

AGENCY FOR INTERNATIONAL DEVELOPMENT
WASHINGTON, D C 20523
BIBLIOGRAPHIC INPUT SHEET

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Batch 94

1 SUBJECT CLASSIFICATION	A PRIMARY Serials	Y-PC00-0000-0000	
	B SECONDARY Population--Family planning		
2 TITLE AND SUBTITLE Program for Applied Research on Fertility Regulation; progress report, Jan.-June, 1978			
3 AUTHOR(S) (101) Northwestern Univ. Medical School			
4 DOCUMENT DATE 1978	5 NUMBER OF PAGES 56p.	6 ARC NUMBER ARC	
7 REFERENCE ORGANIZATION NAME AND ADDRESS Northwestern			
8 SUPPLEMENTARY NOTES (Sponsoring Organization, Publisher, Availability) (Research summary)			
9 ABSTRACT			

10 CONTROL NUMBER PN-AAG-180	11. PRICE OF DOCUMENT
12 DESCRIPTORS Fertility Research	13 PROJECT NUMBER 931054600
	14 CONTRACT NUMBER GSD-3608 Res.
	15 TYPE OF DOCUMENT

PROGRAM FOR APPLIED RESEARCH
ON FERTILITY REGULATION

SEMI-ANNUAL REPORT

JANUARY 1, 1978 - JUNE 30, 1978

Submitted to: Research Division
 Office of Population
 Development Support Bureau
 Agency for International Development
 Department of State
 Washington, D.C. 20523

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

In compliance with Contract AID/csd-3608

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REPORT SUMMARY

Project Title and Contract Number:

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

Principal Investigator:

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

Contractor:

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

Contract Period:

July 1, 1975 - June 30, 1978

Reporting Period:

January 1, 1978 - June 30, 1978

Total Expenditures Through December 31, 1977: \$1,429,278.85

Total Expenditures January 1, 1978 - June 30, 1978: \$ 447,526.02

Outstanding Commitments at June 30, 1978: \$ 502,565.02

CONTRACT OBJECTIVES

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

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

ACCOMPLISHMENTS

PROGRAM ACCOMPLISHMENTS

LDC Involvement

Dr. Gerald I. Zatuchni participated in a project development site visit January 24-28, 1978 in Mexico City to formulate a research protocol for a Phase I clinical trial of a biodegradable polymer long-acting steroid system, developed at the University of Alabama and Southern Research Institute, under PARFR support (PARFR-83N). Dr. Zatuchni was accompanied by Drs. Lee Beck, Reproductive Biologist at University of Alabama, Don Cowsar, Polymer Chemist, Southern Research Institute, and Joseph Goldzieher, Southwest Foundation for Research and Education, San Antonio, Texas. All met with Drs. Jorge Martinez-Manitou, Executive Director of the National Family Planning Program, Ramon Aznar, Gynecologist, Juan Giner, Gynecologist, M. Inagueo, Family Planning Consultant, Harry Rudell, Consultant to the Executive Director, Luis Sobrevilla, Population Council Consultant, Gordon Perkins, Ford Foundation - PIACT, and Cervantes, Andrologist and Mr. Thomas R. Donnelly, AID, to seek interest in several PARFR projects and specifically to investigate a clinical trial for PARFR-83N. Dr. Jorge Martinez-Manitou felt that PARFR could arrange a clinical trial and subcontract to Centro de Investigacion de Fertilidad y Esterilidad (CIFE), with the principal investigators - being Drs. Aznar and Zamora, for a Phase I clinical study on the use of a long-acting biodegradable polymer containing norethisterone.

Dr. Aquiles Sobrero was Program Chairman for the Pan American Conference on Fertility and Sterility in Cancun, Mexico from January 29 to February 5, 1978.

PARFR Staff exhibited at the American Fertility Society, March 30 - April 1, 1978 in New Orleans, Louisiana. Ms. Krier met with Dr. Ivo Brosens, Catholic University of Leuven, Belgium, to finalize negotiations relating to a pilot study, IFRP collaboration, on a reversible female sterilization technique. PARFR Staff met with several Latin American researchers. Dr. Zatuchni met with Dr. van Os to discuss PARFR involvement in an IUD Symposium in June, 1979 in Holland. Dr. Zatuchni suggested a collaboration of Dr. van Os with Dr. Laumas (India) in that an IUD meeting was planned for New Delhi in March, 1979.

April 10-12, 1978, Dr. Zatuchni attended the ACOG Meeting in Anaheim, California and made valuable contacts for PARFR's proposed clinical trials.

PARFR Staff organized, a non-AID supported International Workshop and Postgraduate Course on Pregnancy Termination Procedures, Safety and New Developments, May 23-26, 1978, Nassau, Bahamas. One hundred and seventy-five persons attended with twenty-four countries represented. The countries, with the number of persons in parenthesis, are: Antigua (1), Bangladesh (1), Canada (3), Colombia (5), England (4), India (1), Iran (2), Italy (1), Holland (11), Kenya (1), Korea (3), Mexico (1), Morocco (1), Nigeria (1), Philippines (1), Singapore (1), Sweden (3), Switzerland (2), Sudan (1), Thailand (2), United States (125), West Germany (1), Yugoslavia (2), and Zambia (1). PARFR Staff were able to meet personally with all these individuals and discuss possible collaborative research interests.

Relating to current PARFR interests, Dr. Zatuchni and Ms. Krier met with Drs. Che (Korean Ministry of Health), Hong (Korea University), and Moon (Yonsei University) relating to the PARFR MCA Study (Dr. Hong) and Midtrimester Abortion Study (Drs Moon and Hong). Dr. Hong had arrived in Nassau from a training session in Cologne, Germany on the MCA project.

Drs. Zatuchni and Sciarra met with PARFR Committee to plan the next workshop on Intravaginal Contraception for April, 1979 in Guatemala.

PARFR continued recruitment for a Research Project Development Coordinator and is negotiating with Elizabeth B. Connell, M.D. for acceptance of the position, with a proposed start date of September 1, 1978. This position has been created primarily for project development involving foreign travel aimed at the initiation of Phase I clinical trials and their subsequent monitoring in less developed countries.

PROGRAM ACCOMPLISHMENTSAdministrative Summary

In addition to the routine management of the Program, the efforts of the PARFR Administrative Staff for this period were chiefly directed toward:

- (1) Preparation and development of an information sheet on PARFR for distribution via mailings and medical exhibits.
- (2) The Scientific Advisory Committee agenda for the March 29, 1978 was coordinated which included: one extension proposal, six formal proposals, two pilot studies and six informal proposals; and project monitoring, including three site visit reports and five technical reports on active projects. The June SAC Meeting was postponed to July 10, 1978 due to schedule conflicts. This change necessitated five PARFR projects to be administratively extended three months for continuity of research, until the determination of the committee was made.
- (3) Negotiation and execution of subcontracts for two extended research projects (PARFR-98M and 99N); negotiation and amendment of one subcontract for continuation of previously supported research (PARFR-83N) and development of two formal proposals from acceptable informal proposals submitted. Two pilot studies were negotiated and one executed (PARFR-P13), which had been approved for funding at the December, 1977 SAC Meeting.
- (4) The manuscripts from the December, 1977 Reversal of Sterilization Workshop were submitted to Harper & Row in February. Page proofs were corrected in April. The completed publication is anticipated for November, 1978.
- (5) The publication, Risks, Benefits and Controversies in Fertility Control was released in May, 1978 and 150 copies were distributed to speakers, staff and other participants. USAID purchased 1500 copies at publisher's cost.
- (6) PARFR Exhibit at the American Fertility Society, March 30 - April 1, 1978 in New Orleans, Louisiana.
- (7) Began editing manuscripts from the Workshop and Postgraduate Course on Pregnancy Termination: Procedures, Safety and New Developments.
- (8) Interviewed candidates for the staff position, Research Project Development Coordinator, with the anticipation of candidate selection and acceptance by September 1, 1978.

- (9) N.U. promotion of Ms. Georgia Fackler, PARFR's Project Controller, effective April 1, 1978.
- (10) Acquired IBM Memory Typewriter on February 24, 1978 which increases support staff efficiency and productivity.
- (11) Susan C.M. Scrimshaw, Ph.D. was approved for a one-year term on the Scientific Advisory Committee, beginning with the July 10, 1978 Meeting; one vacancy remains on the SAC.
- (12) Refining and monitoring the recently developed comprehensive financial system.

Staffing of the Program was modified to include the following during this report period.

Program Director	John J. Sciarra, M D., Ph.D.
Director of Administration	Diane H. Krier, M.B.A.
Director of Technical Assistance	Gerald I. Zatuchni, M.D., M.Sc.
Project Coordinator	Aquiles J. Sobrero, M.D.
Project Controller	Georgia L. Fackler, B.A.
Department Assistant I	Hazel Hagen
Two Full-Time Secretaries	Ruvenia Thomas Mary Rose Traylor
One Part-Time Secretary	Juliet Paynter

Hazel Hagen resigned the position of Department Assistant I effective February 24, 1978.

SUBCONTRACT NEGOTIATIONS

<u>PROJECT #</u>	<u>TITLE, INVESTIGATOR & INSTITUTION</u>	<u>ACTION</u>	<u>PERIOD</u>	<u>FUNDING</u>
PARFR-79N	"A Method for Reversible Sterilization in the Female" C. I. Meeker, M.D. Maine Medical Center	Extension w/funds (Amend #1)	7/1/78 - 9/30/78	\$ 5,543.75
PARFR-83N	"Studies to Test an Injectable Delivery System for the Sustained Release of Norethisterone" Lee R. Beck, Ph.D. University of Alabama	Add'l funding (Amend # 4) Extension w/funds (Amend #5)	4/1/77 - 3/31/78 4/1/78 - 3/31/79	\$ 5,000.00 \$29,975.00
PARFR-89N	"Fallopian Tube Cauterization Enclosure by Silver Acetate-Alginate Formulations" Harry P. Gregor, Ph.D. Columbia University St. Luke's Hospital Animal Care Facility	Animal Care Purchase Order Extension w/funds (Amend #1)	11/1/77 - 6/30/78 1/15/78 - 1/14/79	\$17,558.75 \$13,216.00
PARFR-90N	"New Method for Obstructing the Vas Deferens by Direct Injection of Chemical Agents: A Non-Operative Technique of Male Sterilization" Joseph E. Davis, M.D. New York Medical College	Change Project Period (Amend #1) No-cost extension (Amend #2)	7/1/77 - 6/30/78 7/1/77 - 9/30/78	- 0 - - 0 -

PARFR-92N	"Contraception by Induction of Mild Uterine Inflammation" Deborah J. Anderson, Ph.D. Medical Research Foundation of Oregon	Extension w/funds (Amend #1)	1/1/78 - 6/30/78	\$19,252.65
PARFR-94N	"Modern Modified Aldridge Procedure" William Droegemueller, M.D. University of Arizona	Change Project Period (Amend #1)	12/1/77 - 9/30/78	-- 0 -
PARFR-95N	"Development & Evaluation of a Reversible Vas Deferens Blocking Device" L.J.D. Zaneveld, D.V.M., Ph.D. University of Illinois	Add'l funding (Amend #1)	7/1/77 - 6/30/78	\$15,284.00
PARFR-96N	"Long Term Study on the Effectiveness of an Injectable Polymer System in Producing Tubal Occlusion in Rabbits" Ramaa P. Rao, M.D. Michael Reese Hospital & Medical Center	New Sub-contract	3/15/78 - 9/14/78	\$18,805.00
PARFR-P10	"Fertility Regulation by Control of Progesterone Clearance" Robert T. Chatterton, Ph.D. University of Illinois	Change Project Period (Amend #1)	1/1/78 - 7/31/78	- 0 -

PARFR-P11	"Evaluation of Carbohexoxymethyl 2 Cyanoacrylate as a Tube-Blocking Agent"	New Sub- contract	2/1/78 - 6/30/78	\$ 5,970.00
	Ralph M. Richart, M.D. Columbia University	No-cost Extension	2/1/78 - 6/30/79	- 0 -
PARFR-P13	"An Evaluation of the Efficacy of Candidate Fimbrial Prosthesis in Female Rabbits and the Evaluation of Fimbrial Devices as a Reversible Technique of Female Sterilization" Ivo Brosens, M.D., Ph.D. Catholic University of Leuven International Fertility Research Program	New Sub- contract	5/1/78 - 4/30/79	\$ 4,741.38
		Purchase Order	5/1/78 - 4/30/79	\$ 1,700.00

PERSONNEL

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

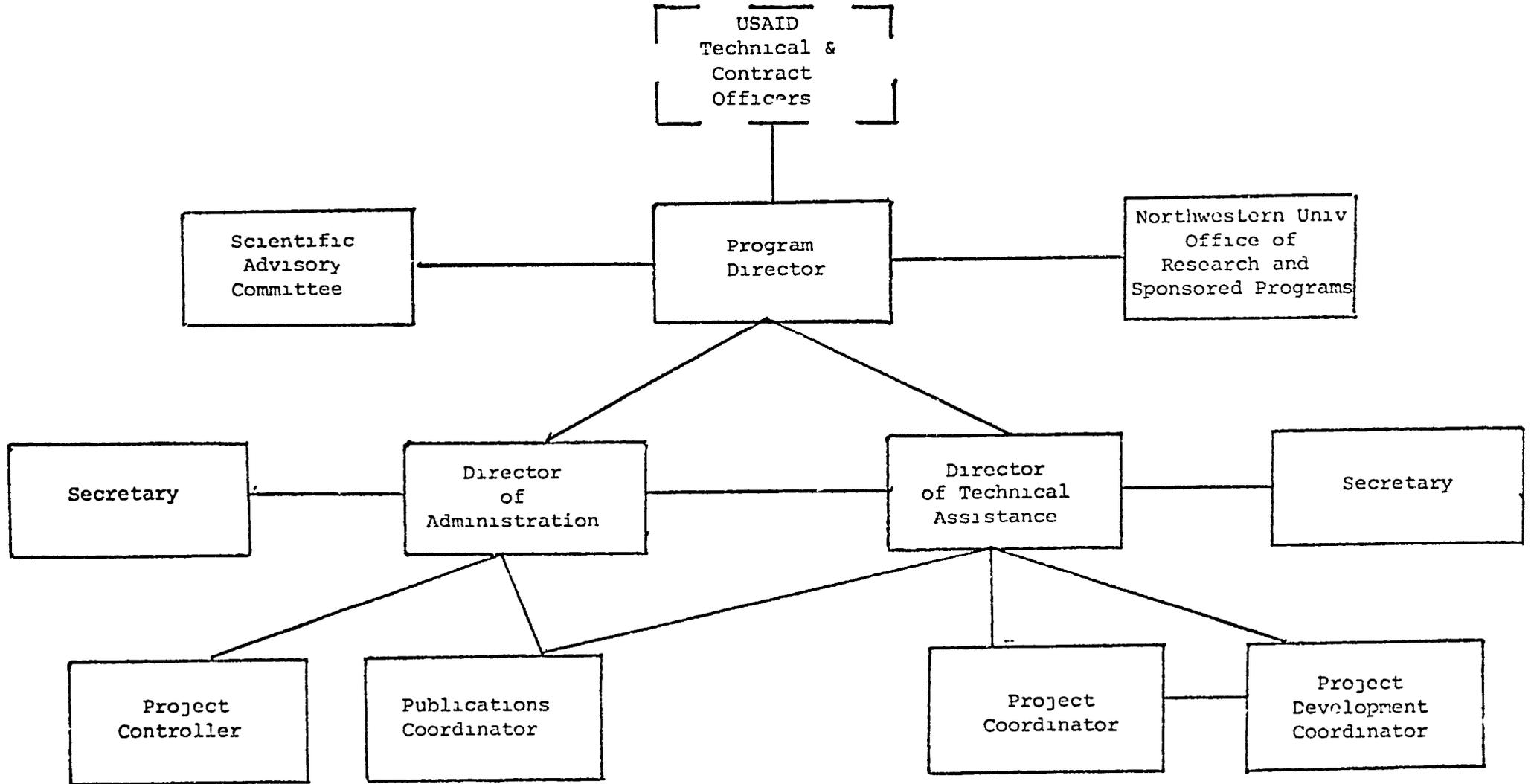
<u>Staff and Title</u>	<u>Effort in Man-Months</u>	<u>Salary</u>
John J. Sciarra, M.D., Ph.D. Director & Principal Investigator	.9	-0-
Gerald I. Zatuchni, M.D., M.Sc. Director of Technical Assistance	4.2	16,624.98
Aquiles J. Sobrero, M.D. Foreign Technical Project Coordinator	1.5	4,500.00
Diane H. Krier Director of Administration	6.0	8,749.98
Georgia L. Fackler Project Controller	6.0	6,441.00
Kelley Osborn Publications Coordinator	.2	1,760.00
Hazel Hagen Department Assistant I	1.9	1,970.16
Ruvenia Thomas Secretary I	6.0	4,701.48
Mary Rose Traylor Secretary I	6.0	4,766.00
<u>Temporary Services</u>		
Temporary Secretary	6.0	6,209.92*
<u>Fringe Benefits</u>		6,931.89
<u>Indirect Costs</u>		14,854.09

* Salary for temporary secretary has been charged to the Supplies budget line item, rather than Salaries, since this is a required procedure at Northwestern University.

Administrative Organization

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

PARFR Organization



Scientific Advisory Committee

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

John J. Sciarra, M.D., Ph.D., Chairman	Northwestern University
Nancy J. Alexander, Ph.D.	Oregon Regional Primate Research Center
Robert T. Chatterton, Ph.D.	University of Illinois
Joseph E. Davis, M.D.	New York Medical College
William Droegemueller, M.D.	University of Arizona
Edward C. Mather, D.V.M., Ph.D.	University of Minnesota
Robert H. Messer, M.D.	University of New Mexico
Kamran S. Moghissi	Wayne State University
Ralph M. Richart, M.D.	Columbia University
Judith L. Vaitukaitis, M.D.	Boston University
A. Albert Yuzpe, M.D.	University of Western Ontario Canada

At the March meeting, Dr. Moghissi joined the Committee, filling the vacancy left by Dr. Bedford. Approval was received to add Susan C. M. Scrimshaw to the Committee, filling a long-standing vacancy. Her membership will begin with the July meeting.

The Scientific Advisory Committee (SAC) held one meeting during this period; March 29, 1978, in New Orleans, Louisiana. Minutes of this meeting are included in the Appendix.

At this SAC meeting, the Committee reviewed Technical Reports for presently funded projects. One project (PARFR-83N) scheduled to expire during this reporting period was reviewed in depth by the Committee, which voted to extend the subcontract.

Six informal proposals were reviewed by SAC, with resultant recommendation that two formal proposals be solicited. These projects are:

"Investigation of New Compounds to Terminate Pregnancy"
Leonard J. Lerner, Ph.D., Jefferson Medical College

"Testing a New Vaginal Barrier Contraceptive, The Anti-Conception Tampon (ACT) with Unique Spermicide Delivery System"
Ernest W. Page, M.D., University of California, San Francisco

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

"Norethisterone Microcapsule Injectable Contraceptive Study"
Ramon Aznar, M.D. and Gustavo Zamora, M.D., Centro De Investigacion Sobre Fertilidad y Esterilidad, Mexico City, Mexico

"Immunoabsorbent Isolation of Specific Spermatozoal Antigens for Use as Anti-Fertility Immunogens"
Duane L. Garner, Ph.D., Oklahoma State University

Two pilot proposals were reviewed by SAC, with resultant recommendation that neither project be funded.

SITE VISITS

Site visits were conducted on four projects during this reporting period:

<u>Project #</u>	<u>Title of Project</u>	<u>Site Visitors</u>	<u>Date</u>
PARFR-80N	Fertility Control Through Local Cervical Injection Of Microencapsulated Pro- gestins David W. Keller, M.D. Washington University	E. Mather, D.V.M., Ph.D. D. Krier	2/15/78
PARFR-85N	Collagen Sponge Contra- ceptive -- Testing of Efficacy in Human Volun- teers Milos Chvapil, M.D., Ph.D. University of Arizona	R. Messer, M.D. G. Zatuchni, M.D.	3/15/78
PARFR-91N	Preparation and Evaluation of Biodegradable Cylindrical Implants for Fertility Con- trol Donald L. Wise, Ph.D. Dynatech R/D Company	G. Whitesides, Ph.D. G. Zatuchni, M.D.	5/18/78
PARFR-P8	Water Soluble Condom Feasibility Study Charles Salivar The Emko Company	E. Mather, D.V.M., Ph.D. D. Krier	2/16/78

The following project development site visits were conducted during this re-
porting period:

<u>Site</u>	<u>Site Visitors</u>	<u>Date</u>
Centro de Investigacion Sobre Fertilidad y Esterilidad Mexico City, Mexico (PARFR-98M)	G. Zatuchni, M.D. L. Beck, Ph.D. D. Cowsar, Ph.D. J. Goldzieher, M.D.	1/24-27/78
* "A Retrospective study of Alpha- Adrenergic Blockade (Bethanidine) on Human Male Fertility" Several Centers in England	A. Markland, M.D.	2/2-3/17/78
* Evangelisches Krankenhaus Cologne, West Germany (PARFR-86N,G,K)	R. Neuwirth, M.D. S. Hong, M.D.	5/12-22/78
* Yonsei University Seoul, South Korea (PARFR-97N,K)	R. Burkman, M.D.	5/29-6/2/78

* No consulting fees were paid for these project development site visits; only
travel expenses were reimbursed by PARFR

CONSULTANTS

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

Consultant	Purpose	Effort	Fee
Nancy J. Alexander, Ph.D. Reproductive Physiology	SAC, 3/28-29/78	2 days	\$300.00
J. Michael Bedford, Vet.M.B., Ph.D. Male Reproductive Physiology	1 Review		25.00
Robert T. Chatterton, Ph.D. Steroid Biochemistry	SAC, 3/28-29/78	2 days	300.00
Joseph E. Davis, M.D. Urology	SAC, 3/28-29/78	2 days	300.00
William Droege Mueller, M.D. Obstetrics and Gynecology	SAC, 3/28-29/78	2 days	300.00
Edward C. Mather, D.V.M., Ph.D. Animal Reproductive Physiology	SAC, 3/28-29/78	2 days	300.00
Robert H. Messer, M.D. Obstetrics and Gynecology	Site Visit (3/15-16/78) SAC, 3/28-29/78	1 1/2 days 2 days	225.00 300.00
Kamran S. Moghissi, M.D. Obstetrics and Gynecology Reproductive Endocrinology	SAC, 3/28-29/78	2 days	300.00
Ralph M. Richart, M.D. Obstetrics and Gynecology Pathology	SAC, 3/28-29/78	2 days	300.00
Judith L. Vaitukaitis, M.D. Endocrinology	SAC, 3/28-29/78 1 Review	2 days	300.00 25.00
A. Albert Yuzpe, M.D. Obstetrics and Gynecology	SAC, 3/28-29/78	2 days	300.00
Lee R. Beck, Ph.D. Reproductive Biology	Project Development Mexico City, Mexico 1/24-27/78	4 days	400.00
Donald R. Cowser, Ph.D. Chemistry	Project Development Mexico City, Mexico 1/24-27/78	4 days	400.00
Erwin Goldberg, Ph.D. Reproductive Biochemistry	1 Review		25.00
J. W. Goldzieher, M.D. Endocrinology	Project Development Mexico City, Mexico 1/25/78	1 day	100.00

Consultant	Purpose	Effort	Fee
George M. Whitesides, Ph.D. Polymer Chemistry	Site Visit (5/18/78)	1 day	150.00
L.J.D. Zaneveld, D.V.M., Ph.D. Physiology	Project Development Cologne W. Germany 6/13/78	1 day	100.00
TOTAL:			4,450.00



PROGRAM ACCOMPLISHMENTSSubcontracts

Below are capsule summaries of work proceeding under subcontracts during this reporting period (January 1, 1978 to June 30, 1978):

Project: PARFR-54N

An Evaluation of Loops C and D with Copper Comparing Results
In a Developed and a Developing Country

Jack Lippes, M.D. -- Planned Parenthood of Buffalo (New York)
Lenworth M. Jacobs, M.D. -- Jamaica Family Planning Association

\$62,844

7/1/75 - 12/31/77

Objectives: To find an improved contraceptive device and comparatively evaluate 2-year results obtained in a developed country vs. a developing country to determine whether copper provides an improved intrauterine device by adding copper to Loops C and D.

Accomplishments:

This study was terminated on December 31, 1977. A final report was received in accordance with the terms of the subcontract. The two year net cumulative event, closure and continuation rates for Loops C and D in Jamaica and Buffalo are as follows:

	<u>Jamaica</u>	<u>Buffalo</u>
<u>Event</u>		
Accidental pregnancy	1.19 + .22	1.93 + .44
Expulsion	20.91 + .99	5.21 + .73
Removal for:		
Medical reasons		
Bleeding, pain	17.90 + .97	30.50 + 1.84
Other medical	2.49 + .35	9.36 + .99
Planning pregnancy	4.47 + .50	4.13 + .69
Other personal reasons	13.82 + .92	4.00 + .70
<u>Closure</u>		
Accidental pregnancy	1.19 + .22	1.93 + .44
Expulsion	15.13 + .84	5.21 + .73
Removal for:		
Medical reasons		
Bleeding, pain	17.90 + .97	30.50 + 1.84
Other medical	2.49 + .35	9.36 + .99
Planning pregnancy	4.47 + .50	4.13 + .69
Other personal reasons	13.34 + .90	4.00 + .70
Continuation rate	45.49 + 2.23	44.85 + 3.25
Woman-months of use	5,466	2,608

PARFR-54N

Accomplishments: (continued)

It would appear that the addition of copper to Loops C and D has improved the effectiveness of this device in reducing pregnancies. However, this advantage has been offset by the greater discontinuation of the devices, both in Jamaica and Buffalo. In Jamaica, the greater discontinuation was accounted for by an increased expulsion rate, while in Buffalo, the greater discontinuation was due to bleeding. From this study, it may be concluded that it is probably better for family planning programs to continue to use the inert loop because it has a higher continuation rate, even though the inert loop has a somewhat greater pregnancy rate.

Project: PARFR-63B

Development of a Reversible and Permanent Uterotubal Blocking Technique by Hysteroscopy

Abdol H. Hosseinian, M.D. -- University of Chicago, Chgo. Med. School
Lourens J.D. Zaneveld, D.V.M., Ph.D., -- University of Illinois

\$53,480

7/1/75 - 6/30/78

Objectives: To negate the present drawbacks of which electrocoagulation of the uterotubal junction by hysteroscopy suffers by mechanically blocking the uterotubal junction by a device which could be easily carried, implanted and/or removed by a suitable hysteroscope: to provide a technique that could be carried out in a physician's office under local anesthesia.

Accomplishments:

The accomplishments were fully described in the previous semi-annual report. During this report period, the animals in whom the devices had been removed were continually bred and an additional two pregnancies resulted. In summary, 21 baboons of proven fertility had the devices implanted and no pregnancy resulted. Removal of the devices was carried out in 14 baboons of whom 11 were bred to evaluate the reversibility of the sterilization technique. A total of 7 pregnant baboons have been observed. Three baboons underwent hysterectomy and the pathology report indicated good tissue tolerance for the devices. As far as could be determined, the tubes were patent upon removal of the devices, even after a period of over two years of use.

The research findings have been incorporated into the Phase I clinical study performed in Iran under PARFR-87N.

Project: PARFR-79N

A Method for Reversible Sterilization in the Female

C. Irving Meeker, M.D. -- Maine Medical Center

\$32,370 2/1/77 - 8/31/77 (Vermont)
\$48,594 9/1/77 - 9/30/78 (Maine)

Objectives: To fabricate a variety of special devices designed for use in the stump-tail macaque monkey and to insert them in 45 animals. Observations will be carried out with regard to effectiveness against pregnancy, and later removal of the devices and fertility restoration.

Accomplishments:

Forty-one animals have had the tubal insertion of the device. Two animals died secondary to trauma received in fights with the male. The other animals have been continuously bred for over ten cycles and no pregnancies have resulted. In the spring of 1978, most of the animals were reoperated and the devices removed. Gross observation revealed imbedding of the suture around the tube with great difficulty for removal in some of them. In two animals, a mild hydrosalpinx was noted proximal to the device. The devices were easily milked out of the tube in all animals. The animals are currently in breeding. Several of the animals have been kept with the devices in the tubes for longer term observation.

Project: PARFR-80N

Fertility Control through Local Cervical Injection of Micro-encapsulated Progestins

David W. Keller, M.D. -- Washington University, St. Louis
Robert E. Sparks, D.Eng.

\$168,526 7/1/75 - 7/11/78

Objectives: The two primary objectives of this project are to demonstrate that low concentrations of progesterone administered locally into the cervix are potentially effective contraceptive agents, and that sustained-release, bioabsorbable capsules can be developed to achieve long-term contraception utilizing the cervical injection technique.

Accomplishments:

Microencapsulation of progesterone has been developed and provides appropriate release rates both in vivo and in vitro. Unfortunately, major difficulties were encountered in the research protocol and the experimental animal model (cow). The animal results were inconclusive with regard to the con-

PARFR-80N

Accomplishments: (continued)

traceptive effect of progesterone released in micro quantities at the cervix. Increasing the dosage to extremely high levels did not seem appropriate as a useful means of contraception.

The Scientific Advisory Committee, at its July 10, 1978 meeting, reviewed an extension request and voted not to extend the project. The project was amended to 7/11/78 to cover animal costs.

Project: PARFR-81N

Clinical Evaluation of Intrauterine Devices Containing Epsilon Aminocaproic Acid (EACA)

Peter F Tauber, M.D. -- University of Essen, West Germany

\$53,187 5/1/76 - 6/30/78

Objectives. The objectives have been to determine the possible uptake of the antifibrinolytic agent, EACA, into the general bloodstream of women following intrauterine administration of the drug; enrollment of a small number of women to determine efficacy and side effects of this medicated IUD, to determine actual blood loss by atomic absorption spectrophotometry of menstrual tampons and napkins collected during two menstrual periods.

Accomplishments:

The investigator has enrolled three groups of sixty women each using the following intrauterine devices: 1) ml-cu250; 2) ml-cu250 with EACA capsule; and 3) plain multi-load device. Two pregnancies resulted in women having the plain multi-load device; accordingly, this device was excluded from the comparison study. The other women had periodic blood loss determinations, and the data are presently being analyzed. A three month extension (to 9/30/78) with additional funding is in process.

Project: PARFR-82N

Measurement of Blood Loss of Women Fitted With Copper-Clad and Standard Lippes Loops

Fouad Hefnawi, M.B., M.S. -- Al-Azhar University, Cairo, Egypt

\$59,329 11/1/75 - 6/30/78

Objectives: To determine the event rate, acceptability and measured blood loss in women having either a standard Lippes Loop or a Copper-Clad Lippes Loop.

Project: PARFR-84N

Evaluation of the Copper-T IUD as a Post-Coital Method of Contraception

Jack Lippes, M.D. -- Planned Parenthood of Buffalo, New York

\$25,693

10/1/77 - 6/30/78

Objectives: To select 100 patients from the Planned Parenthood of Buffalo Clinics requesting post-coital contraception within 96 hours of unprotected mid-cycle intercourse. These patients will have a Copper-T Intrauterine Device inserted. Various tests will be carried out, including the new, extremely sensitive beta-HCG measurements.

Accomplishments:

Because the investigator has found it next to impossible to obtain volunteers for hormonal studies following insertion of the Copper-T IUD, the study has terminated. Instead and at much reduced cost, the principal investigator will collate life-table rates on the 250 women who have had a Copper-T or Copper-7 device inserted following unprotected mid-cycle intercourse. This data will be available by September, 1978.

Project: PARFR-85N

Collagen Sponge Contraceptive: Testing of Efficacy in Human Volunteers

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

\$98,124

12/1/76 - 6/30/78

Objectives. To develop and test an intravaginal long-acting contraceptive made of collagen sponge, capable of self-administration.

Accomplishments:

Post-coital sperm penetration studies have been completed in twenty-one couples. They affirm the effectiveness of the collagen sponge acting as a mechanical block. It now appears that two different sized sponges will be required, mostly depending upon the relaxation of the vaginal walls. Women will be instructed to try to use the larger size first, and if uncomfortable, switch to the smaller size.

A suitable number of sponges with attached tapes have been received from the West German manufacturer. A total of 65 couples have been enrolled as volunteers in this clinical efficacy study. These couples will use only the collagen sponge over the next period of six to twelve months.

Due to delays in manufacture and the necessary completion of the post-coital testing, the project has been delayed. Accordingly, a no-cost extension has been requested and approved for a period of six months to December 31, 1978.

Project: PARFR-86N, G & K

Phase I Clinical Trial of Fallopian Tube Closure Using Methylcyanoacrylate Tissue Adhesive Delivered Through the Single Application Fertility Regulating Device

Robert S. Neuwirth, M.D. -- St. Luke's Institute for Health Sciences
Ralph M. Richart, M.D. -- Columbia University

PARFR-86N \$36,602 6/1/78 - 5/31/79

Objectives: To determine the safety and efficacy of the single application fertility regulation device for the delivery of methylcyanoacrylate to the fallopian tubes of human volunteers.

Accomplishments:

The study will be undertaken in one South Korean institution (Korea University, PARFR-86K, 6/1/78-5/31/79, \$16,080) and one German institution (PARFR-86G, 9/1/78-8/31/79, \$27,159). Dr. Sung-bong Hong (Korea University) participated in a training session in Cologne, Germany in May, 1978. The principal investigators intend to arrange additional clinical trials in other LDCs.

Project: PARFR-87N

Hysteroscopic Sterilization Technique by Using Uterotubal Junction (UTJ) Blocking Devices

Abdol H. Hosseini, M.D. -- Reza Pahlavi Medical Center
Chicago Medical School and Cook County Hospital

\$17,310 11/1/76 - 10/31/77 (Iran)

Objectives: To investigate the efficacy of mechanically blocking the uterotubal junction by means of a device which could be implanted in or removed from the tubal ostium through hysteroscopy.

Accomplishments:

The Phase I human study for UTJ Device insertion and removal has been completed in a satisfactory manner. The investigator has modified the hysteroscope in order to obtain a better lateral angle for the insertion of the devices. This modification has been carried out by Eder Instrument Company, Chicago. The investigator is now using this modified instrument in Iran. If suitable, the investigator proposes a clinical efficacy study in Iran and in two or three other countries. A proposal for this study will be submitted to SAC in the fall of 1978.

Project: PARFR-88N

Study to Determine the Safety and Efficacy of Copper-Releasing IUDs as a Method of Post-Coital Contraception

Louise B. Tyrer, M.D. -- Planned Parenthood Federation of America, Inc.

\$83,020

3/1/77 - 8/31/78

Objectives: To determine the effectiveness of copper-releasing IUDs in preventing intrauterine pregnancy in a population of women following unprotected mid-cycle intercourse to ascertain that in those in whom conception occurs, there is not an unacceptably high rate of extrauterine implantation.

Accomplishments:

This study failed to enroll sufficient numbers of volunteer women willing to accept an IUD as a post-coital method of contraception and to return to the clinic every other day for pregnancy hormone and other studies. Accordingly, the study will be terminated.

Project: PARFR-89N

Fallopian Tube Cauterization and Closure by Silver Acetate-Alginate Formulations

Harry P. Gregor, Ph.D. -- Columbia University, New York

\$82,684

1/15/77 - 1/14/79

Separate agreement with St. Luke's Hospital for animal charges.

\$31,844

11/1/77 - 9/30/78

Total Budget relating to PARFR-89N: \$114,528.

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

PARFR-89N (continued)

Accomplishments:

Working closely with his colleagues at St. Luke's Hospital, the investigator has been successful in developing appropriate formulations of appropriate viscosity in order for the material to be delivered "blindly" via the use of the specially designed administration system. The material has been placed in monkeys to determine tubal closure effects. These results will be available in the fall of 1978. If this formulation appears satisfactory, a parallel study, under WHO auspices, will be carried out in Lucknow, India using the monkey facilities there.

Project: PARFR-90J

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

Joseph E. Davis, M.D. -- New York Medical College

\$59,305

7/1/77 - 9/30/78

Objectives: To test in 100 human volunteers a direct percutaneous injection of a mixture of ethanol and formalin as a vas-occlusive agent.

Accomplishments:

Twenty-seven volunteers seeking vasectomy agreed to participate in this study and underwent bilateral vas injection between October, 1977 and April, 1978. The results are promising. Bilateral vas injection can result in azoospermia, although the results thus far are not consistent. Several problems remain, including standardized delivery of the material, the question of reinjection after an appropriate period of follow-up, and from a scientific point of view, histopathologic examination of the vas in those men who have azoospermia.

The principal investigator is collaborating with biomedical engineers in the development of a more feasible delivery system.

Project: PARFR-91N

Preparation and Evaluation of Biodegradable Cylindrical Implants
for Fertility Control

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

\$80,440

6/1/77 - 9/30/78

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

Accomplishments:

Biodegradable cylindrical implants releasing d-norgestrel have been manufactured and implanted in baboons and small animals, in accordance with the study protocol.

A site visit of this project was done in May, 1978 and suggestions were made to engineer a more appropriate implant configuration. The present implant requires approximately 30 cm. of rod which has to be inserted via a trocar.

The investigators have completed all phases of the first portion of this project, and will be requesting an extension at the September, 1978 SAC Meeting.

Project: PARFR-92N

Contraception by Induction of Mild Uterine Inflammation

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

\$36,145

6/1/77 - 6/30/78

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

Accomplishments:

The investigator has submitted an extension proposal to SAC to continue studies on the use of various matrix substances that provide for a slow release of glycogen which has been found to have a contragestational effect when administered in appropriate doses on certain days of pregnancy.

Project: PARFR-93N

Workshop on Animal Models of Fertility and Contraception

Nancy Muckenhirn, Ph.D. -- National Academy of Sciences,
Institute for Laboratory Animal Resources

\$50,500

8/1/77 - 6/30/78

Objectives: To organize an international workshop on the use of laboratory animals in reproductive research to be held at the National Academy of Sciences in May, 1978. The scientific papers, poster exhibits, and proceedings will be published. The publication should serve as a manual for the use of animals in reproductive research and contraceptive development.

Accomplishments:

The workshop was held May 8-10, 1978 and was received very positively. PARFR has negotiated the publication of the proceedings with Harper and Row Publishers. Publication date is anticipated for May, 1979.

Project: PARFR-94N

Modern Modified Aldridge Procedure

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

\$37,744

12/1/77 - 9/30/78

Objectives: To test in baboons a modern modification of the Aldridge procedure; specifically, a surgical technique of enclosing the fimbria of the fallopian tubes in a stocking made of microporous expanded polytetrafluoroethylene.

Accomplishments:

The tubal hoods were hand manufactured at the University of Arizona and in January, 1978, the animals had the caps implanted. The animals are being observed for fertility. At an appropriate time, the majority of animals will be re-operated, the devices removed, and mating again carried out to establish the reversibility of the procedures.

Project: PARFR-95N

Development and Evaluation of a Reversible Vas Deferens Blocking Device

Lourens J.D. Zaneveld, D.V.M., Ph.D. -- University of Illinois

\$68,102

7/1/77 - 9/30/78

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

Accomplishments:

The study has been extended in order to provide longer term observation of the device in rabbits and in primates. Difficulties were encountered in moving from the rabbit to the primate model. A modified shug device has been developed and inserted in a number of monkeys. Thus far, all monkeys have reached very low or azoospermic levels.

Project: PARFR-96N

Long-Term Study on the Effectiveness of an Injectable Polymer System in Producing Tubal Occlusion in Rabbits

Ramaa P. Rao, M.D. -- Michael Reese Hospital & Medical Center
Antonio Scommegna, M.D. Chicago, Illinois

\$18,805

3/15/78 - 9/14/78

+ agreement with Abcor for providing polymer (\$1,500.)

Objectives: To determine the feasibility of tubal occlusion via an injectable polymer system in rabbits.

Accomplishments:

Abcor has been provided a small amount of funds to produce the polymer that will be used at the Michael Reese Animal Research Facility. Due to manufacturing delays, the polymer has not, as yet, been made.

Project: PARFR-P8

Water Soluble Condom Feasibility Study

Charles Salivar -- Emko Company, St. Louis

\$5,790

7/1/77 - 6/30/78

Objectives: To develop and test a biodegradable condom made of thin polylactate/glycolate containing spermicidal drug.

Accomplishments:

A large variety of biodegradable films have been examined with regard to their suitability for use as a spermicidal-containing condom. Several prototypes have been developed. The investigator has requested an extension for manufacture of a suitable number in order to do Phase I clinical studies. It is likely that these studies will begin in the winter of 1978.

Project: PARFR-P9

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

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

\$6,000

12/1/77 - 6/30/78

Objectives: To fabricate and evaluate in vitro progesterone-releasing fibers and microspheres connected by a fiber for potential contraceptive application in women.

Accomplishments:

Progesterone releasing fibers have been developed and are being studied in small animals for their release rates. An extension request has been approved to further develop the biochemical engineering processes, and to study a variety of uses for the slow releasing fibers. Animal studies will be done in cooperation with the University of Alabama.

Project: PARFR-P10

Fertility Regulation by Control of Progesterone Clearance

Robert T. Chatterton, Ph.D. -- University of Illinois

\$7,217

1/1/78 - 10/31/78

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

Accomplishments:

An antiprogestosterone antibody has been developed and studies indicate its effectiveness in reacting with progesterone. Major technical problems need to be addressed including appropriate encapsulation of the antibody in order to prevent gastric digestion and to provide sufficient residence in the small intestine to bind up like quantities of progesterone circulating through the entero-hepatic circulation.

Project: PARFR-P11

Evaluation of Carbohexoxymethyl 2 Cyanoacrylate as a Tube-Blocking Agent

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

\$5,790

2/1/78 - 6/30/79

Objectives: To determine the feasibility of carbohexoxymethyl 2 cyanoacrylate as a tube-blocking agent in primates.

Accomplishments:

The material, supplied by Ethicon, Inc., has been inserted in the fallopian tubes of six squirrel monkeys. Six months observation will determine its effectiveness and histopathologic findings.

Project: PARFR-P13

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

Ivo Brosens, M.D., Ph.D. -- Catholic University of Leuven, Belgium
Willem Boeckx, M.D.

\$4,741

5/1/78 - 4/30/79

+ agreement with IFRP (\$1,700).

Objectives: To determine the efficacy of a fimbrial hood in rabbits as a
reversible sterilization procedure.

Accomplishments:

The tubal hoods have been hand manufactured at IFRP and the
devices have been inserted in rabbits. They are being observed
via breeding for loss of fertility. After an appropriate period
of time, the rabbits will be reoperated and the devices removed.
Breeding experiments will again be carried out to determine
possible reversibility of these procedures.

WORK PLAN

WORK PLANAnticipated Accomplishments

During the next six months' reporting period, a substantial increase is anticipated in proposals submitted for consideration because of PARFR's attendance at relevant medical and scientific meetings, closer collaboration with other organizations working in the field of reproductive research and contraceptive development, greater effort at solicitation (RFP and Journal Announcements), and Dr. Elizabeth Connell's joining PARFR's Staff.

Completed negotiations with a Guatemalan Institution and possibly another Latin American institution is contemplated by November, 1978 for the Phase I Clinical Study on the use of MCA as a fallopian tube tissue adhesive, delivered by an instrument through the cervix without the need for surgery.

Negotiations should be completed for early Phase II Clinical Studies on the following PARFR-supported developments

Collagen Sponge - The investigator and PARFR are interested in supporting the further testing of the sponge in a variety of socio/cultural settings in both developed and developing countries.

Spermicidal Condom - Additional PARFR support will be requested to permit the small scale manufacture of a suitable number of spermicidal-containing, biodegradable condoms for clinical studies regarding acceptability and effectiveness. These clinical studies are anticipated to be carried out in the United States and in developing countries.

Uterotubal Junction Blocking Plug - The investigator and PARFR are working closely together in the equipment modifications required, and in the development of an appropriate protocol for Phase II human studies to be carried out in the United States, Iran, Thailand, and Germany.

Additional negotiations and eventual contracts support are anticipated for the following research: Continued Development and Testing of a Series of Related Compounds that Prevent the Degradation of Prostaglandins, to be carried out at the Jefferson Medical College, Philadelphia, and Lepetit Research Laboratories, Milan, Italy;

Dr. I. Meeker, Maine Medical Center, and several developing countries, for Phase I Clinical Testing of the Meeker Intratubal Device,

Similar negotiations will be started with several developing countries for the testing of certain new non-surgical methods for vas deferens obstruction, including the percutaneous injection of sclerosing agents, and electrocautery administered through the skin.

Data analysis will be completed on the metabolic differences of ethynyl estradiol administration among women in Nigeria, Sri Lanka, Thailand and The United States (Southwest Foundation; Dr. J. Goldzieher);

A protocol is being developed that will satisfy FDA toxicological requirements for the human use of quinacrine HCL in pellet form administered intrauterine for the purpose of tubal closure. Additionally, a clinical study may be supported by PARFR involving two or three Latin American institutions.

In November, 1978, Harper and Row Publishers will make available the Proceedings of the PARFR Workshop on "Reversal of Sterilization." This conference was held in December, 1977 in San Francisco, California.

The manuscripts and discussion summaries for the sixth PARFR-supported Workshop (PARFR-93N), "Animal Models for Research on Contraception and Fertility," held at the National Academy of Sciences in Washington, D.C. in May, 1978, has been completed and submitted to Harper and Row for expected publication in May, 1979.

The manuscripts and discussion summaries for the seventh PARFR Workshop, "Pregnancy Termination. Procedures, Safety and New Developments," held in Nassau, Bahamas in May, 1978, will be completed in August, 1978, and submitted to Harper and Row for expected publication in May, 1979.

PARFR is planning its eighth Workshop, "Intravaginal Contraception," to be held in April, 1979 in Guatemala. Publication of these proceedings is anticipated.

Procedures and Activities

The remaining Scientific Advisory Committee Meetings for 1978 are scheduled for:

July 10, 1978 (Chicago)
September 6, 1978 (Washington, D.C.)
December 11, 1978 (Chicago)

PARFR will exhibit at the annual meeting of the Association for Planned Parenthood Physicians on October 24-27, 1978 in San Diego, California.

Factors Affecting Accomplishments

PARFR envisions expansion in terms of the number of actively supported projects through the coming-on-board of Dr. Elizabeth Connell, as PARFR's Research Development Coordinator.

Plans for LDC Involvement

During the next six months, PARFR will be supporting collaborative research and development projects in South Korea, Mexico, and Thailand. Beginning negotiations regarding certain contraceptive research projects have been started with interested investigators in two Central American countries, four Middle East and Asian countries, and one country in Africa. With the continued support of USAID, it is entirely likely that PARFR will be able to mount a significant number of contraceptive research projects in developing countries during the next years. In addition, PARFR will continue to strengthen its involvement in developing countries by closer collaboration with international organizations working in the field of fertility control, and by seeking out opportunities in these countries for PARFR-initiated research.

PARFR FINANCIAL REPORT, 6/30/78

		<u>Budget</u> 7/1/75 - 6/30/78	<u>Expended</u> 7/1/75 - 6/30/77	<u>Expended</u> 7/1/77 - 12/31/77	<u>Expended</u> 1/1/78 - 6/30/78	<u>Expended</u> 7/1/75 - 6/30/78	<u>Outstand</u> <u>Commit.</u> a/o 6/30/78	<u>Uncommit.</u> <u>Balance</u>
Salaries	02	141,800.58	78,623.98	28,166.64	35,009.96	141,800.58	---	---
	03	82,828.88	41,890.48	16,014.03	14,503.64	72,408.15	---	10,420.73
Total Salaries		<u>224,629.46</u>	<u>120,514.46</u>	<u>44,180.67</u>	<u>49,513.60</u>	<u>214,208.73</u>	---	<u>10,420.73</u>
Frng. Bnfts.	13	30,259.04	15,734.01	6,134.28	6,931.89	28,800.19	---	1,458.86
Indirect Costs	88	78,050.05	45,795.51	14,274.37	14,854.09	74,923.97	---	3,126.08
Supplies	05	70,081.14	37,737.50	14,218.16	17,447.83	69,403.49	3,017.37	(2,339.72)
	09	135.00	---	---	---	---	---	135.00
	10	36.13	36.13	---	---	36.13	---	---
	12	712.00	---	22.00	645.00	667.00	45.00	---
	78	2,091.89	1,346.44	24.08	94.97	1,465.49	---	626.40
Total Supplies		<u>73,056.16</u>	<u>39,120.07</u>	<u>14,264.24</u>	<u>18,187.80</u>	<u>71,572.11</u>	<u>3,062.37</u>	<u>(1,578.32)</u>
Equipment	06	10,755.55	3,769.23	11.50	6,790.07	10,570.80	1,600.00	(1,415.25)
Consult. Fees	49	10,056.89	---	---	4,250.00	4,250.00	125.00	5,681.89
	50	19,523.11	13,573.11	3,425.00	2,525.00	19,523.11	---	---
Tot. Con. Fees.		<u>29,580.00</u>	<u>13,573.11</u>	<u>3,425.00</u>	<u>6,775.00</u>	<u>23,773.11</u>	<u>125.00</u>	<u>5,681.89</u>
Travel	07	117,950.14	48,850.14	13,130.47	15,253.46	77,234.07	934.00	39,782.07
Moving Expense	18	1,846.17	954.38	---	891.79	1,846.17	---	---
Remodel & Maint.	52	11,249.30	11,249.30	---	---	11,249.30	---	---
Wksp/Publ	91	168,275.21	48,275.21	18,321.18	28,307.94	94,904.33	---	73,370.88
Subcontracts	90	2,543,579.92	721,498.62	219,620.22	291,158.51	1,232,277.35	482,413.77	828,888.80
Pilot Studies	92	120,000.00	19,953.52	6,629.36	8,861.87	35,444.75	14,429.88	70,125.37
Tot. Research		<u>2,663,579.92</u>	<u>741,452.14</u>	<u>226,249.58</u>	<u>300,020.38</u>	<u>1,267,722.10</u>	<u>496,843.65</u>	<u>899,014.17</u>
Tot. Workshop		<u>168,275.21</u>	<u>48,275.21</u>	<u>18,321.18</u>	<u>28,307.94</u>	<u>94,904.33</u>	<u>---</u>	<u>73,370.88</u>
Tot. Admins.		<u>577,375.87</u>	<u>299,560.21</u>	<u>95,420.53</u>	<u>119,197.70</u>	<u>514,178.44</u>	<u>5,721.37</u>	<u>57,476.06</u>
Total Budget		<u>3,409,231.00</u>	<u>1,089,287.56</u>	<u>339,991.29</u>	<u>447,526.02</u>	<u>1,876,804.87</u>	<u>502,565.02</u>	<u>1,029,861.11</u>

SUMMARY FINANCIAL REPORT

7/1/75 - 6/30/78

	7/1/75-6/30/78 PARFR Total Budget at NU	EXPENDED 7/1/75- 6/30/77	EXPENDED 7/1/77- 6/30/78	EXPENDED 7/1/75- 6/30/78
Salaries & Wages	\$ 224,629.46	\$ 120,514.46	\$ 93,694.27	\$ 214,208.73
Fringe Benefits	30,259.04	15,734.01	13,066.17	28,800.18
Indirect Costs	78,050.05	45,795.51	29,128.46	74,923.97
Supplies	73,056.16	39,120.07	32,452.04	71,572.11
Equipment	10,755.55	3,769.23	6,801.57	10,570.80
Consulting Fees	29,580.00	13,573.11	10,200.00	23,773.11
Travel	117,950.14	48,850.14	28,383.93	77,234.07
Moving Expenses	1,846.17	954.38	891.79	1,846.17
Remodeling & Maint	11,249.30	11,249.30	----	11,249.30
Workshops/Publ	168,275.21	48,275.21	46,629.12	94,904.33
Subcontracts	2,543,579.92	721,498.62	510,778.73	1,232,277.35
Pilot Studies	120,000.00	19,953.52	15,491.23	35,444.75
TOTAL	\$3,409,231.00	\$1,089,287.56	\$ 787,517.31	\$1,876,804.87

PARFR Budget 7/1/78-6/30/79
as appropriated
at Northwestern University

SALARIES	166,920.73
FRINGE BENEFITS	23,800.36
INDIRECT COSTS	58,459.58
SUPPLIES	39,484.05
EQUIPMENT	5,184.75
CONSULTING FEES	27,170.89
TRAVEL	64,716.07
MOVING FEE/LEASE	5,000.00
REMODEL & MAINT.	5,000.00
WORKSHOPS/PUBL	101,870.88
SUBCONTRACTS	1,844,916.57
PILOT STUDIES	89,902.25
TOTAL RESEARCH	<u>1,934,818.82</u>
TOTAL WORKSHOP	101,870.88
TOTAL ADMIN	<u>395,736.43</u>
TOTAL BUDGET	<u>2,432,426.13</u>

PARFR SCIENTIFIC ADVISORY COMMITTEE

MEETING IV

NEW ORLEANS, LOUISIANA
March 29, 1978

VOTING SAC MEMBERS PRESENT

John J. Sciarra, M.D., Ph.D.
Nancy J. Alexander, Ph.D.
Robert T. Conaterton, Ph.D.
Joseph E. Davis, M.D.
William D. Genuelle, M.D.
Edward C. Mather, D.V.M.
Robert H. Messer, M.D.
Kamran S. Roghissi, M.D.
Ralph W. Richart, M.D.
Judith H. Vantubatis, M.D.
A. Albert Wozny, M.D.

PARFR STAFF PRESENT

Diane H. Krier
Aguiles J. Sobrero, M.D.
Gerald I. Zatuchni, M.D., M.Sc.

USAID MEMBERS PRESENT

Miriam Labbok, M.D.

The twenty-fourth meeting of the PARFR Scientific Advisory Committee convened on Wednesday, March 29, 1978 at 8:00 a.m. at the New Orleans Marriott in New Orleans, Louisiana. Dr. John J. Sciarra presided as chairman. Minutes of the December 7, 1977 meeting were approved with no voiced corrections.

I. AGENDA ITEMS

- A. Kamran S. Roghissi, M.D. from Wayne State University in Detroit was formally introduced to the SAC Members. A copy of his C.V. was circulated.
- B. The June 19, 1978 SAC Meeting was rescheduled for July 10, 1978 in Chicago at the O'Hare Regency Hyatt. The remaining SAC dates for 1978 remain the same.

September 6, 1978 -- Washington, D.C. International Inn (Thomas Circle)
December 11, 1978 -- Chicago, Illinois, Location to be determined.

II. NEW BUSINESS

A. Extension Proposal Review

1. PARFR-83 -- Lee K. Beck, Ph.D., University of Alabama in Birmingham

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

Dr. Zatuchni reported on his most recent conversation with Dr. Beck concerning this extension request. This extension proposal request was approved by the SAC Committee for PARFR continued funding provided that the vaginal micropheres study be deleted from the protocol. Dr. Zatuchni will confer with Dr. Beck concerning the suggested changes by the SAC Members.

B. Formal Proposal Review

1. Ramon Aznar, M.D. and Gustavo Zamora, M.D., Centro De Investigacion Sobre Fertilidad Y Esterilidad, A.C., Mexico City, Mexico

"Norethisterone Microcapsule Injectable Contraceptive Study"

Funding request \$55,579. Length of project one year.

Dr. Zatuchni reported on the January, 1978 project development site visit to Mexico along with Drs. Beck, Cowsar and Goldzieher. There was considerable discussion in regard to the modification of the proposed protocol and that the informed consent form should be modified. The Committee felt that Dr. Vaitukaitis should consult with Drs. Beck and Zatuchni in reworking this protocol. The SAC Members did vote to approve this project for funding provided that the protocol is modified to incorporate the suggestions of the Committee.

2. Charles M. Lynne, M.D., University of Miami

"Clinical Evaluation of a Reversible Vasectomy Device, The Bionyx Phaser"

Funding requested \$89,735.74. Length of project two years.

The SAC Committee voted not to approve this project for funding in that it would not be an appropriate method applicable to LDC's.

3. H. G. Madhwa Raj, Ph.D., University of North Carolina School of Medicine

"Active Immunization with Follicle Stimulating Hormone Sub-unit in the Male Monkey"

Funding requested \$66,035 for one year. Length of project two years.

The SAC Committee voted not to approve this project in that they felt the research proposed was too basic in nature and too long-term for PARFR consideration.

4. Duane L. Garner, Ph.D., Oklahoma State University, College of Veterinary Medicine

"Immunoabsorbent Isolation of Specific Spermatozoal Antigens for Use as Anti-Fertility Immunogens"

Funding requested \$56,853. Length of project one year.

The Committee felt that this was an area in immunological research that PARFR could support. However, the general consensus was that an immunological consult should be obtained prior to funding. Dr. Zatuchni would contact Dr. Erwin Goldberg, a professor in biological science at Northwestern University to request his consultation on the feasibility of the protocol. The SAC did vote to approve this project for funding provided the immunological consultation was favorable.

B. Formal Proposal Review (continued)

5. Virendra B. Mahesh, M.D., D.Phil., Medical College of Georgia

"Evaluation of Estradiol Pellet Implantation As a Method of Contraception"

Funding requested \$50-35,000 Length of project three years.

Dr. Zatushen presented a review of his conversations with Dr. Mahesh. This proposal is an off-shoot from PARER-66N whereby SAC at that time voted not to proceed with the extension request until an ID has been filed. SAC's primary concerns on this proposal were the potential side effects of estrogen. The Committee voted not to approve this project for funding.

6. T. W. Horna, Ph.D., Mankind Research Foundation, Inc., Silver Springs, Maryland

"Electronic Detection of Ovulation"

Funding requested \$37,900 Length of project one year.

This proposal was not approved for funding in that it was felt that it was not an acceptable or possible method especially for use in LDC's.

C. Pilot Study Review

1. T. K. Roberts, Ph.D., University of Newcastle, Department of Biological Sciences

"The Development of Cell-mediated Autoimmunity to Spermatozoa Following Vasectomy in Primates"

Funding requested \$5,324 Length of project ten months.

The SAC voted not to approve this project for funding in that it was too basic in nature.

2. Allan P. Gray, Ph.D., IIT Research Institute and L. J. D. Zaneveld, D.V.M., Ph.D., University of Illinois at the Medical Center

"Evaluation of Acrosin Inhibitors as Systemic Antifertility Agents"

Funding requested \$6,237. Length of project one year.

The SAC voted not to approve this project for funding because of potential toxicity of the compounds and the lack of evidence demonstrating an oral (systemic) effect.

D. Informal Proposal Review

The SAC voted not to request formal proposals from the following four projects.

1. Michael J. Free, Ph.D., Battelle

"The Electrocoagulator for Male Sterilization: Proposed Improvements in the State-of-the-Art"

Funding requested \$117,300. Length of project two years.

2. Professor Joseph Weinman and Dr. Hillel Armon, The Hebrew University - Hadassah Medical School (Israel)

"Attempt to Predict the Period of Fertility by Monitoring Blood Volume Changes in the Human Vagina During the Menstrual Cycle"

Funding requested \$69,000 Length of project two years.
3. Luis Grana, M.D. and John N. Keller, M.D., Chicago Medical School

"Reversible Female Sterilization Method by Full-Length Intratubal Catheter"

Funding requested \$38,253.40. Length of project one year.
4. Cappy Morris Rothman, M.D., Century City Hospital

"Diamond Ring"

Funding requested \$15,225. Length of project three months.
5. Leonard J. Lerner, Ph.D., Jefferson Medical College

"Investigation of New Compounds to Terminate Pregnancy"

Funding requested \$66,582. Length of project one year.

The SAC voted to request a formal proposal for review and discussion at the July 10th Meeting.
6. Ernest W. Page, M.D., University of California, San Francisco

"Testing a New Vaginal Barrier Contraceptive, the Anti-Conception Tampon (ACT) with Unique Spermicide Delivery System"

Funding requested \$67,792. Length of project one year.

Dr. Messer suggested that Dr. Page contact Dr. Chvapil to discuss his experience with the collagen sponge. The SAC voted to request a formal proposal for consideration at the July 10th Meeting.

E. Subcontract Monitoring

1. Site Visit Reports

- a. Dr. Mather and Diane Krier site visited Dr. Keller (PARFR-80N) on February 15, 1978 in St. Louis Missouri. Dr. Mather reported on the proceedings of the site visit. The site visitors felt that Dr. Keller would not request an extension at this point in time.

1. Site Visit Reports (continued)

- b. Dr. Mather and Diane Krieger met with Mr. Salivar and Mr. Belsky (PARFR-P3) on February 16, 1978 in St. Louis. Dr. Mather reported that Mr. Belsky was encouraged by the results of this pilot study and that he would be submitting an extension request to PARFR for consideration at the July, 1978 Meeting.
- c. Drs. Messer and Zatushni site visited Dr. Chvapil (PARFR-85N) on March 16, 1978 in Tucson, Arizona. Drs. Messer and Zatushni reported on the progress of Dr. Chvapil. He will begin human testing in April, 1978.

All site visit reports were included in the Agenda.

2. Technical Reports

The following technical reports were included in the Agenda for information purposes.

- a. PARFR-54N -- Lippes/Jacobs (Final)
- b. PARFR-87N -- Hosseinian
- c. PARFR-88N -- Tyrer
- d. PARFR-P8 -- Salivar/Belsky
- e. PARFR-P9 -- Lewis

III. OLD BUSINESS

A. Pending From 9/12/77 Meeting

1. PARFR-87N -- Dr. Hosseinian put the modification of the hysteroscope out to bid to KLI, Eder and Wolf. Dr. Hosseinian proposed that the modification be done by Eder and that their bid was very low - \$1600.

Dr. Droegemuller wanted it recorded in the minutes that he felt Dr. Zatushni does a superb job in negotiating PARFR projects, as with Hosseinian's project. The Committee concurred.

2. PARFR-96G -- Rao/Scornegna, Michael Reese - The subcontract has been approved at a funding level of \$18,800 with a start date of March 15, 1978, for a six month period. A purchase order with Abcor totaling \$1,500 has been approved for supplying the polymer to Michael Reese.

3. The following Amendments have been fully executed:

- a. PARFR-81K -- Tauber, Amendment #2
- b. PARFR-82N -- Hefnawi, Amendment #3

B. Updates on Determinations of the December 7, 1977 SAC Meeting

1. Extensions

- a. PARFR-92N -- Anderson has been fully executed.

1. Extensions (continued)

- b. PARFR-89d -- This Amendment has been approved and is currently at Columbia University for signatures. A purchase order with St. Luke's Hospital for the animal charges was approved by AID Technical and Contract Offices.

2. Formal Proposals

- a. Dr. T. King's mid trimester abortion study. A revised protocol has been submitted to PARFR. Ms. Krier is preparing communications with Dr. Moon at Yonsei in Korea regarding this study. Dr. R. Burkman will be doing a site visit to Korea in June, 1978. The Hopkins portion of this project is being negotiated.
- b. PARFR-86f. -- The St. Luke's Institute for Health Sciences, Principal Investigators - Drs. Neuwirth/Richart. This subcontract has been submitted to the AID Contract Office for approval. Dr. Neuwirth is proposing a training session in Cologne, Germany with Professor Zinser and Dr. Sung Bong Hong from Korea University to be scheduled the week of May 15, 1978. Ms. Krier is waiting for additional information before their subcontracts are sent to AID Contract Office for approval.

3. Pilot Studies

- a. Brosens/Bocckx/Laufe (PARFR-P13) -- Dr. Laufe will submit a revised protocol to PARFR in the next week. The subcontract will be prepared to the Catholic University of Leuven in Belgium, and a separate purchase order will be done with IFRP.
- b. PARFR-P10 -- Chatterton is fully executed
- c. Frisch -- Dr. J. Davis reported on his conversation with Dr. Frisch. His report was favorable and he felt that the pilot study should be funded. PARFR Staff will negotiate a subcontract with MIT with a proposed start date of June 1, 1978.

4. Informal Proposals

- a. Lele -- Dr. Davis has spoken with Dr. Lele and Dr. Lele requested to withdraw his proposal at this time.

C. Pilot Proposals (Funded but were not previously submitted to SAC)

1. PARFR-P11 - Richart - Fully Executed.

"Evaluation of Carbohexoxymethyl 2 Cyanoacrylate as a Tube-Blocking Device"

Funding requested \$5,970. Length of project six months.

C. Pilot Proposals (continued)

2. Stanwood S. Schmidt, M.D., University of California Medical School at San Francisco

"The Bipolar Needle for Percutaneous Vas Obstruction"

Funding requested \$3,354. Length of project one year.

PARFR is waiting to hear from the University of California Medical School at San Francisco regarding this proposal.

D. Active Project Updates

1. PARFR-90N -- Joseph E. Davis, M.D., New York Medical College

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

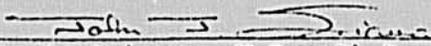
Dr. Davis enthusiastically reported on the progress of his study. He has completed twenty-six patients, eight of these are azoospermic within three months. Dr. Davis asked for suggestions of the SAC Committee in that he feels he needs to modify his delivery system.

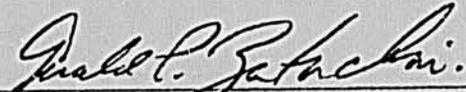
IV. MISCELLANEOUS

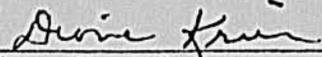
- A. Dr. Nancy Alexander reported on the progress of the NAS/ILAR workshop on Animal Models for Research on Contraception and Fertility, May 8-10, 1978 to be held at the NAS Auditorium in Washington, D.C.
- B. The International Workshop and Postgraduate Course on Pregnancy Termination: Procedures, Safety and New Developments, May 23-26, 1978, Nassau, Bahamas. The Program has shaped up nicely and the attendance response seems promising.
- C. It is suggested that the 1979 PARFR Workshop be held in conjunction with the Ob/Gyn meeting in Tokyo in October, 1979. Suggested sites are Philippines, Thailand, Sri Lanka, Singapore and Seoul. Suggested topics were IUD's, Releasing Devices Both Intravasal and Intravaginal, and Barrier Methods.

There being no further business, the meeting adjourned at 3:00 P.M.

Respectfully submitted,


John J. Sciarra, M.D., Ph.D.
Program Director, Chairman, SAC


Gerald I. Zatychni, M.D., M.Sc.
Director of Technical Assistance
PARFR


Diane H. Krier
Director of Administration
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MAILING ADDRESS

PROGRAM FOR APPLIED RESEARCH
 ON FERTILITY REGULATION
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The Program for Applied Research on Fertility Regulation (PARFR), Northwestern University, in association with the United States Agency for International Development, provides scientific and technical assistance and funding support to foreign and United States institutions for applied research in the field of contraceptive development. Priority is given to proposals of new or improved methods of fertility control appropriate for use in developing countries. Foreign-based research projects or collaborative efforts between United States and foreign institutions are encouraged.

Of major interest to PARFR are fertility control methods which

- Do not require physician services
- Do not require frequent administration
- Do not require high levels of motivation
- Can be self administered
- May be effective on a post coital or hind sight basis
- Minimize supply and distribution problems

Proposals are evaluated by the PARFR Staff and Scientific Advisory Committee. The selection involves two steps: 1) Brief informal proposals are screened and selected for conformity with PARFR's aims; 2) Selected investigators will be requested to prepare and submit formal proposals for further review. Projects selected for funding may receive maximum support of \$66,000 annually through subcontracting on a cost-reimbursable basis.

Specific areas of proposed research could include animal or human investigations leading to the development of contraceptive methods that

- Provide for long acting sustained release of contraceptive drugs or anti-fertility agents,
- Interfere with the maturation process of sperm or egg either at the local site of gametogenesis or at a central level,
- Interfere with the transport of gametes by pharmacologic or mechanical means,
- Interfere with the process of fertilization by pharmacologic or immunologic means,
- Interfere with the process of implantation by pharmacologic or mechanical means

PARFR RESEARCH PROJECTS

The following are research topics which have received PARFR support: biodegradable contraceptive drug release systems, intravaginal barrier methods, immunological approaches, intrauterine delivery systems, contragestational intervention methods, sperm enzyme inhibitors, male pharmacological methods, post-coital contraceptive methods, ovum transport manipulation, and luteolytic contraceptive agents.

Research projects involving male or female sterilization by pharmacological, mechanical, and surgical methods have received PARFR funding. PARFR is also supporting research involving several reversible occlusive sterilization devices in the male and female.

PILOT STUDIES

PARFR also funds short-term research projects designed to produce preliminary results from which extended research proposals may develop. These projects may receive maximum support of \$7,500 for a period not to exceed one year.

SCIENTIFIC WORKSHOPS & PUBLICATIONS

Five workshops have been sponsored by PARFR, bringing together leading national and international scientists and clinicians representing an array of disciplines to present their experiences and exchange ideas on the following topics: Hysteroscopic Sterilization, Control of Male Fertility, Advances in Female Sterilization Techniques, Risks, Benefits, and Controversies in Fertility Control, and Reversal of Sterilization. PARFR is also supporting a workshop sponsored by the National Academy of Sciences/Institute of Laboratory Animal Resources on Animal Models for Research on Contraception and Fertility to be held in 1978.

The proceedings of each workshop are published and are available from Harper and Row, Publishers, Inc. (Control of Male Fertility and Advances in Female Sterilization Techniques) and Intercontinental Medical Book Corporation (Hysteroscopic Sterilization). Risks, Benefits, and Controversies in Fertility Control will be available in April 1978 and Reversal of Sterilization in August 1978 from Harper and Row, Publishers, Inc.

Update: Risk-Benefit Ratio in Contraception

Risks, Benefits, and Controversies in Fertility Control" was the focus for the 1977 workshop sponsored by the Program for Applied Research on Fertility Regulation, PARFR, which is directed by John J. Sciarra, M. D., of Northwestern University, was established in 1972 under a contract with the Agency for International Development (AID). Its objective is to support research in contraceptive development and fertility control.

The 1977 workshop, PARFR's fourth, drew investigators from Australia, Nigeria, and Central America, as well as Great Britain, Canada, and the U. S. The goal was mutual updating on all available methods of contraception, with an eye to the risk-benefit ratio of the various approaches, and their suitability for developing countries.

Relative Risks

Malcolm Potts, M. B., of the International Planned Parenthood Foundation, London, reminded participants at the workshop that all the most effective birth control methods—the pill, IUDs, abortion, and sterilization—entail some risk. But risks need to be seen in perspective, he added, particularly in areas of the world where maternal mortality is high (290 deaths per 100,000 live births in Bombay, or 2,000 in Ethiopia, compared with 12 in England and Wales).

"Unlike astronomers exploring the universe in a purely intellectual way, we as physicians are compelled to make decisions, however weak the data," Potts said. "In the last analysis those decisions are judgments, not scientific conclusions."

To strengthen the basis for such judgments, Potts—in collaboration with the International Fertility Research Program in Research Triangle Park, North Carolina and the AID in

Washington, D. C.—used computer data developed by the World Population Council, indicating the relative risks of various U. S. birth control methods, and extrapolated them to two types of less-developed countries (LDCs): one fairly advanced, as typified by South Korea or Thailand, and the other less so, as typified by rural Bangladesh or Ethiopia.

Where appropriate, the investigators wove in such variables as diet and culture. For instance, since vegetarians on poor diets in India are likely to be anemic, the bleeding problems caused by IUDs could be expected to be especially grave. In the Orient, where thromboembolic disease is rare, the pill would be less risky than in the developed world.

Among the conclusions from Potts' analysis:

- **Abortion:** Though two or five times riskier than in the U. S. (for each category of LDC, respectively), it would still carry a mortality rate only one-fourth or one-twentieth of what it would be if no birth control were used.
- **IUDs:** The risk would be at least two or three times higher in the LDCs, since potentially treatable complications might cause death in areas where medical care facilities are scarce or unavailable.
- **Female sterilization:** The risk is increased two or five times for each category of LDC, respectively.
- **Vasectomy:** While there have been no deaths in most countries, a few have resulted from tetanus in some mass programs, thus making the risk in the poorest countries on the order of one in a million. When the risks associated with tubectomy and vasectomy are "amortized" over a period of five, ten, or 15 years, these methods are among the safest, according to Potts.
- **Condom and diaphragm:** These entail a

Reprinted from CONTEMPORARY OB/GYN, December, 1977.

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CONTRACEPTION *continued*

fairly constant risk entirely associated with method failure and resulting birth-related deaths. Backed up with legal abortion, these traditional methods are by far the safest, Potts contended, in all settings and for all ages.

■ **Oral contraceptives:** It's particularly difficult, Potts said, to evaluate the risks of systemically active agents such as the pill, which may exert long-term effects not yet suspected. Women in less-developed countries have different genetic backgrounds from those in developed countries and also, as a rule, are more slender, more active, and smoke less. For these reasons, the risk of the pill—and ensuing thromboembolic disease—would be lower for them than for women in a developed country.

In both developed and less-developed countries, oral contraceptives are riskier than no birth control for women over 40 who smoke and have other predisposing factors, such as obesity or hyperlipoproteinemia. In the very poorest countries, even these high-risk women are statistically better off taking the pill than using no birth control method. For women who are free of such predisposing factors—even those over 40—the pill is still safer than no control at all.

On the plus side, Potts suggested that the pill may exert a protective effect against breast cancer. "The modern world subjects the human reproductive system to some unusual strains," he said. Women are experiencing menarche earlier than ever, and are having more menstrual periods as they have fewer babies, at later ages, he pointed out. Unlike the woman of earlier times, who probably had no more than 50 ovulatory menstrual cycles throughout her lifetime, today's woman is more apt to have 300 to 350 cycles, of which at least 100 precede her first child.

All these factors are associated with breast cancer, a "fearfully common" malady that kills one woman in 20 by the age of 70, in contrast to thromboembolic disease, with a death rate of a few in 100,000. A small percentage change in the incidence of carcinoma of the breast would be much more significant in public health terms, Potts noted, than the alteration in the incidence of thrombosis that

has been demonstrated for women taking the pill.

Weighing the risks of maternal mortality with an assumed pregnancy rate in a developing country, Potts estimated that the advantages of using birth control outweigh the disadvantages by a ratio of 5.6 to 1 for the IUD, 5.5 to 1 for the pill, and 2.5 to 1 for the condom.

Female Sterilization

Another British investigator, Anthony D. Noble, M. B., took issue with the use of diathermy for female sterilization. In his opinion, diathermy leads to excessive menstrual loss and increased menstrual pain, and the end result is apt to be hysterectomy.

Noble explained that in his small city of Winchester, two gynecologic teams had sterilized nearly 1,000 women in 1972 and 1973. (Excluded from this series were most women who had heavy periods, carcinoma in situ, or other gynecologic problems; those were usually advised to have hysterectomy.) One team used tubal division and diathermy under laparoscopy, while the second team employed tubal division and ligation via laparotomy.

As clinicians in a small, close-knit community, the members of the gynecologic teams realized, to their surprise, that many patients were returning during 1973 and 1974, with complaints of menstrual abnormalities, particularly menorrhagia. In order to confirm this clinical impression, Noble and his associates mailed a 15-point questionnaire to 454 women who had been sterilized (excluding postpartum procedures). The questionnaire inquired whether menstrual loss was the same, heavier, or lighter since the operation. It also asked about frequency of menstruation, dysmenorrhea, pain at intercourse, sexual satisfaction, and libido.

For control purposes, Noble sent the same questionnaire to 198 women whose husbands had been vasectomized. The three groups of women—those sterilized by diathermy, those sterilized by ligation, and the wives of the vasectomized men—were comparable in terms of age, number of children, years of marriage, age of youngest child, and prior use of contraceptives. About half of each group

had taken the pill, though very few had used IUDs.

Of the 493 women who returned the questionnaire, most were well pleased with the operation and its effect on their marriage. Noble reported. Nevertheless, adverse changes in menstrual patterns were not uncommon, particularly among women who had been sterilized by diathermy. The differences among the three groups were most marked in the area of increased menstrual loss; such an increase was reported by 39% of the diathermy patients, in contrast to 22% of the ligation patients, and 10% of the controls. Increases in menstrual pain followed a similar pattern, though less marked.

After a follow-up period ranging from 3½ to five years, 22 women sterilized by diathermy (10% of that group) reported changes so severe that they subsequently underwent hysterectomy. During this period, there were only five hysterectomies in ligation patients (5%) and two in the controls (less than 2%).

While 10% of the controls experienced heavier periods, 10% also had lighter periods. "Part of this change is psychosomatic," Noble said, "part due to natural changes (cause unknown), and part because patients discontinued their previous mode of contraception."

Among the sterilized women, 11% of the diathermy patients and 20% of those sterilized by ligation also had lighter periods. "It is difficult to explain how tubal surgery can affect menstrual function," Noble admitted. Typically, women with post-sterilization menorrhagia or dysmenorrhea present have a mobile, normal-sized but tender uterus, he noted, and at laparoscopy or laparotomy the venous plexus in the infundibular-pelvic ligament usually appears engorged. To him this suggests a disturbance in the utero-ovarian vascular anastomosis, which he would expect to be more severe after tubal diathermy than after tubal ligation "because of the greater degree of tissue destruction with the former."

Noble suspects that prostaglandins may somehow be involved in a "feedback mechanism between uterus and ovary, and that normal ovarian steroidogenesis is dependent on a normal blood circulation between uterus and ovary."

IUDs and Inflammatory Disease

IUDs are clearly capable of causing pelvic inflammatory disease. David A. Eschenbach, M. D., assistant professor of obstetrics and gynecology at the University of Washington, Seattle, said at the workshop that although the rate of infection is low, the degree of infection often mild, and the risk acceptable in most cases, physicians need to stay alert to the possibility. When an IUD user complains of abdominal pain, pelvic inflammatory disease (PID) ought to be considered, Eschenbach noted. Prompt administration of antibiotics may reduce serious complications, including chronic pain, infertility, and recurrent infection.

Eschenbach reported that he had studied 204 women diagnosed as having PID—on the basis of discharge, bleeding, abdominal pain, and pelvic tenderness—by one, two, or three previous physicians. In 54 women, pus was found in the cul-de-sac either at culdocentesis or during surgery. Eschenbach eliminated 8% of the women from the study because their diagnosis was not sufficiently clearcut, and another 8% who had other pathology. He carefully matched the remainder with controls.

While the controls were free of PID, the two groups were the same in respect to age, race, marital status, previous pregnancy, number of sex partners, and the presence or absence of gonorrhea. A subset was matched for socioeconomic status.

Eschenbach found that 30% of the PID patients—but only 11% of the controls—were using an IUD. Like other studies, Eschenbach's showed PID to be more common in lower socioeconomic groups. However, the association between PID and IUD use was strongest among women from the highest socioeconomic group.

Because PID is frequently gonococcal in origin, Eschenbach compared PID patients who had gonorrhea with controls who had gonorrhea. Again, he found that PID was more common among those patients who used an IUD. However, IUD users ran a higher relative risk of developing nongonococcal than gonococcal PID.

Finally, Eschenbach looked at the incidence

of PID in nulligravidas and in women who had been pregnant. With both groups using IUDs, nulligravidas were more likely to develop PID than were women who had been pregnant. Eschenbach's findings agreed with those of other investigators in this respect.

Clinically, there were few differences between the PID that developed in IUD users and in nonusers, Eschenbach reported. One difference was that fever was apt to be higher in nonusers. This perhaps suggests, Eschenbach said, that IUD-associated infection involves anaerobes. A second difference was the frequency of adnexal masses: Among women with nongonococcal PID, masses 6 cm or more in diameter occurred in 40% of IUD users but in only 15% of nonusers.

Although infections are well known to occur immediately following IUD insertion, Eschenbach confirmed that infection is likely to appear again several months later—at about 21 months, in his study. He postulates that the initial infection may well be caused by the insertion procedure itself, with cervical bacteria being carried into the uterus. Later, the risk of infection remains at a steady rate; indicating that bacteria are reintroduced, perhaps during menstruation; PID patients tend to develop their pain at the time of the menses.

The Dalkon shield, found in a disproportionate number of pregnant women who develop infection, has *not* proved more common than other types of IUDs in nonpregnant women with PID. Using an elaborate calculation, Eschenbach estimated that there were 110,000 cases of IUD-associated PID in the U. S. in 1973. While this is quite low in view of the more than three million IUDs now in use, the number of PID patients who use IUDs is likely to rise as IUDs become more commonplace.

Few patients who develop abdominal pain associate it with infection, Eschenbach noted, and even fewer make the link between infection and IUD. As a result, they end up in the emergency room late at night, when severe pain prevents them from sleeping. The clinicians or family-planning clinics responsible for insertion of the IUD may be the last to find out about infections—if they ever do.

IUDs and Pregnancy

What happens when pregnancy occurs while an IUD is in place? Daniel R. Mishell Jr., M. D., of the University of Southern California School of Medicine, Los Angeles, has made the following observations:

■ **Congenital abnormalities:** Since implantation occurs at a distance from the device itself, the IUD is always extra-amniotic. The evidence indicates that an IUD has no adverse influence on embryonic development. Even copper IUDs, or those containing progesterone, have never been shown to be associated with developmental abnormalities.

■ **Spontaneous abortion:** The incidence is consistently increased, Mishell reported. Over half the women who become pregnant with an IUD in place—and who do not choose to terminate the pregnancy electively—will abort spontaneously. If the IUD is expelled or can be removed, the chances of spontaneous abortion drop markedly, to approximately normal levels.

■ **Septic abortion:** If an IUD remains in place during pregnancy, the chances of septic abortion appear to increase. Mishell cited a study from the Center for Disease Control showing that the risk of death from abortion with an IUD in place was 14.8 per 100,000 women years, but only 0.28 without an IUD—an increase of more than 50 times.

However, the device most often involved in septic abortion was a shield, Mishell pointed out. The risk of death with a shield was five times that for other IUDs. With a device other than a shield, he stated, "there is no conclusive evidence of an increased risk of septic abortion."

■ **Ectopic pregnancy:** By its very nature, the IUD is more effective in preventing intrauterine than ectopic pregnancy: As a foreign body, it creates a continuous inflammatory reaction, the byproducts of which are toxic to sperm and blastocyst. The reaction is naturally greater in the uterus, where the IUD is located, than farther along, in the oviducts.

It is because the IUD is so effective in preventing uterine implantation that, if pregnancy occurs at all with an IUD in place, chances that it will be ectopic are increased to about ten times the expected incidence of

0.3% to 0.7%. The longer the device is in place, the greater the chance of the pregnancy being ectopic.

■ **Prematurity.** The data from relatively small studies indicate that prematurity may be more likely when an IUD is left in place. In one study, prematurity was four times more frequent in a group of women with IUDs in place than among women from whom they had been removed.

When a woman becomes pregnant with an IUD in place and wishes to continue the pregnancy, Mishell recommends that the IUD be removed if the threads are visible. If it cannot be removed, her physician should advise her that the risk of spontaneous abortion is definitely increased, as is the risk of ectopic pregnancy; that there is likely to be a risk of premature delivery; and that there may be an increased risk of septic abortion.

If the patient still wants to continue the pregnancy, Mishell said, she must be alerted to call her physician immediately should she develop any signs of lower abdominal pain, bleeding, or fever. At the first sign of infection, she ought to be treated with antibiotics and then the uterus should be evacuated, just as in any other case of septic abortion.

Vasectomy

Male sterilization may also entail a heretofore unsuspected complication. Joseph E. Davis, M.D., of New York Medical College, told the PARFR Workshop that half of all men who are vasectomized develop antibodies to spermatozoa during the year following sterilization. These antibodies cause agglutination or immobilization of donor sperm. In some patients, these antisperm antibodies have been reported to persist for ten to 25 years.

In experimental animals, Davis said, antigen-antibody complexes can be deposited not only in the reproductive tract but in the kidney as well. Some vasectomized rabbits with antisperm antibodies develop a condition resembling serum sickness. If—and Davis emphasized the “if”—such findings were to be extrapolated to man, a proportion of men with large numbers of circulating antibodies might well be expected to develop glomerulonephritis.

According to other investigations, the animals that are the most likely to sustain high antisperm antibody levels are those that have high initial sperm counts. “If high counts more frequently lead to high antibody levels, and if high antibody levels lead to immune complex deposition,” Davis concluded, “then possibly men with kidney disease and high sperm counts might be well advised not to get a vasectomy.”

Hyperosmolar Urea

At the Johns Hopkins Fertility Control Center, mid-trimester abortions are performed with hyperosmolar urea plus an oxytocic agent, Theodore M. King, M. D., reported. This combination, he said, offers a number of advantages over other intra-amniotic methods.

After 200 cc of amniotic fluid are removed, 80 gm of urea, dissolved in 134 cc of 5% dextrose and water, are injected intra-amniotically. This is followed immediately by the augmenting agent. At first the Johns Hopkins investigators used intravenous oxytocin for this purpose. The procedure was carried out in 513 women. Because of oxytocin's anti-diuretic effects, it was necessary to monitor patients carefully, using infusion pumps, making serial determinations of serum electrolytes, and watching over total fluid intake and output.

In order to simplify the procedure, the center subsequently switched from oxytocin to intra-amniotic prostaglandin F-2-alpha. They started out with doses of 20 mg (in 30 women), reduced it to ten mg (in 180 women) and then further reduced it to five mg (in 32 women). It is quite possible that the minimal effective dose may be even lower, King said. However, the prostaglandin is definitely effective, he added. In a prospective randomized series of 16 patients, the Baltimore group compared urea alone with urea plus 5 mg of the prostaglandin. They found that the injection-abortion interval was markedly shortened when prostaglandin was combined with the urea.

In all combinations, hyperosmolar urea with an augmenting agent has proved a satisfactory method for second-trimester abortion, King reported. Injection-abortion intervals

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were reasonably short, with the mean interval ranging from 14 to 20 hours. It is possible to keep the injection-abortion interval to less than 24 hours by attention to two key factors, according to King. One factor is the ultimate concentration of urea in the amniotic fluid—this is high at Johns Hopkins, where a large quantity of amniotic fluid is replaced by a urea solution at a concentration approaching 60%. A second factor is *early* administration of an augmenting agent; a delay of even two hours will lengthen the injection-abortion interval considerably.

Of course the time interval in a given study will be influenced by the proportion of nulliparous to multiparous subjects, King pointed out, since abortion takes longer in nulliparas. In the Baltimore study, urea plus either oxytocin or prostaglandins in various dosages led to mean injection-abortion intervals of 13 to 17 hours in the multiparas, and between 18 and 20 hours in nulliparas.

A complete abortion, as defined by King and his associates, is the noninstrumented passage of fetus and placenta within two hours of each other. Between 53% and 59% of the women in each of the four dosage groups (urea plus oxytocin or urea plus prostaglandin in 20, 10, or 5 mg doses) had complete abortions according to this definition.

Between 37% and 45% of the women had abortions classed as incomplete, when defined as failure to pass all or part of the placenta within two hours of fetal abortion, or a need for instrumental removal of the placenta within two hours due to hemorrhage or infection. Incomplete abortions were managed by curettage with intravenous analgesia. This is a convenient solution, King noted, since the cervix is already dilated.

If it became necessary to remove all products instrumentally, either because the woman failed to abort within 48 hours or because of hemorrhage or infection, the procedure was classed as a failure. In 15 (2.9%) of the 513 patients treated with urea plus oxytocin, in two (6.7%) of the 30 patients who received urea plus 20 mg of prostaglandin and in one (0.6%) of the 180 patients who received urea plus 10 mg of prostaglandin, the procedure was considered a failure. There were no

failures among the 32 patients who were treated with urea plus 5 mg of prostaglandin. The failures were managed by dilatation and evacuation, with intravenous analgesia and paracervical block. D&E are facilitated in these instances by the prior occurrence of labor, King said, and by the maceration of fetal products.

Gastrointestinal side-effects, common in all induced second-trimester abortions, were the most common complications of the urea abortions. Other complications included hemorrhage (one patient required transfusion), infection, and cervical laceration. The most troublesome complication, King reported, was cervical laceration. It occurred in five women in the entire series. "The behavior of cervical scars during future childbearing is unknown, and certainly deserves careful study," he cautioned. No lacerations were found in the women who had received only 5 mg of prostaglandin, and for that reason King suggested reducing the dose of prostaglandin to decrease the likelihood of lacerations.

Hyperosmolar urea offers several advantages for second-trimester abortions, King said. Unlike hypertonic saline, urea rapidly traverses membranes and is an osmotic diuretic; thus, if it is inadvertently injected intravascularly, it is much less dangerous. Life-threatening complications such as coagulopathy are rare. Furthermore, aborted fetuses are seldom alive. The technique is uncomplicated and readily learned, and the shortened injection-abortion intervals facilitate nursing care.

Vaginal Approach

Not only are vaginal abortions possible in the second trimester, they are safer than those done with chemicals, Michael S. Burnhill, M. D., told the workshop. That is, he added, provided they are done by experts and with ultrasonic confirmation of gestational age.

Burnhill, who at the time of the PARFR workshop was director of Preterm, a Washington, D. C., clinic, said that second-trimester abortions had been performed there since July 1976. In general, Preterm's results corroborate those of a recent study from the Center for Disease Control which showed that

in a series of approximately 6,000 vaginal terminations the total complication rate was 6% and the major complication rate was 0.77%, compared with a total complication rate of 43% and a major complication rate of 1.85% in more than 10,000 instillation procedures.

Preterm's decision to undertake second-trimester abortions, Burnhill said, followed the discovery that in some 11,000 abortions performed there, 568 fetuses had turned out to be beyond 12 weeks' gestation (one was 17). This error occurred, Burnhill noted, despite the fact that all the physicians at Preterm were experienced in estimating gestational age, and, at 12 weeks they always sought a second opinion. Yet, in the 10- to 12-week range, the error rate was 25%.

"The first thing I would advise, if you are going to attempt these procedures, is *not* to rely on the clinical estimation of even the most experienced clinicians," Burnhill said. It is essential, he added, to use echograms to determine biparietal diameter.

When Preterm began using ultrasound, "an equally interesting set of errors was discovered," he said. Among the first 184 patients evaluated by ultrasound, all thought to be 13 to 15 weeks pregnant, 25% turned out to be less than 12 weeks. "Whether this was due to excess amniotic fluid, fibromyomas, obesity, or whatever, we immediately retrieved women who, in many instances, would have had to sit around for four or five weeks until the time was right for a saline procedure," he declared. "Then they might have had difficulty because they turned out to be at 15 weeks instead of 18." At the other end of the spectrum, echograms showed that 11% of the 184 patients were 16, 17, or 18 weeks pregnant.

In reviewing the 568 second-trimester procedures done inadvertently, the Preterm staff found only one significant complication, Burnhill told the workshop. Uterine perforation had occurred in four, or 0.7%, of the cases. Though this figure is not out of line with the perforation rate for other types of second-trimester procedures, Burnhill commented that Preterm found it "horrific" when compared with the clinic's first-trimester standard. The rate was 14 times higher than

the rate for abortions done before 12 weeks.

In the 60 or so second-trimester abortions intentionally performed since July 1976, the greatest problem has been excessive blood loss, Burnhill said. Whereas the average blood loss for first-trimester procedures at Preterm is less than 100 cc, there have been seven second-trimester operations in which the patient lost more than 200 cc; one had to be hospitalized and transfused.

Preterm now performs no abortions beyond 14 weeks, as determined by an ultrasonic biparietal diameter of 3 cm. The procedure is carried out under local anesthesia. The patient walks away from the table and leaves the recovery room in an hour, reported Burnhill, who is now associated with Johns Hopkins' program in international education in gynecology and obstetrics.

Despite the obvious advantages of the vaginal approach, Burnhill commented, any clinician who considers performing second-trimester procedures must take several factors into account. First, it must be understood that considerably more expertise is required than for first-trimester procedures. "No matter how many first-trimester abortions you've performed, you're not qualified to do second-trimester procedures," Burnhill declared.

"Second-trimester abortions demand a quantum leap in experience." He recommended that a practitioner begin by gaining wide experience with 12-week abortions. Only when he feels confident at this level should he move up to 13 weeks. When he has gained experience with these, he can advance to 14-week terminations.

Finally, Burnhill cautioned, doing second-trimester abortions exacts a tremendous emotional toll from the staff. "You are clearly the instrument of termination and dismemberment," he warned. "If you choose to perform second-trimester abortions you must be absolutely clear in your commitment to choice, to women's rights, and to the necessity of these procedures."

In the ensuing discussion, nurse-midwife-epidemiologist Judith Rooks of the Center for Disease Control urged speakers and audience to weigh not only the biological aspects of second-trimester abortions, but the emotional

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costs from the standpoint of the patient. Nearly half of those who have delayed their decision until the second trimester are teenagers, she reported. Though vaginal termination is a very bloody procedure and distasteful to the physician, it is not much different for the patient than a routine first-trimester procedure.

This is in sharp contrast to chemical abortion, which may put the patient through two or three days of labor followed, in some cases, by delivery of a fetus in bed, alone, without any support. Rooks pointed out "Surely it's much easier on the physician to give a drug than to deal with the gross reality of doing a delayed abortion through the cervix." Rooks added, "but when judging the advantages and disadvantages please don't ignore the psychological and experiential aspects. It is the patient, after all, with whom we're supposed to be concerned."

The Pill and Liver Tumors

Data from a registry of liver tumors associated with oral contraceptives were reviewed by Edward D. Nissen, M.D., of the University of California—Irvine, Medical Center. The registry, which was set up at Irvine in early 1975, has entered 32 new cases. In addition, Nissen has analyzed 46 cases from the literature. Among his findings:

- **Age** More than three-fourths of the women are between 20 and 35 when the tumor is first discovered—not unexpected, since this is the age group most widely exposed to oral contraceptives. "This early age peak stands in striking contrast to the age-related incidence of nearly every other form of neoplasm, benign or malignant," Nissen noted.

- **Type of contraceptive** More patients were exposed, for more months of contraceptive use, to products containing mestranol. However, these products were first on the market and probably are still the most widely prescribed.

- **Exposure** More than half the patients had used birth control pills for longer than five years, and over 85% for more than four years.

- **Histopathology** Efforts to classify the tumors have created a "semantic nightmare," Nissen pointed out. One problem has been

caused by attempts to describe "an entirely new pathologic phenomenon utilizing antiquated classifications." Another classification problem arises from the vascularity of the tumors, since hemorrhage and necrosis easily distort their features. Nissen, however, believes "nearly all benign liver tumors in oral contraceptive users are closely related to the prototypic lesion—the hepatic adenoma."

- **Screening** No reliable technique for detecting the patient at risk is widely available, according to Nissen. Since liver enzyme levels are elevated in most oral contraceptive users, they're useless in diagnosing hepatic adenoma. Selective celiac angiography will usually demonstrate the lesion, but it is much too risky to use for routine screening, cautioned Nissen. Ultrasound may prove to be the most practical approach to screening, he added.

- **Diagnosis** It is complicated because tumors in the parenchyma produce no pain until they are large enough to impinge on the capsule or bleed extensively.

- **Treatment** "Even under ideal circumstances, surgical treatment of these tumors may be extremely difficult," said Nissen. There is evidence that some lesions may regress once the pill is withdrawn, but the clinician should judge each case individually, Nissen declared. "weighing the risks of hazardous surgery against the possibility of life-threatening liver rupture."

Additional links between oral contraceptives and benign liver tumors also have been forged in a case-control study conducted by the Center for Disease Control in collaboration with the Armed Forces Institute of Pathology in Washington, D.C. Rooks outlined the preliminary results of the study, which involved 105 cases of hepatocellular adenoma (HCA). The research team found that the risk of developing HCA was estimated to be nine times higher for women with one to four years of pill use compared to those who had taken the pill for a year or less. The risk jumped to 120 times for women with four to seven years of use and 500 times for those with eight or more years of use. Findings of the completed study have appeared in the CDC's *Morbidity and Mortality Weekly Report* (26:293) [66].

—LYDIA WOODS SCHINDLER