Contraceptive Microbicide Research and Development Program

A Vision of the Future

National Institute of Child Health and Human Development

National Institutes of Health

CONTRACEPTIVE MICROBICIDE RESEARCH AND DEVELOPMENT PROGRAM

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NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

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Foreword

The National Institute of Child Health and Human Development (NICHD) has an ongoing and longstanding commitment to HIV/AIDS research, particularly related to the prevention of perinatal, pediatric, adolescent, and maternal HIV transmission. The Institute's support for research related to the development, use, and acceptability of contraceptive microbicides remains an important part of this commitment, especially given the increasing rates of heterosexually transmitted HIV-infection among teenage girls and women, both domestically and internationally.

This report on the Institute's *Contraceptive Microbicide Research and Development Program* provides an overview of our currently supported activities and anticipated short-term plans and priorities in this area. It also describes briefly the Institute's wide range of collaborative partnerships with other National Institutes of Health (NIH) Institutes and Centers, federal and non-governmental agencies, and private sector organizations interested in microbicide research.

Within the Institute, the NICHD HIV/AIDS Coordinating Committee contributes to the overall coordination, integration, planning, and assessment of our AIDS program. During the past year, the AIDS Committee has formed a Contraceptive Microbicide Coordinating Subcommittee to provide additional attention to the Institute's expanding research agenda related to the development of contraceptive methods that also are effective in preventing HIV infection and other sexually transmitted infections. The members of this Subcommittee (listed in Appendix B) were instrumental in the development and writing of this report.

We anticipate that this report will be updated periodically and serve as a foundation for ongoing assessment and planning of NICHD's future research efforts and related program activities in the area of contraceptive microbicides.

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NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

CONTRACEPTIVE MICROBICIDE RESEARCH AND DEVELOPMENT PROGRAM

I. BACKGROUND

The National Institute of Child Health and Human Development (NICHD) supports and conducts basic, applied, clinical, and epidemiologic research on the reproductive, neurobiological, developmental, and behavioral processes that determine, maintain, and advance the health of women, children, families, and populations. Its scientific mission includes conducting research that contributes to the prevention of unwanted pregnancies, HIV/AIDS, and other sexually transmitted infections (STIs), both domestically and globally.

The Institute's HIV-prevention research agenda focuses on the development of contraceptive microbicides and the prevention of perinatal, pediatric, adolescent, and maternal HIV transmission. The NICHD also supports prevention research and training on behavioral factors that may influence the use and acceptability of microbicides and other preventive measures, including barrier methods and other contraceptives.

The NICHD has been committed to reproductive health research since its inception in 1962 and has remained committed to HIV/AIDS research for more than a decade. Since 1987, the Institute has supported research and training activities that helped to establish and define the field of contraceptive microbicides.

The U.S. Congress recognized and encouraged the NICHD's contraceptive microbicide research activities in its fiscal year 1999 House Appropriations Bill:

> The Committee appreciates the leadership role that NICHD has taken in the evaluation and development of physical and chemical contraceptive methods that are also effective in preventing [sexually transmitted diseases] and HIV infection. The Committee encourages further effort in this area as well as research on hormonal methods of contraception that influence susceptibility to STDs and HIV infection.

In subsequent years, both House and Senate Conference Reports reiterated the expectation that the NICHD would remain active in this research area and urged the Director of the National Institutes of Health (NIH) to enhance microbicide research and development in coordination with the NICHD, the Office of AIDS Research (OAR), the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Mental Health (NIMH), the National Institute of Drug Abuse (NIDA), and the Office of Research on Women's Health (ORWH).

A. Research Responsibilities

The NICHD has identified several areas of responsibility relevant to its contraceptive microbicide research agenda. Consistent with congressional expectations and the Institute's mission, goals, and priorities, these areas include:

- Basic and epidemiologic research on reproductive health
- Identification and development of new and promising contraceptive microbicides
- Exploration, improvement, and validation of new assays for assessment of anti-HIV activity, activity against other STIs, and toxicity
- Screening of new compounds for anti-HIV activity
- Formulation of promising compounds
- Toxicology studies
- Development of clinical testing protocols
- Clinical trials in the NICHD Contraceptive Clinical Trials Network and other networks
- Social and behavioral research, including acceptability studies
- Post-marketing surveillance studies
- Coordination of research efforts in the area of contraceptive microbicides
- Training of biomedical, social, and behavioral scientists and institutional capacity-building, both domestically and internationally
- Establishment of linkages and partnerships with NIH Institutes and Centers and other nonprofit and private sector organizations

Within the NICHD, four Extramural Program branches share primary responsibility for research related to HIV/AIDS, as well as to aspects of contraceptive microbicide research.

- **The Contraception and Reproductive Health Branch (CRHB),** at the Center for Population Research (CPR), provides overall leadership and coordination for the Institute's research efforts related to contraceptive microbicides. The CRHB focuses its research agenda on the development and evaluation of products that prevent fertilization and the transmission of HIV and other STIs.
- **The Demographic and Behavioral Sciences Branch (DBSB),** CPR, sponsors research on behavioral and social factors at the individual, dyadic, and societal level that may influence the use and acceptability of contraceptive microbicides.
- **The Pediatric, Adolescent, and Maternal AIDS Branch (PAMA),** at the Center for Research on Mothers and Children, supports basic and clinical research on HIV infection in women, children, adolescents, and families. PAMA implements research relevant to microbicide development through studies in the REACH (Reaching for Excellence in Adolescent Health and Care) Program and Adolescent Trials Network of the Adolescent Medicine HIV/AIDS Research Network, and co-sponsorship of or collaboration with the

Pediatric and Adult AIDS Clinical Trials Groups, the Women's Interagency HIV Study, and the Women and Infants Transmission Study.

- **The Reproductive Sciences Branch (RSB),** CPR, supports basic research on reproductive processes relevant to transmission of HIV and other STIs.

The NICHD Division of Intramural Research (DIR) also conducts relevant research in these areas. The DIR conducts basic research related to the study of HIV pathogenesis in human lymphoid tissue and on contributions of host and viral factors to HIV disease.

NICHD contraceptive microbicide activities are coordinated and facilitated by a cross-Institute subcommittee. Its membership is listed in Appendix B.

B. Scientific Accomplishments

NICHD-supported research and training activities have resulted in significant advances related to HIV/AIDS prevention and treatment. Some of the contributions that are specific to contraceptive microbicide research are highlighted below.

- Established an *in vitro* screening program for virucidal activity of spermicides and other non-spermicidal compounds
- Supported the development of a simian model to study sexual transmission of SIV (an HIV-like virus in monkeys) and provided a clearer understanding of vaginal HIV transmission and the potential preventive impact of microbicides and spermicides
- Increased understanding of the role of seminal fluid in the transmission of HIV and recognized the importance of dual purpose contraceptive and antimicrobial compounds
- Developed the ME180 cell model system for assessing cell-to-cell transmission of HIV
- Established a contraceptive research centers program that conducts pre-clinical research on new contraceptive microbicides
- Developed a research program in vaginal physiology and biology related to HIV infection
- Developed a clinical trial to examine contraceptive efficacy of currently marketed spermicides
- Established the NICHD Contraceptive Clinical Trials Network (CCTN) to conduct safety and efficacy trials on new contraceptive microbicidal products
- Supported research on the integration of family-planning with HIV prevention
- Explored attitudinal, behavioral, and cultural barriers to dual-use and supported interventions to promote dual use of contraception and disease prevention methods
- Solicited research on the acceptability of microbicides and other methods of protection from HIV/STI
- Co-funded the National Survey of Family Growth to assess women's sexual, contraceptive, and protective behaviors

C. Overview of the Research Program

The NICHD's contraceptive microbicide research and development program reflects the interests and involvement of the various groups within the Institute that have been active in HIV/AIDS research. Figure 1 (see Appendix C) provides a schematic overview of NICHD-supported efforts in such research. The program positions most projects along a continuum of activity, ranging from basic science through pre-clinical and clinical development, and includes behavioral research and post-marketing surveillance. The selected bibliography included in this report (see Appendix A) provides examples of published NICHD-supported research results of relevance to this field.

This document briefly describes the Institute's currently funded and proposed projects in this area. In addition, it identifies significant research gaps and opportunities, suggests needed capacity-building activities, and summarizes collaborations and strategic alliances in support of enhanced microbicide research. Figure 2 in Appendix C demonstrates the interrelationships among these collaborating entities.

II. CURRENT PROJECTS

A. Basic Biomedical Research

The NICHD supports basic biomedical research on systemic, cellular, and molecular aspects of reproductive health that could influence conveyance of STIs. This section summarizes currently active, basic biomedical research projects that may have relevance for contraceptive microbicide development. Ongoing basic behavioral and social science research is discussed in Section II. D.

Vaginal Physiology and Immunology

The NICHD funds research on vaginal physiology and immunology, with a focus on the inter-relationships among hormones, coitus, and intravaginal products and their effect on systemic and local immune systems. Some projects currently underway include:

- ***Mucosal Immunity in the Female Genital Tract*.** This study is examining how changes in female genital tract immunity may influence susceptibility to STIs. It is evaluating changes in humoral and cellular immunity, both naturally over the menstrual cycle and induced by steroid hormone levels in the genital tract, and the effect of semen and spermicides on the natural variation. Additionally, the project is assessing the effects of the menstrual cycle, semen, and spermicides on antigen-specific immune responses induced by mucosal immunization.

- ***Mucosal Immunity in the Murine Genital Tract*.** This project studies the immune mechanisms that protect mice against vaginal viral infection. It tests the hypotheses that specific antibodies and lymphocytes contribute to vaginal immunity to herpes simplex virus-2 and cells release interferons that inhibit viral replication in response to stimulation by this virus.

- ***Effect of Intravaginal Products on Vaginal Physiology*.** This research includes studies on: variations in bacterial attachment during the menstrual cycle; effects of hormonal contraception on bacterial growth, bacterial cell attachment and the epithelium; effects of nonoxynol-9 (N-9) or povidone-iodine use on bacterial flora and resulting changes to vaginal epithelia; conditions where intravaginal lactobacillus instillation leads to vaginal colonization; and the effects of menopause and estrogen replacement on vaginal flora and bacterial attachment.

- ***Ectopy, Hormonal Contraception, and STIs in Adolescents.*** This study is assessing the relationship between oral contraceptives and Depot medroxyprogesterone acetate (Depo-Provera™ or DMPA) on cervical ectopy and STI acquisition in sexually active adolescents. It also examines the natural history of cervical ectopy and the transformation zone in this population.

- **In Vitro *Model of Human Epithelium.*** This project aims to develop a model of primary, cultured vaginal cells for basic investigations of epithelial differentiation and susceptibility to bacterial infection, before and after exposure to hormonal and vaginal products.

- ***Novel Anti-HIV Microbicides.*** HIV requires intact lipid rafts, which are highly specialized subregions in cell membranes for entry into cells and budding of fully infectious particles. Beta-cyclodextrin, a cyclic heptasaccharide that removes cholesterol from cell membranes and disperses lipid rafts, blocks HIV infection and drastically reduces the infectivity of budding HIV particles. It is non-toxic in humans and used as a carrier for polar drugs. This project relies on *in vitro* models to test the effect of lipid raft dispersion by beta-cyclodextrin on potential modes of sexual transmission of HIV.

- ***Viscoelasticity and Protein Composition of the Cervical Mucus.*** Various factors regulate the quantity and quality of the cervical mucus, a critical component in controlling the access of pathogens and sperm to the upper reproductive tract. These factors influence viscoelastic properties, protein interactions, and the thickness of cell layers. This project investigates the mechanism of ethylenediaminetetraacetic acid (EDTA)-induced viscoelasticity changes in cervical mucus.

Steroidal Contraceptives and Hormone Replacement Therapy

Steroidal contraceptives and hormone replacement therapy are widely used. At least 72 million women globally, including 18 million women in the U.S., use oral contraceptives (OCs). An estimated 80 percent of women in the U.S. will use OCs at some point during their reproductive years. Because HIV infection in women primarily affects those of reproductive age, understanding the impact of steroidal contraception on HIV acquisition is a critical, unanswered public health question. Since many HIV-positive women use steroidal contraceptives, it also is important to understand the role of steroidal hormones in HIV progression.

About 10 million women worldwide used injectable Depo-Provera™ or DMPA in 1990. Since then its use has increased rapidly. Preliminary data on Depo-Provera™ use in women showed much less thinning of the human vaginal epithelium than was found in an earlier NICHD-supported study of the effect of progesterone implants on the risk of vaginal SIV acquisition in the macaque model. In that study, progesterone-treated monkeys had a markedly thinned vaginal epithelium and increased numbers of SIV-positive cells in the vaginal lamina propria than the controls. Physiologic and anatomical differences between the macaque and the human genital tract may account for the differences in the results. The macaque study reported a seven-fold greater risk of transmission in progesterone-treated

monkeys. The study also suggested that progesterone treatment accelerated the rate of progression to disease and death.

Effects of Contraceptive Steroids on Risk of HIV Acquisition. The NICHD supports a multi-site, international, prospective observational study in Africa and Asia that focuses on the possible effects of contraceptive steroids (both oral and injectable) on the risk of HIV acquisition in women. Additional substudies on genital shedding, viral fitness/host response, herpes simplex virus, human papillomavirus (HPV), bacterial vaginosis, and other important factors are nested within this protocol.

Viral Shedding from the Genital Tract

Knowledge of the basic pathogenic mechanisms underlying shedding of the virus from the genital tracts of men and women is critical in designing effective microbicides for prevention of HIV transmission. The NICHD, NIAID, and NIDCR have co-sponsored important clinical studies on viral shedding from the genital tract of HIV-infected women. The research questions concern the etiology and pathogenesis of HIV infection and its manifestations in women, including studies on parameters that affect genital-tract and oral-cavity shedding of HIV-1, as well as the effect of the menstrual cycle on virologic and immunologic parameters in HIV-infected women. A listing of currently funded research follows.

- ***Factors Affecting Detection of HIV-1 in Vaginocervical Secretions.*** Specific studies in this protocol focus on: antiviral resistance and genetic diversity in women; unintegrated HIV-1 proviral DNA as a marker for the level of virologic containment in blood; Epstein-Barr Virus genital shedding in HIV-1-infected women; characterization of cytomegalovirus strains isolated from vaginocervical secretions; association of specific factors in vaginocervical secretions that enhance expression of HIV-1 *in vitro* with increased shedding *in vivo*; HIV-1 sequence variation in plasma, cervico-vaginal lavage and saliva; and measurements of immunoglobulin A_1 and immunoglobulin A_2 subclasses in plasma and vaginocervical secretions.

- ***Effect of the Menstrual Cycle on Virologic and Immunologic Parameters in HIV-1-infected Women.*** Ongoing analysis assesses the effect of the menstrual cycle on cytokine and immunoglobulin levels; the variability of multiple collection methodologies on detection of HIV-1 in the genital tract; the effect of the menstrual cycle on other genital tract opportunistic infections; and factors that influence the ability to recover infectious virus from the genital tract.

- ***Effect of Herpes Simplex Virus (HSV) Shedding on Plasma HIV-1 RNA Levels in HIV/HSV Co-infected Women.*** While studies in men have shown an association between seminal HSV and increased levels of HIV-1 RNA in plasma, the same effect has not been seen in women. It is unclear if this lack of effect is hormonal or otherwise controlled. This study is assessing the impact of cytokine levels on HSV- and HIV-shedding.

Membrane Properties and Sperm/Microbe Susceptibility

One of the challenges in developing microbicides is to generate agents that target pathogens without damaging healthy tissue. Currently marketed spermicides are surfactants that dissolve cell membranes indiscriminately, affecting pathogens, sperm, and epithelial cells alike, and that have been shown to irritate or damage vaginal epithelium. The ideal contraceptive spermicide would not affect epithelial cells, while killing spermatozoa and pathogens. There may be similarities among spermatozoa, bacteria, and enveloped viruses that can be used to advantage. All these have membranes that are capable of external membrane fusion, an integral process for both fertilization and infection of cells. Since the

mechanism by which cell membranes are differentially susceptible to external fusion is not well understood, the NICHD supports research on models of membrane fusion that may help identify the critical components in the process. Additionally, identification of factors involved in the entry of the virus into cells, including the process of cell fusion, is an area of scientific interest and need. Currently funded projects include:

- ***Membrane Properties: Exploration of Sperm/Microbe Susceptibility*.** Through a Program Announcement (PA) issued in fiscal year 2000 (and to be reissued in fiscal year 2001), the NICHD is encouraging research on the similarities between membranes of spermatozoa and pathogens, and the properties that contribute to differential fusibility of membranes at the molecular level. Study results are expected to have implications for the design of products for contraception and prevention of HIV and other viral or bacterial infections.

- ***Transmembrane Mucin Studies.*** The NICHD supports a long-standing and ongoing research program related to this area. A thick mucus-like layer is present on the surface of the uterine epithelium. One important component of this layer is the transmembrane mucin, MUC-1, which performs a barrier function in the reproductive tract, protecting it from microbial infection. Genetically engineered mice with low levels of MUC-1 are predisposed to reproductive tract infections. Hence, enhancement of MUC-1-expression represents a new opportunity for reducing microbial infections.

The Women's Interagency HIV Study (WIHS)

Since 1993, the WIHS, a multi-center prospective study, has investigated comprehensively the impact of HIV infection in women. Sponsored by the NICHD, NIAID, NIDA, National Cancer Institute (NCI), and National Institute of Dental and Craniofacial Research (NIDCR), the study has enrolled 2,068 HIV-infected and 560 HIV-uninfected, but at-risk women, in five cities. Over 80 percent of the women are from minority populations, reflecting the epidemiology of HIV infection domestically. Through the primary study, substudies, and investigator-initiated proposals utilizing repository specimens, WIHS has contributed greatly to the understanding of the natural history and complications of HIV infection and its therapies in women and how these differ from those in men.

Ongoing WIHS activities include investigation of concentrations of antiretroviral agents in the genital tract after systemic administration and effects of these drugs on HIV detection in the genital tract, differences in viral populations such as co-receptor utilization between systemic and genital isolates, and the rate of detection of HIV resistant to antiretroviral therapy in the genital tract. A proposal currently being reviewed will evaluate the effect of treatment of bacterial vaginosis on HIV levels in the genital tract.

Adolescent Medicine HIV/AIDS Research Network (AMHARN)

Since 1996, the NICHD, with co-funding from NIAID, NIDA, and NIMH, has sponsored the AMHARN, a multi-center, observational, prospective study, to examine HIV disease progression and manifestations in adolescents in the U.S. The AMHARN enrolled 578 subjects (271 HIV-positive females, 164 HIV-negative females, 94 HIV-positive males, 49 HIV-negative males) at 15 sites in 13 cities. Over 90 percent of those enrolled are from minority populations, reflecting the epidemiology of HIV infection among American youth.

This adolescent population at high risk represents an important group for evaluation of potential microbicide use.

The AMHARN base protocol provided for in-depth immunologic characterization and focused

on the interaction between HIV and other STIs, notably HPV. Another study examined the interaction of HPV and HIV in the genital tract of young women and demonstrated higher rates of HPV infection and squamous intraepithelial lesions in HIV-infected young women, compared to HIV-uninfected, despite similar sexual risk behaviors and the relatively healthy state of the HIV-infected group. This finding suggests that HIV may enhance HPV proliferation through mechanisms other than immunosuppression of CD4T cells. Examination of cytokines (Interleukin [IL]-2, IL-10, and IL-12) in cervical secretions showed HIV-infected subjects to have significantly higher concentrations of IL-10 and IL-12, but not IL-2. Further, concomitant genital tract infection with HIV and other viral, bacterial, or protozoan pathogens influences local concentrations of some immunoregulatory cytokines. The longitudinal analyses of these data continue in the last year of the study.

B. Pre-clinical Development

The NICHD's pre-clinical development program is an important component in the process of identifying and developing new active agents for use as contraceptive microbicides. Institute-supported pre-clinical activities include:

- Screening of candidate compounds for spermicidal and antiviral (HIV) activity
- Chemical modification of compounds for optimal dual activity
- Assessing vaginal irritation in animal models
- Product formulation

Through periodic announcements in the *Commerce Business Daily*, the NICHD maintains an open call for compounds with dual spermicidal and microbicidal activity. The Institute has supported the screening of more than 200 chemical entities for *in vitro* spermicidal activity (Sander Cramer assay) and anti-HIV activity (cell-free and cell-associated assays or viral binding-inhibition assay).

Historically, the Institute has consulted with the developers of dual-use products to assist in re-design of candidate agents when improvements are indicated. NICHD has worked with several companies (and products) including: Biosyn (C31G), ReProtect (Buffer Gel™), Biotek (Foaming N-9 gel), Novavax (Novasomes), Procept (Pro2000™), Magainin Pharmaceuticals (Magainins), and Jelling (polybiguanides). Other tested products did not pass a rabbit vaginal irritation assay and, therefore, were not researched further.

A description of ongoing projects associated with the pre-clinical development of contraceptive microbicides follows.

- ***Vaginal Bioprotection by Controlled Acidification*.** This grant aims to develop a microbicidal, virucidal, and spermicidal vaginal gel that combines acidic buffering with concentrations of N-9 that are much lower and potentially less irritating than those used in current vaginal contraceptives. The researchers will assess vaginal irritation, and effects on vaginal pH *in vivo* in animals, and examine *in vitro* the effect of the gel on lactobacilli, human sperm, and various sexually transmitted pathogens, including HIV.

- ***Novel Contraceptives with Anti-HIV Activity*.** Pre-clinical studies are evaluating the clinical potential of two previously synthesized AZT derivatives (WHI-05 and WHI-07) that show promise as spermicides with anti-HIV activity. This project is assessing their contraceptive activity in rabbits, their ability to prevent transmucosal and perinatal transmission of feline immunodeficiency virus in cats, and their efficacy in preventing transmucosal transmission of HIV-1 in chimpanzees. Researchers will also conduct *in vivo* embryonic development, reproductive toxicology, and carcinogenesis studies in rodents.

- ***Biological Testing and Support Facility.*** This contract supports testing of potential contraceptive microbicide products in the rabbit model for spermicidal activity and vaginal irritation. The U.S. Food and Drug Administration (FDA) requires such testing prior to further evaluation of any product intended for human vaginal use. This facility enables testing of contraceptive activity both *in vitro* and *in vivo* in animal models.

- ***Testing of Anti-HIV Activity* in Vitro.** Through an Interagency Agreement with the U.S. Agency for International Development (USAID), the NICHD supports testing products for anti-HIV activity using multiple *in vitro* assay systems.

- ***Small Animal Models for Microbicide Testing.*** A specialized Contraceptive Development Research Center project aims to develop small animal and *in vitro* models for testing both the safety and efficacy of vaginal microbicides. Some of the work has resulted in development of an HIV-infection assay to screen compounds for potential use as a microbicide, achieved by employing both primary cells and established epithelial cell lines derived from the human cervix, vagina, and foreskin, which are the potential target cells of HIV infection. Using the HIV-infection assay, a number of compounds have been identified that show potential for use in a vaginal microbicide. *In vivo* mouse systems are being developed to expand testing of potential microbicide products for anti-microbial activity, including mouse systems for Neisseria gonnorrhoeae and murine leukemia virus (the mouse retrovirus analogous to HIV). An inactivated HIV/mouse system has also been developed to assay the blocking abilities of compounds in preventing HIV from crossing the reproductive tract epithelium.

- ***Reproductive Toxicology and Carcinogenicity Studies*.** The NICHD supports animal studies on reproductive toxicology and carcinogenicity for BufferGel™ and C31G, two promising contraceptive microbicidal agents. BufferGel, an acid-buffering agent that may prevent acquisition of HIV, is contraceptive by acidifying the vagina during intercourse. C31G is an antimicrobial agent with spermicidal activity. Toxicology studies are required prior to larger clinical trials in humans, while carcinogenicity studies ensure safety prior to product marketing. Initiated in 1999/2000, these studies will take two years to complete.

C. Clinical Research

The NICHD supports clinical studies to assess the safety and effectiveness of contraceptive microbicides. At the present time, clinical development of contraceptive microbicides takes place through the Contraceptive Clinical Trials Network (CCTN) and through the Efficacy Trial of Spermicidal Agents (ETSA). A description of recently completed Phase I studies and the ongoing ETSA trial follows.

- ***Phase I Clinical Trials.*** Four products, two containing N-9, one containing octoxynol-9, and one containing a new contraceptive microbicide (C31G), have undergone randomized, controlled, double-masked, Phase I clinical trials in the CCTN. The product containing octoxynol-9 was discontinued from the study because of severe vulvar irritation. C31G was found to produce more vulvar irritation than the control (Gynol II™). As a result, C31G was reformulated and is currently in Phase I clinical trials. The two N-9 products did not appear to be less irritating than the control.

- ***Phase II Clinical Trials and Pharmacokinetics of C31G.*** C31G represents a novel contraceptive microbicide compound that has been shown to have broad antiviral, antibacterial, and antifungal properties in addition to spermicidal activity. The compound C31G can be absorbed through the vagina into the circulatory system. An ongoing contract monitors the pharmacokinetics of C31G. The goal is to conduct the appropriate chemical, analytical, and metabolic studies to qualify the material for Phase II clinical trials to test spermicidal efficacy and to supply a sufficient amount of Good Manufacturing Practices material to conduct the study.

- ***Phase III Clinical Trials.*** The active ingredient in most marketed spermicides is N-9, which was monograph-approved by the FDA as safe and effective in the early 1980s, along with closely related octoxynol-9. In 1995, as part of its notice of proposed rulemaking for marketing approval of vaginal products, the FDA expressed concerns about the conflicting evidence available on both the safety and efficacy of N-9 and proposed requiring stringent new clinical evidence for such products. In July 2000, scientific reports indicated that HIV-negative women who were enrolled in the United Nations AIDS (UNAIDS)-funded clinical trial of "AdvantageS™," a microbicidal product containing N-9, were more likely to sero-convert than women who had used the non N-9 comparison product (Replens™). The Centers for Disease Control and Prevention (CDC) subsequently stated that "…N-9 should not be recommended as an effective means of HIV prevention." The NIH has not yet issued a statement on this matter and continues to discuss the issue.

The NICHD is undertaking the ETSA study, a Phase III trial of five N-9 vaginal spermicidal products, for contraceptive efficacy (through detection of both clinical and pre-clinical pregnancies), and for a comparison of product safety (through colposcopy, effects on vaginal microflora, levels of vaginal cyto- and chemo-kines, and reports of adverse reactions). The trial will take place at 11 clinical sites in the U.S., and has a target accrual of 1,800 women, ages 18-35, to be followed for 30 weeks. The study will require five years for patient recruitment, follow-up, and analysis. The products chosen for the trial will allow for a comparison of dose response to N-9 independent of formulation, as well as a comparison of formulations at the same dose of N-9.

D. Behavioral and Social Science Research

Complementing its biomedical research, the NICHD also supports a portfolio of behavioral and social science research on the potential use of contraceptive microbicidal products. A three-pronged strategy to establish the groundwork for research in this area focuses on:

- How people choose methods for HIV and pregnancy prevention;
- Use of currently available products, e.g., spermicidal products and male and female condoms; and
- Readiness to adopt new methods with specific characteristics within various populations.

This research aims to improve understanding of the acceptability of microbicides and other female-controlled methods for the prevention of HIV and/or other STIs. It is part of a larger portfolio that includes: interventions for young people to decrease their risk of exposure to STIs and unintended pregnancy; basic behavioral research relating to the determinants of sexual behavior and protection from STI in adolescents as well as adults; and studies of social and sexual networks and their influences on individual risk behaviors. The NICHD also funds research on community-level determinants of risk behavior.

Current NICHD-supported research relevant to the acceptability of microbicides includes the following:

Use of Dual Methods of Protection

- An interactive video is encouraging women at high-risk of HIV/STI to consider adopting or improving use of two methods of protection. It uses the "Stages of Change" model to tailor intervention messages to the women's readiness to adopt new ideas and practices.
- An observational study is examining the use of dual methods of protection in a Texas family-planning clinic and has found rates of dual-use quite low in a group of primarily Hispanic women, whose partners' behavior may put them at risk of both unwanted pregnancy and exposure to STIs.
- A study is following women interviewed in a STI clinic and is giving them information and materials needed for prevention of unwanted pregnancy and avoidance of further STIs.
- A longitudinal follow-up study of women, who accepted NORPLANT™ when it was first introduced, is finding that few of them, including those at increased risk of HIV/STI, are adopting consistent STI-prevention behavior.

Barrier Methods of Contraception

A project directly addresses correct, consistent, and continuing use of barrier methods of contraception by young women in the U.S., in situations in which they are given free choice among male condoms, female condoms, spermicides, and diaphragms. The study is finding that women prefer to have their partners use the male condom.

Basic Behavioral Science Research on Sexual Behaviors Related to HIV Risk

- A longitudinal study of the determinants of adolescents' health-related behavior is providing a range of information on the attitudes of young people and their parents toward sexual risk and protection.
- An AMHARN study is evaluating the influence of the disclosure of HIV serostatus and discrepancy in partner age on condom use.
- Studies of social and sexual networks are focusing on how, and in what manner, partners, other peers, and family influence individuals in their decisions to have sex, to have protected sex, and to maintain or change sexual partnerships. These studies are demonstrating that partner change is a strong predictor of the introduction of protection

from STI, and that in partnerships of long duration, dual methods of protection are not often used. Individuals from different racial, ethnic, or class groups have widely varying patterns of sexual partnerships. This has powerful implications for the use of protection, including the use of microbicides.

Promotion of Dual Protection Behavior

This study among rural South African youth is designed to identify factors influencing the choice of pregnancy-and HIV-prevention methods and to develop and test a school-based intervention.

III. RESEARCH NEEDS, GOALS, AND PROPOSED ACTIVITIES

The NICHD has identified current issues, questions, and gaps for each major area of research related to contraceptive microbicides. These findings are presented in this section, along with the Institute's goals and proposed activities to address such needs. To a considerable degree, investigator-initiated endeavors will continue to define future research directions.

A. Basic Biomedical Research

There remains a shortage of basic biomedical research in virology, microbiology, and immunology in relation to HIV dynamics in the genital tract. In addition, there are understudied areas in formulation technology of contraceptive microbicide development. The effect of the reproductive health of women on disease presentation, diagnosis, and acquisition is largely unknown. The relationship of immune decline in women to conditions such as female genital tract and reproductive organ infections needs to be determined. There is limited information on the effect of therapy or prevention efforts on gender-specific aspects of HIV infection and disease manifestation.

Goal: Expand Understanding of Factors Affecting HIV Transmission and Acquisition.

- ***Establish a Women's HIV Pathogenesis Program.*** In fiscal year 2001, the NICHD will award program project grants under a Request for Applications (RFA) titled *Women's HIV Pathogenesis Program*. Projects will focus on increasing understanding of the causal relationship between HIV-1 pathogenesis and factors unique to women, such as reproductive physiology. Studies will help identify gender-specific biological factors that influence viral shedding in the genital tract, HIV-1 transmission, disease acquisition and manifestations in women. Such research may be useful in the design of microbicides to reduce viral shedding. Additionally, investigators will identify mechanisms for assessing microbicidal activity in HIV-infected women. The results of studies under this program also are anticipated to have practical applications for improving the care of HIV-infected women.

- ***Establish an Adolescent Medicine Trial Network (ATN).*** The NICHD will fund a Leadership Group, Data and Operations Center, and Clinical Trials Units to implement HIV-related interventions, including microbicide research in adolescent populations. Adolescents and young people contribute over half of all incident HIV infections each year. The ATN will provide the clinical research infrastructure and adolescent behavioral expertise for effective collaboration with microbicide researchers.

- ***Support Additional Basic Biomedical Research.*** As appropriate to the purview of the NICHD, the Institute will implement the recommendations for additional basic research that are identified in the report produced by the *Biology of Transmission Think Tank,* sponsored by the NIH OAR in April 2000. Specifically, the NICHD DIR plans to conduct collaborative research on a topical microbicide for HIV-1 and HIV-2. Potentially this product could be formulated into one or more products for vaginal delivery and tested for safety in the rabbit vaginal irritation model and other animal models.

B. Pre-clinical Development

In the area of pre-clinical development, the NICHD has identified the need to develop the following:

- New and innovative compounds for microbicidal and dual-use contraceptive microbicidal activity
- Microbicidal products that are effective against genital infections, such as bacterial vaginosis, HPV, and chlamydia
- Inexpensive, easy-to-use methods appropriate for use in resource poor settings, particularly in developing countries
- Improved models of *in vivo* activity
- Standardization and validation of pre-clinical assays and correlation of non-human test results with human test results
- Improved tracking and coordination of products in development

Although the NICHD and other NIH Institutes and Centers have supported research activities to develop and maintain a pre-clinical screening program to evaluate the contraceptive and microbicidal activity of numerous compounds, there is little evidence that existing pre-clinical assays for microbicidal efficacy are predictive of positive activity during clinical use. One of the major problems in comparing results between studies is the lack of standardization and quality control. The NICHD intends to follow the model that has been implemented by NIAID to ensure quality control of its HIV vaccine efficacy methodology.

The NICHD anticipates funding several microbicidal pre-clinical development projects for the purpose of developing novel, non-vaccine approaches for prevention of sexual transmission of HIV-1. Additionally, the Institute is working actively with private companies to help develop potential contraceptive microbicidal products. Several products are in the early stages of development.

Goal: Expand and Coordinate Pre-clinical Compound Development Activities and Improve Models of *in Vivo* Activity.

- ***Microbicide Pre-clinical Development Program*.** In fiscal year 2001, the NICHD, in co-sponsorship with NIAID, anticipates supporting research through a new Microbicide Pre-clinical Development Program (MPDP) that will use multidisciplinary, multi-project approaches involving academic, nonprofit, and/or commercial/industrial institutions. The MPDP will encourage the discovery and pre-clinical development of novel microbicides, with or without contraceptive activity, and new non-vaccine strategies to prevent sexual transmission of HIV. The active participation of industry will be encouraged, which will allow that segment of the scientific community to contribute both intellectual and material resources. The interaction of academic and non-profit research institutions with industry and the government will facilitate subsequent development and marketing of the new products.

- ***Coordination Contract for Microbicide Development Program*.** The Institute plans to award a Coordination Contract for Microbicide Development in 2002, to help track products at all stages of development, from basic research through clinical trials; evaluate their status in the pipeline; and make recommendations as to future development. This resource would be shared by other NIH Institutes and Centers.

- ***Alternative Test Models for Assessing Genital Irritation.*** Irritation of epithelial surfaces of the genital organs is of concern in developing vaginal contraceptive microbicidal products. If resources become available, the NICHD will consider a PA with funds set aside in fiscal year 2003, to support studies that allow discovery or validation of new test models, comparing multiple *in vitro* assay systems with the current rabbit vaginal irritation (RVI) test and other possible *ex vivo* models, such as mouse/human xenographs. Proposals would be solicited for use of any non-RVI system as a possible pre-clinical vaginal irritation screen to aid safety assessments for products and product formulations.

- ***BufferGel™and Diaphragm Stability Studies.*** A study of BufferGel™, used in conjunction with a diaphragm, is planned for Phase II/III contraceptive efficacy studies in fiscal year 2001 (See Clinical Research section below). An issue beyond the efficacy of BufferGel™/diaphragm use is whether prolonged exposure to BufferGel™ has any adverse effect on the physical integrity of the diaphragm material. Two simple tests will be conducted to address this issue: tensile strength measurement of the post-exposure diaphragm dome material, and visual/water integrity inspection for defects in the physical barrier of the dome.

- ***Standardization and Validation of Pre-clinical HIV Assays*.** Several groups possess research data, including a common set of controls, that would permit a comprehensive evaluation of various technologies used in the pre-clinical assessment of anti-HIV activity, toxicity, and spermicidal activity. Phase I clinical trial data on toxicity could also be linked to various pre-clinical studies to validate their predictive value. In fiscal year 2002, the NICHD plans to award a contract to coordinate access to such databases, help standardize and validate pre-clinical assays, and establish an integrated and comprehensive set of pre-clinical testing guidelines.

- ***Toxicology Evaluation of Products*.** A survey of microbicide development researchers (conducted by the Alliance for Microbicide Development) found that two-thirds of respondents were unable to progress to clinical trials because support for toxicology testing was lacking. The NICHD plans to continue its support for toxicology testing of

leading products, as promising compounds are reviewed by the Scientific Advisory Committee to the Institute's CRHB.

- ***Microbicide Formulation Support Contract.*** If resources are available in fiscal year 2003, the NICHD is considering awarding a contract to develop or optimize new clinical formulations for microbicides, with or without contraceptive activity, that demonstrate good drug or formulation stability, targeting, bioavailability, and acceptability. Additionally, this contract would assess physical/chemical properties of drugs identified for formulation development. The contract would also identify potential drug excipient interactions and drug solubility. The overall goal would be to provide capacity for optimization of effectiveness and ease of delivery

- ***Natural Product Microbicide Development Groups.*** Historically, complementary and alternative medicine has been a source of leads on pharmacologically active agents with efficacy against a wide variety of human diseases and conditions. The NICHD is interested in encouraging the development of natural products from natural sources for the prevention of conception, HIV, and other STIs. If resources are available, the NICHD may issue an RFA in fiscal year 2003, to support Natural Product Microbicide Development Groups that would conduct studies on mechanisms of action, characterization of active ingredient(s), and pre-clinical development. A workshop on this research will be held in September 2001.

C. Clinical Research

Goal: Increase the Number of Contraceptive Microbicide Products that Undergo Clinical Development and Testing.

While the NICHD has programs and projects in place or planned to support pre-clinical development of promising contraceptive microbicides, additional resources are needed to move potential products into and through clinical development and testing. Specific clinical trials are required to assess the safety and effectiveness in humans of new contraceptive microbicides. The NICHD also collaborates with the NIAID in programs that are designed to bridge the gap between the pre-clinical and clinical development of microbicides. A description of proposed projects for fiscal year 2001, and fiscal year 2002, follows.

- ***Expansion of CCTN Involvement.*** The NICHD plans to expand research in the CCTN and to address additional questions of clinical relevance in the ETSA trial for fiscal year 2001, and Fiscal Year 2002. One of these projects is described below. Other products may also be included in the CCTN studies. The Scientific Advisory Committee for the CCTN meets regularly to advise CRHB program staff on which compounds should be priorities for study. This practice creates a dynamic process that encourages flexibility in the clinical development of contraceptive microbicides.

- ***Contraceptive Efficacy Trial of BufferGel™.*** Funds have been committed to a contraceptive efficacy trial in the CCTN of BufferGel™ with a diaphragm compared to Gynol II™ with a diaphragm. The protocol is currently under development, with the trial anticipated to start in fiscal year 2001. In addition to contraceptive efficacy, several microbiologic endpoints, including bacterial vaginosis, *E. coli* colonization, and monilial vaginitis will be included. A total of 975 subjects will be recruited over an 18-month period for a six-month study. A subset of patients will be recruited to continue use of the product

for an additional six months. The BufferGel™ trial may also expand to possible sites in Africa and India.

- ***Colposcopic Evaluation Studies*.** Colposcopy, a clinical technique that allows inspection and evaluation of the vaginal and cervical epithelia, is used in diagnosis and treatment of vaginal and cervical conditions. This technology has potential to contribute to the development and evaluation of vaginal spermicides and microbicides. If resources are available, the NICHD may propose a new RFA in fiscal year 2002, to help define the applicability and feasibility of colposcopic examination as a part of vaginal product safety assessment. The RFA would focus study on: definition of the components of the colposcopic exam; description of intra- and inter-observer variability; definition of causes and natural history of diagnosed lesions; value and reliability of colpophotographs; and correlation of visual findings with other objective measures of disease.

D. Behavioral and Social Science Research

Goal: Expand the Current Program of Behavioral and Social Sciences Research and Improve Understanding of Sexual Behavior Related to HIV Transmission.

The absence of new contraceptive microbicidal products limits the behavioral and social science research on this specific issue that can be supported by the NICHD. Research on the choice and use of methods to prevent pregnancy and STIs reveals the importance of individual, partner-specific, method-specific, and socio-cultural factors. Further research is needed to study the acceptability of new and potential anti-microbial products, and the likely characteristics of such products, in a variety of populations, domestically and internationally.

There also is a need to develop new models for studying acceptability within the context of clinical trials and in the population at large. The NICHD plans to encourage the inclusion of behavioral research in clinical studies, including those undertaken through the new Women's HIV Pathogenesis Program, which will assure that the important behavioral components of microbicide and contraceptive testing and application are considered at all stages of product development. Questions related to microbicide use are especially important in international settings where young women are at particular risk for HIV infection. Research needs to address cultural and social differences to assure that products developed in the U.S. are appropriate and effective when used in other countries and societies.

- ***National Survey of Family Growth.*** The NICHD will continue to fund the National Survey of Family Growth, last conducted in 1995, with the next round to be fielded in fiscal year 2002. This continuing series of interviews, with a nationally representative sample of more than 10,000 women of reproductive age, tracks the use of all methods of contraception and prophylaxis. In fiscal year 2002, the survey will include a nationally representative sample of men as well as women. Another longitudinal study of young adults also will be conducted in fiscal year 2006.

- ***Acceptability Research for HIV/STI Prevention.*** In fiscal year 2001, the NICHD, in co-sponsorship with the NIMH, awarded several new grants for research on the acceptability of microbicides for HIV/STI prevention. Given the paucity of products in clinical trials, the NICHD is encouraging investigators to use analog models and work in conjunction with ongoing trials. Under this program of research, the NICHD is supporting five grants and the NIMH is supporting two grants. Summarized below are the five NICHD-funded

projects, which will address a broad range of questions related to acceptability issues, both among domestic and developing country populations.

- One study will explore how individual, relationship, and socio-cultural factors influence acceptability of actual male and female condoms and hypothetical methods for both people in the relationship.

- A second set of studies conducted in South Africa will involve focus group discussions and in-depth interviews among participants who had previously used an N-9 product in a clinical trial, to determine cultural factors that affected the use of the microbicides during the trial. In addition, Rapid Assessment Procedures will be used among sex workers who have participated in a long-term trial in order to develop an appropriate measurement for acceptability among this high-risk population.

- A third study will examine developmental factors that are associated with use of microbicide-like formulations among adolescent girls recruited from a teen health center. It will provide information on how adolescent females and males and significant adults (mothers of adolescent girls and health care providers) anticipate the use of microbicidal products. The study will also evaluate how discussion of use, initial use, and sustained use varies as a function of developmental characteristics and experience with the product.

- A fourth project will interview both adults and teenagers in a STI clinic and a family-planning clinic, to provide comparisons among three groups of potential users of a microbicide. It will include a short-term, prospective study of women randomly assigned to test two forms of spermicide delivery systems, gel and suppository, and will test for socio-demographic differences between women who agree and those who decline to participate in the study.

- The fifth study will address issues of acceptability using an actual, but under-utilized product, the vaginal diaphragm. In addition to the possible parallels of acceptability of the vaginal diaphragm to the acceptability of microbicides, there is increasing interest in the diaphragm as a device for holding microbicidal products in place.

- ***Gender Issues and Microbicide Use.*** Some studies have suggested that women may feel they must inform their partners about any plan to use microbicides, and must comply with their partners' wishes. The implications of varying gender and power dynamics across populations for use of protection are important and have been little studied. An NICHD RFA issued in fiscal year 2001 will fund studies on this topic.

- ***Institutional Pathways Toward Strengthening HIV Prevention in Minority Communities.*** In fiscal year 2002, the NICHD plans to fund a two-stage initiative. Initial support will focus on basic research demonstrating the mechanisms through which organizations in minority communities support and contribute to development and continuation of local cultural and social norms concerning appropriate sexual and protective behavior. After this formative research phase, an RFA will support development and implementation of intervention programs grounded in existing community organizations. Results from these studies will enhance understanding of community norms and socio-cultural factors involved in acceptability and use of dual protection products in minority populations.

- ***Research on HIV/STI Prevention Messages.*** In fiscal year 2002, the NICHD also plans to issue an RFA that will support research to improve understanding of how individuals and their sexual partners, in a wide variety of settings domestically and internationally, interpret HIV/STI-prevention messages and how these interpretations influence their prevention practices. It is anticipated that these studies will contribute to knowledge of cultural differences, myths, and misconceptions about risk and protective behaviors that may hinder prevention efforts, including acceptability and use of potential contraceptive microbicidal products.

E. Post-marketing Surveillance

The NICHD anticipates that as more contraceptive microbicidal agents are developed and marketed there will be an ongoing need to provide safety and efficacy surveillance through traditional mechanisms. Thus, while there are no new agents available for marketing at the present time, the NICHD foresees a future need for research in this area.

F. Capacity-building

Given the urgency of the HIV epidemic and the need for development of promising contraceptive microbicide products, it is critically important to expand the pool of trained and committed researchers, domestically and internationally, who are involved in microbicide-related studies. Investigators need to be brought into the field and encouraged in the development of innovative approaches in contraceptive microbicide research. The capacity of organizations in both the private and public sector (particularly small companies and organizations in countries profoundly affected by HIV) to conduct research in this area needs to be developed or enhanced. New training approaches and workshops may need to be designed to meet the capacity-building needs of investigators within such organizations, particularly in international settings.

The expansion of U.S. support for microbicide development also needs to be enhanced by increasing pharmaceutical industry interest and involvement in the development and marketing of microbicidal or dual-use products. The conviction that there is a limited income-producing market for these products contributes to the historic lack of industry interest. Significant industry concerns about litigation and consumer dissatisfaction are not outweighed by the expected return on the research and development (R&D) investment. Finally, industry cites problems with FDA regulatory requirements.

Goal: Expand U.S. and Global Support for Microbicide Research and the U.S. Capacity to Develop, Evaluate, and Improve Microbicidal and Dual-use Compounds.

- ***Indo-U.S. Joint Working Group Workshop on STIs/RTIs*.** In November 2000*,* the Indo-U.S. Joint Working Group on Contraceptive and Reproductive Health Research sponsored a research agenda-setting workshop in New Delhi, India, on the diagnosis, antecedents, outcomes, prevention, and treatment of STIs, including HIV, and reproductive tract infections (RTIs). This workshop is generating joint scientific projects in the area of STIs/RTIs. It is anticipated that research results will have relevance for the prevention of HIV transmission and acquisition in India.

- ***Contraceptive/Infertility Research Loan Repayment Plan.*** With increased funding in fiscal year 2001, the NICHD will continue to encourage qualified health professionals (including graduate students) to remain engaged in contraceptive microbicide and reproductive health research through an educational loan debt repayment program. Those individuals who accept repayment commit to a period of obligatory service of not less than two years, conducting research with respect to contraception and/or infertility. This is a competitive program.

- ***Ongoing Meetings with Pharmaceutical Industry Representatives*.** The NICHD program staff will continue to meet with pharmaceutical industry representatives to encourage their expanded involvement with contraceptive microbicides. The NICHD will also work with the FDA to standardize regulatory requirements for contraceptives and microbicides. It is expected that this would make it more appealing to industry to develop microbicidal and dual-use compounds. The Institute will consider the use of outside consultants to facilitate industry involvement in the contraceptive microbicide R&D field and help clarify FDA regulatory revisions.

- ***Supplements to Funded Grants.*** In fiscal year 2000, grant supplements were awarded to increase international capacity to conduct studies relating to sexual risk. Two of these studies will have particular relevance for behavioral research on the use of microbicides: a study of "sugar daddies" in Zimbabwe, and a study of teenagers' sexual behavior in South Africa.

- ***Behavioral and Social Science Training and Career Development in HIV/AIDS.*** Through a PA issued in fiscal year 2002, the NICHD will support the initiation of training and career development activities to strengthen behavioral and social science research capabilities and capacity related to HIV/AIDS research, including contraceptive microbicides. This program will actively encourage applications from minority investigators and institutions, domestically, and from scientists in developing countries.

IV. COLLABORATIVE EFFORTS

The NICHD collaborates with many groups working in the microbicide development area. Many of these organizations also work with each other. Figure 2 (see Appendix C) delineates the interrelationships among them. Brief descriptions of several of these groups and the nature of their partnerships and collaborations with the NICHD follow. Please note that the acronyms in parentheses for the organizations described below are also used in Figure 2 in Appendix C.

- ***NIH Office of AIDS Research (OAR).*** The OAR coordinates microbicide research across the various NIH Institutes and Centers. The NICHD has had numerous meetings with the OAR regarding the NICHD contraceptive microbicide research agenda. Additionally, NICHD staff has worked with the OAR and others in developing the first International Conference on Microbicides in 2000. A second meeting will be held in Europe in 2002.

- ***National Institute of Allergy and Infectious Diseases (NIAID).*** The NICHD and NIAID collaboration in microbicide development ranges from the basic sciences to clinical trials. The NICHD is listed as a co-sponsor on the NIAID Mechanisms of AIDS Pathogenesis PA and on the NIAID Integrated Pre-clinical /Clinical Program in HIV Topical Microbicides PA. Together the Institutes have also co-sponsored a workshop on *in vitro* assays used in the evaluation of anti-HIV activity. NICHD staff members are represented on the STD, perinatal, behavioral science and microbicide working groups for the NIAID Prevention Trials Network, of which NICHD is a co-sponsor. The NIAID staff is present during NICHD/CRHB Scientific Advisory Committee review of products for the CCTN. The NICHD RFA on the Microbicide Pre-clinical Development Program is also co-sponsored by NIAID.

  Extramural and intramural staff of the NICHD have entered into several collaborative efforts with NIAID in the area of microbicide research. Models have been developed by NICHD intramural staff, and similarly, by the British Medical Research Council (MRC), London, United Kingdom, which may prove useful in elucidating mechanisms of action and selecting potential new microbicidal agents. In addition, through the NIAID-administered Biological Technology Evaluation Program, NICHD extramural and intramural staff will be working with Russian scientists to develop a new class of promising microbicides.

- ***Fogarty International Center (FIC).*** The NICHD collaborates with the FIC in supporting seven U.S. institutions that have provided training in population and health-related research for investigators from developing countries. During the past five years, this training program has been very effective, not only in training of individual investigators, but also in establishing institutional collaborations aimed at strengthening research capabilities in developing countries. The overall program entails support for biomedical training as well as support in the demographic and behavioral sciences. In fiscal year 2000, an RFA was issued to solicit applications for the continuation of this successful initial program. These training grants were awarded and are administered by the FIC. Programmatic overview is provided by the Center for Population Research, a component of the NICHD.

- ***Food and Drug Administration (FDA).*** The NICHD collaborates, both formally and informally, with the FDA. Informally, discussions take place at multiple levels for product development and evaluation. More formally, the NICHD and FDA have had several meetings regarding contraceptive microbicide development. Additionally, through interactions with the International Working Group on Microbicides, NICHD and FDA have been involved in developing pre-clinical and clinical guidelines for product development.

- ***U.S. Agency for International Development (USAID).*** The NICHD and USAID have a long-standing Interagency Agreement that has helped support studies with the Contraceptive Research and Development (CONRAD) Program of Eastern Virginia Medical School, Family Health International (FHI), and the Population Council. Screening of NICHD-supported compounds for anti-HIV activity is funded through USAID and done in collaboration with the CONRAD program.

- ***Family Health International (FHI).*** The NICHD also funds Family Health International directly. FHI staff has been active in the contraceptive and reproductive health efforts of the NICHD for many years. At the present time FHI is the primary contractor for the Hormonal Contraception and HIV Acquisition study, the ETSA study, and the planned Indo-U.S. STI/RTI activities.

- ***The Population Council (Pop Council).*** NICHD provides funds to the Population Council through a Contraceptive Development Center Grant. Population Council efforts, which have been supported by the NICHD, include the development of small animal models for evaluating microbicide efficacy.

- ***The Alliance for Microbicide Development (AMD).*** AMD is a non-profit organization comprised of individuals from government (ad hoc), industry, and advocacy groups. NICHD program staff works with AMD staff to update its database, assist in provision of developmental materials, and facilitate, in whatever capacity possible, the development of microbicides.

- ***The International Working Group on Microbicides*** **(IWGM).** Organized under the auspices of the World Health Organization (WHO), the IWGM serves as a scientific and policy forum to stimulate microbicide research globally. The IWGM is committed to the development, production, and distribution of safe, effective, affordable and acceptable, topically applied, self-administered preparations to prevent the sexual transmission of HIV and other STIs. The IWGM facilitates communication and collaboration on scientific, technical, social, ethical, and industry issues relevant to microbicides and helps identify needs and opportunities to promote product development. Its members seek consensus on recommendations for pre-clinical and clinical investigations and criteria for selecting promising leads for evaluation. The NICHD helped in the formation of the IWGM and remains an active member.

V. SUMMARY

The NICHD Contraceptive Microbicide Development Program is a dynamic program. Its goals and projects reflect expert guidance on the type of research and programmatic efforts that are needed to drive and advance ongoing and future science in this area. The Institute recognizes that, as additional contributions to its knowledge regarding HIV and its prevention become available, program priorities may need to be revised. The NICHD welcomes other insights and knowledge that may help expedite and expand research in the development of contraceptive microbicides.

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Appendix B: NICHD HIV/AIDS Coordinating Committee (HACC) Contraceptive Microbicide Coordinating Subcommittee (CMCS)

CMCS Co-chairs

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Acting Deputy Director, Center for Population Research (CPR)

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APPENDIX C

Figure 1: NICHD Contraceptive Microbicide Research and Development Program

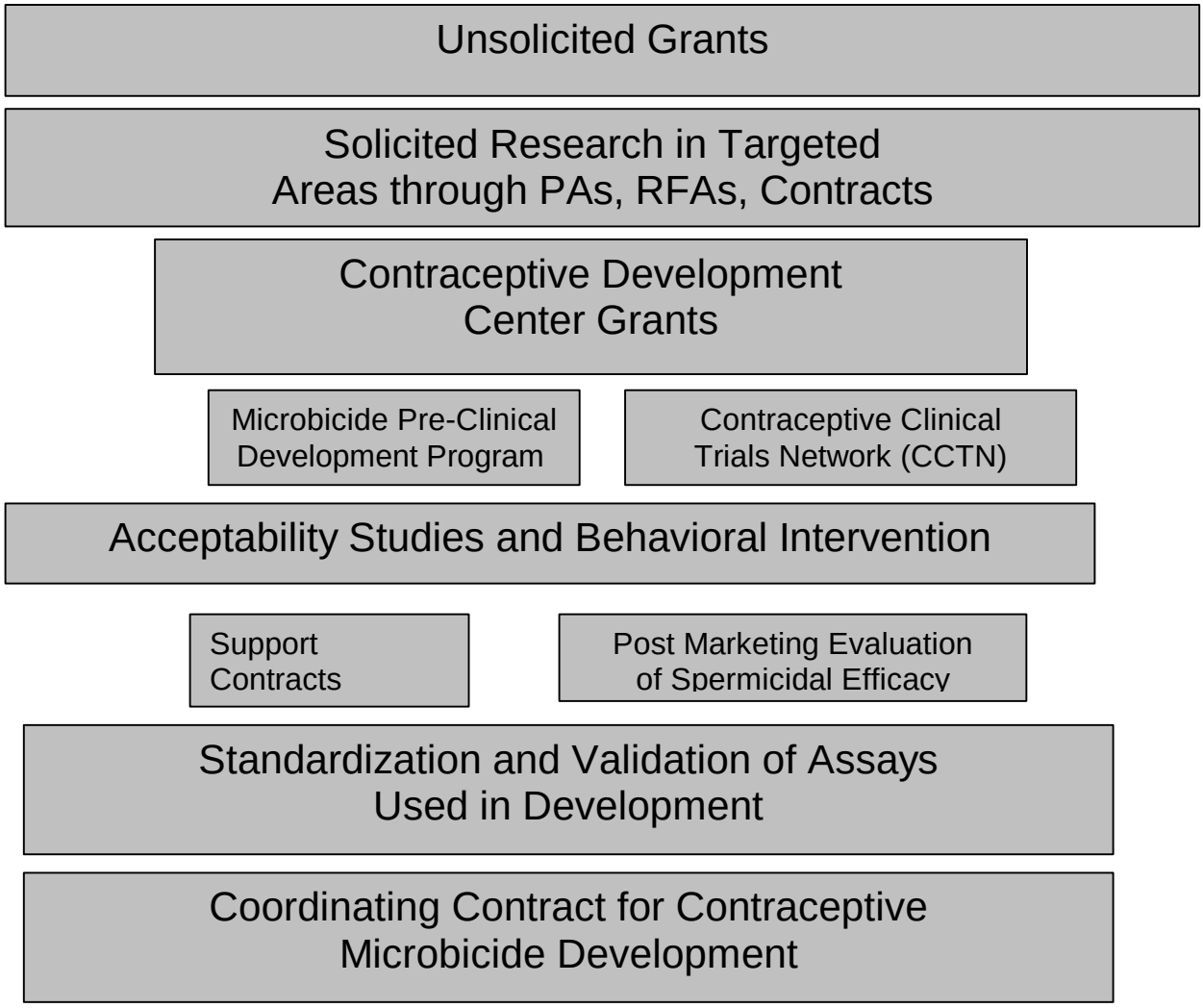

Figure 2: NICHD Contraceptive Microbicide Collaborations