, 1986.

David Archer MD

SIGNATURE

July 14, 1986

DATE

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

PARFR- 387T

TITLE: "Phase I Poly NET 90 Injectable Study - Pharmacokinetics"

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

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

FUNDING PERIOD: 12/1/86 - 11/30/86 AMOUNT FUNDED: \$99,241

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

A total of 14 out of 20 patients have now completed the study. So far the side effects are minimal: slight weight gain (3 to 8 pounds), and complaints of spotting throughout the cycle. No allergic reactions have been reported.

NET samples were sent to Stolle on June 23, 1986. The last five used syringes and needles containing norethindrone were shipped to Dr. Beck on May 21, 1986.

The last two patients of the NET 90 study were injected on May 16, 1986. On July 17, 1986, the completed information for the month proceeding was sent to FHI.

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

PARFR- 388

TITLE: "Preparation and Characterization of Poly NET 30 Microspheres
for Phase I Clinical Study"

INSTITUTION: Stolle Research and Development Corporation

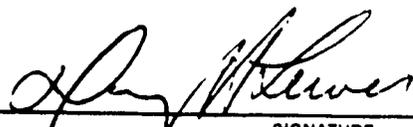
PRINCIPAL INVESTIGATOR: Danny H. Lewis, Ph.D.

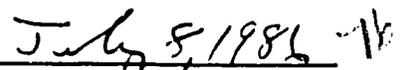
FUNDING PERIOD: 11/1/85-3/31/86

AMOUNT FUNDED: \$29,307

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

The objective of this project was the preparation and pre-clinical characterization of Poly NET 30 microspheres for a Phase I clinical study. Clinical supplies were produced under GMP in the Stolle Parenteral Drug Facility in Cincinnati, Ohio. The microspheres were manufactured by the patented Stolle micro-encapsulation process previously used to produce a similar Poly NET 90 system. The clinical materials were completely characterized in vitro and in two baboons. Drug-loaded syringes were delivered to PARFR during the first quarter of 1986 for the Phase I study. A formal storage stability study was initiated at Stolle on the Phase I supplies. This 30-day NET system is essentially developed, and expanded Phase II trials could be initiated at the completion of the Phase I study. Future research and development efforts will be aimed at scale up and stability studies as the basic formulation is now in place.


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

PARFR- 388M

TITLE: "Phase I Poly NET 30 Injectable Study"

INSTITUTION: Instituto de Investigacion Cientifica

PRINCIPAL INVESTIGATOR: Roberto Rivera, M.D.

FUNDING PERIOD: 3/1/86-12/31/86

AMOUNT FUNDED: \$5 3,064

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

Telex sent July 26, 1986. No response.

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

PARFR- 389

TITLE: "Insertion Technique of a Reversible Vas Deferens Occlusive Device"

INSTITUTION: PROPATER: "Promocao da Paternidade Responsavel:"

PRINCIPAL INVESTIGATOR: Marcos Paulo P. de Castro, M.D.

FUNDING PERIOD: 1/18/86-1/28/86

AMOUNT FUNDED: \$1,795

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

Objective: To test the techniques for insertion of a reversible vas occlusive device (the Shug) in human subjects.

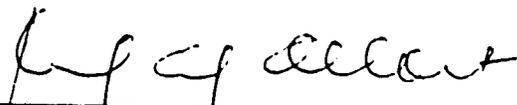
Summary: A total of 10 patients were used for the study, ranging in age from 31 to 43 years old. Various different insertion devices were tested, and the technique that proved to be optimal was:

- 1) surgical exposition of the vas;
- 2) introduction of telescoping trochar into the vas lumen;
- 3) remotion of the trochar and insertion of the Shug into the vas lumen;
- 4) the same procedure is repeated on the other side, so that one end of the Shug was directed towards the testis and the other end towards the seminal vesicles;
- 5) removal, by pulling the Shug out of the vas.

After remotion of the Shug, a standard vasectomy was performed in each patient.

Follow-up: Follow-up interviews at one week, one month and 3 months after surgery were uneventfull.

Conclusion and expected outcome: It can be concluded that the implantation of the Shug can be performed successfully and relatively simply, requiring about 5 min. for each side. The Shug fits the vas snugly and the patient experiences no additional pain. Some improvements can still be made in the implantation technique but this is not essential for a Phase I Clinical Trial (although it would be preferable).



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June 24, 1986

DATE

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

PARFR- 391

TITLE: "Phase I Progesterone Microcapsule Clinical Trial"

INSTITUTION: Northwestern University

PRINCIPAL INVESTIGATOR: Robert W. Rebar, M.D.

FUNDING PERIOD: 1/1/86-12/31/86

AMOUNT FUNDED: \$69,352

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

The Northwestern University clinical trial of progesterone microcapsules to examine pharmacokinetics and pharmacodynamics of controlled release progesterone microcapsules was designed to originally involve postpartum women, who had undergone a postpartum tubal ligation, were not breast feeding their infants, and could be injected within 5 days of delivery. Since the original proposal two years have past and our clinic population, from whom we were to draw our subjects, has increasingly decided to breast feed their newborns and to undergo interval tubal ligation procedures, leaving no subjects eligible for our study. We have therefore re-designed the protocol to study normally cycling women who have undergone a tubal ligation. The study design allows the subject to serve as her own control, with an intensive study in the Clinical Research Center of both the follicular and luteal phases of the cycle during the month prior to the progesterone injection. The injection is scheduled for the first 1 to 3 days of the menstrual cycle, prior to recruitment of the dominant follicle, and follow up is for six months afterward, with an intensive study eight weeks after injection. The study as redesigned has been approved by the Institutional Review Board of Northwestern University, and pending FDA approval should begin shortly.

Robert W. Rebar

SIGNATURE

7/14/86

DATE

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FINAL REPORT SUMMARY

AUG 1 1986

PARFR CD-RI-001

Title: Training and Collaboration in Molecular
Biology

Institution: Joslin Diabetes Center

Principal Investigator: William W. Chin, M.D.

Funding Period: 10/1/85 - 6/30/86

Introduction:

The major objective of this proposal was the transfer of the technologies of the "new biology" (molecular biology and recombinant DNA) to biomedical research establishments in India. It is likely that these fields will play important roles in the solution of some of the multitude of biomedical problems that face this developing nation. It was in the spirit of encouraging the growth and development of a critical mass of scientists and technical individuals who are proficient in these areas that the original work was proposed.

Specific Aims

The two specific aims for this funding period were: (1)

instruction and training of Dr. Swatantra K. Jain in the major techniques of molecular biology and recombinant DNA technology. These methods included (a) cDNA and genomic DNA cloning with construction of DNA libraries, (b) clonal isolation and selection via in situ hybridization, (c) gene expression in foreign cells including gene transfer, and (d) DNA characterization including restriction enzyme mapping and nucleotide sequence analysis; and (2) arrangement of transfer of these technologies to India.

Specific Approaches

In order to effect this anticipated transfer of technology, it was proposed that Dr. Swatantra K. Jain, an accomplished biochemist who has had scientific training both in India and in the United States, pursue specific objectives during the brief tenure of this funding period. It was proposed that many of the techniques of molecular biology and recombinant technology would be obtained by pursuing a well-defined project. In general, work focused on the production of large quantities of authentic, biologically active gonadotropins for use in immunization trials in the ongoing immunocontraceptive program.

The specific objectives included:

1. To prepare cDNA and genomic DNA libraries from ovine and bovine anterior pituitary glands and ruminant liver, respectively, using conventional and expression vectors. To identify cDNA and genomic clones encoding the α and β subunits of LH and FSH. To determine the structure and DNA sequence of these DNAs.

2. To express these DNAs in foreign mammalian cells and lower eucaryotes in order to produce authentic ovine and bovine gonadotropins.
3. To isolate the biologically active hormones from these gonadotropin-producing cells in anticipation of large-scale production for immunization protocols.
4. To assemble a procedures manual in molecular biology for use upon return to India.

Progress

Over the nine months of the funding period, considerable progress has been made in the original specific goals. First, Dr. Jain received extensive training in various aspects of gene cloning.

Second, efforts to clone cDNAs and genomic DNAs encoding the subunits of ovine and bovine LH and FSH were successful. After initial difficulties in our attempts to obtain good mRNA using commercially available pituitaries, we were successful with fresh ovine pituitaries from a local slaughterhouse that were rapidly frozen in liquid nitrogen. The pituitary mRNA was isolated by conventional methods and was intact as judged by agarose gel electrophoresis. The mRNA was then transferred to a nitrocellulose filter and the blot was hybridized to labeled rat α and LH β cDNAs which are available in our laboratory. Since extensive homology between rat and ovine gonadotropins was expected, we anticipated that the rat probes would

-4-

hybridize with ovine RNA and DNA. At moderate stringencies of hybridization of 3X SSC at 55°C, our prediction proved to be correct. The Northern blot analysis revealed that the RNA preparation contained intact α and LH β mRNA and hence that the rat probes would be useful to isolate ovine gonadotropin subunit cDNAs.

Then, cDNA was prepared from pituitary mRNA using reverse transcriptase. The DNA-RNA hybrids were treated with RNase H and E. coli DNA polymerase I--Klenow fragment which produced double-stranded cDNAs. The analysis of the cDNAs showed that their sizes were distributed between 0.2 -- 2 Kb. To obtain an ovine pituitary gland cDNA library, two approaches were utilized. The first approach involved the addition of homopolymeric dC "tails" to cDNAs and the annealing of these cDNAs to G-tailed pBR 322 (Pst I digest). The resulting recombinants were used to transfect E. coli. Screening of about 350 colonies with the rat α probe resulted in one clone encoding the α subunit of ovine pituitary gonadotropins. This clone contains a 450-500 bp insert and an internal Pst I site. Further characterization of the clone including partial sequencing indicates that it contains much of the coding region of the α subunit precursor.

The screening of about 1500 colonies from the same library with rat LH β probe yielded one clone encoding the ovine LH β subunit. This clone contains an insert of about 650 bp and gives a single insert upon digestion with Pst I. A comparison of the size of this insert with the approximate size of LH β mRNA as seen by Northern blot analysis of mRNA suggests that this cDNA appears to be a

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-5-

near full-length clone for LH β . Again further sequence analysis confirms its identity as a cDNA encoding ovine LH β subunit.

An additional 25,000 colonies were further screened with a small region of bovine FSH β subunit cDNA. A few putative FSH β clones have been isolated. These clones contain inserts of about 1.4 Kb which are appropriate inasmuch as the size of human and bovine FSH β subunit mRNAs are 1.7 Kb in size. However these clones need further characterization before we can be sure of their identities.

In the second cDNA cloning approach, EcoRI linkers were ligated to blunt-ended ovine pituitary cDNA which were then recombined to EcoRI-digested arms of bacteriophage λ gt10. A library was constructed using this approach. The initial screening of this and a human genomic DNA library in λ Charon 26 with the FSH β probe has provided several other putative FSH β cDNA clones. These cDNAs are also being characterized further to confirm their identities.

In conclusion, Dr. Jain has received extensive training in several aspects of molecular cloning that were not in his previous extensive molecular biology experience. Specifically, he has familiarized himself in the use of phage vectors for molecular cloning. These included: λ gt 10, λ gt 11 and λ Charon 26 vectors. Since use of phages requires totally different processes than the use of plasmids (an area where Dr. Jain had the experience), this training will be very helpful in carrying out his future projects at the National Institute of Immunology. He also received training in DNA sequence analysis using the M13 system. DNA sequencing is a critical

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tool to characterize agene as well as to understand its regulation. Dr. Jain also received training in tissue culture techniques and use of mammalian cell lines as hosts for the growth and expression of recombinant DNAs.

Summary

Considerable progress has been made in achieving the goals set at the beginning of the project. Also, arrangements have been made to continue the collaboration. The present project has thus laid a foundation for a long and mutually beneficial understanding and collaboration between two groups interested in related research problems. Even though Dr. Jain had prior expertise in various aspects of molecular biology, he obtained further training in cDNA and genomic DNA cloning techniques in which he had much less experience. During this funding period, Dr. Jain was able to obtain first hand knowledge of all of the techniques described in the original specific objectives.

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

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PARFR- CR-RI-002

TITLE: "Training and Collaboration in Bovine and Murine In Vitro
Fertilization and Gamete Culture"

INSTITUTION: University of Wisconsin - Madison

PRINCIPAL INVESTIGATOR: Neal L. First, Ph.D.

FUNDING PERIOD: 10/21/85 - 3/31/86

AMOUNT FUNDED: \$7,292

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

No response.

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

PARFR-CD-RI-005

TITLE: "Training and Collaboration in Immunocontraception"

INSTITUTION: Brigham and Women's Hospital

PRINCIPAL INVESTIGATOR: Deborah J. Anderson, Ph.D.

FUNDING PERIOD: 4/27/86-6/30/86

AMOUNT FUNDED: \$7,884

Below is a project summary for the January 1, 1986 - June 30, 1986 period.

The objectives of this program were: 1) to enable Dr. Upadhyay to participate in the WHO-sponsored workshop on sperm antigens; 2) to enable Dr. Upadhyay to further characterize anti-sperm monoclonal antibodies produced at the NII in India; and 3) to expose Dr. Upadhyay to basic immunology concepts and techniques including immunohistology and immunoblotting.

Dr. Upadhyay has just finished his 2 month stay in my laboratory and has successfully accomplished the objectives listed above. In addition we have written a collaborative research proposal to investigate the role of cell-mediated immunity in infertility.

Deborah Anderson
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7/27/86
DATE

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