

PD-ABS-617
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The CONRAD Program

MAKING PROGRESS TOWARD MORE EFFECTIVE, SAFE, AND ACCEPTABLE CONTRACEPTIVES

1996

Annual

Report

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CONRAD'S

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Highlights of recent CONRAD achievements are:

Achievements:

Clinical studies on the Reality® female condom

This work was instrumental in getting the condom approved by the U.S. Food and Drug Administration (FDA).

Clinical studies on Lea's Shield® and Femcap®, cervical barriers

The FDA is reviewing the data on Lea's Shield®; approval is pending. Data should be available next year on Femcap® to present to FDA for approval of the device.

Clinical studies on new formulations of nonoxynol-9 (N-9), a spermicide

One new N-9 product appears to last longer and coat the vagina better than available products. A U.S. patent will be issued in 1996.

Clinical studies on exogenous testosterone

Early findings are promising and these studies could lead to a new and effective male contraceptive.

HIV studies in monkey models

These studies, which focus on heterosexual transmission of the virus, could result in better contraceptives with microbicidal activity.

The Contraceptive Research and Development (CONRAD) Program has made great strides over the past 10 years in fulfilling its mission of developing more effective, safe, and acceptable contraceptive methods suitable for use in developing countries. The focus of CONRAD is on the early stages of contraceptive research and development, with an emphasis on moving promising approaches through the first two phases of clinical testing for safety and efficacy.

As a result of CONRAD-supported research, women and men worldwide will have expanded choices in contraceptive methods. They also will reap the benefits of improved reproductive health through contraceptives that help prevent the transmission of the human immunodeficiency virus (HIV) and other sexually transmitted diseases (STDs).

An Overview

Major

Resources

for

Research

FEDERAL FUNDING

CONRAD was established in 1986 at the Eastern Virginia Medical School under a cooperative agreement with the U.S. Agency for International Development (USAID). The research supported by CONRAD is conducted in its intramural laboratories and clinics at the Medical School and by investigators at public and private sector research institutions in the United States and abroad.

Although USAID continues to be the primary source of funds for CONRAD, as the linkage between the prevention of HIV transmission and contraceptive practice became clear, an expanded program on STDs was supported first by the National Institutes of Health (NIH) for mechanism of transmission and animal model studies and then by the Centers for Disease Control and Prevention (CDC) for epidemiological studies. The contributions of NIH and CDC continue to play a synergistic role in the activities of the CONRAD Program. CONRAD, in turn, provides these agencies with an ability to achieve a rapid response to ever-changing research needs.

PHILANTHROPIC SUPPORT

The role of philanthropic foundations in the activities of CONRAD became much more important in the past year. Not only has CONRAD's role in the research center twinning program of The Andrew W. Mellon Foundation been significantly expanded, but also an important new initiative to enhance collaboration between the not-for-profit and for-profit sectors for the development of new contraceptives began with major funding from The Rockefeller Foundation and The Mellon Foundation.

The role of philanthropic foundations became much more important in the past year.

Small Grants Program/ Research Twinning Program

The Andrew W. Mellon Foundation gave CONRAD a three-year grant starting in 1993 to fund small research projects and fellowship training in contraceptive research. A key feature of the Mellon grant is that it allows CONRAD to fund projects on more fundamental research and in countries proscribed by USAID. In 1994, CONRAD was asked to manage an expansion of Mellon's ongoing twinning program between investigators at the Mellon Reproductive Biology Centers and selected centers outside of the United States. CONRAD recently was awarded a three-year grant to support continuation of the small grants program and further expansion of the twinning program.

The objective of the small grants program is to support innovative, high-risk research that may lead to new contraceptive technology.

Recently funded projects include characterization of gonadal surge-inhibiting factor and an intragonadal steroidogenesis-inhibiting protein, and two immunocontraceptive leads, one an epididymis-specific protein found on the sperm surface and the other an oviduct-specific glycoprotein. Planned projects encompass further development of an assay for immature sperm in men using systemic male contraceptives.

The primary goals of the twinning program are to promote research relevant to contraceptive development and to build partnerships with centers of excellence in developing countries. Current and pending projects include male and

female reproductive tract biology, characterization of potential immunocontraceptives, a primate fertility trial of a plant extract, and two clinical trials: a hormonal implant in Chinese men and a new spermicidal formulation in Brazil.

Consortium for Industrial Collaboration in Contraceptive Research (CICCR)

CICCR was initiated in 1995 as a new CONRAD project by The Rockefeller Foundation and The Andrew W. Mellon Foundation. CICCR awards grants for contraceptive research and development to not-for-profit research institutions working in collaboration with for-profit industrial partners. The industrial partners are required to provide matching funds.

The idea behind CICCR is to revitalize industry's commitment to developing new contraceptive products. In the early 1960s, 12 multinational pharmaceutical companies were active in contraceptive research and development. Today there are only four—two in the United States and two in Europe. The research and development process is long and costly, and pharmaceutical manufacturers perceive many barriers to entering the market with a new contraceptive. For example, contraception involves treating healthy individuals, failed contraception could cause fetal malformations with attendant litigation, and the market—at least in developed countries—is considered mature.

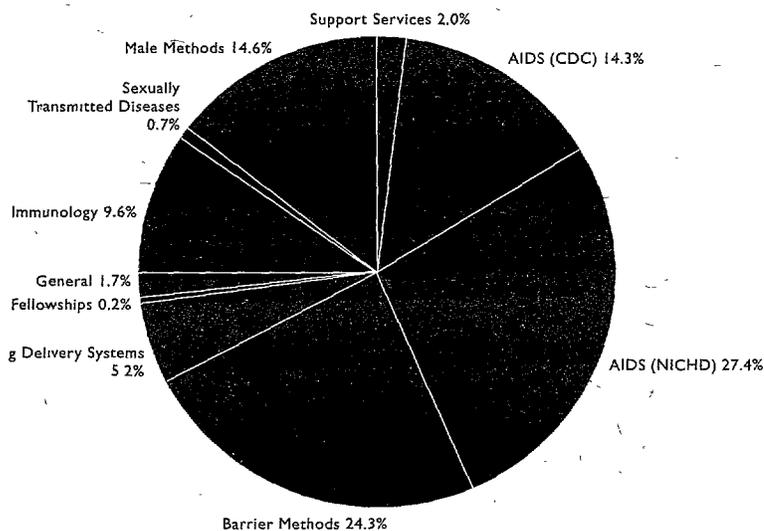
CICCR's priority areas for research, which are based on a woman-centered agenda, feature:

- ▶ male methods of contraception;
- ▶ vaginal methods that prevent both pregnancy and STD transmission; and
- ▶ monthly regimens, which could be postcoital, anti-implantation, or menses-inducers.

Since CICCR began operating on October 1, 1995, seven projects have been funded or approved for funding in three countries. The projects include three vaginal contraceptive/microbicide preparations (two new chemical entities and one new formulation of N-9), one male-hormonal method, plus three feasibility studies. Several potential projects are under review.

CONRAD PROJECTS

June 1, 1992-May 31, 1996



Recognizing the pressing needs to develop new contraceptives for use in developing countries as well as acknowledging contraceptive research being done by other institutions, CONRAD has identified five priority areas where it can make a special contribution:

- ▶ Barrier contraceptives
- ▶ Development of microbicides to prevent the transmission of HIV/AIDS and other STDs
- ▶ Systemic hormonal methods for women
- ▶ Male methods
- ▶ Immunocontraceptives

The following sections describe CONRAD-supported projects that are recently completed, underway, and/or in the planning stage.

BARRIER CONTRACEPTIVES

When the CONRAD Program first began, attention was focused exclusively on preventing pregnancy. As AIDS became increasingly

prevalent, it became clear that contraception also had to be considered in the context of STD prevention. This caused CONRAD to increase its work in the area of barriers that reduce disease transmission as well as prevent pregnancy.

Chemical and mechanical barrier methods not only are contraceptives but may prevent STDs, to varying degrees. Both pregnancy and infection may be prevented by mechanical interference with transmission or chemical interference with sperm or microbe viability or function. The goal is to find a method that is efficacious without side effects that compromise safety or acceptability.

Researchers face two challenges in developing new barrier contraceptives to prevent both pregnancy and disease:

Finding a method that prevents microbial attachment and penetration of the vaginal wall. This is a new area of contraceptive research because protecting or coating of the vaginal wall is not needed to prevent pregnancy.

Finding a method that is less disruptive of the vaginal environment than nonoxynol-9. High doses or frequent use of N-9, a widely-used spermicide, can disrupt the vaginal epithelium and may upset the vaginal flora. Disruption of the epithelium raises problems concerning safety and acceptability since it may create a portal of entry for STD-causing organisms as well as vaginal irritation.

CONRAD has completed or is working on

several projects involving barrier methods, including the Reality® female condom, Lea's Shield® and Femcap® (two cervical barriers), a silicone diaphragm, contraceptive sponges, spermicidal films, and male condoms. Work on new barriers that prevent STD transmission as well as pregnancy is being carried out in partnership with private sector research groups. To make these products feasible for use in less-developed countries, it is preferred that they can be manufactured locally, do not require frequent resupply, and can be easily disposed of.

MECHANICAL BARRIERS

LEA'S SHIELD®

In collaboration with Family Health International (FHI), CONRAD sponsored Phase I, Phase II, and over-the-counter feasibility studies of Lea's Shield®, a new silicone rubber device that comes in one size for all users. It covers the cervix and when used with spermicide appears to prevent pregnancy at least as well as traditional barriers. The device may reduce upper reproductive tract infection as do traditional barriers, although this was not studied specifically. There is no reason to expect that the shield itself will prevent vaginal transmission of STDs; the microbicidal activity of the spermicide used with it, however, may prevent such transmission. The developer, Yama, Inc., has applied for FDA approval of the device for contraception. A report on the multicenter Phase II study appeared in the journal *Contraception* (see table).

SAFETY AND EFFICACY OF LEA'S SHIELD®

A Six-Month Life Table Analysis

BASELINE CHARACTERISTICS (N=90)

Mean age	29.6
% Caucasian race	80.0
Mean years in school	14.2
% Married	63.3
% Parous	81.1

GROSS CUMULATIVE PREGNANCY RATE PER 100 WOMEN 8.7

GROSS CUMULATIVE DISCONTINUATION RATES FOR REASONS OTHER THAN PREGNANCY

Personal, not device-related	4.4
Personal, device-related	8.5
Medical reasons	1.2
Protocol violations/exclusion	11.8
Lost to follow-up	6.4

Source: Mauck C et al (1996). *Contraception*, 46:511-19.

FEMCAP®

CONRAD has completed Phase I postcoital testing on the Femcap®, a silicone rubber cervical cap available in three sizes, and is conducting a Phase II/III study on it in 10 sites in the United States. Fitting is determined by obstetrical history and clinician judgment. Its design follows the anatomy of the cervix and proximal vagina and it is expected to provide a snug fit that is comfortable and not easily dislodged. Its ability to prevent STDs is expected to be about the same as the Lea's Shield®.

The Phase II/III study involves 800 women, half of whom were selected randomly to use the Femcap® and half to use a standard latex diaphragm. There will be a six-month follow-up of each volunteer. Researchers will measure the incidence of pregnancy, adverse experiences, Pap smear changes, and acceptability by the women. The study will be completed around the end of 1996 with data analysis and premarketing approval (PMA) submission to follow. FHI is being funded by CONRAD to help with clinical monitoring and data analysis. Separate studies using the same protocol involving 50 women will be carried out at Instituto Chileno de Medicina Reproductiva (ICMER) in Santiago, Chile, and in India in collaboration with the Indian Council for

Medical Research. Evaluation of the Femcap®'s acceptability to women in Chile will be incorporated into the final study report.

EASY FIT DIAPHRAGM

Prototypes of an easy fit silicone diaphragm have been sequentially developed by the Program for Appropriate Technology in Health (PATH) in Seattle with CONRAD collaboration, with each subsequent iteration modified as a result of fittings and input from volunteers and clinicians. The major features that have been adjusted are the thickness of the membrane, size, and position of a cervical cup, position and number of grip dimples, location and size of removal handles, and, most important, rim spring changes. The most recent prototype is scheduled for extended wear (eight hours) evaluation in volunteers.

A preproduction prototype, fully contoured and optimized for assembly, is expected to be developed soon from these final fittings.

TACTYLON®

New materials and designs have resulted in improvements in male condoms. CONRAD is conducting a slippage and breakage study at two centers on three styles of condoms made from Tactylon®, a thermoplastic elastomer produced by Tactyl Technologies. Tactylon® does not cause allergic reactions in persons sensitive to latex and is more resistant than latex to degradation. The study will compare the new condoms with latex condoms at centers in Los Angeles and Minneapolis. Work will involve a total of 440 couples not at risk for pregnancy who will use each type of condom three times. Detailed questionnaires will be completed after each use to record problems with slippage, breakage, and acceptability.

REALITY®

CONRAD and FHI conducted the Phase II/III clinical trials of Reality®, a female condom, that was approved by FDA in 1994 and is on the market in the United States. CONRAD has received several proposals for new female condoms that purport to have aesthetic advantages over the Reality® condom—such as having improved physical appearance and producing less noise—and is considering conducting acceptability studies on a new prototype.

CONRAD has received many proposals for new female condoms and may test one.

CHEMICAL BARRIERS

NONOXYNOL-9

CONRAD is directing some of its efforts at better characterization of existing spermicides as well as at developing new ones. N-9 is the most commonly used spermicide in the United States, but little is known about its optimum dose, timing of administration before intercourse, need for additional application with subsequent acts, and efficacy in perfect use once an optimal regimen is

defined. In addition, there may be safety problems with high doses or frequent use that require additional investigation.

CONRAD has completed a study at its

intramural clinical research center at the Eastern Virginia Medical School in Norfolk on a marketed N-9 film called VCF®, in which the concentration of N-9 remaining in the vagina was determined at different time periods up to four hours after insertion; intercourse did not occur. The concentration of N-9 stayed relatively high for about 90 minutes, then fell. Pieces of undissolved film were still present after four hours in some women. A follow-up study is being planned to evaluate the concentration of N-9 present when intercourse follows insertion by up to four hours. In addition, postcoital testing will be done to correlate N-9 concentration with its ability to prevent the passage of progressively motile sperm into midcycle cervical mucus.

The intramural clinical researchers have completed a postcoital study on a new formulation of N-9 film called the Allendale film. This film uses a different base, which, it is hoped, will be more stable in hot, humid climates, and possibly

less irritating than VCF®. In the study, two different doses of this film performed as well as VCF® in reducing the number of progressively motile sperm present in midcycle cervical mucus to below the level considered compatible with fertility.

Another Allendale film containing benzalkonium chloride in two doses performed as well as VCF® in the postcoital tests. It is hoped that benzalkonium chloride will offer a spermicidal alternative to persons sensitive to N-9 and may offer better microbicidal activity than N-9. Pending identification of a commercial partner, further studies will be done on both.

CONRAD is involved with a commercial partner through CICCR in developing a long-acting sustained-release formulation of N-9. Phase I trials on safety (irritation) after varying doses are underway and postcoital studies are being planned.

A number of new formulations for N-9 are being explored at Integra, Inc., in Plainsboro, New Jersey, to optimize bioavailability while at the same time minimizing dose and thereby reducing the likelihood of irritation. In addition, the manufacture of derivatized polysaccharides has been scaled up to provide sufficient material for rabbit vaginal irritation testing, which is underway. These polysaccharides enhance the utility of N-9 by coating the vaginal walls and blocking penetration of sperm into cervical mucus.

Preclinical evaluation for efficacy and toxicology of the N-9 products, as well as new chemical entities, is being carried out in animal models when warranted. Such agents could potentially be delivered as vaginal films or suppositories, which might be more acceptable to users than creams and gels, or delivered in conjunction with barrier devices such as sponges or

diaphragms. The cost and practicality of providing such products through public sector programs is an important consideration.

VAGINAL SPONGES

There have been no vaginal sponges on the market in the United States since Today® was removed from sale in 1995. Several vaginal sponge prototypes recently have been presented to CONRAD, and the developer of one is seeking a commercial partner for possible support through CICCR.

FUTURE DIRECTIONS

CONRAD will continue to develop new mechanical and chemical barriers with an emphasis on those that prevent the transmission of STDs in addition to pregnancy. Most of this work will be in the area of chemical barriers, including defining N-9's duration of action and the work through CICCR with sustained-release formulations of N-9. In addition, work has begun with other industrial partners to develop new chemical entities that show promise as both contraceptives and antimicrobials, and preclinical screening of candidate products will continue to take place. CONRAD also may test a new female condom.

SCREENING PLAN AND DECISION TREE

To aid in the discovery and screening of new leads for spermicides and microbicides, CONRAD staff developed a decision tree process in collaboration with the TOPCAD Program at Rush-Presbyterian-St. Luke's Medical Center in Chicago and other consultants. This process permits researchers to evaluate contraceptive antimicrobials in a way that allows for the continuous comparison and selection of lead compounds for possible clinical development. A group of *in vitro* tests have been selected that comprise the primary and optional tests deemed valuable in characterizing a compound as a contraceptive antimicrobial. More than 20 specific tests are used to characterize compounds in the following areas:

- ▶ Sperm activity
- ▶ Effects on conception
- ▶ Toxicity
- ▶ Sperm function
- ▶ Effects on STD organisms
- ▶ Effects on fertilization

The specific tests are arrayed in a diagrammatic scheme which, if followed, will automatically eliminate compounds that do not have enough activity to justify continued testing. This diagrammatic scheme is called the Contraceptive Antimicrobial Screening Plan and Elimination Tree (CASPET).

Compounds that survive the elimination tree become the lead compounds for development consideration. The leads are ranked on scoring sheets against each other on the basis of their activities in the characterization tests. These scoring sheets allow for easy selection of candidates for clinical development.

A supplemental scoring sheet, called the Review Before Development, captures additional information important for the decision-making process of selecting a candidate for clinical development. Items to be scored on this sheet are:

- ▶ Business partner characteristics
- ▶ Control
- ▶ Cost (project)
- ▶ Cost (compound)
- ▶ Formulation
- ▶ Patent matters
- ▶ Physical/chemical profile
- ▶ Safety data (existing)
- ▶ Synthesis
- ▶ Technical success
- ▶ Time to complete
- ▶ Value

CASPET is supported by a comprehensive test protocol summary package and a detailed diagram of the product development process.

**MICROBICIDES
TO PREVENT THE
TRANSMISSION
OF HIV/AIDS AND
OTHER STDs**

Because of the urgency to develop vaginal barrier methods that not only prevent unwanted pregnancy but also offer protection against

HIV/AIDS and other STDs, CONRAD has targeted some of its research activities specifically to:

- ▶ Develop new products that prevent the transmission of HIV/AIDS and other STDs;
- ▶ Better define how existing and potential contraceptive methods might either reduce or enhance the risk of HIV/AIDS and other STDs; and
- ▶ Contribute to more appropriately tailored and responsible family planning services, including improved counseling and products.

**DEVELOPMENT OF NEW
MICROBICIDAL AGENTS AND
FORMULATIONS**

At the Southern Research Institute in Birmingham, Alabama, CONRAD is investigating the use of *in vitro* models to evaluate the ability of various compounds to inactivate cell-free and cell-associated HIV or to prevent the attachment of HIV to target cells in the reproductive tract. Several classes of compounds have been identified that appear to be promising leads with high spermicidal and virucidal activity and potentially low levels of tissue irritation. CONRAD-sponsored investigators in the United States and abroad are conducting targeted synthesis programs to optimize the structure and activity of these compounds. Several series of hemicholini-

um compounds have been synthesized, and lead compounds have been selected for rabbit vaginal irritation testing.

An *in vitro* model has been developed to study the mechanisms by which a virus is transmitted from infected blood cells like those in semen to epithelial target cells like those in the cervix. This model is being used to evaluate the efficacy of various compounds in preventing this mode of HIV transmission; it has yielded promising data for sulfated polysaccharides.

Several classes of compounds have been identified that appear to be promising leads with high spermicidal and virucidal activity.

Another *in vitro* system using vaginal and ectocervical cell lines is under development. A number of cytokines appear to be promising markers for toxicity and inflammation, and it is hoped that this *in vitro* test will serve as a good screening assay before *in vivo* irritation testing is undertaken.

In addition, CONRAD has provided substantial funding to the TOPCAD Program in Chicago to evaluate and develop a number of promising agents with substantial antifertility and anti-STD properties. Development of topical products using antibodies to prevent pregnancy and infection also is under consideration.

MECHANISMS OF SEXUAL HIV TRANSMISSION

A CONRAD project at Harvard University has examined the mechanisms and cofactors of HIV secretion in the male reproductive tract. The investigators identified cells in semen that carried HIV, the tissues from which infected cells and free virus are secreted, and their relationship to disease stage, therapy, and immune function. The project also tested a number of relevant hypotheses and found that:

- ▶ Vasectomy reduces but does not prevent HIV in the ejaculate.
- ▶ HIV in semen is greatly reduced by zidovudine treatment.
- ▶ HIV is not carried by sperm.
- ▶ Survival of free and cell-associated HIV is highly pH dependent.

Using surgical and autopsy tissues, which are now increasingly available, researchers are studying the localization and secretion of HIV in the female reproductive tract. Data are being correlated with disease stage; pathological condition; therapy; coinfections such as cytomegalovirus (CMV), human papillomavirus (HPV), and Epstein-Barr virus (EBV); and other factors such as menstrual stage and endometriosis.

A much improved ELISA-based polymerase chain reaction (PCR) method to quantitatively measure HIV has been developed and is being used to examine factors that influence HIV levels in tissues and fluids of the reproductive tract. *In situ* PCR also has been improved and used to demonstrate that testicular HIV is in macrophage-like cells but not in germ cells. A double-labeling technique is planned to determine definitively if HIV-positive lymphocytes bind

to and infiltrate across the intact human endocervical mucosa. Work is underway to identify inflammatory cytokines in lower genital tract secretions that may be associated with HIV-1 shedding. These data will be useful in looking at the influence of a variety of cofactors in the transmission of HIV.

ACTIVITY OF EXISTING AND NEW AGENTS AGAINST OTHER STDS

Investigators working in the pig-tail macaque model of sexually transmitted chlamydial infection at the University of Washington found that a single vaginal application of a spermicidal product containing 4% N-9 inhibited infection. They also noted only a minimal temporary shift in vaginal flora and mild irritation to the vaginal and cervical mucosa. In contrast, with 1.2% benzalkonium chloride the alteration of vaginal flora and irritation were more marked. The protective effect of the 1.2% benzalkonium chloride against chlamydial infection was similar to that of the 4% N-9. Researchers believe that this model could be used to evaluate the *in vivo* antichlamydial activity of other spermicides and/or microbicides.

Other CONRAD investigators, including those in the TOPCAD Program, are conducting *in vitro* studies to define the efficacy of promising agents against a variety of microbes, such as chlamydia, herpes virus, gonococci, hemophilus, trichomonas, and candida, while minimizing the impact on normal lactobacilli.

DEVELOPMENT OF ANIMAL MODELS FOR HIV TRANSMISSION

Initial CONRAD investigations in the late 1980s included immune deficiency viruses in African green monkeys, mice, cats, and chimpanzees. The

rhesus monkey and simian immunodeficiency virus (SIV) model developed with CONRAD and National Institute of Child Health and Human Development (NICHD) funding continues to be promising. Past studies have characterized the relevant biology in this model and have shown partially protective effects of N-9-containing foam and gel contraceptives against highly infectious inocula of SIV. Current studies are examining the role of seminal plasma, pH, repeated N-9 exposure, and other factors on transmission.

Animal model work shows protective effects against highly infectious inocula of SIV.

In a preliminary study, investigators found that a rigorous regimen of exposure to an N-9-containing vaginal spermicide (twice a day for 28 days) did not increase the likelihood of SIV infection following vaginal inoculation. The effects of this treatment regimen and others, including controls and a group treated for 42 days, have been more extensively characterized using video colposcopy and histological analysis of vaginal biopsies. As a part of the study, researchers were able to determine a profile of N-9 concentration in the vagina following treatment: N-9 remains detectable for up to 72 hours after treatment, but cannot be detected after seven days.

In another study at the Aaron Diamond AIDS Research Center in Tuxedo, New York, progesterone-implanted and placebo-implanted monkeys were vaginally inoculated with a dose of SIV that infected 1 of 10 monkeys in the placebo group and 14 of 18 monkeys in the progesterone group. Histological evaluations suggested that this

enhancement of transmission might be attributable to the progesterone-induced thinning of the vaginal epithelium. A follow-up study determined that a thinner epithelium also correlates with more virus in the subepithelial layers and in the blood at three to four days after inoculation.

Additional studies are underway at Aaron Diamond to characterize changes in infectability during the normal menstrual cycle in monkeys and, with the CONRAD Clinical Research Unit, to compare vaginal epithelial thickness in women before and during the use of Depo-Provera.

EPIDEMIOLOGICAL STUDIES

Work is underway in Chiang Mai, Thailand, to identify fac-

tors associated with the sexual transmission of HIV, including contraceptive practices, types and frequency of sexual contact, STDs, and other possible cofactors. This epidemiological study is attempting to identify factors associated with infectiousness from those associated with susceptibility. Researchers are addressing the dynamics of heterosexual HIV transmission cross-sectionally by following the serostatus of the multiple female sexual partners of the seropositive index males. Collection of semen samples to quantitatively measure HIV load by PCR is underway and will be related to seroconversion of the female partners. The immunological parameters of women who remain seronegative despite being highly exposed to seropositive men will be compared with those who seroconvert upon exposure.

Investigators in Brooklyn are studying the impact of HIV/AIDS on gynecologic health by observing the natural history of biological and

behavioral events in HIV-infected women. Of particular interest to the researchers are the incidence and progression of HPV disease and cervical neoplasia, including vaginal candidiasis, chlamydial infection, trichomoniasis, syphilis, pelvic inflammatory disease (PID), and bacterial vaginosis. The study includes recording the women's contraceptive use and other potential factors affecting disease incidence or progression.

A behaviorally focused project is assessing how high-risk Latino men and their heterosexual partners perceive the role of men in contraceptive decision making and condom use for preventing the transmission of HIV and other STDs. Investigators are exploring the inner-city context of relationships and how it relates to communication and decision making about condom use, the power differentials between male and female partners, and the effects of traditional Latino cultural norms and beliefs about gender roles. Initial data have been collected and are being used to prepare a questionnaire for further data collection.

FUTURE PLANS

CONRAD will continue to develop microbicide product leads, including formulation, preclinical evaluation, and clinical testing. In addition to completing projects underway, future studies regarding the heterosexual transmission of HIV are likely to address the effect of steroids on epithelial structure and immune function in the reproductive tract and the role of additional contraceptive methods, specific STDs, or other phenomena as cofactors for transmission of HIV to or from infected individuals. Other studies will be considered if justified in the context of contributing to better products, service delivery, and reproductive health.

SYSTEMIC HORMONAL METHODS FOR WOMEN

Over the years, CONRAD has worked on several long-acting hormonal delivery systems to prevent pregnancy. The empha-

sis has been on methods that are suitable for lactating women and/or that use natural rather than synthetic steroids. The delivery systems for CONRAD's work include injectables, vaginal rings, and suppositories.

NATURAL STEROID MICROSPHERES

Work on two types of injectables based on natural steroids is underway at the Instituto Nacional de la Nutricion Salvador Zubiran (INNSZ) and Aplicaciones Farmaceuticas in Mexico using a pulsating jet of melted drug to form microspheres, which are then annealed and formulated to provide relatively stable and long-acting aqueous suspensions. One injectable containing 250 mg of progesterone and 5 mg of estradiol has been tested in 30 women for a single cycle and appears to block ovulation for a month. Researchers will conduct reproducibility studies and evaluate the impact of multiple injections on bleeding patterns.

The other injectable uses progesterone alone and is designed to be used postpartum in lactating women and to last approximately two months. A clinical evaluation of the pharmacokinetics of this preparation in women is underway.

PROGESTERONE IN POLYMERIC MICROSPHERES

Investigators at Biotek, Inc., have developed an alternative approach to a sustained-release injectable, progesterone delivery system. Using

poly (lactide-co-glycolide) matrixes, a sufficiently high loading of drug in the polymer has been achieved to enable delivery of adequate amounts of progesterone for approximately 90 days *in vitro* and at least 77 days in rabbits. The process uses a solvent that is FDA approved but whose safety is now being questioned. As a result, no further work is planned.

PROGESTERONE VAGINAL RINGS

The concept of a woman-controlled long-lasting delivery system for progesterone has long had considerable appeal and has been part of the development programs of WHO and the Population Council for many years. ICMER and the Silesia Laboratories in Santiago produced and evaluated a ring that was originally developed at the Population Council. A multicenter Phase II clinical trial is ongoing in the Santiago area. The preliminary results look promising with respect to acceptability and pregnancy prevention. ICMER also is evaluating a daily use progesterone suppository in a Phase I pharmacokinetic study.

FUTURE PLANS

Concerns about the impact of progesterone on SIV transmission in monkeys and the yet unknown implications for women have raised questions about the continuing priority of research on injectable and vaginal ring progesterone delivery systems for lactating women. With respect to a monthly injectable, the issue is whether sufficient resources are available to continue this development given the considerable work that remains and the uncertainties about stability and reproducibility. CONRAD is considering entering the implant field using synthetic steroids such as levonorgestrel.

MALE METHODS OF CONTRACEPTION

Vasectomy is a highly effective method of contraception for males, and it is the method of choice for many couples. It is,

however, largely irreversible. With only one reversible male method of contraception on the market—the condom—the development of new male contraceptives has long been a high priority for CONRAD. Currently available latex condoms, while relatively effective in preventing sexual transmission of infectious disease agents, are unacceptable for many men and are much less effective in preventing pregnancy than methods readily available to women.

Most of the new male methods under development by CONRAD are systemic ones focused on suppression of spermatogenesis. Suppression is achieved by exogenous administration of hormones that inhibit the production and release of endogenous male hormones critical for spermatogenesis. Most of the ongoing clinical studies are at the stage of trying to establish the degree of suppression needed for high contraceptive efficacy. However, they involve suboptimal prototype drug formulations and have typically only been assessed in small numbers of men. CONRAD is investigating nonhormonal methods as well, including nonlatex condoms, follicle-stimulating hormone (FSH)-based immunocontraception, post-testicular agents, and vas deferens-blocking devices/plugs.

ANDROGENS ALONE

Gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone-releasing hormone (LHRH), is a hypothalamic peptide that stimulates gonadotropins in the pituitary to

secrete FSH and LH. In males, FSH stimulates and maintains spermatogenesis and LH acts on testicular Leydig cells to stimulate testosterone (T) production. GnRH antagonists compete with the endogenous molecule for pituitary binding sites and thereby prevent the release of LH and FSH. This leads to suppression of T in the short term and inhibition of spermatogenesis in the long term. Exogenous administration of androgens also inhibits GnRH production by the hypothalamus and FSH and LH production by the pituitary, and leads to suppression to azoospermia in many men and severe oligospermia ($\leq 3 \times 10^6/\text{ml}$) in almost all remaining men. When exogenous androgen is terminated, sperm production returns to normal.

CONRAD began collaborating nearly a decade ago with the WHO Task Force on Methods for the Regulation of Male Fertility to establish a multicenter, systematic assessment of the efficacy and safety of hormonally-induced azoospermia and oligospermia, using high-dose testosterone enanthate (TE) injections weekly as the prototypic agent. Studies involving more than

high circulating testosterone can result in undesirable, though reversible, side effects, such as acne and reduction in HDL-cholesterol.

Over the years, CONRAD investigators have attempted to devise more physiologic and acceptable formulations of androgens. Both long-acting esters and microcapsules have been investigated. Currently, testosterone bucyclate, a long-acting ester, is the most promising.

ANDROGEN/PROGESTIN COMBINATIONS

CONRAD has supported a number of studies designed to determine whether the addition of a progestin allows for the use of less testosterone (thus having fewer adverse effects on serum lipids) and increases the proportion of men who achieve azoospermia. Investigators at the University of Washington are working on a study to determine the lowest dose of the synthetic progestin, levonorgestrel (LNG), which suppresses spermatogenesis in combination with TE.

Earlier studies using oral dosing of 500 μg LNG per day were very promising. The primary drawback was that lipids were adversely affected (primarily a small reduction of HDL). This reduction was significant enough to warrant testing lower LNG dosages (125 $\mu\text{g}/\text{day}$ and 250 $\mu\text{g}/\text{day}$).

Preliminary data indicate

that all men receiving LNG have similar suppression to azoospermia or oligospermia, and that these men suppress sooner and to a higher percent than men receiving only TE. Preliminary analysis of serum lipids reveals that men receiving the lower LNG doses experience less of a

PREGNANCY RATES DURING EXPOSURE TO WEEKLY DOSE OF TE

Sperm Level	Concentration (million/mL)	Exposure (person-years)	Rate (per 100 person-years)
Azoospermia	0.0	230.4	0.0
Severe oligospermia	0.1 to 3.0	49.5	8.1
Combined	0.0 to 3.0	279.9	1.4

Source: WuFCW et al (1996). *Fertility and Sterility* 65(3): 626-36

400 men in nine countries clearly demonstrated the high contraceptive efficacy of this approach (see table). Findings show consistent azoospermia in 70% of the men overall and severely inhibited sperm production in almost all (98%) of the men. However, investigators also found that the

reduction in HDLs than men receiving the highest dose, thus indicating that further investigation of this promising approach is warranted.

Multicentered studies recently were initiated to verify whether lipids are adversely affected in men when desogestrel is used as the progestin in combination with TE (weekly) for suppression of spermatogenesis. Since these represent the first clinical studies of desogestrel in men, the men will be monitored for FSH and LH suppression, pharmacokinetic characteristics of desogestrel, and effects on lipid and carbohydrate metabolism. Recruitment was delayed because of reports that women taking oral contraceptives (OCs) containing desogestrel experienced a statistically greater risk of deep vein thrombosis than women taking other OCs. There are no data to suggest that this risk is present in men, and concerns over use of these OCs in most women appear to be overridden by other significant benefits. They provide effective contraception, regular cycles, are reversible, can prevent ovarian and endometrial cancer, and can protect against pelvic inflammatory disease and benign breast disease. The results from this study should be available by mid-1997 and will be compared with the results from the University of Washington studies using LNG.

Although preliminary results suggest that progestin/androgen combinations are more effective and safer than androgen administration alone, daily administration of a progestin/androgen combination is not an acceptable male contraceptive formulation because it can lead to pregnancy in cases where the male may not use it consistently. Because of this, long-acting testosterone and progestin esters, which were developed by WHO and NIH researchers, are more desirable, and preliminary studies using T bucy-

clate in men and LNG butanoate in women show promising results. They only have to be taken every three months and they have good pharmacokinetic profiles. Negotiations are underway with a major pharmaceutical company for the product development rights for the esters. If the development path appears too protracted, CONRAD may pursue development of other long-acting formulations.

GNRH ANALOGS

Because of their purely antagonistic effect on pituitary FSH and LH secretion in both women and men, GnRH antagonists are a potentially useful approach toward developing a practical male contraceptive. One drawback is that an androgen, such as testosterone, must also be administered to maintain libido and potency. Another is that most of the antagonists and agonists studied in small clinical trials are relatively expensive synthetic peptides and require frequent (if not daily) administration, some of which can cause local skin irritation. The two antagonists studied by CONRAD are Nal-Glu and Nal-Lys (Antide). Nal-Glu is more water-soluble than Nal-Lys and is easier to formulate; Nal-Lys is relatively free of local side effects and has an extended duration.

Studies show that azoospermia is readily induced by administration of Nal-Glu. Daily doses were sufficient to reach azoospermia by 12 weeks in six of eight men in a study conducted by investigators at Vanderbilt University. Increasing the dose resulted in azoospermia in the remaining two men. Subsequent studies carried out at the University of Washington on metabolic effects of testosterone replacement when used in conjunction with the GnRH antagonist indicated that any adverse metabolic and/or

behavioral effects were related to the level of replacement androgen administered.

Research is underway at the University of Washington and at Harbor Hospital-University of California, Los Angeles (UCLA) Medical Center on ways to eliminate the need for long-term daily administration of the antagonist, Nal-Glu.

Investigators recently began studies to determine whether androgens alone can maintain azoospermia or severe oligospermia induced with a priming dose of Nal-Glu plus testosterone enanthate. If this drug regimen is found to be effective in

spermatogenesis suppression, the effects of the treatment regimen on hormonal levels, lipoprotein levels, and sexual and/or behavioral changes also will be determined. Results from this study should be available by the end of 1996.

CONRAD has supported more limited clinical studies using the GnRH antagonist, Antide. A Phase I clinical study was initiated in 1990 to characterize the antigonadal effects of single-dose administration of the antagonist in eight normal men, evaluate its potency and duration of action, and identify any adverse reactions.

Although all the men in the trial apparently achieved azoospermia, problems with the drug formulation and inadequate patient follow-up by the investigator prevented completion of the clinical study.

The GnRH antagonist of choice might still be Antide if researchers can resolve formulation problems so that a sufficient dose can be obtained with reproducible duration of action. New GnRH antagonists are being developed

continually by private companies and other public sector organizations with the hope of increasing potency (and thus lowering the amount of drug needed) and decreasing side effects and costs. Should any of the new antagonists appear highly promising in preclinical or clinical testing, CONRAD would be interested in participating in

Improved condoms are likely in the short term, but it will be many years before acceptable hormonal and nonhormonal systemic methods are developed.

additional clinical trials.

Earlier studies using GnRH agonists, rather than antagonists, to suppress spermatogenesis are now thought to have used an insufficient dosage. Investigators at the University of Washington and Harbor-UCLA have begun a two-site study in normal men to see whether greater efficacy or a shorter lag time can be obtained using higher doses of the agonist, D-tryp6. Results from this study should be available by mid-1997. Even if the GnRH analogs prove to be highly effective in suppressing spermatogenesis, and can do so without adverse side effects, the acceptability of daily administration remains an issue. It is not known whether a potent nonpeptide will be identified that does not need to be administered daily.

POST-TESTICULAR AGENTS

Another important area of CONRAD research is developing systemic male methods by synthesizing and testing novel compounds that would disrupt sperm functions in the epididymis.

Evaluations are underway by the International Organization for Chemical Sciences in Development on *in vitro* sperm immobilization and *in vivo* effects on reproductive function in the male mouse. Although completely novel compounds will require significant preclinical toxicology testing, CONRAD has chosen a few promising leads for fertility trials, mechanism-of-action studies, and toxicity tests.

Gossypol, extracted from the cotton plant gossypium, has long been known to suppress spermatogenesis without suppressing testosterone. At higher doses, however, this effect has been irreversible in some men and associated with hypokalemia in others. Using plasma samples from men participating in an ongoing clinical trial conducted by the South to South Cooperation in Reproductive Health in Bahia, Brazil, plasma levels of gossypol are being measured to determine if hypokalemia, inadequate antifertility effects, or reversibility are associated with the different blood levels of gossypol achieved in this trial.

VAS-BLOCKING DEVICES

One of CONRAD's high priorities is developing reversible methods of tubal occlusion for men or women. However, few leads tested by CONRAD or collaborating agencies have demonstrated safety and high efficacy in clinical trials. For example, clinical testing of a device consisting of silicone plugs known as the Shug has not yet been shown in humans to have the significant potential

indicated in earlier animal studies. The developer is proceeding without additional CONRAD funding to make Shugs that are more flexible and expected to result in less adverse tissue interaction. If this design proves to induce azoospermia in men without damaging the vas, CONRAD would consider funding additional clinical studies.

CONRAD continues to monitor the expanded clinical trials of Vasoc, a cured *in situ* silicone rubber plug device in trials in China, Indonesia, and several countries in Europe. Support for a U.S.-based study would be considered if results continue to be favorable. Even if the method is highly effective and causes no damage to the vas, researchers would have to address the issue of whether an autoimmune response can lead to irreversible infertility.

FUTURE PLANS

The only new male contraceptives likely to complete product development in the short term will be improved condoms. It will be many years before acceptable formulations for hormonal and nonhormonal systemic methods are developed that are highly effective, safe, and relatively inexpensive.

CONRAD expects to continue research collaborations on long-acting androgen formulations for male contraception. These products, some of which are already in the marketplace, include 90-day testosterone ester injectables, 6- to 12-month implants, 60- to 90-day testosterone microspheres, and daily transdermal patches. Even though GnRH analogs are very effective in suppressing sperm production, CONRAD's continued support of related studies may decrease considerably unless analogs can be found that have significantly fewer negative

characteristics (i.e., local reactions, high cost, poor formulations, and the need for replacement androgen). Nonpeptide analogs may well solve several of these problems.

Several other issues must be resolved before any of the systemic male methods can reach the marketplace:

- ▶ Well-designed studies are needed to verify that exogenous administration of androgens does not adversely affect behavior, as has been suggested anecdotally (but not found in clinical trials).
- ▶ Since it can take about three to four months to achieve azoospermia with hormonal methods, other contraceptive methods must be used at the same time to provide protection.
- ▶ A home test kit needs to be developed so men using hormonal methods can confirm that they have reached azoospermia or adequate oligospermia.

IMMUNO- CONTRACEPTIVES

Immunocontraceptives have many potential advantages for preventing pregnancy including:

- ▶ Lack of side effects typical of current hormonal methods for women;
- ▶ Suitability for either men or women, depending on the target antigen;
- ▶ Sustained, reversible duration of action;
- ▶ Use during all stages of a man's or woman's reproductive life;
- ▶ Low manufacturing and storage cost; and
- ▶ Ease of distribution and administration within health care infrastructure.

CONRAD's main immunocontraceptive projects focus on interfering with spermatogenesis or fertilization by the production of antibodies against sperm and epididymal antigens, zona pellucida antigens, and peptide hormones (and their receptors) related to reproduction. Several other organizations have focused on hCG development because the hormone is usually only produced in women when fertilization and pregnancy occurs and should not interfere with ovulation or the production of sex steroid hormones. Because of the USAID prohibition against developing methods that target postfertilization events and the absence of evidence that hCG immunization would result in high clinical efficacy, CONRAD has followed other antigen leads.

Before any Phase I trials can be conducted, it is necessary to fully characterize the native antigen, verify tissue and cell specificity to minimize any risk of autoimmune disease, and demonstrate efficacy, safety, and reversibility in

relevant animal models, preferably nonhuman primates. CONRAD projects that have led to primate trials for either immunogenicity or antifertility effects include the sperm antigens, LDH-C4 and SP-10, in baboons and several zona pellucida antigens in macaques. Recent studies include testing contraceptive efficacy and safety in nonhuman primates. Additionally, CONRAD has supported limited studies on enhancing secretory immunity in the reproductive tract.

CONRAD has pursued a number of approaches to immunocontraceptives using sperm antigens, and two have advanced to primate fertility trials.

Unfortunately, selection of formulation components (e.g., adjuvant and carrier molecules), timing of primary and booster immunizations, level of antibody titers needed, and other efficacy trial procedures have proven difficult to predetermine and may need to be empirically derived. These factors have hampered rapid progress, especially given limited funding available. In addition, none of the current leads being explored is expected to protect against STDs. Nevertheless, CONRAD is moving ahead with a more modest effort on immunocontraceptives based on some encouraging antifertility results in animal trials and the possibility of achieving an innovative new contraceptive method.

SPERM ANTIGENS

CONRAD has pursued a number of approaches utilizing sperm antigens. Monoclonal antibodies generated against human sperm have been useful in defining candidates and producing purified sperm antigens. Some of the difficulties in this approach lie in the identification of antigens relevant to fertilization (even when *in vitro* sperm-egg interaction can be demonstrated) and the availability of suitable animal models for antifertility

testing. Other investigators have characterized sperm-specific proteins themselves, then identified their possible roles in fertilization. Unfortunately, antifertility trials in small-animal models have tended to demonstrate moderate to high efficacy that

has sometimes not been replicated in the more expensive and time-consuming primate trials.

A few candidate antigens have continued to show promise, and over the years CONRAD has pursued development of a number of leads, including LDH-C4, SP-10, TCTE1, acrosin, and SAA-1. Only two of these have advanced to primate fertility trials: LDH-C4 and SP-10.

LDH-C4

Investigators at Northwestern University and the Institute for Primate Research in Kenya have completed several fertility trials to assess the antifertility effects of improved formulations incorporating LDH-C4 epitopes. Immunization of female baboons with a synthetic peptide of human LDH-C4 conjugated to diphtheria toxoid (DT) carrier or a synthetic peptide bearing a T-

cell epitope from tetanus toxoid (TT) elicits strong immune response and suppresses fertility by approximately 70% to 80%. Suppression was reversible after cessation of immunizations.

The ability to prepare immunogen formulations without carrier conjugation results in simpler formulations and improved quality control and reproducibility. The investigators propose to study the duration and reversibility of the antifertility effect, test immunogenicity of a sustained-release antigen formulation (biodegradable microspheres), and make plans to prepare an investigational new drug (IND) application for FDA submission. However, because of fiscal limitations on the support of research on long-term methods and the modest antifertility effect observed, it is unlikely that continued CONRAD support will be available for the additional studies.

SP-10

SP-10 is a sperm-specific antigen that remains associated with the sperm head following the acrosome reaction. Immunogenicity and fertility trials of human SP-10 (produced by recombinant DNA technology) conducted in baboons by investigators at the University of Virginia demonstrated that SP-10 is a strong immunogen with moderate antifertility effects.

Unexpectedly, immunization of female baboons with the homologous sperm antigen did not generate any antifertility effect. When serum antibody titers were compared with antibody levels found in the cervical mucus of SP-10-immunized baboons, no correlation could be made between fertility status, serum antibody titers, and/or cervical mucus antibody levels. Whether this signifies that intra-acrosomal antigens are not good candidates is unclear.

ZONA PELLUCIDA ANTIGENS

An early step in mammalian fertilization is the penetration of sperm through the extracellular glycoprotein matrix (known as the zona pellucida or ZP) surrounding the oocyte. Since some of the ZP peptides appear to be developmentally expressed, it has been thought that the production of antibodies against late-stage epitopes would inhibit sperm penetration without interfering with normal oogenesis. In some species, including primates, immunization with zona proteins results in altered ovarian function and varying degrees of ovarian pathology. Now that the genes for ZP proteins have been sequenced from several species, including nonhuman primates, recent CONRAD projects have focused on identification of epitopes that do not induce ovarian pathology and on testing the immunogenicity and contraceptive potential of recombinant ZP peptides.

In the first of three zona-based projects, investigators at Baylor College of Medicine were able to generate high antibody titers against a recombinant rabbit homolog of human ZP in primates, but without significant antifertility effects. Because previous immunizations have generated antibodies that block primate sperm-zona binding *in vitro*, induce the acrosome reaction in primate sperm, react with primate zona, and do not induce ovarian pathology, epitope mapping studies have been undertaken to determine the differences in peptide antigenic determinants recognized by two sets of antisera. The goal of this research is to identify the most important epitopes for sperm binding. This approach is considered to be one of the most viable tactics for a zona-based immunogen.

Investigators at the University of California, Davis, are testing the contraceptive effect of

immunization with a well-characterized ZP peptide in an homologous animal model (cynomolgus macaques). They also are studying whether immunization alters ovarian function. All immunized females developed significant antibody titers, some of which produced measurable secretory IgA antibodies. A significant antifertility effect was observed during the time that monthly immunizations were given. As antibody titers

There are encouraging results in reversible male infertility following immunization of nonhuman primates with FSH.

declined, fertility was restored. The ability of antibodies from the immunized macaques to bind to native macaque ZP and inhibit sperm-zona binding is being assessed. Ovarian histology and immunohistochemistry are underway to fully characterize any effects on the ovary.

Because testing recombinantly expressed zona antigens in a homologous primate system has not been adequately tested, investigators at the National Institute of Immunology in New Delhi have immunized bonnet monkeys with recombinant bonnet monkey ZP and synthetic peptides of ZP. Monkeys have been immunized with the entire recombinant ZP protein and selected synthetic peptides. Immune responses and effects on cycling in all of the peptide-immunized monkeys are being monitored in anticipation of a mating trial. Thus far, significant titers have been generated in almost all immunized females.

FOLLICLE-STIMULATING HORMONE (FSH)

Based on encouraging results demonstrating reversible inhibition of spermatogenesis and subsequent infertility following immunization of nonhuman primates with native FSH by investigators in India and Germany, CONRAD has pursued the development of an FSH-based immun contraceptive. The work is being continuously

reviewed, since its actual feasibility has not been established. There appear to be significant species differences in endocrinological and developmental control of spermatogenesis by FSH and testos-

terone. However, unpublished Phase I clinical studies do indicate that immunization of men with purified FSH results in anti-FSH antibodies and suppressive effects on sperm production.

To provide a reliable and reproducible source of FSH for further clinical trials, investigators at the Indian Institute of Sciences (IISc) are producing recombinant FSH in a yeast expression system and characterizing the biological properties of antibodies to this FSH. Continued interest in this project area will take into account results from ongoing clinical trials in men in India by IISc.

Based on the premise that inhibition of FSH action at two levels would provide more effective fertility regulation, recombinant peptides of the extracellular domain of the FSH-receptor are being tested for their immunogenicity and their ability to inhibit fertility alone and in combination with an FSH vaccine. The goals of a collaborative CONRAD project between the Population Council and IISc are to identify the receptor

domains involved in FSH binding and signal transduction and to begin characterization of antibodies generated against monkey FSH-receptor epitopes.

FUTURE PLANS

CONRAD's funding for immunocontraceptive research has become more restrictive in recent years, in part because of a commitment to expensive multicenter clinical trials of barrier methods. With more limited funding available for vaccines and other immunocontraceptives, it becomes ever more important for CONRAD to focus on leads that have the potential to become a product.

One project that received wide support by reviewers of potential CONRAD immunocontraceptive projects is the development of a peptide hormone-based vaccine. Support for this project was based more on its potential than on data generated from CONRAD projects. The reviewers were also enthusiastic about a zona pellucida antigens project, although identification and use of specific epitope(s) critical for sperm-zona binding is probably the only promising route. Sperm antigens for which efficacy and specificity could be demonstrated also received a high level of interest, although CONRAD has no such projects pending.

In spite of the large investments of time and money without achieving a major breakthrough, CONRAD believes that continued efforts in immunocontraceptives must be pursued to reach the goal of having effective and inexpensive methods of fertility regulation that are easy to provide in the field.

Looking Ahead

Over its 10-year history, the mix of CONRAD's work has changed with the times, moving from pregnancy prevention work only to research on products that prevent pregnancy as well as the transmission of STDs, from conducting basic research to undertaking preclinical and Phase I and Phase II/III clinical trials, and from receiving funds only from USAID to embracing a wider range of government and philanthropic support.

No doubt changes will mark CONRAD's next year—and its next 10 years. The areas most likely to change, based on today's research, are:

- Extension of clinical studies on chemical barriers;
- More extensive testing of hormonal delivery systems; and
- Clinical trials to obtain approval of a systemic male contraceptive.

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CONRAD

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PROJECT

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Detection of HIV in
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Bioavailability of Testosterone
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Pharmacodynamics in Chinese
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Safety and Efficacy of Femcap®
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Male Contraception: Effects of
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Effects of Androgens Alone on
Maintenance of Severe
Oligo/Azoospermia in Men after
Induction with a Combination of
GnRH Antagonist and Androgen

High Dose GnRH Agonist Effect
on Spermatogenesis

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Topical Compositions for
Fertility-STD Control

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Zona Pellucida Self Peptides for
Immunocontraception in
Primates

Mitchell Creinin, M.D.

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Safety and Efficacy of Femcap®
Used with Spermicide and the
Ortho All-Flex® Diaphragm
Used with Spermicide

Horacio Croxatto, M.D.	Instituto Chileno de Medicina Reproductiva (ICMER), <i>Santiago, Chile</i>	CONRAD Collaborating Center for Clinical Research
Roy Curtiss, Ph.D.	Washington University, <i>St. Louis, MO</i>	Development of Recombinant Avirulent Salmonella Antifertility Vaccines
Rajan Dighe, Ph.D.	Indian Institute Science, <i>Bangalore, India</i>	Recombinant Expression of Bovine FSH α and FSH β in the Yeast
Bonnie Dunbar, Ph.D.	Baylor College of Medicine, <i>Houston, TX</i>	Immunocontraception Using Zona Pellucida Antigens
Josué Garza-Flores, M.D.	Instituto Nacional de la Nutricion Salvador Zubiran (INNSZ), <i>Mexico City, Mexico</i>	Development of Improved Injectable Sustained Release System for Natural Contraceptive Steroids
Michael Free, Ph.D.	Program for Appropriate Technology in Health (PATH), <i>Seattle, WA</i>	Development of an "Easy Fit" Silicone Diaphragm
Ron Frezieres, M.S.P.H.	Los Angeles Regional Family Planning Council, <i>Los Angeles, CA</i>	Comparative Evaluation of Three Tactylon [®] Condoms with a Latex Condom During Vaginal Intercourse: Breakage and Slippage
Richard Gandour, Ph.D.	Virginia Polytechnic Institute and State University, <i>Blacksburg, VA</i>	Hemicholinium and Related Lipids: A New Class of Contraceptive Spermicidal Agents
Erwin Goldberg, Ph.D.	Northwestern University, <i>Evanston, IL</i>	Immunosuppression of Fertility in Female Baboons by Sperm-Specific LDH-C4
Satish Gupta, Ph.D.	National Institute of Immunology, <i>New Delhi, India</i>	Evaluation of the Efficacy of Recombinant Bonnet Monkey ZP3 and its Corresponding Synthetic Peptides to Regulate Fertility in Primates

Polly Harrison, Ph.D.	National Academy of Sciences, <i>Washington, DC</i>	Applications of Biotechnology to Contraceptive Research and Development: New Opportunities for Public/Private- Sector Collaboration
S. Marie Harvey, Ph.D.	Pacific Institute of Women's Health, <i>Los Angeles, CA</i>	The Context and Meaning of Reproductive Decision Making Among Inner City Hispanic/ Latino Couples
Wayne Heine, M.D.	University of Arizona, <i>Tucson, AZ</i>	Safety and Efficacy of Femcap® Used with Spermicide and the Ortho All-Flex® Diaphragm Used with Spermicide, Protocol B94-027
John C. Herr, Ph.D.	University of Virginia, <i>Charlottesville, VA</i>	Baboon Fertility Trial of a Recombinant Baboon Contraceptive Vaccine
Mohamed Isahakia, Ph.D.	National Museums of Kenya, <i>Nairobi, Kenya</i>	Efficacy of Human LDH-C4 as a Contraceptive Vaccine in the Baboon
David Katz, Ph.D.	Duke University, <i>Durham, NC</i>	Targeting Cervical Mucus for Topical Contraceptive and Prophylactic Action
Annie Kung, M.D.	University of Hong Kong <i>Hong Kong</i>	Bioavailability of Testosterone from a Testosterone Microcapsule Formulation in Chinese Hypogonadal Men: A Comparative Assessment of Its Pharmacokinetics and Pharmacodynamics in Chinese and Caucasian Hypogonadal Men
Mark Maltzer, M.D.	Sutter Medical Foundation, <i>Sacramento, CA</i>	Safety and Efficacy of Femcap® Used with Spermicide and the Ortho All-Flex® Diaphragm Used with Spermicide
Mark Martens, M.D.	Minneapolis Medical Research Foundation, <i>Minneapolis, MN</i>	Comparative Evaluation of Three Tactylon® Condoms with a Latex Condom During Vaginal Intercourse: Breakage and Slippage

Preston Marx, Ph.D.	Aaron Diamond AIDS Research Center, <i>Tuxedo, NY</i>	Effects of Progesterone Implants on the Heterosexual Transmission of AIDS: A Simian Model
Alvin Matsumoto, M.D.	University of Washington, <i>Seattle, WA</i>	Male Contraception: Progestin-Androgen Combinations Using a Reduced Dose of LNG Plus TE
John Mattox, M.D.	Good Samaritan Medical Center, <i>Phoenix, AZ</i>	Safety and Efficacy of Femcap® Used with Spermicide and the Ortho All-Flex® Diaphragm Used with Spermicide
Christopher Miller, D.V.M., Ph.D.	University of California, <i>Davis, CA</i>	The Heterosexual Transmission of AIDS: A Simian Model
Howard Minkoff, M.D.	State University of New York (SUNY), <i>Brooklyn, NY</i>	Gynecologic Manifestations of HIV Disease
Kenrad Nelson, M.D.	School of Hygiene and Public Health, The Johns Hopkins University, <i>Baltimore, MD</i>	Factors Affecting the Heterosexual Transmission of HIV Infection in Northern Thailand
Nancy Padian, Ph.D.	University of California, <i>San Francisco, CA</i>	The Effect of the Use of Intravaginal Preparations on the Vaginal Mucosa and Flora and on the Likelihood of Being HIV/STD Infected in Zimbabwean Women
Dorothy Patton, Ph.D.	University of Washington, <i>Seattle, WA</i>	Effects of Nonoxynol-9 and Benzalkonium Chloride on Vaginal Flora and Chlamydia Trachomatis Infection <i>in vivo</i>
Alfred Poindexter, M.D.	Baylor College of Medicine, <i>Houston, TX</i>	Safety and Efficacy of Femcap® Used with Spermicide and the Ortho All-Flex® Diaphragm Used with Spermicide
Marcus Reidenberg, M.D.	Cornell University Medical College, <i>New York, NY</i>	Clinical Pharmacology of Gossypol in the South to South Male Clinical Trial Contraceptive

Bruce Rosenzweig, M.D.	College of Medicine, University of Illinois, <i>Chicago, IL</i>	Safety and Efficacy of Femcap® Used with Spermicide and the Ortho All-Flex® Diaphragm Used with Spermicide
Anthony Sacco, Ph.D.	Wayne State University, <i>Detroit, MI</i>	Evaluation of the Efficacy of Synthetic Peptides Corresponding to Primate/Human ZP3 to Regulate Fertility in Primates
William Shannon, Ph.D.	Southern Research Institute, <i>Birmingham, AL</i>	Evaluation of the Anti-HIV Activity of Spermicides and Virucides <i>in vitro</i>
Alfred Shihata, M.D.	Femcap, Inc., <i>Del Mar, CA</i>	Clinical Evaluation of Femcap®
Ronald Swerdloff, M.D.	Harbor-UCLA Medical Center, <i>Torrance, CA</i>	Effects of Androgens Alone on Maintenance of Severe Oligo/Azoospermia in Men after Induction with a Combination of GnRH Antagonist and Androgen
Derek VanAmerongen, M.D.	Johns Hopkins Medical Service Corporation at Wyman Park, <i>Baltimore, MD</i>	Safety and Efficacy of Femcap® Used with Spermicide and the Ortho All-Flex® Diaphragm Used with Spermicide
Anne Viselli, M.D.	Vermont Women's Health Center, <i>Burlington, VT</i>	Safety and Efficacy of Femcap® Used with Spermicide and the Ortho All-Flex® Diaphragm Used with Spermicide
Ronald Wiehle, Ph.D.	Baylor College of Medicine, <i>Houston, TX</i>	Protein and Lipid Markers of Vaginal Mucosa
Fred C.W. Wu, M.D., F.R.C.P.	University of Manchester, <i>Manchester, England</i>	Effects of Oral Desogestrel Intramuscular Testosterone in Normal Men: A Pharmacokinetic and Pharmacodynamic Study
Lourens Zaneveld, Ph.D.	Rush-Presbyterian-St. Luke's Medical Center, <i>Chicago, IL</i>	Identification, Evaluation and Development of Contraceptive Antimicrobials