

CONRAD
PROGRAM

Making Progress Toward
More Effective, Safe, and Acceptable
Contraceptives

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Major Advances in 1998-1999

During the past two years, the Contraceptive Research and Development (CONRAD) Program has made tremendous strides in the development and improvement of safe, effective, and accessible contraceptives for women and men.

Systemic Hormonal Methods for Men. In conjunction with CONRAD'S Consortium for Industrial Collaboration in Contraceptive Research (CICCR) and industrial partners, Phase I clinical testing of various androgen and progestin combinations has identified several regimens that effectively suppress spermatogenesis with minimal adverse side effects. A Phase II clinical trial on the contraceptive efficacy of testosterone pellets with injectable Depo-Provera® began in 1999. Plans are underway to begin a multicenter study in 2000 of a long-acting injectable testosterone formulation in combination with the progestin norethindrone enanthate.

FemCap™. Clinical studies of this cervical cap have been launched to verify ease of insertion and removal of the latest modification, which has a removal strap, and to obtain additional acceptability information. It is expected that the inventor will submit this device to the U.S. Food and Drug Administration (FDA) for approval upon completion of these studies in 2000.

Silcs Intravaginal Barrier Device. Development of the final prototype of a reusable, silicone, diaphragm-like device progressed into Phase I clinical testing for acceptability, safety, and cervix-blocking capability. Successful completion of Phase I testing will be followed by a Phase II contraceptive efficacy trial. Over-the-counter (OTC) availability is targeted.

Lea® Contraceptive. CONRAD renewed its collaboration with the inventor of this device to complete clinical studies requested by the FDA prior to approval. Lea Contraceptive, a silicone rubber device that covers the cervix, has demonstrated contraceptive efficacy equivalent to that of existing barrier methods.

Cellulose Sulfate Formulation. A Phase I clinical trial on the safety of this contraceptive anti-microbial gel was completed and revealed minimal vaginal irritation. Clinical trial plans for expanded Phase II/III studies will be presented to the FDA in early 2000. Preparations are underway to synthesize adequate quantities of drug substance to conduct all the required toxicological and Phase II/III studies in collaboration with the formulation developers and their industrial partners.

CONRAD's Mission and Funding Sources

THE CONRAD PROGRAM IS DEDICATED TO developing better, safer, and more acceptable methods of contraception that are suitable for use in developing countries. The ultimate goals of CONRAD's research are to expand the contraceptive choices of women and men throughout the world and to help prevent the transmission of the human immunodeficiency virus (HIV) and other sexually transmitted diseases (STDs).

Established in 1986 under a cooperative agreement with the U.S. Agency for International Development (USAID) and the Eastern Virginia Medical School in Norfolk, Virginia, CONRAD's top priority is to move promising leads through Phase I and II clinical trials. Research is conducted at CONRAD's intramural laboratories and clinical facilities in Norfolk and by investigators at public and private sector research institutions in the United States and abroad.

In addition to USAID, CONRAD has received funding from the National Institute of Child Health and Human Development (NICHD) and the Centers for Disease Control and

Prevention (CDC) to support projects that are of mutual interest.

CICCR was created within CONRAD in 1995 with the primary objective of revitalizing the commitment of industries to developing new contraceptive products. For some time, innovation has been impeded by a costly and cumbersome research and development process and by pharmaceutical manufacturers' perceptions of significant barriers to market entry of new contraceptives. CICCR was launched with funding from The Rockefeller Foundation and The Andrew W. Mellon Foundation; additional contributors include The William and Flora Hewlett Foundation, The Bill and Melinda Gates Foundation, the United Nations Population Fund, and others.

CICCR identifies leads under investigation by not-for-profit organizations in developed and developing countries that may result in new contraceptive methods for men; new vaginal methods that prevent pregnancy and STD transmission; and monthly regimens that are postcoital, anti-implantation, or menses-

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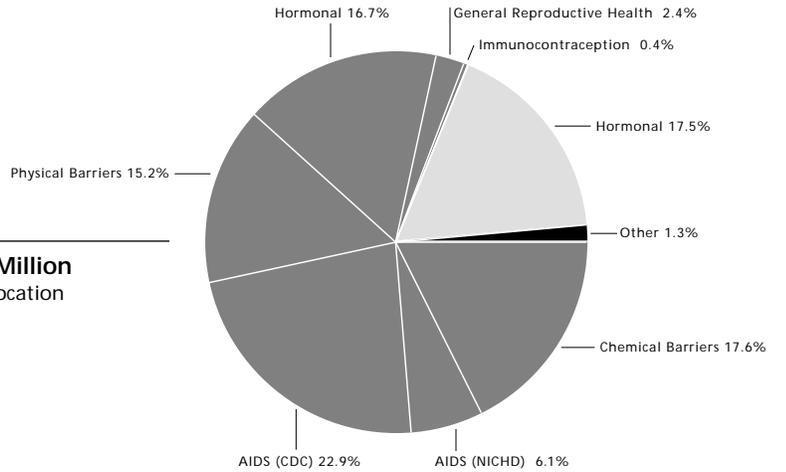
inducers. It encourages the for-profit sector to support these endeavors and provides funds to investigators through three types of mechanisms:

- **A feasibility project** program supports innovative, high-risk research relevant to CICCR's objectives. Initial funding from CICCR helps bring these projects to a point where they can attract interest in further development from an industrial partner.
- **A matching funds** program fosters collaboration between industry and not-for-profit research centers. Support is limited to the early stages of drug development and may also be used to explore the feasibility of commercial development of methods validated in these trials, obtain patent protection for their invention, and identify industrial partners for collaboration.
- **The Mellon Foundation** provides sole funding for twinning projects between Mellon-supported reproductive biology centers in the United States and selected research centers in developing countries.

Research Activities

CONRAD Projects Funded: \$8 Million
1998-1999 in percent by dollar allocation

- Female Methods
- Male Methods
- Other

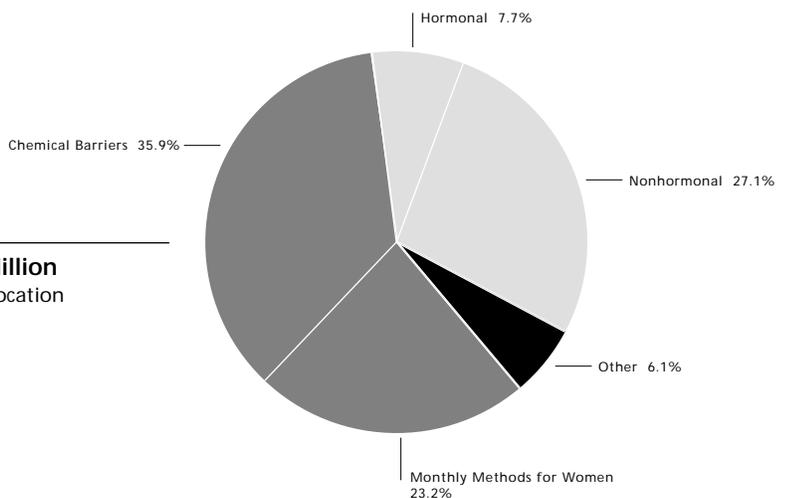


PEOPLE IN DEVELOPING COUNTRIES ARE IN urgent need of new contraceptives that prevent pregnancy and the transmission of STDs, especially HIV/AIDS. Over the past two years, CONRAD has made great progress in meeting that need. As CONRAD looks toward the future, it will continue to focus its work on five high-priority areas of research:

- Systemic methods for men
- Chemical barriers
- Mechanical barriers
- Systemic methods for women
- Microbicides that prevent transmission of STDs

CICCR Projects Funded: \$5.5 Million
1998-1999 in percent by dollar allocation

- Female Methods
- Male Methods
- Other



Contraceptives for Use by Men

AN IDEAL MALE CONTRACEPTIVE HAS TO BE highly effective, but it must also be much more. It must produce minimal adverse side effects, and it must be acceptable, suitable, and affordable to men in developing countries and the United States. Although CONRAD has pursued several approaches to male contraception, it has made the most progress with systemic administration of exogenous hormones designed to inhibit the production and release of endogenous hormones that are critical for spermatogenesis. This remains CONRAD's highest priority in this research area. Other approaches will continue to be considered and developed as their feasibility is established. These methods include the use of:

- nonhormonal agents that block the production or functionality of sperm (e.g., immunocontraceptives),
- orally active agents that act post-testicularly to impair sperm function, and
- physical barriers to the release of sperm (e.g., vas-blocking devices).

CICCR resources for male method development enhance CONRAD's ability to investigate

novel leads and then pursue those leads through preclinical testing and into clinical trials.

Systemic Hormonal Methods

The hypothalamic peptide, gonadotropin-releasing hormone (GnRH), and pituitary proteins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), play critical roles in spermatogenesis. CONRAD's work in this area has focused largely on regimens that inhibit FSH and LH release either by exogenous androgens alone or in combination with other sex steroid hormones or by GnRH antagonists. These methods help suppress endogenous testosterone in the short term and inhibit spermatogenesis in the long term.

Androgen/Progestin Combinations

In general, combinations of a progestin and an androgen have induced azoospermia and significant oligospermia more quickly and at a higher rate than androgens alone. This combination effectively suppresses release of FSH and LH, thus also suppressing testosterone and sperm production. The addition of a progestin to these regimens also permits the use of less testosterone—resulting in

fewer side effects, such as acne, weight gain, or adverse reductions in serum lipids, especially HDL-cholesterol.

The main goal of several ongoing clinical trials involving androgen/progestin combinations is to determine optimal dose combinations that induce high rates of azoospermia and severe oligospermia while maintaining normal serum lipid levels. Unfortunately, the specific pharmacodynamic outcome of a given hormonal combination in a group of men is not completely predictable. As a result, different hormonal combinations and their formulations and delivery systems must be investigated to identify a regimen that provides high efficacy and acceptability and minimizes adverse side effects.

Several trials of new long-acting androgen/progestin formulations are in progress, and others are planned. CONRAD and its CICC expect to play major collaborative roles with the World Health Organization (WHO) and industrial partners in expanded clinical testing for contraceptive efficacy in larger groups of men. Following is a description of several ongoing studies.

- Enrollment is nearing completion in a study at the University of Washington to determine the lowest oral dose of levonorgestrel (LNG), a synthetic progestin that can be used in combination with testosterone enanthate (TE) to suppress spermatogenesis. Preliminary findings indicate that lower doses of LNG (63 µg per day) induce azoospermia and severe oligospermia in nearly the same percentage of men as higher doses (125-500 µg per day).
- Comparative work is underway at Harbor-UCLA Medical Center to test an alternative combination of the Population Council's two-rod LNG-releasing implant system

with daily testosterone-releasing patches. Preliminary data revealed that administration of four LNG rods plus two testosterone-releasing patches did not suppress sperm adequately. Thus, in continuing studies, one group of men will receive four rods plus weekly TE injections, and another group will receive daily treatment of both testosterone patches and oral LNG.

- Preliminary results from a two-center study in Australia confirm observations of highly effective sperm suppression from a combination of six-month depo-testosterone with depo-medroxyprogesterone acetate (DMPA). Although there have been no major adverse effects, symptomatic androgen deficiency was observed in a few men in the sixth month following implantation of testosterone pellets. As a result, testosterone pellets are now being replaced every four months. CONRAD is supporting this study with both USAID and CICC funding.

It is unclear why responses to androgen-based regimens vary, but inadequate suppression of intratesticular androgen may be a factor. Monkey studies are underway at the University of Washington to address the mechanisms by which testosterone suppresses spermatogenesis, whether conversion of testosterone to dihydrotestosterone within the testes limits optimal effectiveness, and whether these mechanisms are augmented when an anti-androgenic progestin is combined with testosterone treatment. Monkeys have begun receiving hormone treatment, and preliminary data are pending.

Several clinical studies completed during 1998 and 1999 assessed combinations that included progestins, which seem to induce fewer side effects when used as oral contraceptives for women. Investigators at the University of

Washington and St. Mary's Hospital in Manchester, United Kingdom, tested oral desogestrel combinations and found that spermatogenesis was significantly suppressed, but adverse effects on lipids were still evident. Lower desogestrel doses did not yield long-lasting suppression, nor did transdermal testosterone patches release adequate androgen.

Development of new male contraceptives is one of CICCR's three priority areas. In addition to the efficacy trial of depo-testosterone plus DMPA, a clinical study of an injectable testosterone, undecanoate (TU), plus oral cyproterone acetate (CPA), a progestin with anti-androgenic activity, is nearing completion in Bologna, Italy. A high percentage of men achieved azoospermia during the maintenance phase, and all men's sperm production had been suppressed to extremely low levels. An expanded multicenter study is under consideration, but will not proceed without the participation of an industrial partner.

Although oral administration of progestin in combination with androgens has proved to be very successful, sustained-release formulations of LNG have not suppressed spermatogenesis adequately in limited clinical trials to date. Because the need to take a daily pill increases the potential for noncompliance, a more effective sustained-release regimen is desired. A pilot study of a Chinese LNG-releasing implant system plus TU did not produce acceptable results, most likely because of inadequate dosages. Testing of a regimen with four rods plus TU is ongoing.

There are concerns that long-term testosterone treatment for male hormonal contraception could have adverse effects on the prostate. However, it is believed that an androgen under development by the Population Council, 7 α -methyl-19-nortestosterone (MENT™), can be administered at

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doses that suppress gonadotropins without adversely affecting prostate growth. This compound may be useful for development of a male contraceptive administered either alone or in combination with other steroid hormones. Investigators in the United States and India are using CICCR twinning funds to test the contraceptive efficacy of MENT alone in monkeys, and its possible enhancement when administered in combination with a low dose of estradiol.

GnRH Analogs

Administration of GnRH antagonists essentially suppresses sperm production as effectively as androgen/progestin combinations. Results of a two-center study (University of Washington and Harbor-UCLA Medical Center) demonstrated that TE alone maintained azoospermia or severe oligospermia after suppression with the GnRH antagonist Nal-Glu for at least 20 weeks. Although this regimen was highly effective in suppressing spermatogenesis, it also induced irritation at the injection site in several men. This is typical of most of the GnRH analogs studied by CONRAD and others in limited clinical trials.

In addition, GnRH analogs are relatively expensive and generally require daily injection. CONRAD's interest in GnRH analogs will remain very limited until analogs with significantly fewer negative characteristics—such as local reactions, high cost, and poor formulations that require frequent administration—are identified. Thus, CONRAD and NICHD are looking into the formulation of acyline, a more promising agent. In addition, nonpeptide analogs that may well solve several of these problems are in development. CONRAD will pursue any highly promising leads that emerge from preclinical studies.

Systemic Nonhormonal Methods

Nonhormonal methods fall into two main categories: orally active agents and immunocontraceptive approaches. Testing of these approaches, however, lags behind testing of hormonal approaches. Although this general area has been the focus of numerous animal studies during the past several years, there are few promising leads. Accordingly, CONRAD support in this area remains limited to CICCR-funded projects.

Previous research has shown that lonidamine, an anticancer drug developed in the 1970s, resulted in significant antispermatogenic activity, but development of lonidamine as an antispermatogenic agent was abandoned in the 1980s because high doses caused kidney damage. More recent research has focused on identifying analogs of lonidamine that will be equally effective but not toxic. More than 20 analogs of lonidamine have been synthesized and screened *in vitro* by investigators at the Population Council and their industrial collaborators. Two orally active lonidamine derivatives appear very promising. In a small animal model, these compounds promoted the release from the testes of immature sperm lacking fertilizing capacity. As a result of these successful findings, the compounds are

undergoing further development in partnership with two Italian companies.

Refined plant extracts used in Chinese medicine have been shown to produce antifertility effects in male mice and human males without significant toxicity or side effects. One such extract, highly purified triptolide from *Trypterygium wilfordii*, may prove suitable as a male contraceptive if adequate safety and efficacy can be established. Investigators at the University of Wisconsin-Madison and Mahidol University in Thailand are collaborating to study the effects of oral triptolide as an antifertility agent in male marmosets.

A CICCR collaborative project between investigators at the Population Council and in China is studying the role of activin C proteins in gonadal function. In gonadal tissues, activins and inhibins act locally to modulate steroid hormone production, spermatogenesis, and oocyte maturation. Because of its expression in reproductive tract tissues, it is believed that activin C may have a unique role in controlling reproductive functions.

Immunization of males against sperm proteins has not been vigorously pursued, largely due to concerns about autoimmune reactions. These concerns, however, are hypothetical for the most part, and have not been validated. Accordingly, a primate fertility trial of a well-characterized sperm enzyme, LDH-C4, is underway by Northwestern University researchers. Results from this trial, and those from planned immunogenicity and fertility studies by investigators from the University of North Carolina of epididymal proteins found on sperm, are expected to provide answers regarding the likely success of male immunization. □

Contraceptives, HIV/AIDS, and Other

Contraceptive products that protect against the sexual transmission of HIV/AIDS and other STDs, and that can be used by women at their own discretion, are urgently needed.

THIS IS A TOP RESEARCH PRIORITY FOR CONRAD.

Clinical trials to assess the efficacy of new test agents against heterosexual transmission of STDs and HIV/AIDS continue to face a number of severely challenging constraints, including:

- the need to provide and conscientiously promote the use of condoms and the test formulation, and then to analyze by stratified degree of compliance;
- the need to conduct such studies in populations at very high risk of exclusively sexual HIV infection, which is likely to occur only in developing countries; and
- the very high cost of doing such studies.

CONRAD is seeking to prioritize potentially active agents for further testing and development. Potential antimicrobial contraceptive compounds are screened and evaluated for *in vitro* and *in vivo* effects of the test agent on:

- sperm motility,
- other sperm functions,
- fertilization in rabbits,
- infectiousness of STD pathogens, including HIV, and
- toxicity, including rabbit vaginal irritation and effects on lactobacilli (the predominant microflora organism that supports good vaginal health).

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CONRAD is continuing its efforts to improve both *in vitro* and *in vivo* primate models for HIV transmission. In addition, CONRAD is seeking to expand scientific knowledge on the mechanisms for HIV transmission in humans. Models for other STDs are also under development.

Considerable progress has been made in 1998 and 1999 with respect to animal models for HIV and other STDs. Current studies are building on the results of earlier work co-supported by NICHD to investigate the specific effects of existing or potential contraceptives on factors relevant to the heterosexual transmission of HIV. Researchers at Primedica are using the rhesus macaque/SIV model to test prototype vaginal microbicides. A recently completed study of three formulations of new agents (that were very active against HIV and SIV *in vitro*) found, unexpectedly, that none of them reduced the rate of infection in this model. Further validation of this primate model and extrapolation of the experimental parameters to human use are needed before firm conclusions based on this model can be made.

These same three formulated agents were also tested for their ability to prevent chlamydial infections in the pigtailed macaque at the University of Washington using a model that was developed with support from CONRAD and the National Institute of Allergies and Infectious Diseases (NIAID). The results suggested a slight inhibition of chlamydia infection by only one of the tested agents. The impact of all three agents on the normal vaginal microflora and inflammation was minimal.

Meanwhile, new feasibility studies are underway to test other models that may be cheaper, more validated, and more useable than the monkey models. The three new formulated agents that were tested in monkey models are also being evaluated for preventing vaginal infection with HSV-2 in mice at the Population Council. Studies continue to confirm *in vitro* anti-HIV activity of promising agents. The viral-binding inhibition assay is now more specific for this stage of infection, and work will begin on incorporating additional assays.

The development of vaginal methods that protect against STD pathogens, including HIV, is a high priority for CONRAD and its CICCR program. One project involves testing of several of the lead agents that were assessed for antimicrobial activity using the primate, small animal, and *in vitro* models. The objectives of a feasibility study at Brigham and Women's Hospital are to investigate the effect of various steroids, including progestins and antiprogestins, on the function of the immune cells, and how this may relate to STD infection.

In another study, Brazilian investigators in São Paulo and at Brigham and Women's Hospital are testing whether antimicrobial vaginal preparations under development are able to inactivate HIV shed vaginally by HIV-positive Brazilian women. This approach

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is an attempt to model the efficacy of these potential products to prevent heterosexual transmission of HIV.

Prevention and Epidemiology Studies

Research on the prevention and epidemiology of STDs/HIV is of utmost importance to CONRAD and several of its collaborating agencies. In 1998 and 1999, for example, CDC provided CONRAD with funds for epidemiological and clinical studies to:

- identify the risk factors associated with heterosexual HIV transmission and the extent to which contraceptive use affects those risk factors;
- address condom acceptability among users of injectable contraceptives;
- determine the immunological, virological, and genetic factors that may be related to resistance of women who are regularly and highly exposed to a seropositive partner; and
- identify high-risk groups for STDs among women refugees of reproductive age.

The main epidemiologic study supported by CDC through CONRAD to identify psychosocial and other risk factors associated with the sexual transmission of HIV in Thailand is complete. Researchers at Johns Hopkins University, Chiang Mai University, CDC, and CONRAD collaborated to evaluate factors such as contraceptive practices, types and frequency of sexual contact, STDs, immune status, and HIV clade. More than 620 couples were enrolled in an attempt to separate factors associated with infectiousness from those associated with susceptibility.

Overall HIV seroprevalence in regular female partners was 45 percent. The seroconversion rate among regular female partners was approximately seven per 100 person-years, and the estimated transmission probability per act of intercourse among newly married couples was 1.7 per 1,000 acts. A retrospective study of 91 of the enrolled couples with a defined period of exposure to HIV found an estimated infectivity ratio of 1.44 for DMPA, compared with nonhormonal/nonbarrier methods. The 95 percent confidence interval, however, was 0.12-17.3.

Follow-up studies are evaluating HIV in semen and characterization of seronegative women with high-level exposure to HIV-infected men, compared with women found to be seropositive after a short period of exposure. Higher viral load in semen samples from a subgroup of men was found to be associated with a greater likelihood of transmission to their female partners. Data collection is underway on the natural history of morbidity and mortality of individuals infected with HIV in Thailand. Reliable data are needed to evaluate interventions to prevent or delay infection. The investigators continue to interview and examine Thai women for HIV status, CD4+ levels, and other STDs.

Consistent use of condoms with DMPA is particularly important because of the sharp rise in the incidence of HIV and other STD infections among reproductive-age women. In one of the ongoing behavioral studies, investigators at Baylor College of Medicine are attempting to identify the psychosocial factors that best predict the use of condoms among injectable contraceptive

users. Another study is designed to help identify high-risk groups for STD infection in Azerbaijan among women refugees of reproductive age.

Highly active antiretroviral therapy (HAART) is a therapeutic regimen that significantly reduces morbidity and mortality in HIV-positive individuals. Studies are underway at Brigham and Women's Hospital to determine the extent to which HAART can eradicate virus from tissue compartments in HIV-positive women.

Contraceptives for Use by Women

CONRAD'S KEY OBJECTIVE IN DEVELOPING contraceptives for women is to expand the range, availability, and use of safe, effective, and acceptable technologies for the prevention of pregnancy and STDs. This is also a strategic objective of USAID, CONRAD's primary funding agency and closest collaborator. Because user acceptance of new reproductive health products is so important, CONRAD formally incorporates user perspectives and feedback into the development process and the earliest stages of clinical evaluation.

New vaginal chemical and physical barriers have been brought through preclinical design and testing and into Phase I and II clinical trials. These include several devices that do not require physician fitting, such as Lea Contraceptive, FemCap, and the Silcs intra-vaginal barrier device. Presumably, these products would be more accessible and more acceptable to users. FDA approval of the Lea Contraceptive and FemCap is anticipated in the near future. In addition to proprietary compounds under development through CICC, CONRAD's extensive spermicide and

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microbicide screening program has resulted in several promising leads. The ideal product would be spermicidal and/or microbicidal without irritating vaginal tissue. Finding that product, however, is a challenge. Also, new delivery systems and formulations are being developed to better protect the vaginal epithelium, increase coverage, and lengthen duration of action.

Barrier methods have several advantages, and CONRAD continues to pursue developments in this area. Barrier methods are likely to provide some protection against STDs; they are required only at the time of coitus; they

Two projects are underway to better understand how spermicidal formulations spread and coat the vaginal epithelium and cervical os.

are nonhormonal and do not produce systemic side effects; and their use is initiated by the woman. However, barrier methods are frequently messy, which reduces user acceptability, and have relatively low efficacy. Research in barrier development focuses on overcoming these deficiencies and on producing new chemical and physical barriers that are more effective and more acceptable than existing methods.

Chemical Barriers

Spermicidal and Microbicidal Compounds

CONRAD has directed major efforts at improving existing spermicides, including nonoxynol-9 (N-9), the only marketed free-standing spermicide in the United States, and developing new ones. High dosage or frequent use of N-9 can irritate the vaginal epithelium and may disturb the vaginal flora, which can create a portal of entry for STD pathogens. In addition, even minor vaginal symptoms can reduce user acceptability. Accordingly, much of the research in this area has focused on answering questions surrounding optimum dosage, timing of administration before intercourse, additional appli-

cation with subsequent acts, efficacy in perfect use, and vaginal irritation with high doses or frequent use.

Lead compounds identified through *in vitro* screening are advancing toward clinical testing. In collaboration with CONRAD, investigators at the University of Kentucky have fractionated and iodinated N-9 (IN-9) and found that several fractions appear to be higher in spermicidal activity than unfractionated N-9. Several compounds, including those based on N-9 and iodinated derivatives, were evaluated for rabbit vaginal irritation, and were found to cause only minimal or mild irritation. In addition, a collaboration between CONRAD and Integra LifeSciences Corporation has resulted in the development and patenting of Q2, a hydrophobe-modified cationic polysaccharide excipient for the delivery of topical microbicides and spermicides. A Phase I safety study of an N-9/Q2/dextran sulfate formulation is expected to begin by the end of 2000.

Methodologies to Assess Spreading and Safety of Chemical Barriers

New technology has been developed to assess and improve the delivery of agents that inhibit the migration, function, and survival of sperm and possibly of STD pathogens. It is hoped that the specific physical properties that most significantly affect the spreading of vehicles in the vagina can be identified and used to predict factors such as the extent of tissue coverage, depth of coating, and maintenance of adhesion. That information will then be used to improve the contraceptive and prophylactic performance of vaginal formulations *in situ*.

Two projects are underway to better understand the dynamics of how spermicidal formulations spread and coat the vaginal epithelium and cervical os, and the adhesion of the formulations to these surfaces over time.

These include a comparison of Conceptrol® and Advantage™ gels used in the recumbent position, followed by a comparison of the recumbent position versus sitting, standing, and then resuming the recumbent position, at Duke University.

An alternative approach to assessing the distribution of formulations in the vagina, using gamma scintigraphy, is under development at the University of Kentucky. Gamma scintigraphy combines radiology imaging with different pharmaceutical dosage forms. This project is completing *in vitro* tests to finalize a computer-assisted analysis program. The analysis software will be validated and the *in vivo* imaging conditions refined to optimize data quality in a clinical trial that monitors the distribution and elimination rates in the vaginal cavity of a currently marketed spermicide radiolabeled with IN-9.

Validation of new *in vitro* technology to assess the potential inflammatory effects of new microbicidal agents is progressing at Brigham and Women's Hospital in Boston. To date, correlations have been good for limited comparisons among cell lines generated from human vaginal and cervical epithelium, primary tissues, and cervical and vaginal lavages collected from women. Tests are planned to correlate *in vitro* results with animal and human outcomes.

Development of vaginal methods that prevent pregnancy and STDs has been the most active and successful of CICCR's activities. New leads for topical vaginal spermicide and microbicide preparations are moving to clinical efficacy trials as rapidly as possible. Several of the most promising initiatives were developed in conjunction with the Program for the Topical Prevention of Conception and Disease (TOPCAD) at Rush-Presbyterian-St. Luke's Hospital in Chicago.

- A Phase I study of a long-acting formulation of N-9 (LASRS) and a Phase I safety study of ACIDFORM, a low pH-buffered formulation containing N-9, were completed. Clinical testing of LASRS continues. The initial ACIDFORM formulation induced excessive vaginal irritation and is being modified to remove N-9 prior to continued clinical testing, since it is believed that maintaining a low pH may be sufficient to prevent fertility and pathogen transmission.
- Additional leads developed through TOPCAD include cellulose sulfate (CS), polystyrene sulfonate (PSS), and SAMMA, a low-molecular-weight noncytotoxic antimicrobial contraceptive. A single- and multiple-exposure tolerance study of a CS gel was successfully completed, with minimal evidence of vaginal irritation. Clinical trial plans for Phase II/III studies of CS will be presented to the FDA by summer 2000. A Phase I clinical trial of PSS is underway to assess signs of irritation, product leakage, and product acceptability. Recently completed preclinical development work on SAMMA found that biological activity was similar to that of PSS. Additional preclinical toxicity and vaginal irritation testing continues.

CONRAD is exerting considerable effort to enhance technology transfer of lead candidates developed by TOPCAD to experienced industrial partners. Results have been encouraging. Advance Care Products (ACP) is a partner in the development of LASRS and PSS. Polydex Pharmaceuticals is a partner in CS development. AO Pharmaceutico, a Brazilian company, is manufacturing the ACIDFORM gel.

- Concerns over the safety and efficacy of spermicidal products using N-9 have led to the development of monoclonal antibodies at the University of Virginia that completely

agglutinate sperm in the ejaculate. Novavax, Inc., is formulating these monoclonal antibodies with the proprietary Novasome® liposomes for Phase I safety studies. Preliminary studies have shown that this preparation inhibits sperm penetration into cervical mucus and immobilizes sperm over a wide range of pH concentrations.

Mechanical Barriers

Lea Contraceptive. CONRAD, in collaboration with Family Health International (FHI) and the device inventor at YAMA, Inc., has sponsored numerous studies, including Phase I, Phase II, and OTC feasibility studies, for this silicone rubber device that covers the cervix. When used with spermicide, this device appears to prevent pregnancy as well as traditional barriers. In response to issues raised by an FDA advisory panel, the most recent study addresses colposcopic and microbiological changes after eight weeks of use.

FemCap. This silicone rubber cervical cap comes in three sizes and has several advantages over other existing barrier devices, including more durable and less sensitizing materials, fewer dislodgments, a lower risk of urinary tract infection (UTI), and size determination based on obstetrical history. Phase II/III studies comparing FemCap to Ortho All-Flex® found a higher use rate and significantly fewer UTIs among FemCap users. In addition, there were no significant differences between the devices in the number or severity of vaginal lesions. Acceptability rates were high for both, but removal was more difficult with FemCap. The inventor at FemCap, Inc., developed an improved, strapped version of the device that underwent limited testing and was found to be easier to remove for most women than the strapless version. Additional studies are underway comparing the two versions for removal problems, dislodgments,

user and partner genital pain or discomfort, and cervical and vaginal irritation.

Silcs Intravaginal Barrier Device. A reusable, one-size-fits-all silicone device developed at the Program for Appropriate Technology in Health (PATH) in Seattle in conjunction with Silcs, Inc., integrates numerous design elements that improve on the standard latex diaphragm. The Silcs device is being studied for function, acceptability, and safety at several clinical centers, including Eastern Virginia Medical School. The new device may be feasible for OTC distribution, especially given the potential for a one-size, easy-fit, comfortable diaphragm free of the material and maintenance problems currently associated with other latex products. A Phase I post-coital test and safety study is underway comparing the Silcs device with the Ortho All-Flex diaphragm.

Female Condom. Development of an improved female condom is a high priority for CONRAD. Medtech Products Ltd., in India, is developing prototypes for acceptability studies. The acceptability and functional performance of the new Reddy condom will be compared with that of the Reality® female condom. Also, PATH is collaborating with a Colombian company to develop a female condom for which user feedback is being incorporated into an iterative development process. Preclinical work on design and materials is underway.

Cervical Cap and Sponge. Limited Phase I safety and acceptability studies are planned for two new barrier devices, the Oves™ Contraceptive Cap and the AVERT sponge, in conjunction with their developers. Oves, a medical-grade silicone cap with a removal loop at the base, is currently sold in Europe. It will be evaluated for fit, dislodgment, and acceptability. The AVERT sponge, a

polyurethane foam sponge infused with an N-9 formulation, will be tested for safety following single and multiple exposures.

Progestin Delivery Systems

CONRAD has made significant progress in its efforts to develop long-acting progestin delivery systems that are suitable for lactating women, use natural progestins, or otherwise improve on existing methods. Investigation continues on two fronts: a progesterone-releasing vaginal ring and a progestin-releasing single-rod implant that is easier to insert than currently available implants. Both of these products are expected to result in lower costs.

Phase II work is underway on a long-lasting progesterone-releasing vaginal ring. Preliminary findings indicate that it can be used safely for four months, instead of replacing it every three months, which is the current practice in Chile. If confirmed, this finding could result in substantial savings for users and providers. No in-treatment pregnancies have been observed in more than 1,100 women-months.

CONRAD has been collaborating with FEI Technologies, Inc., to develop simpler, low-cost alternatives to progestin implants than are currently available. A Phase I pharmacokinetic trial comparing a new, single-rod LNG implant with the marketed six-rod Norplant® system was completed recently. The data from that study are being analyzed to determine pharmacokinetic profiles, ovarian follicular development, patterns of uterine bleeding, adverse experience, and ease of product insertion and removal. Meanwhile, FEI is conducting stability tests and monitoring *in vitro* release rates.

With the assistance of a Chinese pharmaceutical company, CICC is supporting a small

Phase II work is underway on a long-lasting progesterone-releasing vaginal ring. Preliminary findings indicate that it can be used safely for four months, instead of replacing it every three months.

Phase II study of a hormonal monthly oral contraceptive regimen devoid of estrogen. This study will investigate whether sequential treatment with an antiprogestin followed by a progestin can provide effective contraception, even in the few cycles where ovulation occurs.

Emergency Contraceptives

Because of political and religious factors, work in this area is not as advanced as that in other areas of contraceptive research. Still, significant early research is underway.

In one important project, researchers in Santiago, Chile, and Santo Domingo, Dominican Republic, are investigating the mode of action of the Yuzpe regimen for emergency contraception when administered during the follicular phase of the menstrual cycle. The supposition has been that ovulation inhibition is one of the primary mechanisms of action. Although earlier data indicated limited effect on ovulation, the recently completed two-center, randomized, controlled study found that the Yuzpe method causes profound alterations in the ovulatory

The goal of investigators is to identify

epitopes that do not induce ovarian

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process. These effects seem to be more apparent with the full dose and when administered at follicular size of less than 18 mm. Ovulation may be inhibited or delayed. Even if ovulation is not inhibited, the increased production of LH and FSH that normally occurs is blunted. These findings are critical for acceptance and dissemination of this method. Preliminary results suggest that the full dose is more effective than the half-dose, though the incidence and severity of side effects are similar for both doses.

CICCR is also supporting a Phase II trial of an emergency contraceptive regimen in China designed to expand the recommended three-day window of efficacy after unprotected intercourse and reduce the side effects of current therapies. The regimen under investigation is a combination of the antiprogestin, mifepristone, and tamoxifen, an antiestrogen. The idea is that the antagonism of both progesterone and estrogen will delay endometrial development and prevent implantation. Future studies may benefit from the participation of commercial partners in China.

Systemic Nonhormonal Methods

This remains a difficult area of research, in large part because the complex biologic processes under investigation are not well understood. Industrial involvement has also been limited. With few promising leads, projects have been limited in scope. The general objectives in this area of research are to continue developing promising leads toward Phase I clinical testing and to pursue and support limited feasibility studies of new leads. Support for new leads will likely rely primarily on CICCR feasibility funding, as well as on the recently established Indo-U.S. Collaboration on Contraceptive and Reproductive Health Research. A key aim of this collaboration is to support research needed to bring potential leads to the clinical evaluation stage. Feasibility research will continue on immunocontraception, local control of oocyte development, specific inhibition of follicular rupture, and implantation prevention.

Zona Pellucida Antigens. The zona pellucida (ZP) is an extracellular matrix that surrounds mammalian oocytes. It mediates the initial recognition and binding of sperm to oocytes, as well as the subsequent activation process during fertilization in a species-specific manner. Because of this critical role in reproduction, ZP proteins are potential candidate antigens for immunocontraception. Active immunization with ZP purified from native material can significantly lower fertility, though often in concert with ovarian pathology. The goal of investigators at the National Institute of Immunology (NII) in New Delhi and at Baylor College of Medicine is to identify epitopes that do not induce ovarian pathology, and to test the immunogenicity and contraceptive potential of recombinant ZP peptides.

ZP antigens produced by recombinant DNA technology and peptide synthesis have been tested in mating groups of bonnet monkeys,

with mixed results. Investigators at NII immunized female bonnet monkeys with recombinant bonnet monkey ZP3 and synthetic peptides of ZP3 that correlate with peptides that are important for sperm-zona binding in other species. They observed reductions in fertility among some mating groups, but the number of females per mating group was small, limiting the generalizability of those findings. In addition, ovarian disturbances occurred among immunized monkeys, although these disturbances were reversible. Accordingly, primate studies using ZP1 epitopes, which may induce less ovarian disruption, have been launched. Menstrual cycle disturbances were noted in some monkeys, but they were probably related to normal summer amenorrhea. Fertility in all of the immunized female monkeys was reduced. However, expression of the recombinant antigen in a eukaryotic system for more optimal protein processing remains problematic.

Sperm Antigens. Investigations of newly characterized sperm surface antigens are continuing. Unfortunately, antifertility trials targeting some sperm antigens in small animal models have demonstrated moderate to high efficacy that has not been consistently replicated in more expensive and time-consuming primate trials.

A CICCR twinning collaboration between investigators at the University of Virginia and NII in New Delhi has focused on isolating and characterizing gene-encoding sperm surface antigens by screening human testis gene libraries. Several antigens appear promising, and their utility will be evaluated further in monkey fertility trials.

Anti-Implantation Approaches. Several CICCR feasibility projects are pursuing leads for preventing fertilization by blocking ZP antigens

Several CICCR feasibility projects are pursuing leads for preventing fertilization by blocking ZP antigens or hindering meiosis, or by inhibiting implantation.

or hindering meiosis, or by inhibiting implantation. A number of novel anti-implantation approaches are under investigation. They include methods to inhibit:

- progesterone levels,
- obligatory endometrial hormones,
- cytokines/growth factors, such as leukemia inhibitory factor (LIF) and Interleukin-11 (IL-11),
- GnRH,
- angiogenesis (the growth of new blood vessels), and/or
- other signal pathways.

Although the scientific rationale for these projects is sound, they are still a long way from showing practical results and may even be unsuccessful.

Despite these caveats, significant progress has been made in establishing the potential of LIF and IL-11, angiogenesis, and GnRH as good targets. In mice, LIF is essential for induction of blastocyst implantation, and it is likely that LIF is also essential for implantation in humans. Recent studies have shown that intrauterine treatment of rhesus monkeys

with an antibody to recombinant human LIF following ovulation and mating significantly reduces the incidence of pregnancy, compared with controls that received an unrelated antibody.

Blastocyst implantation is crucial to establishing pregnancy. Because implantation involves angiogenesis and increased local capillary permeability, these processes may serve as viable targets. Vaginal delivery of two angiogenic inhibitors to rhesus monkeys at the All India Institute of Medical Sciences in New Delhi produced a dose-dependent inhibition of pregnancy. This successful outcome is impressive and somewhat unexpected. If this method works for other blocking molecules, delivery and timing of angiogenic inhibitors can be greatly simplified.

Various studies have shown that chorionic GnRH, which is found in the human placenta and chorionic membranes, plays a significant role in maintenance of normal pregnancy, and that GnRH analogs can disrupt and terminate early pregnancy. GnRH appears to induce the earliest production of hCG, a hormone secret-

ed in large quantities during the initial stages of pregnancy in primates. CICCR has supported studies at the University of Texas Health Science Center, San Antonio, to identify new GnRH analogs that have a much higher affinity for trophoblast receptors and are more resistant to metabolism than analogs that have been synthesized to date. These novel analogs would inhibit the action of GnRH to stimulate secretion of hCG from the trophoblast and thus inhibit pregnancy. A patent application covering these analogs has been filed. □

Research Agenda for the 21st Century

CONRAD IS WELL POSITIONED TO MAKE major advances during the next two years and beyond in the development of new contraceptive methods for use by women and men. Our top research objectives continue to be:

- systemic male methods that have minimal side effects and are readily reversible;
- intravaginal barriers that are simple to use and highly acceptable;
- improved hormonal delivery systems for women; and
- improved reproductive health through better understanding of how contraceptive use affects transmission of STDs, including AIDS.

Key project objectives during the next two years include:

- Barrier methods
 - Complete the clinical studies of FemCap and Lea Contraceptive needed for the inventors' submissions to the FDA
 - Complete Phase I clinical testing of the Silcs intravaginal barrier device and begin contraceptive efficacy trials

Continue clinical assessment of the new Reddy female condom and initial Phase I testing of the new PATH female condom

Continue clinical trials of chemical barrier formulations—Phase II/III studies of CS for contraceptive efficacy and Phase I studies of LASRS for duration of action and PSS for safety assessment

Begin Phase I safety studies of the AVERT sponge

Initiate clinical testing of the spermicidal microbicide formulation Q2/DS/N-9 and of the non-N9-containing acid-buffered formulation ACIDFORM

Complete antimicrobial assessment and formulation of an acylcarnitine analog, a novel nonirritating spermicide with high antifungal potency

Pursue innovative vaginal contraceptive leads with sperm- and HIV-inactivating properties

Interest in basic reproductive-fertility
 research has been rekindled
 among young researchers, who bring
 new biotechnology techniques to
 contraceptive development.

of an optimal, hormonally based, systemic method for contraceptive efficacy and expanded safety. Significant industrial collaboration is expected during work on this objective.

Collaborate with other organizations to obtain new long-acting formulations of androgens and other hormones, including nonpeptide GnRH analogs

Continue developing current nonhormonal systemic leads toward Phase I clinical testing

Provide limited support for feasibility studies of new leads

- Hormonal methods for women

Conduct Phase I and Phase II clinical trials of improved long-acting progestin formulations

Initiate and complete pharmacokinetic and pharmacodynamic studies of Cyclofem in the United States as part of the Indo-U.S. bilateral research effort in contraception and reproductive health

- Male methods

Complete ongoing Phase II clinical trial of androgen (testosterone pellet) and progestin (DMPA injection) combination

Complete ongoing Phase I safety and efficacy clinical trials of androgen plus progestin combinations

Conduct Phase I clinical trials of improved long-acting androgen and progestin formulations

Begin multicenter, Phase II clinical trial(s)

- STDs and HIV epidemiology

Conduct controlled clinical trials of the ability of diaphragm use to prevent STD infection in high-risk settings

CONRAD's Strategic Plan

To accomplish these objectives, CONRAD must interact closely with various entrepreneurs and industrial collaborators. Consolidation in the pharmaceutical industry, combined with pressure from managed care organizations and possible Medicare prescription reimbursement, will directly affect how much money large pharmaceutical companies are willing to risk on future contraceptive and prophylactic microbicide research and product development. As a result, most large pharmaceutical companies will not show interest or participate in this research until clear product potential has been established during or after Phase III clinical trials.

Industrial partners will demand a relatively rapid, though well-planned, product development pace so that they can successfully introduce products to the private sector. Without

this, industry will not be interested in supplying products for the public sector. Therefore, CONRAD, particularly for CICCRR projects, will need to increase financial support for concurrent analytical, manufacturing, and toxicology services for investigational new drugs through Phase II clinical stages of development.

In addition, CONRAD will continue to refine and implement a decision tree for biological and pharmaceutical tests during Phase I clinical trials so that we can rank drug candidates and take the best to the more resource-intensive Phase II clinical and supportive toxicology studies.

Interest in basic reproductive-fertility research has been rekindled among young researchers, who bring new biotechnology techniques to contraceptive development. The new tools, skills, enthusiasm, and early success have been impressive. Private foundations, particularly The Andrew W. Mellon Foundation, have supported this type of effort through CICCRR. Much more funding is necessary to move this research forward. The CICCRR program will focus on recruiting new grants in this area.

CONRAD will continue its partnerships with start-up companies and independent inventors. Development of products, such as the Reality female condom, FemCap, PSS, CS, and others, has sharpened our experience and helped us to evolve so that we can meet society's challenge to deliver more and better contraceptive products more quickly. CONRAD is acutely aware of consumers' needs and the development path for new contraceptives and antimicrobial agents. CONRAD, through CICCRR, will endeavor to work with inventors and pharmaceutical and device manufacture professionals to move potential products quickly into clinical trials

and assess their contraceptive value within a reasonable period of time.

CONRAD's focus is on the needs of developing countries. The globalization of the pharmaceutical industry will work to our favor in both contraceptive and microbicide research and development areas. The market size for both is much larger internationally than domestically. The pharmaceutical industry will focus on international product growth as domestic pricing constraints caused by managed care and looming government pressures develop. Our current goals are consumer-oriented and on target for future discoveries and development. □

Selected Bibliography, 1998-1999

Systemic Hormonal Methods for Men

Bremner WJ, Cheng CY, Cuasnicu PS, Habenicht UF, Colvard DS, Doncel GF

(1999) Current Approaches to Systemic Male Contraception: An Update. Excerpta Medica International Congress Series—10th World Congress on Human Reproduction, Elsevier Science, Amsterdam.

Swerdlow RS, Bagatell CJ, Wang C, Anawalt BD, Berman N, Steiner B, Bremner WJ

(1998) Suppression of spermatogenesis in man induced by Nal-Glu gonadotropin releasing hormone antagonist and testosterone enanthate (TE) is maintained by TE alone. *J Clin Endocrinol Metab*, 83:3527-33.

Wu FC, Balasubramanian R, Mulders TMT, Coelingh-Bennink H

(1999) Oral progestogen combined with testosterone as a potential male contraceptive: Additive effects between desogestrel and testosterone enanthate in suppression of human spermatogenesis and the pituitary-testicular axis. *J Clin Endocrinol Metab*, 84:112-22.

Barrier Methods for Women

Ballagh SA

(1999) Female Barrier Contraception. Excerpta Medica International Congress Series—10th World Congress on Human Reproduction, Elsevier Science, Amsterdam.

Fichorova RN, Anderson DJ

(1999) Differential expression of immunobiological mediators by immortalized human cervical and vaginal epithelial cells. *Biol Reprod*, 60:508-14.

Gabelnick HL, Harper MJK

(1999) The promise of public/private sector collaboration in the development of vaginal microbicides. *Int J Ob Gynecol*, 67(2):S31-8.

Mauck C, Callahan M, Weiner DH, Dominik R, FemCap Investigators Group

(1999) A comparative study of the safety and efficacy of FemCap™, a new vaginal barrier contraceptive, and the Ortho All-Flex® Diaphragm. *Contraception*, 60:71-80.

Owen DH, Dunmire EN, Plenys AM, Katz DF

(1999). Factors influencing nonoxynol-9 permeation and bioactivity in cervical mucus. *J Controlled Release*, 60:23-34.

Owen DH, Katz DF

(1999) A vaginal fluid simulant. *Contraception*, 59:91-5.

Patton DL, Kidder GG, Sweeney YC, Rabe LK, Hillier SL

(1999) Effects of multiple applications of benzalkonium chloride and nonoxynol-9 on the vaginal epithelium in the pigtailed macaque (*Macaca nemestrina*). *Am J Obstet Gynecol*, 180:1080-7.

Rencher WF, Jr. (Ed)

(1998) Vaginal Microbicide Formulations Workshop, New York: Lippincott-Raven.

Savle PS, Doncel GF, Bryant SD, Hubieki MP, Robinette RG, Gandour RD

(1999) Acylcarnitine analogues as topical, microbicidal spermicides. *Bioorg Med Chem Lett*, 9: 2545-8.

Systemic Hormonal Methods for Women

Croxatto H, Salvatierra AM, Fuentealba B, Massai MR

(1998) Contraceptive potential of mifepristone-nomegestrel acetate sequential regimen in women. *Human Reproduction*, 13:3297-302.

Massai R, Miranda P, Valdes P, et al

(1999) Preregistration study on the safety and contraceptive efficacy of a progesterone-releasing vaginal ring in Chilean nursing women. *Contraception*, 60:9-14.

Mauck CK, Callahan MM, Baker J, Arbogast K, Veazey R, Stock R, Morrison CS, Chen-Mok M, Archer D, Gabelnick HL

(1999) The effect of one injection of Depo-Provera® on the human vaginal epithelium and cervical ectopy. *Contraception*, 60:15-24.

Systemic Nonhormonal Methods for Women (Immunocontraceptives)

Govind CK, Hasagawa A, Koyama K, Gupta SK

(2000) Delineation of conserved B cell epitope on bonnet monkey (*Macaca radiata*) and human zona pellucida glycoprotein-B by monoclonal antibodies demonstrating inhibition of sperm-egg binding. *Biol Reprod*, 62:67-75.

Gupta SK, Yurewicz EC, Sacco AG, Kaul R, Jethanandani P, Govind CK

(1998) Human zona pellucida glycoproteins: Characterization using antibodies against recombinant non-human primate ZP1, ZP2 and ZP3. *Mol Hum Reprod*, 4:1058-64.

HIV/AIDS and Other STDS

Nelson KE, Ruengruengthanakit K, Margolick J, Suriyanon V, Niyomthai S, de Boer MA, Celentano D, Nagachinta T, Duerr A

(1999) High rates of transmission of subtype E human Immunodeficiency virus type 1 among heterosexual couples in Northern Thailand: Role of sexually transmitted diseases and immune complex. *J Infectious Diseases*, 180:337-43.

Quayle AJ, Xu C, Tucker L, Anderson DJ

(1998) The case against an association between HIV-1 and sperm: Molecular evidence. *J Reprod Immunol*, 41:127-36.

Rugpao S, Nagachinta T, Wanapirak C, et al.

(1998) Gynaecological conditions associated with HIV infection in women who are partners of HIV-positive Thai blood donors. *Int J STD AIDS*, 9:677-82.

Sodora, DL, Gettie A, Miller CJ, Marx PA

(1998) Vaginal transmission of SIV: Assessing infectivity and hormonal influences in macaques inoculated with cell-free and cell-associated viral stocks. *AIDS Res Hum Retroviruses*, 14(Suppl 1):S119-23.

CONRAD- and CICCR-Supported Investigators, 1998-1999

CONRAD-Supported Investigators, 1998-1999

Investigator	Institution	Project
Frank Alvarez, M.D.	PROFAMILIA Santo Domingo, Dominican Republic	Phase I Clinical Trial of the Yuzpe Regimen
Deborah Anderson, Ph.D.	Brigham and Women's Hospital Boston, MA	Development of Human Cervical and Vaginal Epithelial Cell Culture Systems for Testing Toxicity of Spermicides and Vaginal Microbicides Effects of Contraceptive Methods on Urogenital Tract Inflammation and HIV-1 Titers in Women
Luis Bahamondes, M.D.	Centro de Pesquisas das Doenças Materno-Infantis de Campinas (CEMICAMP) São Paulo, Brazil	The Effect upon the Human Vaginal Histology of the Long-Term Use of the 90-Day Injectable Contraceptive Depo-Provera
Michael Bernhard, Ph.D.	FEI Technologies Plainsboro, NJ	Contraceptive Drug Delivery Systems Development
Shrikant Betrabet, Ph.D.	Institute for Research in Reproduction Mumbai, India	Development of an <i>in vitro</i> Screening System for Progestins Developed for Therapeutic and Contraceptive Applications
William Bremner, M.D., Ph.D.	University of Washington Seattle, WA	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
William Bremner, M.D., Ph.D.	University of Washington Seattle, WA	Effects of a Non-5 α Reducible Androgen and an Anti-Androgenic Progestin in the Suppression of Primate Spermatogenesis Using Androgen-Based Hormonal Contraception Strategies
Robert McLachlan, M.D., Ph.D.	Prince Henry's Institute of Medical Research Clayton, Victoria, Australia	
George Brode, Ph.D.	Integra LifeSciences Corporation Plainsboro, NJ	Reproductive Health-STD Control Compositions
Sharon Camp, Ph.D.	Women's Capital Corporation Washington, DC	A Two-Period Crossover Study of the Relative Bioavailability of Levonorgestrel 0.75 mg Tablets Orally to Fasting Female Volunteers
Craig Cohen, M.D., M.P.H.	University of Washington Seattle, WA	A Randomized Control Trial of the Diaphragm to Prevent Sexually Transmitted Infections
Mitchell Creinin, M.D.	Magee-Women's Hospital Pittsburgh, PA	Safety and Acceptability of FemCap with Removal Strap Lea Contraceptive: Colposcopy and Microbiological Testing

		A Phase I Comparative Post-Coital Testing and Safety Study of the Silcs Diaphragm versus the Ortho All-Flex Diaphragm
Horacio Croxatto, M.D.	Instituto Chileno de Medicina Reproductiva (ICMER) Santiago, Chile	CONRAD Collaborating Center for Clinical Research
Eric Dadey, Ph.D.	University of Illinois at Chicago Chicago, IL	Evaluation of the Bioadhesive Nature of Dextran Sulfate and Q2
George Digenis, Ph.D.	University of Kentucky Lexington, KY	Development of a Novel Spermicidal Compound and Its Preliminary Evaluation as a Possible Drug Candidate Development of Scintigraphic Techniques and Preliminary Studies to Non-Invasively Evaluate the <i>in vivo</i> Deposition of Vaginal Products in Healthy Women
Raina Fichorova, M.D., Ph.D.	Brigham and Women's Hospital Boston, MA	Use of Immortalized Vaginal and Endocervical Epithelial Cells for <i>in vitro</i> Testing of Spermicides and Vaginal Microbicides
Michael Free, Ph.D. Glenn D. Austin	Program for Appropriate Technology in Health (PATH) Seattle, WA	Development of the Silcs Silicone Diaphragm Development of a New Female Condom Using an Interactive Design Process
Richard Gandour, Ph.D.	Virginia Polytechnic Institute and State University Blacksburg, VA	Quaternary 2-Oxo and 2-Hydroxy Ammonium Salts: Potential Spermicidal Agents with Anti-HIV Activity
David Grimes, M.D.	Family Health International Research Triangle Park, NC	North America Coordinating Site for the Fertility Regulation Review Group of the Cochrane Collaboration
Satish Gupta, Ph.D.	National Institute of Immunology New Delhi, India	Evaluation of the Efficacy of Recombinant Bonnet Monkey ZP3 and Its Corresponding Synthetic Peptides to Regulate Fertility in Primates
Rim Hamzaoui, M.D.	Office National Famille et de Population Ariana, Tunisia	Acceptability of the Female Condom in Tunisia
David Handelsman, M.D.	Royal Prince Alfred Hospital Sydney, Australia	Efficacy, Safety, and Service Feasibility of an Androgen/Progestin Depot Regimen for Hormonal Contraception
Umashashi Hegde, Ph.D.	Institute for Research in Reproduction Mumbai, India	Epididymal Sperm Maturation Antigen: Molecular Cloning of Epididymal Antigen and Evaluation of Antifertility Effect of Epididymal 26 kDa Antifertility
David Katz, Ph.D.	Duke University Durham, NC	Observation and Analysis of Intravaginal Spreading and Adhesion of Spermicidal/ Microbicidal Vehicles
Jamila Kerimova, M.D.	Relief International Los Angeles, CA	Reproductive Health Rapid Assessment Tools and Approaches for Refugees and Internally Displaced People (R/IDPs): An Azerbaijan Case Study

Alvin Matsumoto, M.D.	University of Washington Seattle, WA	Male Contraception: Progestin-Androgen Combinations Using a Reduced Dose of LNG plus TE
Tarala Nandedkar, Ph.D.	Institute for Research in Reproduction Mumbai, India	Evaluation of Antifertility Effect of FSH Binding Inhibitor (FSHBI)
Kenrad Nelson, M.D.	The Johns Hopkins University Baltimore, MD	Factors Affecting the Heterosexual Transmission of HIV Infection in Northern Thailand Survival of HIV-1 Infected Male Blood Donors and Their Infected Partners in Northern Thailand
Nancy Padian, Ph.D.	University of California at San Francisco San Francisco, CA	Acceptability of Using the Diaphragm with Spermicide in a Population of Unsuccessful Condom Users
Dorothy Patton, Ph.D.	University of Washington Seattle, WA	Effects of Three Microbicidal Agents and a Generic Vehicle on Vaginal Flora and <i>Chlamydia trachomatis</i> Infection in the Pigtailed Macaque
Melissa Puliafico	Primedica Milford, MA	A Study to Evaluate the Efficacy of Three Microbicidal Agents against Vaginal Challenge with SIV in Rhesus Monkeys
Allison Quayle, Ph.D.	Brigham and Women's Hospital Boston, MA	Mucosal Immune Reconstitution in Women after Initiation of HAART
Sungwal Ruggao, M.D.	Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand	DMPA Use and HIV Transmission in Northern Thailand
Haleh Sangi-Haghpeykar, Ph.D.	Baylor College of Medicine Houston, TX	Psychosocial Predictors of Condom Use among Injectable Contraceptive Users
Alfred Shihata, M.D.	Femcap, Inc. Del Mar, CA	FemCap's PMA Test Completion, Preparation, and Submission
Ronald Swerdloff, M.D.	Harbor-UCLA Medical Center Torrance, CA	High-Dose GnRH Agonist Effect on Spermatogenesis
James Turpin, Ph.D.	Southern Research Institute Frederick, MD	Evaluation of the Anti-HIV Activity of Spermicides and Virucides <i>in vitro</i>
Christina Wang, M.D.	Harbor-UCLA Medical Center Torrance, CA	Comparison of the Efficacy of a Progestagen Implant (Norplant II) in Combination with Transdermal Androgen versus Transdermal Androgen Alone in Suppression of Spermatogenesis in Normal Men
Fred C.W. Wu, M.D., F.R.C.P.	University of Manchester, Manchester, United Kingdom	Effects of Oral Desogestrel and Intramuscular Testosterone in Normal Men: A Pharmacokinetic and Pharmacodynamic Study
Lourens Zaneveld, Ph.D.	Rush-Presbyterian-St. Luke's Medical Center Chicago, IL	Development and Evaluation of Novel Vaginal Antimicrobial Contraceptive Formulations

CICCR-Supported Investigators, 1998-1999

Investigator	Institution	Project
David Abbott, Ph.D.	Wisconsin Regional Primate Research Center Madison, WI	Effect of Pure Extract of Triptolide from <i>Trypterygium wilfordii</i> on the Fertility of Male Marmoset Monkeys, <i>Callithrix jacchus</i>
Vichai Reutrakul, Ph.D.	Mahidol University Bangkok, Thailand	
Eliana Amaral, M.D.	Centro de Pesquisas das Doenças Materno-Infantis de Campinas (CEMICAMP) São Paulo, Brazil	Studies of Tolerance and Spermicidal Effect of a Bio-Adhesive ACIDFORM Gel Containing Nonoxynol-9
Deborah Anderson, Ph.D.	Brigham and Women's Hospital Boston, MA	The Effects of Synthetic Progestins, Mifepristone, and Testosterone on Immune Cell Function and HIV Infection <i>in vitro</i>
William Bremner, M.D., Ph.D.	University of Washington Seattle, WA	Comparative Study on LNG Implants plus TU for Male Contraception in China
Gao Er-Sheng, M.D., M.P.H.	Shanghai Institute for Planned Parenthood Research Shanghai, P.R. China	
James Catterall, Ph.D.	The Population Council New York, NY	Structure and Function of the FSH Receptor: A Potential Immun contraceptive
ORajan Dighe, Ph.D.	Indian Institute of Science Bangalore, India	
Ching-Ling Chen, Ph.D.	The Population Council New York, NY	Expression and Functional Analysis of Novel Activin C Proteins in Reproductive Tissues
Han-Zheng Wang, Ph.D.	Shanghai Institute for Planned Parenthood Research Shanghai, P.R. China	
Yan Cheng, Ph.D.	The Population Council New York, NY	Induction of Release of Premature Germ Cells from Seminiferous Epithelium by Analogs of Lonidamine
Bruno Silvestrini, M.D., Ph.D.	Fondazione di NOOPOLIS Rome, Italy	
Austin Cooney, Ph.D.	Baylor College of Medicine Houston, TX	Multihormonal Effects of 19-Nor Contraceptive Synthetic Progestins: An Approach to Design Steroid Agonists/Antagonists with Tissue-Specific Actions
Fernando Larrea, M.D.	Instituto Nacional de al Nutricion Salvador Zubiran (INNSZ) Mexico D.F., Mexico	
James Cosentino, Ph.D.	Millersville University Millersville, PA	Testicular Dihydrofolate Reductase: Preliminary Isolation, Characterization, and DNA Expression
Mitchell Creinin, M.D.	Magee-Women's Hospital Pittsburgh, PA	A Phase I Comparative Post-Coital Testing and Safety Study of Two Concentrations of Nonoxynol-9 Formulated in Long-Acting, Sustained Release Vaginal Spermicide (LASRS) Suppositories Single- and Multiple-Exposure Tolerance Study of Polystyrene Sulfonate Gel

Horacio Croxatto, M.D.	Instituto Chileno de Medicina Reproductiva (ICMER) Santiago, Chile	Contraception with an Antiprogestin-Progestin Sequential Regimen: A Phase II Study
Patricia Cuasnicu, Ph.D.	Instituto de Biología y Medicina Experimental (IBYME) Buenos Aires, Argentina	Potential Contraceptive Use of an Epididymal Protein
Paul Primakoff, Ph.D.	University of California at Davis Davis, CA	
Eric Dadey, Ph.D.	University of Illinois at Chicago Chicago, IL	Supplemental Analysis of Polystyrene Sulfonate (PSS) and PSS-Containing Formulations
Jacqueline E. Darroch, Ph.D.	The Alan Guttmacher Institute New York, NY	Balancing Concerns: Assessing Women's Potential Interest in Using Microbicides
Bonnie S. Dunbar, Ph.D.	Baylor College of Medicine Houston, TX	Identification of Regulators of Novel Receptor Molecules of Meiosis and Gametogenesis as Contraceptive Agents
Fernando Larrea, M.D.	Instituto Nacional de al Nutricion Salvador Zubiran (INNSZ) Mexico D.F., Mexico	Identification of Human ZP Peptides Involved in Sperm-Zona Interaction
Frank French, M.D.	University of North Carolina at Chapel Hill Chapel Hill, NC	Human Epididymal Protein Targets for Male Contraception
Gao Er-Sheng, M.D., M.P.H.	Shanghai Institute for Planned Parenthood Research Shanghai, P.R. China	Clinical Comparative Study on Regimens of Mifepristone Alone and in Combination with Tamoxifen for Emergency Contraception
Robert Garfield, Ph.D.	University of Texas Medical Branch Galveston, TX	Synergistic Effects of Mesoprogesterins and Antiprogestins with iNOS and COX-2 Inhibitors on the Inhibition of Pregnancy
Geula Gibori, Ph.D.	University of Illinois at Chicago Chicago, IL	Use of a 20-Hydroxysteroid Dehydrogenase as a Potent Contraceptive
Erwin Goldberg, Ph.D.	Northwestern University Evanston, IL	Immunosuppression of Fertility of Male Baboons by Sperm-Specific LDH-C4
Susan Hall, Ph.D.	University of North Carolina at Chapel Hill Chapel Hill, NC	Human Epididymal Protein Targets for Male Contraception
A. Jagannadha Rao, Ph.D.	Indian Institute of Science Bangalore, India	
David Handelsman, Ph.D.	Royal Prince Alfred Hospital Medical Centre Sydney, Australia	The Efficacy and Safety of Low-Dose Estradiol Supplementation for Depot Testosterone-Induced Suppression of Human Spermatogenesis
Matthew Hardy, Ph.D.	The Population Council New York, NY	Suppression of the Pituitary-Gonadal Axis in the Primate by a Synthetic Androgen, 7 α - Methyl-19-Nortestosterone, Alone and in Combination with Estradiol
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John C. Herr, Ph.D.	University of Virginia Charlottesville, VA	Isolation and Characterization of Genes Encoding Sperm Surface Antigens by Screening Human Testis Expression cDNA Library: Identification of a Candidate Molecule(s) for Development of Contraceptive Vaccine
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Joan Hunt, Ph.D.	University of Kansas Medical Center Kansas City, KS	Biochemical and Molecular Characterization of an HLA-G-like Gene Expressed in Baboon (<i>Papio anubis</i>) Placentas
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Gabor Huszar, M.D.	Yale University New Haven, CT	Sperm Creatine Kinase M-Isoform Assay for the Assessment of Residual Fertility in Men Treated with Suppressants of Spermatogenesis
Stephen Killick, M.D., FRCOG	Princess Royal Hospital Hull, United Kingdom	The Contraceptive Action of Progestogens on Cervical Mucus
Paul Leavis, Ph.D.	Boston Biomedical Research Institute Boston, MA	Development of Antibodies against Preimplantation Factor (PIF) and Investigation of Their Contraceptive Potential
Cristina Meriggiola, M.D.	S. Orsola Hospital University of Bologna Bologna, Italy	Effects of a Sequential Regimen of Cyproterone Acetate and Testosterone Undecanoate Followed by Lower-Dose Cyproterone Acetate and Testosterone Undecanoate in Normal Men
Patricio Morales, Ph.D.	Instituto Chileno de Medicina Reproductiva (ICMER) Santiago, Chile	Effects of GnRH Antagonists upon Human Sperm-Zona Pellucida Binding
Lorraine Robb, M.D., Ph.D.	Walter and Eliza Hall Institute for Medical Research Victoria, Australia	Investigation in the Role of Interleukin-11 in Human Female Fertility
Lois Salamonsen, Ph.D.	Prince Henry's Institute of Medical Research Clayton, Victoria, Australia	Inhibition of Embryo Implantation by Inhibitors of Matrix Metalloproteinases
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Jaysaree Sengupta, Ph.D. Debabrata Ghosh, Ph.D.	All India Institute of Medical Sciences New Delhi, India	Effect of Fumagilin and Magainins on Blastocyst Implantation in the Rhesus Monkey
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Theresa Siler-Khodr, Ph.D.	University of Texas Health Science Center San Antonio, TX	Gonadotropin-Releasing Hormone Analogues as a Luteolytic, Menses-Inducing Agent or a Post-Coital Contraceptive

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