Contraception and Reproductive Health Branch

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About the Cover…

One of the overarching goals of the NICHD's Contraception and Reproductive Health Branch is support for the development of safe and effective methods of contraception. In a role that preceded that of the Branch, **Katherine Dexter McCormick**, pictured on the cover, provided critical financial support for the development of the first oral contraceptive for women.

In the 1920s and 1930s, researchers identified many of the body's natural steroid hormones and began synthesizing them and their analogs. In 1928, scientists at the University of Rochester identified progesterone; in 1929, researchers at Washington University in St. Louis isolated and identified estrone. While ethynylestradiol, today the most widely used estrogenic agent, was commercially available in 1938, progesterone availability was more problematic. It was difficult and expensive to extract progesterone from naturally occurring sources, making its use impractical. In addition, progesterone was not orally active, and therefore had to be given as an injection.

By 1943, Russell Marker, an organic chemistry professor at Pennsylvania State College (now Pennsylvania State University) had devised a technique to extract a precursor compound, diosgenin, from Mexican wild yams that could be chemically modified into progesterone. Marker's process allowed affordable mass production of progesterone, but it still had to be injected. In the early 1950s, Frank Colton and Carl Djerassi, two chemists working independently, created orally effective forms of synthetic progesterone that were many times more potent than natural progesterone.

At that time, however, many of the commercial sources for research support were not interested in supporting further research to develop these compounds into an oral contraceptive. Some did not want to get involved in the controversy that surrounded such a product, while others simply saw no commercial market for it. So, although inexpensive and potent synthetic forms of steroids were available, there was little progress in developing them into effective oral contraceptives.

Enter Katherine Dexter McCormick. McCormick was the second woman to earn a degree from the Massachusetts Institute of Technology where she received a BS in biology in 1904. She married Stanley McCormick, the heir to the International Harvester fortune, that same year and devoted her life and fortune to philanthropy and to championing women's rights. It was in 1917, during her efforts to secure women's right to vote, that she met Margaret Sanger, founder of the Planned Parenthood Federation. McCormick and Sanger shared concerns about the problem of population growth.

In the early 1950s, McCormick met with Gregory Pincus, a leading researcher in reproductive physiology, to discuss oral contraceptive research. Over the next decade, McCormick anonymously invested more than $2 million (the equivalent of $30 million today) in Pincus' research. Pincus developed the first affordable, effective contraceptive pill, using funds from McCormick and others. The pill was first tested in large-scale human studies beginning in 1956 and was licensed by the U.S. Food and Drug Administration in 1960.

The development of the oral contraceptive pill required the pioneering work of reproductive biologists and medicinal chemists, the visionary scientific drive of Pincus, and the farsighted philanthropy of McCormick. If not for the financial support of Katherine McCormick, development of the oral contraceptive from research concept to licensed product would have taken much longer. The NICHD's Contraception and Reproductive Health Branch extends the pioneering effort of McCormick in its support of multidisciplinary research on new, safe, and effective contraceptives, as well as other areas of reproductive health.

Cover image courtesy of the Massachusetts Institute of Technology Museum

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EXECUTIVE SUMMARY

The mission of the Contraception and Reproductive Health Branch (CRHB), part of the Center for Population Research (CPR) within the National Institute of Child Health and Human Development (NICHD), has traditionally been to support research on the discovery, development, efficacy, safety, and mechanisms of action of various methods of contraception, as well as on reproductive health and epidemiology. In 1997, two Branches within the CPR, specifically the Contraceptive Development Branch and the Contraceptive and Reproductive Evaluation Branch, merged to form the CRHB. The CRHB combines the research foci of these two components and has undertaken development of a broad program that includes exploration of new reproductive health and contraceptive technologies, establishment of research programs on HIV/AIDS and sexually transmitted infections (STIs), female pelvic floor disorders, and design of multicenter contraceptive clinical trials. During the past several years, CRHB-sponsored research on these and other topics has significantly expanded.

Throughout the history of the CRHB and its predecessor Branches, there have been extensive collaborative efforts with other organizations, reflecting the worldwide need for safe and effective contraceptives. Development of new contraceptives involves the efforts of governmental agencies, academic institutions, non-governmental organizations, and private industry and cuts across national borders.

The Branch seeks to advance research in contraception and reproductive health. In support of this mission, the Branch pursues five major program areas, based upon specific goals:

- Contraceptive research and development;
- Contraceptive and reproductive evaluation;
- Prevention of HIV/AIDS and other STIs;
- Selected reproductive and gynecologic health issues; and
- Research training.

This report highlights the scientific activities and achievements of the CRHB since its last report to the National Advisory Child Health and Human Development (NACHHD) Council in 1999. It notes progress in the five program areas, lists goals for these areas, and projects future directions for the Branch.

For more information about the contraception and Reproductive Health Branch, visit its Web site at http://www.nichd.nih.gov/cpr/crh/crh.htm.

PROGRAM AREAS AND GOALS

PROGRAM AREA 1: CONTRACEPTIVE RESEARCH AND DEVELOPMENT

Within this program area, the goal of the CRHB is to promote contraceptive research and development for preventing or reducing unintended pregnancies by:

- Developing new male and female contraceptive methods that employ hormonal and non-hormonal agents
- Developing new hormonal methods for emergency contraception
- Supporting contraceptive research and development that may lead to new methods for inhibiting ovulation, fertilization, or spermatogenesis
- Conducting experimental studies in animals and clinical trials in humans to determine optimal formulations and dosages of contraceptive agents

Contraceptive research and development is critical for providing safer, more efficacious methods of preventing unintended pregnancies, especially in light of the continued growth of the global population. Although a range of contraceptive methods is currently available, the proportion of unintended pregnancies in the United States still approximates 50 percent of all pregnancies. The CRHB recognizes that part of this problem results from failure to use available methods because of an individual's dissatisfaction with those methods, which illustrates the critical need for contraceptive methods that enhance use by meeting the diverse needs of women and men throughout their reproductive lives. Having a variety of contraceptive methods available for widespread use that recognize and meet the needs of individuals with different ethnicities, cultures, and religious values, but adapt as the needs of individuals change over time would be ideal, and it is to this optimal situation that the Branch strives.

The CRHB uses a variety of funding mechanisms to promote contraceptive research and development (See Figure 1). New ideas are generated by the Cooperative Contraceptive Research Centers Program, by staff generation of research contracts for new contraceptive leads, through conferences, and by investigator-initiated grants. Selected new contraceptive leads move forward with assistance from one of the Branch's support contractors. For instance, the Chemical Synthesis and Peptide Synthesis Facilities prepare compounds for the Branch and for other extramural scientists involved in contraceptive research. The Biological Testing Facility studies biological activity, pharmacology, and toxicology of compounds of interest. The Contraceptive Clinical Trials Network conducts Phase I through Phase III trials of promising contraceptives developed from Branch-sponsored projects and from other investigators.

The Branch continues its efforts to develop new contraceptive methods for women. In addition, when the NICHD established strategic goals for *Reproductive Health in the 21st Century* in 2000, researchers concluded that a successful reproductive health agenda must include development of effective, safe, and acceptable contraceptive methods for men beyond those presently available (e.g., periodic abstinence, withdrawal, condoms, or vasectomy). Effective new methods for male fertility regulation would not only benefit men, but would also be a major contribution to women's health. In order to implement this strategic goal, the CRHB, in collaboration with the other two components of the CPR, initiated and restructured research

programs to encourage development of male contraceptives using a combination of basic, applied, clinical, and behavioral research.

The Department has supported contraceptive research and development activities since 1968, when the Secretary of the Department of Health, Education, and Welfare established the CPR at the NICHD, with the goal of developing new contraceptives using contracts and grants. Further support came in 1993, when congress passed legislation directing the NICHD to establish three extramural centers devoted to contraceptive research and development. The 1996 Amendment to the Public Health Service Act (Title X) reemphasized this goal. Congress continues to support the efforts of the CRHB in its appropriations and by highlighting contraceptive research and development as important to the NICHD's mission.

PROGRAM AREA 2: CONTRACEPTIVE AND REPRODUCTIVE EVALUATION

Within this program area, the goal of the CRHB is to expand contraceptive and reproductive evaluation, by:

- Conducting epidemiological, statistical, and clinical studies for post-marketing surveillance of drugs, devices, and procedures utilized for contraception and reproductive health
- Collecting and disseminating results of research on the effects of drugs, devices, and procedures utilized for contraception and reproductive health

These two objectives are temporally related; the first supports the conduct of research, the second ensures appropriate interpretation and distribution of research findings.

Traditionally, the CRHB has evaluated contraceptive methods through epidemiological studies and clinical trials. Although the contraceptive discovery and development activities of the Branch, discussed earlier, allow the detection of acute side effects, the clinical trials required for approval for U.S. marketing involve sample sizes that are too small and/or follow-up periods that are too short to detect less frequent events. Thus, the CRHB also supports Phase IV, or post-marketing studies of available contraceptive methods, devices, or drugs. Further, some associations between contraceptive methods and reproductive or other outcomes require larger populations, special populations, or longer observation periods than those presently required for marketing approval.

Specific examples of such research are outlined in the *Highlights from CRHB-Funded Research* section of this report, including research on the effects of hormonal contraceptives and postmenopausal hormone therapy on the risk of breast cancer.

PROGRAM AREA 3: PREVENTION OF HIV/AIDS AND OTHER STIS

The goal of the CRHB within this program area is to promote research on the prevention of HIV/AIDS and STIs and to increase understanding of gender-specific HIV issues by:

- Increasing understanding of the transmission, acquisition, and prevention of HIV/AIDS and STIs in the female genital tract
- Developing new microbicides, especially those with contraceptive activity
- Determining optimal formulations and dosages of microbicides
- Reviewing current models and developing new ones for investigating heterosexual HIV-infection mechanisms and prevention of HIV transmission
- Evaluating hormonal and barrier contraceptive methods for their effects in preventing or enhancing heterosexual HIV and STI transmission
- Evaluating the safety and efficacy of contraceptives and infertility treatments in HIV-positive women
- Evaluating the effect of gender (i.e., exogenous and endogenous steroid hormones) on HIV/AIDS disease

The NICHD's research program on HIV/AIDS and STIs includes activities central to the HIV prevention research endeavors of the National Institutes of Health (NIH). The HIV prevention research agenda of the NICHD focuses on preventing heterosexual and perinatal transmission of HIV/AIDS. Microbicides, defined as products designed for intravaginal application by women prior to intercourse, could offer a female-controlled alternative for preventing transmission of HIV and other STIs. Research on these substances is an important part of the Institute's overall prevention agenda.

Worldwide, as well as in the United States, HIV prevalence in women is increasing, with transmission during heterosexual intercourse as the primary means, globally, by which women become infected. HIV acquisition and progression must be considered in the context of sexual practices (i.e., vaginal cleansing), fertility regulation methods (e.g., contraceptives), and other STIs. Additionally, some aspects of HIV disease in women differ from features observed in men. For example, more rapid disease progression has been observed in HIV-infected women, and occurs at lower HIV viral loads than in men. As the absolute number and percentage of HIV-positive women increases, interest in prevention of heterosexual acquisition/transmission also increases.

The effect of endogenous and exogenous steroid hormones on risk of HIV acquisition and subsequent disease progression is unknown. In addition, incident cases of HIV occur overwhelmingly among women during their early reproductive years. Thus, understanding the role steroid contraceptives play in HIV acquisition, progression of disease, and transmission is critical. It is also important to determine if peri- or postmenopausal hormone therapy has any effect on HIV/AIDS. As HIV vaccine development advances, it will also be important to examine steroid contraceptives and hormonal therapies for possible influence on the immunogenicity of potential vaccines. More research on the possible interactions of antiretrovirals and exogenous steroid hormones will also be needed.

Encouragement and support for the NICHD program comes from many sources, among them:

- The fiscal year 2002 House Appropriations Committee Report and the fiscal year 2003 Senate Appropriations Committee Report urged the NIH (including NICHD) to continue implementing its strategic plan for microbicide research and development, and to accelerate and strengthen efforts to coordinate research among Institutes and with other federal agencies.
- The NIH Office of AIDS Research (OAR) has stated that microbicide development should be given as much attention as that placed on vaccine prevention strategies. The OAR has also created a special emphasis area for research on HIV in women and girls.

PROGRAM AREA 4: SELECTED REPRODUCTIVE AND GYNECOLOGIC HEALTH ISSUES

Within this program area, the goal of the CRHB is to advance research into selected reproductive and gynecologic health issues by:

- Sponsoring research efforts on reproductive health issues that have been either overlooked or under funded
- Focusing research efforts on gynecologic and reproductive health issues that are considered important to women's health, and on issues of minorities and aging as these relate to reproductive health within the purview of the CRHB

The Institute of Medicine (IOM) of the National Academy of Sciences noted a need for additional NIH research attention to obstetrics/gynecology research as early as 1992 in its report, *Strengthening Research in Academic OB/GYN Departments*. Further recommendations from congress, professional societies, and women affected by reproductive/gynecological disorders over the last decade have also led the NICHD to increase its research in this area.

Although the Institute has been among the major funding sources for research in obstetrics and gynecology, the CRHB recognizes that research on some gynecologic topics is still underfunded. For example, as many as 10 percent of women in the United States will undergo a major surgical procedure to correct urinary incontinence or pelvic prolapse. The NICHD has expanded its funding for research on female pelvic floor disorders, including pelvic prolapse, urinary and fecal incontinence, and other sensory and emptying abnormalities of the lower urinary and gastrointestinal tract. As the population in the United States ages, the need for treatments for these disorders will also increase. The fiscal year 2003 Senate Appropriations Committee encouraged the NICHD's efforts in developing a program in urogynecology, specifically its funding of tissue structure, epidemiology, urinary incontinence, and intervention programs. The Committee also encouraged the NICHD to include the effects of pregnancy on a women's chance for later urogynecologic problems in the *National Children's Study*, a longitudinal cohort study set to begin in 2005 that will follow mothers and their children from before birth to age 21.

In addition, the NICHD has increased its support for research into the etiology, diagnosis, treatment, and prevention of reproductive disorders. For instance, the CRHB has supported research on the mechanisms and treatments of abnormal uterine bleeding and the effects of peri- and postmenopausal hormone therapy. These topics are among the most common reasons

women seek gynecologic care, and the CRHB has extended its research program to encompass and address these aspects of reproductive health.

PROGRAM AREA 5: RESEARCH TRAINING

The goal of the CRHB within this program area is to promote training in areas of contraception and reproductive health that attract new investigators to the field by:

- Supporting training of obstetricians and gynecologists in epidemiology and clinical research to ensure future cadres of investigators in contraception and reproductive health
- Providing training for pharmacologists, biologists, and epidemiologists to promote future research in this field

The 1992 IOM report, *Strengthening Research in Academic OB/GYN Departments*, noted that few academic obstetricians and gynecologists received formal research training, which it called, "an important obstacle to successful applications for research funding." The IOM went on to recommend that: "NICHD program staff should exercise to the fullest extent possible their ability to target training support to expand the number of research training opportunities for physicians in OB/GYN."

A 1994 IOM report, *Careers in Clinical Research: Obstacles and Opportunities*, recommended that academic centers develop interdisciplinary programs to award advanced degrees in evaluative sciences related to clinical research. The CRHB has supported one such program, training obstetricians/gynecologists in epidemiology and clinical research since 1996, and has supported four additional programs since 2001. Support for research training of obstetricians and gynecologists in these areas is a CRHB priority.

HIGHLIGHTS FROM CRHB-FUNDED RESEARCH

CONTRACEPTIVE RESEARCH AND DEVELOPMENT

Cooperative Contraceptive Research Centers Program

Since 1993, congress has included language in its annual appropriations bill to fund three Contraceptive Research Centers that focus their efforts on research that may lead to new contraceptive products. Recognizing that the complexity of contraceptive research and development can severely limit progress achieved by individual investigators working alone, the NICHD funds these Centers through a specialized cooperative research center award mechanism (U54), in which there is substantial NIH scientific and programmatic involvement with the awardees during performance of the activity. Under this mechanism, the NICHD supports three Centers, composed of researchers and technical service core facilities that are interactively organized to conduct research for discovering and/or developing promising new leads in regulating fertility, as well as additional relevant projects. The focus of individual projects includes basic, preclinical, or clinical research, or a combination of these areas. The Centers also

serve as a national resource for career development of young scientists who elect to pursue research in fertility regulation. Funding for each of the Centers and related projects runs to 2007.

Each Center consists of three or more projects that are devoted to basic or clinical research on new contraceptives using a variety of approaches: inhibition of spermatogenesis via a number of possible mechanisms, including phosphodiesterase inhibitors, calcium-channel blockers, adherence junctions, and adhesion molecules; hormonal suppression of the hypothalamic-pituitary-gonadal axis in men or women; development of novel vaginal delivery systems for drugs that inhibit ovulation; and analysis of paracrine regulation of oocyte development by cumulus cells. The three Centers share common resources and research information throughout their five-year funding period. Emphasis on training opportunities within the Centers is also a priority. A description of selected Center projects appears below.

University of Washington
Principal Investigator (PI): William Bremner
Title: *Male Contraception Research Center Grant*
This new Center is conducting clinical studies on contraceptive methods for males, as well as basic research to identify new targets for fertility regulation in males. One important goal is to attract new fellows and support new investigators in male contraception research. Subproject 1 (PI: W. Bremner) proposes to conduct a clinical trial of new contraceptive agents in men. Subproject 2 (PI: R. Braun) is a basic research project designed to conduct genetic studies on the control of spermatogenesis in mice. Subproject 3 (PI: J. Beavo) is investigating the roles of phosphodiesterases and their inhibitors in the testis. Subproject 4 (PI: M. Griswold) examines the cell-specific patterns of gene expression and their control in the testis.

University of California, Davis
PI: Paul Primakoff
Title: *Center for Development of Anti-Sperm Contraceptives*
The focus of this Center is new drug development using promising targets that have demonstrated involvement in fertility regulation, as well as the continued search for new contraceptive targets. Subproject 1 (PI: P. Primakoff) is designed to screen for contraceptive agents to block sperm function in fertilization. Subproject 2 (PI: D. Myles) is exploring gamete surface metalloproteases as contraceptive targets. Subproject 3 (PI: H. Florman) investigates ion-channel-based anti-fertility agents in sperm.

The Population Council
PI: Regine Sitruk-Ware
Title: *Cooperative Contraceptive Research Center*
This Center is supporting all new subprojects because the successful projects developed during the previous funding cycle were transferred to commercial entities for final product development. Subproject 1 (PI: Y.Y. Tsong) is conducting studies to develop a vaginal ring that delivers a progesterone receptor modulator for contraception. Subproject 2 (PI: R. Sitruk-Ware) is examining the effectiveness of a Carraguard-levonorgestrel combination in providing dual protection against STIs and pregnancy.

Subproject 3 (PI: C.Y. Cheng) is investigating the possibility of developing contraceptive agents to affect cell junction dynamics that are specific to the testis.

Two additional, non-center grants were funded from the Request for Applications (RFAs) for the Cooperative Contraceptive Research Centers Program. The PIs for these two grants will serve as members of the Program's Steering Committee, and their research efforts will be integrated within the overall Program.

Jackson Laboratories
PI: John J. Eppig
Title: *Trapping Cumulus Products for Contraceptive Targeting*
This project explores the interactions of cumulus cells, which produce paracrine regulators that promote oocyte development. The project uses novel methodology (e.g., signal sequence trapping) to screen the cumulus cell library and identify specific membrane and secreted targets. The knowledge gained from these studies will provide new insight into cumulus-oocyte communication and will identify exciting new targets for regulation of fertility.

University of Virginia
PI: Kenneth Tung
Title: *Autoimmune Oophoritis: Consequences of Gamete Vaccines*
This project, to be carried out in experiments with animals, examines the factors that control development of autoimmune ovarian disease following immunization with certain gamete-specific antigens. The development of ovarian pathology appears to be dependent upon unknown factors within the B cell epitope and may manifest effects in progeny, rather than in the immunized animals. The knowledge gained from these studies is not only critical to the potential development of immunocontraception, but also has broader implications for understanding the etiology of autoimmune diseases in general.

Cooperative Research Program on Male Fertility Regulation

Developing contraceptives for males is among the goals of the NICHD strategic plan, *Reproductive Health in the 21st Century*. In order to implement that plan, the CRHB, in collaboration with the other Branches in the CPR, has initiated or restructured existing programs to encourage a spectrum of activities leading to development of male contraceptives, including a combination of basic, applied, and clinical research. These programs include the following:

- Redirection of the Contraceptive Development Research Centers, which focus on basic and clinical contraceptive research (see previous section), to include a number of projects devoted specifically to male contraception.
- Support of a Fertility Defect Phenotyping Program (currently at Baylor University and Northwestern University). Supervision of this Program resides in the Reproductive Sciences Branch of the CPR, and it is part of a collaborative effort involving the Male Fertility Regulation Cooperative Agreement described in the next bulleted item.
- Support of solicited Male Fertility Regulation Cooperative Agreements to elucidate novel contraceptive methods for males. Of the 33 applications that were reviewed, eight were

recommended for funding. The PIs will form a steering committee to foster communication among the participants, review progress within the individual projects, and make recommendations regarding future directions of the projects. The anticipated period of support for these agreements is 2003 through 2008. The investigators and projects included in this program are:

  - Cheng, CY; The Population Council, New York City, New York—Junction dynamics and male fertility regulation
  - Clapham, D; Children's Hospital, Boston, Massachusetts—Male contraception/CatSper 1,2 sperm-specific ion channels
  - Hinton, B; University of Virginia, Charlottesville, Virginia—C-Ros pathways as targets for contraceptive development
  - MacGregor, G; University of California, Irvine, California—A novel gene required for sertoli-spermatids adhesion
  - O'Brien, D; University of North Carolina, Chapel Hill, North Carolina—Novel sperm glycolytic enzymes as contraceptive targets
  - Platt, F; University of Oxford, Oxford, United Kingdom—Glycosphingolipids as targets for male contraception
  - Wang, PJ; University of Pennsylvania, Philadelphia, Pennsylvania—Regulation of spermiogenesis in mice
  - Xu, E; University of California, San Francisco, California—Functional genomic approach to male contraception

- Utilization of existing contracts for Chemical Synthesis and Peptide Synthesis Facilities to synthesize bulk quantities of drugs, under current Good Manufacturing Practices, for use in clinical trials. These contracts will assist in the conduct of translational research by scaling-up synthesis of specific male contraceptive agents that have been identified as candidates for clinical trials.
- Utilization of Biological Testing Facilities to conduct biological evaluation and toxicology testing prior to utilization of promising male agents in clinical trials approved by the U.S. Food and Drug Administration (FDA).
- Funding of clinical sites within the Contraceptive Clinical Trials Network that are capable of conducting Phase I, II, or III clinical trials in males. Sites have been selected and the contracts are currently in negotiation.

Contraceptive Clinical Trials Network (CCTN)

The CCTN has been in existence since 1996. It originally consisted of nine centers for female contraceptive research, as well as a Statistical and Clinical Coordinating Center. The CCTN utilizes the CRHB Scientific Advisory Committee, which is composed of outside experts in the fields of basic and clinical contraceptive research, pharmacology, and epidemiology. The CCTN contract was recently recompeted, and there are now 12 sites for female contraceptive research, and two sites for male contraceptive research. The clinical field centers were selected on the basis of their capacity to carry out Phase I, II, and III trials of oral, injectable, implantable, or topical contraceptive drugs and contraceptive devices. Each research site has, at a minimum, a qualified obstetrician/gynecologist (for the female-focused sites), or an andrologist/urologist (for the male-focused sites), as well as a study coordinator, data/research manager, and access to clinical facilities capable of recruiting subjects for Phase I and II trials, at both male- or female-focused sites, and for Phase III trials at the female-focused sites.

Two trials have been completed in the CCTN:

- A Phase I trial of four spermicides, with the most successful candidate scheduled to move into a Phase II/III trial in 2004
- A Phase II/III trial, limited to one center, which involved efficacy and breakage/slippage testing of a non-latex condom

Two clinical protocols are currently active in the original CCTN:

- A Phase II/III trial of contraceptive efficacy comparing the use of Buffergel or Gynol gel with a diaphragm—The Buffergel project, funded by the CRHB, is a Phase II/III trial of a new vaginal contraceptive whose mechanism of action is maintenance of the natural low pH level of the vagina by buffering the elevated pH of semen (Buffergel, Johns Hopkins University). Buffergel inactivates sperm by preventing the semen-induced rise in vaginal pH, which *in vivo* also inactivates multiple microorganisms including HIV, Herpes Simplex Virus (HSV)-1, HSV-2, *N. gonorrhoeae, Treponema pallidum, Hemophilus ducreyi,* Human Papillomavirus (HPV), *Chlamydia trachomatis*, and organisms associated with bacterial vaginosis. Unlike agents that contain detergents, Buffergel does not cause epithelial disruption, and is generally well tolerated by women and their partners. Previous research on this formulation demonstrated that the carbopol gel base is stable in the presence of 1-percent hydrogen peroxide, that lactobacilli remain viable, and that the compound does not adversely affect condom integrity. In the reconstituted CCTN, the project will be a contraceptive efficacy trial of another potential microbicide with contraceptive activity, C31G, as compared with an existing, marketed nonoxynol-9 (N-9) containing gel.
- A Phase II/III trial of CDB-2914, a selective progesterone receptor modulator (SPRM), for emergency contraception. Additional information on CDB-2914 appears later in this report.

Male Condoms

Until relatively recently, the latex male condom was the only condom product available to U.S. couples; now, however, non-latex condoms for both men and women are available on the U.S. market. In part, this availability reflects the fact that a measurable percentage of individuals are allergic to latex, and, therefore, cannot use latex condoms. Although the polyurethane condom was being marketed under the FDA provision for "substantial equivalence," no clinical trial had published a comparison of its performance to the latex condom until the Contraceptive Development Branch (now the CRHB) funded such a study. In this crossover study, 360 couples were randomly assigned to use three Avanti™ (polyester polyurethane) condoms, during three sequential acts of intercourse, either before or after using three latex condoms. Although the breakage rate of the polyurethane condom was significantly higher than that of the latex condom, nearly half of the users nonetheless preferred the polyurethane condom. This outcome demonstrated that the polyurethane condom could provide an option for couples that cannot or would not use latex condoms.

In a subsequent CRHB-supported study, 805 monogamous couples were randomized to use either polyurethane male condoms, or standard latex condoms for six months. Couples recorded the frequency of intercourse and condom use, breakage, and slippage throughout the trial in diaries, and in detailed reports on the first five uses. Reported clinical failure rates (including breakage and slippage that occurred during intercourse or withdrawal) in this study also differed

significantly: 8.5 percent for the polyurethane condom, and 1.6 percent for the latex condom. In contrast to the earlier study, however, male participants were more satisfied with the latex than with the non-latex condom. In fact, latex condom users were significantly less likely to drop out of the study for condom-related reasons than were polyurethane condom users. The six-month pregnancy rates for the two groups during "typical use" did not differ significantly: 4.8 percent and 6.3 percent for the polyurethane and latex condom users, respectively (after adjustment for use of emergency contraception). Pregnancy rates during "consistent use" over six completed menstrual cycles also did not differ significantly: 2.4 percent for the polyurethane condom, and 1.1 percent for the latex condom group (after adjustment for use of emergency contraception, although results were similar without such adjustment). Thus, the polyurethane and latex male condoms tested in this study gave equivalent levels of contraceptive protection.

The CRHB subsequently supported a randomized, double-masked trial that compared the performance of another non-latex condom, Tactylon™, composed of styrene ethylene butylene styrene, to that of two different latex condoms. The 830 couples, who were assigned to use either the Tactylon™ condom or one of two commercially available latex condoms for six months, were required to record their frequency of intercourse, condom use, condom breakage and slippage, and genital discomfort in detailed reports on the first five condom uses and in diaries throughout the trial.

Even among the highly motivated couples willing to participate in this clinical trial, couples reported failing to follow one or more instructions for correct condom use in nearly one-third of the events. During the first five uses, the non-latex condom had a higher frequency of breakage or slippage during intercourse or withdrawal (4.0 percent) than did latex condoms (1.3 percent); the breakage rate for the non-latex condom was about eight times that of latex condoms. Although the six-cycle "typical-use" pregnancy rate did not differ significantly between users of non-latex (10.8 percent) and latex condoms (6.4 percent), the six-cycle "consistent-use" pregnancy rate was higher for non-latex users (4.9 percent) than for latex condom users (1.0 percent. These data are consistent with a difference in efficacy between the latex and non-latex condoms. The results also support the use of latex condoms and, for individuals who cannot or will not to use latex condoms, the use of non-latex condoms for prevention of pregnancy and disease.

Three Phase I and one Phase II grants, which relate to condoms, have been completed under the Small Business Innovative Research Program since the last CRHB report to the NACHHD Council. Two projects demonstrated the safety and effectiveness of a condom applicator designed to test condom integrity and to make it easier to put condoms on properly. This product was approved by the FDA in November 2003 and is expected to be marketed in the spring of 2004. Another grant supported tests of the safety and effectiveness of a condom designed for use by men with erectile dysfunction. The other grant supported the development and testing of a prototype optical testing technology designed to provide more information than the standard condom testing techniques currently available.

Male Hormonal Methods

The CRHB sponsored research that led to the following important developments in hormonal steroids for male contraception.

Dimethandrolone Undecanoate

In the search for new androgenic steroids with melting points high enough to permit formulation as aqueous microcrystalline suspensions, the CRHB synthesized and evaluated the biological properties of several esters of 7 alpha, 11 beta-dimethyl-19-nortestosterone (dimethandrolone) resulting in domestic and foreign patent applications. Not only do some of these esters exhibit prolonged androgenic activity following parenteral administration in aqueous suspensions, but they also possess potent oral activity.

Single subcutaneous injections of 1.2 mg dimethandrolone in rats induced and maintained increases in size of sex accessory structures (the classical measure of androgenic activity) for 14 weeks. The initial elevations in serum levels of free alcohol (dimethandrolone) dropped over the first four or five weeks, and then remained steady until the end of the 14-week study. In addition, small elevations in prostate-specific antigen could be induced in orchidectomized rhesus monkeys, which indicates that these compounds are also active in primates. Several esters showed oral androgenic activity greater than that of methyltestosterone, the only oral androgen currently available in the United States. Methyltestosterone, like other orally active 17-alkylated steroids, induces hepatotoxicity, which limits chronic administration.

Esters of dimethandrolone are being developed for use in male hypogonadism, for use as replacement therapy in aging men (andropause) and possibly women (menopause), and for use as the add-back androgen necessary in hormonal methods of male contraception. Available bulk quantities of dimethandrolone are sufficient to undertake preclinical drug safety studies up to and including Phase II clinical trials.

MENT™

The development of MENT™ *(7 alpha-methyl-19-nortestosterone)* for male contraception and for male hormonal therapies holds promise. This synthetic androgen was developed by the Upjohn Company and was subsequently provided to the Population Council, with partial grant support for additional studies from the CRHB. The compound is considerably more potent than testosterone in its effects on muscle and the pituitary gland, while its stimulatory effect on the prostate is less than that of other testosterone derivatives. Because MENT™ has a high binding affinity to androgen receptors, but does not undergo enzymatic 5-alpha-reduction in the prostate, it is believed to cause less stimulation of the prostate than observed with testosterone. In contrast to MENT™, testosterone is 5-alpha-reduced to dihydro-testosterone, an androgen with higher affinity for androgen receptors and greater potency in stimulating growth of the prostate. The Population Council has developed a relationship with Schering AG to continue development and marketing of MENT™.

Levonorgestrel Butanoate (LB)

A collaborative effort between the Special Programme of Research, Development, and Research Training in Human Reproduction at the World Health Organization (WHO) and the NICHD resulted in the discovery of LB, an ester of levonorgestrel, which is a synthetic progestational

agent that is widely employed in progestin-only and combination (with estrogen) oral contraceptives. LB was tested at the Biological Testing Facility, where its potent long-term progestational activity was discovered. This drug has been extensively studied in rodents and primates, in efforts that included completion of a one-year toxicology study, and a pharmacokinetic study to support Phase I/II clinical investigation of the drug as a long-acting injectable contraceptive for women. In addition, the free alcohol moiety, levonorgestrel, has been successfully employed in oral form in combination with a supplemental androgen by intramuscular injection, often with testosterone enanthate, in experimental studies to induce azoospermia or oligospermia in normal men. Thus, the foundation existed for the use of LB in aqueous microcrystalline suspension as a sustained source of active steroid. Formulation studies are in progress to develop a stable and clinically acceptable aqueous suspension.

Indenopyridine

The CRHB continues to study the anti-spermatogenic activity of a series of indenopyridines (nitrogen heterocycles). A single oral dose of 2.5 mg/kg of the lead compound is sufficient to produce irreversible infertility in rats. Pharmacological studies are now directed at identifying the mechanism of action of indenopyridines, which could elucidate mechanisms to reverse this infertility effect on the germinal epithelium. These efforts include studies of Sertoli cell function in the production of inhibin, histocytological studies of Sertoli cells, and examination of the effects of pretreatment with gonadropin-releasing hormone (GnRH) agonists and antagonists. Leydig cell function does not seem to be impaired by indenopyridines; thus, no supplemental androgen therapy would be required if an indenopyridine was used as a male contraceptive.

This work has already identified the active and inactive isomers of the lead candidate indenopyridine. The active enantiomer appears to be more than twice as potent as the racemic mixture and, at relatively low dose levels, exhibits some azoospermia reversibility. Ultrastructural studies of Sertoli cells from treated rats have been undertaken, using transmission electron microscopy, to identify the initial locus of injury. Alterations in Sertoli cell cytoarchitecture can be observed within three hours of a single oral dose of the drug.

Studies of the lead candidate indenopyridine in rats also indicate that testosterone is obligatory for induction of irreversible anti-spermatogenic activity. Anti-fertility activity of this indenopyridine is reversible in immature rats and in adult animals pretreated with a GnRH antagonist to suppress the hypothalamic-hypophyseal-gonadal axis. Studies of this phenomenon in primates are under way. In addition, because Inhibin B levels are severely suppressed both *in vivo* and *in vitro* (Sertoli cell cultures) by this nitrogen heterocycle, Inhibin B appears to be a good marker of anti-fertility activity in this situation.

Bioisosteres of Lonidamine

In vitro binding assays of testis-specific adenylate cyclase and CDK2/Cyclin A1 have been used to identify a class of novel spermatogenesis inhibitors derived from lonidamine. This discovery could be critical in the development of new male contraceptives. Preliminary screening results of a newly synthesized, 7-azaindazolecarboxylic acid demonstrate that it possesses anti-spermatogenic activity in the male rat. Research supported by the CRHB found that this lonidamine analog has anti-spermatogenic activity after oral administration in the rat and is devoid of mutagenic activity by the Ames test.

Acyline

Acyline is one of the most potent and promising GnRH antagonists for reproductive and contraceptive use in humans. This peptide was originally synthesized and patented by the Salk Institute for Biological Studies with NICHD funding. Structural modifications of GnRH made by substituting natural amino acids with unnatural amino acids (e.g., D-amino acids with unnatural L-amino acids) enhanced potency and reduced concomitant histamine release to a minimum. Early clinical studies in men found that acyline, given as a single subcutaneous dose of 300 ug/kg, suppressed testosterone levels for two weeks without discernible side effects. Currently, the University of Washington and Massachusetts General Hospital are undertaking Phase I clinical trials of acyline in healthy male volunteers.

To minimize injections, a long-acting and/or slow-release formulation of acyline is necessary for broad clinical use. Structural modifications of acyline and its analogs have already produced several antagonists that are as active as acyline, but with fewer gelling problems. For instance, one modification puts a polyethylene glycol moiety at positions 5 and 6 in the formulation of acyline. Investigation of a slow-release formulation that uses polylactide-coglycolide beads is also being tested by Newport Scientific, Inc. Planning is under way to conduct Phase II trials.

Female Hormonal Methods

Emergency Contraception

CDB-2914 is a synthetic selective progesterone receptor modulator (SPRM) that binds to the progesterone receptor with relatively high affinity, yet lacks progestational activity. It is reasonable to project that this class of compounds may have promise for use in postcoital contraception, in treatment for uterine fibroids and endometriosis, in treatment of breast cancer and gliomas, and in a variety of other clinical uses, including cervical ripening for induction of labor.

Three Phase I clinical studies of CDB-2914 have been completed to date: an initial safety study in normally cycling women (mid-luteal phase administration), and two additional studies to determine the effect of the menstrual cycle (follicular and luteal phases) on the action of CDB-2914, vis-à-vis ovulation and endometrial maturation. No safety problems were observed with the administration of a single dose up to 200 mg. A Phase II/III trial of CDB-2914 is now under way to determine efficacy in preventing pregnancy when used within 72 hours of unprotected intercourse. Preliminary results from the trial demonstrate that a single 50 mg dose of CDB-2914 is as effective as the standard levonorgestrel regimen for postcoital contraception. Studies in monkeys have indicated that micronization of the drug increases its bioavailability, as measured by serum levels after oral dosing. Based on the demonstration of different bioavailability, the ongoing Phase II/III trial was expanded to include a dose comparison of 10 mg micronized versus 50 mg unmicronized CDB-2914.

New SPRMs

Domestic and foreign patent applications have been filed for a series of 21-substituted analogs of CDB-2914. These compounds exhibit greater tissue selectivity than CDB-2914 or mifepristone, as well as reduced anti-glucocorticoid activity. These features, in turn, should permit chronic administration at dose levels sufficient for therapeutic applications in the absence of elevated cortisol levels. After availability of these compounds for commercial development was

advertised, a small pharmaceutical company negotiated a license for their further development through the NIH Office of Technology Transfer. The licensee is exploring the potential use of these compounds for treatment of uterine fibroids, endometriosis, and breast cancer.

In addition, researchers found that one compound from the second generation of SPRMs, called CDB-4124, had three times the anti-progestational activity of CDB-2914, with reduced anti-glucocorticoid activity. The CRHB's Synthetic Chemical Facility contractor successfully accomplished the process development chemistry for this new class of compounds. Patent applications for both the composition of matter and the production process have been submitted in the United States and internationally. Subsequent bulk production of CDB-4124 under current Good Manufacturing Practices starting from commercially available 17 beta-cyano-17alpha-hydroxyestra-4,9-dien-3-one has produced 900 grams of the substance at greater than 99 percent purity. The Drug Master File has been filed with the FDA.

New Estrogens

One facet of oral contraceptive (OC) technology that has received little attention over the last three decades is the development of new, orally active estrogens with better pharmacologic profiles. Specifically, research seeks estrogens that have fewer side effects than those associated with the currently available estrogens, such as ethynylestradiol and mestranol, and include, notably, nausea, vomiting, alterations in liver function and histopathology, and clotting disorders. Some clinicians have suggested that the presence of the 17-ethynyl moiety, which protects the steroid from rapid metabolism by the liver (the so-called "first-pass" effect) and thus confers oral activity, is also responsible for many of the side effects observed with these drugs.

In an effort to develop nonethynylated estrogens, researchers synthesized a series of estradiol nitrate esters, many of which exhibit estrogenic activity in rats and rhesus monkeys in both oral and/or subcutaneous administration. Measuring increases in the uterine weight of immature rats as an endpoint, the most potent compound of this series, 7 alpha-methyl estradiol, 11 beta-nitrate ester (CDB-1357), was more than 14 times as potent as ethynylestradiol; it was 40 times as potent in the rat postcoital test when administered orally. However, following oral administration in ovariectomized rhesus monkeys, this compound was found to be less than half as active as ethynylestradiol in inducing estrogen withdrawal bleeding, and blood levels of CDB-1357 were lower than anticipated when compared with levels for estradiol. Since the compound was highly active in inducing estrogen withdrawal bleeding after subcutaneous administration in monkeys, one can speculate that either rapid metabolism due to the "first-pass" effect and/or poor absorption were responsible for the reduced activity seen after oral administration in primates. Indeed, all of the nitrate esters of estradiol, which seemed more potent than ethynylestradiol after oral administration in the rat, were less active when given to monkeys. This reduction in potency could be more than offset by an increase in dose, if the nitrate esters induced fewer side effects; however, the potential for reduction in side effects has not yet been demonstrated in animal studies.

Notwithstanding the findings summarized above, studies have identified several good candidates in this series of estradiol nitrate esters. However, it seems that their superiority to ethynylestradiol or its methyl ether as the estrogenic component of OC tablets will depend upon

clinical and histopathological findings from toxicity studies in animals and/or in clinical observations in Phase I and II studies in humans.

Biological Testing Facility

Under contract with the CRHB, the Biological Testing Facility undertakes more than 150 screens, assays, safety tests, and analytical procedures for the evaluation of new drugs, formulations, and delivery systems. This Facility screens submissions of drugs for classical endocrine and anti-fertility activity and establishes potency ratios for those that exhibit significant effects. It has also developed methods for determining the duration of hormonal activity following oral, subcutaneous, or transdermal administration. The work done by the Biological Testing Facility allows researchers to assess the potential clinical utility of new compounds and formulations.

In recent years, this Facility has extended its capabilities to include development of radioimmunoassays (RIAs) for proteins and steroid hormones including generation, harvesting, and characterization of antibodies, iodination of tracers, and validation of the assay procedure. These processes permit researchers to determine alterations in endogenous hormone levels, as well as to conduct pharmacokinetic studies required by the FDA for new drug applications. The tests are also essential for determining the best clinical formulations for each route of administration.

The Biological Testing Facility has developed a procedure for evaluating of relative binding affinities for the receptors of: progesterone (rabbit uterus), estrogen (rat and rabbit uterus), glucocorticoid (rat thymus), and androgen (rat ventral prostate receptors). This development was undertaken because of the wide variation in relative binding affinities frequently reported from different laboratories. As a result, researchers are now able to test a broad spectrum of compounds within a standardized testing system.

Historically, the rabbit vaginal irritation test has been the standard used to evaluate formulations of spermicides and antimicrobials and this test is often done under Good Laboratory Practice guidelines, so that the results may be submitted to the FDA in support of an investigational new drug to initiate clinical investigation. In this test, a board-certified pathologist performs both gross and microscopic pathology. New compounds and formulations must pass the test before clinical work can begin.

In addition, the Biological Testing Facility recently broadened its high-performance liquid chromatography (HPLC) capabilities to include analysis of specific steroids and their putative metabolites. This expansion will permit stability studies of drugs that are scheduled for toxicology testing and permit metabolic studies, where metabolites have already been identified. The Facility also undertakes short-term toxicology studies (up to six months) in rats and rabbits, using consultants for necropsy, gross and microscopic pathology, clinical chemistries, urinalysis, and hematology.

Chemical Synthesis Facility

The Chemical Synthesis Facility provides the Biological Testing Facility, the Peptide Synthesis Facility, and extramural scientists with drugs, chemicals, chemical intermediates, steroids, and optically pure and/or resolved unnatural amino acids, which are either commercially unavailable or unduly expensive to purchase for contraceptive research and development.

During the past four years, the Facility synthesized gram quantities of a number of steroids, steroid heptans, putative metabolites of CDB-2914 and CDB-4124, unnatural optically active amino acids, heterocycles (i.e., indenopyridines, carbocycles), and other non-steroids that were evaluated for contraceptive activity. Bulk production of several steroids in one-kilogram quantities, including CDB- 4124 and CDB-4521, under current Good Manufacturing Practices was necessary for toxicology studies and for preclinical and clinical evaluation. In addition, the Facility prepared radiolabeled steroids and indenopyridines for RIAs and metabolism studies with specific activity of approximately 60 to approximately 80 Ci/mmol. The Facility has conducted HPLC, ^{1}H, and ^{13}H nuclear magnetic resonance, Fourier-transform infrared, and mass spectral analyses for samples that came from other laboratories, including micronized CDB-2914 and 11 beta-[4-(N,N-dimethylamino)phenyl]-17 beta-hydroxy-17 alpha-(3-hydroxy-1-propynyl)-estra-4,9-dien-3-one (CDB-4163A).

Peptide Synthesis Facility

The Peptide Synthesis Facility continues to provide bulk non-Good Manufacturing Practice-grade acyline, a potent GnRH antagonist, to qualified investigators, as well as a clinical formulation (Good Manufacturing Practice-grade), which requires simple reconstitution with sterile water, for studies with human subjects. The Facility also produces new peptides for evaluation by the Biological Testing Facility and for investigators who are interested in gonadotropin suppression and regulation of the gene that encodes both a new class of steroid/sterol sulfotransferases, and zona pellucida glycoprotein for immunocontraception.

Acyline has been structurally modified to render greater water solubility without gelling, and to increase biological activity to four weeks or longer. So far, the Facility has completed synthesis of 38 analogs of acyline, and anti-ovulatory assays are now in progress. Most of the analogs tested to date either retained the same potency as acyline, or showed less gelling propensity in water. Several analogs were modified by substitution of a polyethylene glycol moiety at positions 5 and 6, resulting in improved solubility. Among them, CDB-4676 showed anti-ovulatory activity at 8 micrograms per rat. Further modification with polyethylene glycol moiety may result in better GnRH antagonism than exists for acyline.

Newport Scientific, Inc., subcontractor to the Peptide Synthesis Facility, has also initiated studies of sustained-release formulations of acyline. In the initial approach, researchers will prepare microcapsules (beads) of acyline using polylactic-glycolate polymer. The Facility has submitted the following to the FDA Drug Master File: Ames test results, as well as Volume 7-Study of acyline (CDB-3883F) in In Vitro *Test for Chemical Induction of Micronucleated Polychromatic Erythrocytes in Mouse Bone Marrow Cells.*

CONTRACEPTIVE AND REPRODUCTIVE EVALUATION

Contraceptive Steroid Hormones and Risk of Breast Cancer

Although the relationship between OCs and breast cancer has been investigated extensively for more than two decades, the association between OC use, including hormonal use for other than contraceptive purposes (e.g., therapy for other gynecologic conditions, postmenopausal hormone therapy), and lifetime risk of breast cancer has only recently been evaluated. Women now in the ages at highest risk for breast cancer (middle age and older) are the first cohort likely to have taken OCs early in life in significant proportions and may have taken the highest dose pills for the longest period of time.

In fiscal year 2003, investigators published results from the NICHD Women's Contraceptive and Reproductive Experiences (Women's CARE) Study, a retrospective case-control study of approximately 5,000 women, ages 35 to 64. Women's CARE was designed to study the associations between lifetime hormone use and breast cancer risk with primary objectives to:

- Compare breast cancer risk of OC users to never-users;
- Evaluate the impact of various patterns of OC use to breast cancer risk;
- Examine the use of OCs in different time of life on breast cancer risk;
- Elucidate the role of formulation, dose, and type of estrogens/progestins; and
- Assess postmenopausal hormone therapy in modifying the impact of OC use on breast cancer risk.

Secondary objectives included the identification of breast cancer risks other than OC use (including the effect of race), and the examination of biologic specimens (i.e., blood and tumor tissue). The study relied on contracts with five academic clinical sites and an interagency agreement for data coordination support with the CDC.

The relative risk of breast cancer was not elevated for women who were currently using OCs (relative risk: 1.0; 95 percent confidence interval: 08-1.3), or for those who had previously used them (relative risk: 0.9; 95 percent confidence interval: 0.8-1.0). The relative risk did not increase with longer periods of use or with higher doses of estrogen, and the results were similar among white and African American women. Use of OCs by women with a family history of breast cancer was not associated with an increased risk of breast cancer, nor was there any association of increased breast cancer risk with the initiation of OC use at a young age.

Postmenopausal Hormone Therapy and Risk of Breast Cancer

The safety and efficacy of postmenopausal hormone therapy (also called hormone replacement therapy, HRT, and menopausal hormone therapy) have recently become of greater public interest because of results reported from one arm of the NIH Women's Health Initiative (WHI) Study, which indicated an increased risk of cardiovascular disease and breast cancer among women using estrogen plus progestin (E+P). The WHI results for breast cancer risk posed by this therapy were generally consistent with those from the NICHD Women's CARE Study. The WHI found, however, that continuous (E+P) among those who had been on the therapy for five or more years was associated with an increased breast cancer risk (odds ratio: 1.54; 95 percent confidence interval: 1.10-2.17). Additionally, a statistically significant trend of increasing

breast cancer risk with longer duration of continuous E+P was observed among current users (P=0.01), when compared with those who were never on postmenopausal hormone therapy. There were no positive associations between breast cancer risk and other postmenopausal hormone therapy regimens. However, some evidence did suggest that after women discontinued therapy, their breast cancer risk declined to control levels.

Efficacy Trial of Spermicidal Agents

The only spermicidal agent presently approved for marketing as a vaginal product in the United States is N-9. Originally approved in 1976, this compound has recently been subjected to increased scrutiny relative to both efficacy and safety. In 1997, the FDA issued a Notice of Proposed Rule Making, a proposal to require each N-9 spermicide marketed in the United States to undergo extensive new clinical testing to retain approval for U.S. marketing. It appeared unlikely, however, that the spermicide manufacturers would be able to afford such clinical testing, which was then estimated to cost a minimum of $1 million per product. Recognizing that spermicides represent a "niche" market, that is, for customers who would otherwise lack an acceptable contraceptive method, the NICHD planned a comparative trial of N-9 products. In 1997, the FDA's Advisory Committees recommended to the agency that it postpone further action on the Notice until the NICHD's study results were available.

In fiscal year 2003, the Efficacy Trial of Spermicidal Agents was completed. The study was a randomized trial of five N-9 products designed to estimate their efficacy and safety over six to seven months of use. The trial compared products to determine whether product efficacy or safety was influenced by either the amount of N-9 per use (52.5 mg, 100 mg, or 150 mg); or the type of formulation (gel, film, or suppository). The five products tested included a gel at each of three dose levels, and two non-gel products at 100 mg per dose (film and suppository).
The study successfully recruited 1536 women. The statistical analysis of primary outcomes has been completed. A manuscript presenting and discussing six-month pregnancy rates has been accepted for publication in early 2004. The six-month pregnancy rates, using the life-table method, showed no difference in failure (pregnancy) rates by formulation (gel, film, or suppository), but did show a dose-related statistically significant difference among gel products. There were no differences in safety (measured by reported serious adverse events) observed among the products tested. These results will be considered by the FDA in determining future regulatory requirements for clinical trials of vaginal products. Future analyses from this study will consider compliance, loss-to-follow-up, colposcopic findings, and effects on vaginal microflora.

Vasectomy and Prostate Cancer

In the early 1990s, some studies were published suggesting that vasectomy might increase the risk of prostate cancer. In response, the CRHB supported a large, national population-based case-control study of this issue in New Zealand, which was well suited to such a study because of a particularly high prevalence of both vasectomy and prostate cancer. This study had 99 percent statistical power to detect a 50 percent or greater increase in risk. After studying 923 new cases of prostate cancer and 1,224 age-matched controls, the investigators found no association between prostate cancer and vasectomy (relative risk: 0.92; 95 percent confidence interval: 0.75-1.14). The analysis took into account time since vasectomy, social class, geographic region, religious affiliation, and family history of prostate cancer. The authors

concluded that vasectomy did not increase the risk of prostate cancer, up through at least 25 years after the procedure, a finding consistent with those of other studies in recent years.

Depo-Medroxyprogesterone Acetate (DMPA) Use and Bone Mineral Density in Young Women

DMPA is an injectable contraceptive popular among American women. The CRHB currently supports five studies of DMPA's effect on bone mineral density with participants in a wide range of ages.

Early results indicate that DMPA use decreases bone density in a matter of months, which might lead to an increased risk of osteoporosis in later life. There was also a correlation between long-term use and greater bone density loss. Although substantial recovery of bone mineral density has been reported after discontinuing DMPA in older women, bone mineral densities were not fully recovered among 18- to 21-year-olds up to at least two-and-a-half years after stopping DMPA use. Further results from this study, and the others still under way, are expected to shed more light on this issue.

Body Weight and OC Failure

Among women using reversible birth control methods in the United States, approximately 50 percent use OCs. Among OC users, 500,000 pregnancies occur annually and are routinely attributed to noncompliance (failure to use the method), rather than to method failure.

Currently, no recommendations indicate the need to take weight or body mass index into consideration when prescribing OCs. A CRHB-supported retrospective cohort study found that women in the highest quartile for weight, after controlling for parity, had a significantly greater risk of OC failure than did women of lighter weight (relative risk: 1.6; 95 percent confidence interval: 1.1-2.4). This risk persisted after estrogen dosage, parity, race, religion, and menstrual cycle regularity were accounted for. The mechanism of observed reduction in OC efficacy among obese women is unknown, but could be due to deposition of hormones in adipose tissue; or, it might reflect an altered basal metabolic rate that occurs with increasing weight. These results suggest that body weight should be a consideration in prescribing OCs to women.

Semen Biomarkers

Tests of condom failure need to be more sensitive and faster than the traditional measurements of incident pregnancies, visual condom inspection, or permeability testing after use. Accordingly, the NICHD supported research to determine which of several semen components was suited to serve as a biomarker of semen exposure in vaginal fluids. This study found that prostate-specific antigen was the most useful of the three biomarkers tested for suitability. Thus, condom failure and vaginal exposure to semen can now be accurately detected by biochemical testing of vaginal fluids.

Another study examined the usefulness of prostate-specific antigen measurements when using condoms with known puncture size. All 24 vaginal samples collected immediately after unprotected intercourse tested positive for prostate-specific antigen; none of the 90 vaginal samples collected more than 24 hours after intercourse tested positive for prostate-specific antigen. Excluding uses where the condom had failed, prostate-specific antigen was detected in

2 percent (1/47) of the postcoital vaginal samples collected after use of intact condoms and in 41 percent (14/34) of the samples collected after use of condoms with known 1 millimeter punctures. These results support the possibility of routinely using prostate-specific antigen as a semen biomarker in clinical trials of physical barrier methods.

Another study sought to determine the usefulness of semen biomarkers to quantitate vaginal semen exposure due to condom failure. Couples collected a baseline sample of ejaculate from the inside of the first study condom they used and were asked to collect a postcoital vaginal sample whenever a study condom broke or slipped off during intercourse. All samples were tested for prostate-specific antigen and were inspected microscopically for the presence of sperm. Results indicated that 68 baseline ejaculate samples collected from the inside of the first study condom, by couples that subsequently experienced a condom failure, averaged 13.4 micrograms prostate-specific antigen per swab; 79 percent of these samples averaged one or more sperm per high power field (hpf). In addition, 79 postcoital vaginal samples obtained after a condom break averaged 5.7 micrograms prostate-specific antigen per swab, and only 38 percent averaged one or more sperm per hpf. These results document a significant reduction (approximately 50 percent) in vaginal semen exposure among broken condom users compared to intact condom ejaculate. Although 17 vaginal samples obtained after condom slip-off averaged 2.5 micrograms prostate-specific antigen per swab, none of these samples averaged one or more sperm per hpf. Results indicated a highly significant 80 percent reduction in semen exposure with condom use even if it was not "perfect" use when compared to baseline levels. These results also suggest that, even if a condom fails, it still reduces the risk of pregnancy and, theoretically, the transmission of STIs when compared to unprotected intercourse.

Evaluation of Sterilization Methods

The Collaborative Review of Sterilization (CREST) study was conducted by the Centers for Disease Control and Prevention (CDC) with partial support from the NICHD. This study, which spanned 1978 to 1994, followed 11,232 women at 15 medical centers, in nine U.S. cities for up to 14 years after sterilization. It is the largest longitudinal study of U.S. women who underwent tubal sterilization (commonly known as tubal ligation) to date.

Since the CRHB's last report to the NACHHD Council, the CREST study reported that laparoscopic sterilization was a safe procedure and rarely resulted in serious morbidity. For example, complication rates for interval sterilization (i.e., not done shortly after delivery) were less than 2 percent for each of the four major methods of tubal occlusion, with no significant differences among them. Of the 9,475 interval sterilization procedures studied, no deaths occurred, and only one life-threatening event took place.

With regard to effectiveness, the five-year cumulative probability of pregnancy after bipolar coagulation was very low (12.9 cases per 1,000 procedures) when three or more sites of the fallopian tube were coagulated. Long-term failure rates after silicone rubber-band and spring-clip applications were less than one percent, which demonstrated that the procedures could be as effective as other laparoscopic sterilization methods. Although low overall, pregnancy risk in the CREST study varied widely by various clinical and demographic characteristics, particularly study site, which reflected extent of experience with the procedure. For example, site-specific cumulative pregnancy rates ranged from 0.0 to 42.5 (at 10 years) per

1,000 silicone rubber-band applications, and from 7.1 to 78.0 (at five years) per 1,000 spring-clip applications.

The CREST study found that women who underwent tubal sterilization were not at greater risk of menstrual abnormalities, thereby resolving the decades-old debate over the existence of what was known as "post-tubal ligation syndrome."

The study also examined trends in the desire for and completion of sterilization reversal. Among women who were 18 to 24 at the time of sterilization, the cumulative probability of asking about sterilization reversal within 14 years was 40 percent, compared to 14 percent among all women combined. Additionally, women who were 18 to 30 years old at sterilization were almost eight times as likely as older women to actually obtain reversal, with an overall cumulative probability of 1.1 percent. No difference was seen in the probability of a woman expressing regret about her sterilization, and that of a woman regretting her husband's vasectomy (7 percent and 6 percent after five years, respectively). However, women who reported substantial conflict with their husbands before vasectomy or tubal sterilization were significantly more likely to request reversal than women who did not report such conflict.

The CREST study's most recent paper reported that interval tubal ligation was unlikely to result in changed sexual interest or pleasure. However, among those who did experience such change, the majority experienced a positive change.

The Cochrane Collaboration

The CRHB makes use of an international network of medical and scientific organizations that perform ongoing systematic reviews of randomized, controlled clinical trials on specific medical interventions. Known as the Cochrane Collaboration, this network provides clinicians with up-to-date and valid information for decision making, thus reducing the lag time in transfer to clinical practice of scientific knowledge from individual randomized trials. Most of the major areas of medicine are included in one of the 50 review groups; the review reports are made widely accessible through the Cochrane Library and are also available on disk, CD-ROM, and via the Internet.

At present, the CRHB is supporting the development and publication of a book compiling all the Cochrane Collaboration Fertility Regulation Reviews. It is expected that this support will allow the Collaboration to produce approximately three to four reviews annually, and that the reviews will be made available on the Internet. These reviews could markedly enhance decision making by practitioners in the field. In addition, the development of this database will assist the CRHB in identifying gaps in knowledge and will contribute to defining the Branch's future research agenda.

Funding from CRHB also allows Family Health International to contribute to the Cochrane Fertility Regulation Review Group, based in Leiden, the Netherlands. The Fertility Regulation Review Group coordinates worldwide efforts to identify, analyze, and disseminate the scientific evidence on effective family planning in easily understood format. To date, Family Health International has completed and published nine reviews in the Cochrane Library, six of which were also published in peer-reviewed journals. The reviews evaluated different contraceptive

methods, including the sponge versus diaphragm, the cervical cap versus the diaphragm, the diaphragm alone versus the diaphragm with spermicides, biphasic versus monophasic OCs, and biphasic versus triphasic OCs. Completed reviews have also examined antibiotic prophylaxis for intrauterine contraceptive device insertion and immediate post-abortal and immediate post-partum insertion of intrauterine devices.

In addition, 12 Cochrane review topics have been registered and are currently in progress:

- 20 mcg versus >20 mcg estrogen OCs;
- Combined OC pills for treatment of acne vulgaris;
- Combination hormonal contraceptive use: effects on body weight;
- Expectant care versus surgical treatment for miscarriage;
- Hormonal contraception during lactation;
- Non-latex versus latex male condoms for contraception;
- Scalpel versus no-scalpel incision for vasectomy;
- Skin patch and vaginal ring versus combined OCs for contraception;
- Strategies to improve compliance and acceptability of hormonal methods of contraception;
- Strategies to increase concurrent barrier use among women using OCs;
- Triphasic versus monophasic OCs for contraception; and
- Vas occlusion techniques for male sterilization.

Progestins and Endometrial Bleeding

For more than 20 years, the NICHD and the WHO have supported research on the association between progestin-only contraceptives and irregular endometrial bleeding. Unlike the onset of normal menses, which is triggered by spiral artery constriction, irregular bleeding associated with parenteral progestin exposure is thought to originate from the subepithelial capillary plexus. Factors regulating the endometrial microvasculature are poorly understood, but it is known that ovarian hormones coordinate microvascular growth and development.

A meeting of researchers, sponsored jointly by the WHO and the NICHD, was held at Monash University in Melbourne, Australia, May 4 and 5, 1999. The group issued recommendations that clinical research be pursued for specific therapeutic agents in this area. In fiscal year 2001, the CRHB issued a call for such research in the RFA entitled *Progestin Contraception and Endometrial Bleeding*, to encourage proposals for clinical trials or animal studies of promising candidate drugs for the prevention and treatment of irregular endometrial bleeding in women using progestin contraceptives. Grants were awarded to four institutions in fiscal year 2002.

Global Guidance for Family Planning Based on the Best Available Science

In 2002, with input from the NICHD, the WHO Department of Reproductive Health and Research produced the *WHO Selected Practice Recommendations for Contraceptive Use,* the first evidenced-based, global consensus guidelines on how to safely and effectively use contraceptive methods. The document serves as a companion to the second edition of the *WHO Medical Eligibility Criteria for Contraceptive Use (2001*), also produced with input from the NICHD, that defines who can safely and effectively use contraceptive methods. From these two evidence-based documents, two tools for improving the global quality of family-planning care

will be developed: the *Decision-Making Tool for Family-Planning Clients and Providers* and the *Handbook for Family-Planning Providers*.

A system to provide global family-planning guidance was developed and pilot tested in fiscal year 2003, with NICHD support. The system assures continuous and comprehensive identification, critical appraisal, and synthesis of new research results as they become available. It is a collaborative effort between the Department of Reproductive Health and Research at the WHO, the Johns Hopkins University Bloomberg School of Public Health Center for Communication Programs (JHU/CCP), and the CDC/WHO Collaborating Center for Reproductive Health (CDC/WHOCC).

The first step, undertaken by the JHU/CCP, consisted of ongoing, comprehensive bibliographic surveillance using the POPLINE database to identify studies of relevance to the guidance topic, by: screening input to the POPLINE database (averaging 850 records per month) to identify research reports that may be relevant; posting bibliographic information to a database; and categorizing the bibliographic data according to the research issue it addressed.

The next step, undertaken by the CDC/WHOCC, consisted of: determining which new pieces of evidence were relevant; critically appraising relevant new evidence; getting peer reviews and, subsequently, creating final appraisals; and conducting systematic reviews. The CDC will also assist the WHO in determining whether the new evidence necessitates revision of existing recommendations.

The third step, conducted by the WHO, was the determination of whether an update to the guidance was warranted, pending the next expert working group meeting to establish the medical eligibility criteria for contraceptive use and the selected practice recommendations for contraceptive use. Updates will be provided electronically pending the next printing of the guidance. The system has been in full operation since November 2002.

PREVENTION OF HIV AND OTHER STIS

In earlier years, the CRHB began its HIV activities with funded studies on: factors that influence detection of HIV in semen; the possible cellular vectors of AIDS, which led to the development of the ME180 cell model system for assessing cell-to-cell transmission of HIV; and use of spermicidal agents to inactivate HIV, which led to the establishment of the present *in vitro* screening program for virucidal activity of spermicides and other non-spermicidal compounds. More recent CRHB research activities in this area are described below.

Microbicide Development

Microbicides are an important component of the NICHD's efforts in HIV prevention. To date the CRHB has focused on development of dual-use products, e.g., those that have both a contraceptive effect and an anti-microbial action.

In October 2001, the CRHB commenced a Phase II/III clinical trial of the contraceptive efficacy of Buffergel within the CCTN. This clinical trial is currently under way at 10 institutions and

will continue through June 2004. Approximately 975 women will participate for six months, with a smaller subset continuing for 12 months in this randomized, controlled, and double-masked study. Two-thirds of the women will receive Buffergel for use with a diaphragm during each act of intercourse; and the other one-third will receive a control product containing N-9, together with the diaphragm.

In addition to the endpoint of pregnancy, the trial will collect data on secondary microbiologic endpoints, including incidence of bacterial vaginosis, *E. coli* colonization, and urinary tract infections. A subset of women will undergo colposcopic examination, performed at the first visit and repeated at each of the three or five subsequent visits.

The CRHB has also supported the preclinical development and Phase I clinical testing of a promising microbicidal spermicide, C31G or SAVVY (Biosyn, Inc., Philadelphia, Pennsylvania). *In vitro* tests and animal studies indicated high potency against sperm and pathogens, with acceptable results in a rabbit vaginal irritation assay. C31G has successfully completed Phase I clinical testing for safety, acceptability, and postcoital efficacy. In addition, the C31G formulation (1-percent C31G poloxamer gel) performed well in a rabbit contraceptive efficacy trial. C31G will undergo a Phase II/III comparative spermicidal efficacy trial in the new CCTN beginning in the second quarter of fiscal year 2004.

In addition, the CHRB sponsors Small Business Innovative Research and R01 grants on microbicide development. This work is further supported through a unique arrangement with the Office of Population Affairs, U.S. Department of Health and Human Services (DHHS), and the NICHD's Division of Intramural Research (DIR). In this program, to conduct microbicide research, Russian scientists are paired with U.S. scientists. Program staff from the CRHB and the DIR have participated in this project and are working presently with Russian scientists on a topical microbicide. An additional collaboration in this area is anticipated for fiscal year 2004. The microbicide grant portfolio for which CRHB is responsible also includes projects on the following topics: vaginal physiology and vaginal immunology as they influence STIs and HIV infection; interrelationship between hormones, coitus, and intravaginal products, and their effects on systemic and local immune systems in HIV infection and disease; and cervical and vaginal factors that heavily influence transmission of HIV from female-to-male, male-to-female, and mother-to-newborn. Hence, a better understanding of virologic, immunologic, and disease co-factors in women is key to the prevention of HIV transmission.

Microbicide Support Contracts

Two NICHD contracts have been awarded to support the microbicide development program. One is the portfolio management system, which will help the NICHD and the National Institute of Allergy and Infectious Diseases (NIAID) to track the progress of the many compounds under development. The second, the microbicide quality assurance contract awarded in fiscal year 2003, will assist in standardizing and validating the various assays used in preclinical microbicide development. The standardized assays will be used in many projects, such as: examinations of inductions of mucosal immunity in women; the difference between the dynamics of T-cell turnover in men versus women, as well as the difference in antiretroviral drug metabolism in women versus men; and the difference in HIV viral evolution in women versus men, and the impact of bacterial vaginosis on HIV shedding and potential transmission. The

latter project recently received a supplement from the NIH Office of Research on Women's Health (ORWH) to study the effect of use of a topical disinfectant in men on re-acquisition of bacterial vaginosis in women.

HIV and Contraception

The CRHB has had an active role in research on contraceptive drug development since its founding and, to a lesser extent, in research on STIs and the reproductive health of women. In recent years, the Branch has come to more fully appreciate the interrelationship between HIV, STIs, and fertility regulation methods.

Since its last report to the NACHHD Council, the CRHB has greatly expanded support for research related to the development of contraceptive microbicides. An overview of currently supported activities and priorities in this area can be found in *Contraceptive Microbicide Research and Development Program: A Vision for the Future*, published in January 2001 by the NICHD. This document provides a foundation for assessment of current research and for planning of the NICHD's future microbicide research efforts and related program activities. Its background section outlines NICHD research responsibilities, scientific accomplishments, and an overview of the research program, while the body of the report describes current projects in the areas of basic biomedical research, preclinical development, clinical research, and behavioral and social science research. The research needs, goals, and proposed activities, as well as post-marketing surveillance and capacity building, are also outlined. Because the NICHD effort in this area is highly integrated with the other groups also working in the area, a description of many of the collaborations is included in the *Vision* report.

Hormonal Contraceptives and Risk of AIDS Transmission Study

Incidence of HIV infection and AIDS has been increasing among women for some time, but it is not known whether hormonal contraceptives have any effect on susceptibility to HIV infection. To address this issue, in fiscal year 1997, the NICHD began a prospective, observational study of 6,400 women in three countries with high HIV risk: Thailand, Uganda, and Zimbabwe. After enrolling equal numbers of HIV-seronegative women using OCs, DMPA, or no steroidal method of contraception, the participants have been followed for seroconversion over a time period of 15 to 35 months. Recruitment into this study is complete, and its primary outcome data will be available in fiscal year 2005.

Study participants who become HIV-seropositive during the study are offered enrollment in a further study of genital shedding of HIV, which includes research on HIV subtype fitness and host-immune response during the acute phase of infection, and into the chronic phase of HIV infection. This cohort, therefore, allows examination of possible hormonal contraceptive effects on the progression of HIV disease. This study, with a seroincident cohort of approximately 250 women, will continue for an extended period of follow up and includes comparison of systemic and cervico/vaginal HIV viral loads. It may also yield information on the possible interaction of hormonal contraception with efficacy of antiretroviral therapy.

Condoms and STI Prevention as a Proxy Measure of HIV Transmission

The CRHB has also examined research needs relative to STIs other than HIV. In a collaboration with the NIAID and other government agencies in June 2001, the Branch supported a scientific meeting on condom efficacy that later issued a report on the scientific evidence about the effectiveness of the male latex condom in preventing HIV and other STIs. The conclusion of the review effort was that, with the clear exception of HIV and gonorrhea in males, the available scientific evidence did not allow conclusions on condom efficacy against the other STIs that were considered (i.e., HSV, HPV, trichomonas, syphilis, etc.).

Subsequent to this report, new findings are emerging from a CRHB prospective observational study to determine the efficacy of the male and female latex condoms in preventing transmission of STIs, specifically gonorrhea, chlamydia, and HSV, in a cohort of women at high risk of STIs. Findings from the initial study are based on a cohort of 920 women, followed monthly for six months, who were tested routinely and interviewed for interval diagnosis of gonorrhea or chlamydial infection. The cohort reported using a male condom in 42 percent of encounters, and a female condom in 27 percent of encounters. Among women who reported consistent and correct use of either condom, there was a 70 percent reduction in STI rates when compared to inconsistent condom use. Consistent use of either type of condom resulted in a similar reduction in incident cases. These new data are adding to the scientific evidence that both the male and female condoms can be highly effective in preventing gonorrhea and chlamydia. Results of study analyses on condom use and risk of HSV infection are pending.

To further address the shortcoming of available research evidence, the CRHB sponsored a workshop on the design of such studies in December 2002. Workshop participants reviewed, in detail, the critical decisions to be made in designing research studies on condom effectiveness in prevention of STIs. A guidance paper is currently in development and is intended as a reference for individuals planning such studies.

The Branch continues its efforts to expand the scientific knowledge base concerning prevention of STIs other than HIV, through collaborations with the CDC, FDA, other NIH Institutes, and the United States Agency for International Development (USAID). There have also been collaborations with the National Institute of Dental and Craniofacial Research to assess parameters associated with shedding of HIV in the oral cavity.

Microbicide Scientific Meetings

Between 1999 and 2002, CRHB staff were instrumental in organizing several international conferences on microbicides. The NICHD sponsored the first organizational meeting, which led to the establishment of an international conference series on HIV microbicides. The International AIDS Society president and NICHD program staff proposed a biannual series of international meetings for the HIV microbicide research community. The first meeting, *Microbicides 2000,* funded by the NIH OAR, with more than 700 attendees, was the largest meeting on the topic ever held. CRHB staff were part of the original and subsequent organizing committees for the basic sciences and acted as rapporteur for both. A second meeting in the series, *Microbicides 2002*, held in Antwerp by the Institute of Tropical Medicine, with a broad base of organizations offering financial support, was also attended by more than 700 international scientists. The major accomplishments of the first two meetings were to attract new

investigators from relevant disciplines, and to increase recognition of the importance of microbicides at a level equal to vaccines in the HIV prevention science agenda. The third meeting, *Microbicides 2004*, will take place in March 2004 in London, England. At this time, *Microbicides 2006* is planned for a developing country, such as South Africa.

In January 2003, in collaboration with the NIAID, OAR, and ORWH, the CRHB sponsored a meeting on Fertility Regulation in HIV-Infected and At-Risk Women. Meeting attendees included scientists from the HIV and contraception communities. This meeting allowed interaction between members of the HIV-infectious disease community, the family-planning community, the FDA, and organizations such as the Alliance for Microbicide Development and the American Society for Emergency Contraception. Publication of the presentations from this meeting is anticipated in fiscal year 2004. Since then, two symposia on contraceptive choices and HIV have been held at major STI/HIV/AIDS meetings. In addition, the Women's Health Committee of the NIAID AIDS Clinical Trials Group has made contraception a research priority.

HIV in Women and Girls

The NICHD sponsors an increasing number of research projects on HIV in women and girls. In the past, the NICHD has collaborated with NIAID to sponsor several studies on HIV in women and girls, including the effect of the menstrual cycle on HIV shedding and cytokine levels in the female genital tract. Other projects include:

- Women's HIV Interdisciplinary Network (WHIN). In 2001, the NICHD awarded three program projects on HIV in women to the WHIN. The scope of these projects covers immunology, HIV and associated co-factors, and molecular biology of HIV in women. All these projects use explant tissue models to study various aspects of HIV in women. In 2002, the projects were supplemented by the OAR to continue this endeavor by establishing a virtual tissue repository.
- Centers for AIDS Research (CFAR). In 1998, the NIAID opened the CFAR program to sponsorship from other NIH Institutes. Presently, the CFARs are co-sponsored by seven NIH Institutes and are directed by a steering committee composed of members representing each Institute. The CFARs are generally located at institutions that support more than $20 million in AIDS research, with the task of coordinating the AIDS research at a local level, much as the CRHB does at an extramural level. Over the last several years, NICHD has funded supplemental grants to the CFARs on microbicides and on issues related to women and girls. In addition, in 2003, the CFARs produced a report on all activities in which they were involved that were supported by the NICHD.

At present, the NICHD collaborates with NIAID on the CFAR program by serving as the primary funder of the North Carolina CFAR; CRHB is the sponsoring Branch. This CFAR has a strong interest in genital HIV and microbicide/STI prevention research, as well as in behavioral research.

SELECTED REPRODUCTIVE AND GYNECOLOGIC HEALTH ISSUES

Up to one-third of adult women in the United States may suffer from one or more pelvic floor disorders (e.g., pelvic organ prolapse, urinary or fecal incontinence, or other sensory and emptying abnormality of the lower urinary and gastrointestinal tract), while an estimated 11 percent of women will undergo a major surgical procedure to correct urinary incontinence or pelvic organ prolapse. The aging population in the United States will markedly increase the need for treatment of these disorders; as a result, there is an urgent need for research into their etiology, diagnosis, treatment, and prevention. In response to this ongoing need as identified in the professional communities and with congressional direction, the Branch, in collaboration with the American Urogynecologic Society, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the ORWH, and other Branches within NICHD, has undertaken a number of activities in the area of pelvic floor disorders.

Epidemiologic Research on Female Pelvic Floor Disorders

The NIH issued 10 awards to support epidemiologic research in this area; eight awards came through the NICHD, one through the NICHD and ORWH, and one through the NIDDK. The grants included the studies of: reproductive risk factors and the natural history of pelvic organ prolapse; the epidemiology of fecal incontinence after childbirth and later in life; genetic and racial determinants of pelvic floor disorders; and risk factors for urinary incontinence, including the analysis of familial (genetic) and acquired (childbirth) factors.

Clinical Trials Network for Female Pelvic Floor Disorders

Using the cooperative agreement mechanism, the Pelvic Floor Disorders Network (PFDN), which consists of seven clinical sites and one data-coordinating center, was funded by the NICHD. The first PFDN protocol is the Colpopexy and Urinary Reduction Efforts Study, a randomized trial to determine whether continent women with advanced prolapse should receive a procedure to prevent stress incontinence (called the Burch colposuspension) at the same time that abdominal sacral colpopexy is performed to correct prolapse. Enrollment for this study should be completed by June 2005.

The second PFDN protocol is the Childbirth and Pelvic Symptoms (CAPS) Study, which will determine the prevalence and incidence of fecal incontinence, urinary incontinence, and sexual dysfunction in women after childbirth. The study will follow three groups of women after the delivery of their first child: 400 women after vaginal delivery with anal sphincter laceration, 400 women after vaginal delivery without anal sphincter laceration, and 100 women after cesarean delivery without labor. This study is the largest ever performed with American women; because obstetric practices in Europe, especially the use of midline episiotomy, vary so widely, data comparisons cannot be used to estimate the occurrence of symptoms after childbirth. The results of this study will be important in identifying risk factors for pelvic floor disorders after delivery; in addition, these data will be used to design a trial of pelvic muscle physiotherapy to prevent or treat fecal incontinence and other symptoms after childbirth. Enrollment of the full sample is complete.

A supplementary study is being performed on a subset of 255 women who will complete questionnaires and receive physical examinations, anal ultrasound, and pelvic magnetic

resonance imaging to correlate symptoms with imaging. The results will guide evaluation and management of women after anal sphincter disruption and repair at delivery, a serious complication that occurs in up to 20 percent of women who deliver their first baby vaginally.

Competitive renewal of Network sites is planned for 2006, with the goal of increasing the number of clinical sites from seven to 12. This increase should enhance the effectiveness of the PFDN, allowing high-impact, high-quality multicenter studies to be performed more efficiently, especially surgical trials that cannot be performed by single sites.

Other Activities

The Urinary Incontinence Treatment Network (UITN), initiated in 2000 by the NIDDK, consists of nine clinical sites and one biostatistical coordinating center. The NICHD fully funds one clinical site and partially funds two other sites in the Network. The first UITN protocol is a randomized trial comparing two of the most commonly performed surgical procedures for treating incontinence in women: Burch colposuspension versus autologous fascial sling. The study's results on 650 subjects, available by mid-2006, will provide critically important information about the relative effectiveness of these two procedures and will help guide clinicians in choosing the most appropriate treatments. The second UITN protocol, although still in development will be a randomized trial to compare behavioral and pharmacologic therapies for overactive bladder symptoms (i.e., urgency, frequency, and urge incontinence).

In October 2002, the NIH held a Grant Fundamentals Workshop at the annual meeting of the American Urogynecology Society. The workshop, with four NIH speakers and 75 participants, was well received. A similar program is planned for July 2004, when the American Urogynecologic Society and the Society of Gynecologic Surgeons hold their annual meetings jointly.

In November 2002, the Branch was involved in a scientific meeting on Basic Science and Translational Research in Female Pelvic Floor Disorders. At this meeting, 50 participants presented research findings, discussed important knowledge gaps, and identified educational and training needs to accelerate progress in female pelvic floor disorders research. CRHB staff will use the proceedings of this meeting, submitted for publication, in developing new initiatives. Efforts will also be made to stimulate collaboration between basic and clinical scientists to address the most pressing needs; for example, until pathophysiology is clearly understood, treatment is necessarily empiric and prone to high rates of failure. In addition, new research findings have the potential for huge public health impact because pelvic floor disorders are so common and frequently require expensive, invasive treatment, such as surgery.

RESEARCH TRAINING

Reproductive Epidemiology Training

The NICHD funded the establishment of a two- to three-year formal postgraduate training program that includes the following components: a core curriculum in clinical epidemiology, research methods, and biostatistics; elective courses in reproductive biology and basic science; research symposia; and independent research in basic and clinical epidemiology. To date, two

postgraduate M.D.s have been in training: one for two years (1996-98), and one for one year (1997-98). The senior fellow has also obtained funding from outside sources for several studies (12 publications in peer-reviewed journals).

In collaboration with the Fogarty International Center at the NIH, the NICHD is also co-funding training programs for foreign scientists in contraceptive vaccinology, as well as in male reproduction/contraception.

In response to the needs for obstetricians/gynecologists, as outlined in the two IOM publications (mentioned earlier), the CRHB issued an RFA, *Training in Epidemiology and Clinical Trials for Obstetricians and Gynecologists* and awarded grants to four institutions in 2001. These T32 grants support fellows for two or three years in programs jointly based in departments of obstetrics and gynecology and in departments of epidemiology in medical schools or schools of public health. The fellows receive training in biostatistics, and in the design and execution of clinical research, and are required to participate actively in clinical research at their institutions. There are currently a total of 11 fellows in training at the four institutions.

Career Development Program for Contraceptive Research

The U54 Contraceptive Research Center at the University of Washington initiated a program to attract new investigators to the field of clinical reproductive biology and its applications to contraception. This program will recruit Ph.D. fellows as well as physician scientists to conduct one- to two-year pilot projects in reproduction research related to contraception. The Center will use its experience in partnering with domestic research institutions, as well as with research institutes in developing countries, to attract talented new investigators to the field. A steering committee for this program is composed of senior investigators in the Center, who will serve as mentors.

Mid-Career Investigator Awards in Patient-Oriented Research in Female Pelvic Floor Disorders

In 2001, the NICHD and NIDDK released a program announcement (PA) for K24 awards for mid-career clinician-scientists to support time devoted to mentoring junior faculty and performing research in pelvic floor disorders. Consideration is being given to re-issuing this PA, and to developing a funding mechanism to encourage basic scientists who are early in their careers to focus on research in female pelvic floor disorders.

FUTURE DIRECTIONS

The CRHB looks forward to an exciting future. New developments in genomics and proteomics are rapidly identifying new targets for contraceptive agents. The cadre of new investigators trained in clinical research will add new energy and ideas to clinical trials. Greater utilization of the Internet and its resources will enhance communication among investigators, and between investigators and the public. Based on ongoing internal planning efforts and discussions with colleagues and collaborators, the Branch is pleased to set forth its ideas for future research. Planned and potential specific research ideas are described in this section.

CONTRACEPTIVE RESEARCH AND DEVELOPMENT

The CRHB is planning a number of future activities in contraceptive research and development.

A Meeting on the Future of Male Contraception

In fiscal year 2004, the Branch will begin planning to enhance activities related to discovery and transition from discovery of basic contraceptive leads in males through to clinical trial testing. The CRHB plans to sponsor a meeting in September 2004 at the University of Washington in Seattle, *The Future of Male Contraception.* The investigators who will be invited to participate include members of the: Cooperative Contraceptive Research Centers (supported by the NICHD); Male Contraceptive Cooperative Program (supported by the NICHD); Fertility Defect Phenotyping Program; Male Research Focus Group within the Specialized Cooperative Centers Program in Reproduction Research (supported by the NICHD); International Summit on Hormonal Male Fertility Regulation; private-sector groups, including pharmaceutical companies; and collaborating organizations such as USAID, the WHO, Family Health International, and the Contraceptive Research and Development Program. Other interested parties may also attend the conference.

The goal of the conference will be to evaluate the progress to date in male contraception, and to identify the obstacles that remain to transition discoveries into products. Recommendations from the meeting will be used to determine additional government activities in support of developing male contraceptives.

Hepatotoxicity Measurement

A reliable *in vitro* method of predicting potential hepatotoxicity in human subjects is urgently needed to assess new contraceptive candidates. The CRHB will explore the use of human hepatocytes from several sources for assaying comparative liver cytotoxicity. Currently, the Branch is studying a subclone of hepatocytes , called C3A from Amphioxus for apoptosis (Apo-ONE homogenous Caspase 3/7 assay), viability (ATP production), cytotoxicity (LDH release), and cell proliferation (MTS assay). Testing for effects on metabolic activity utilizes CYP1A2 or CYP3A4 inhibition or stimulation serves as an endpoint in these efforts.

Angiogenesis Inhibitors

Angiogenesis is the process of forming new blood vessels. Molecules that play a role in angiogenesis may also be important for follicular development, ovulation, and/or endometrial development and differentiation. Angiogenesis inhibitors are under intensive study as cancer therapeutics, but are also potential candidates as contraceptive agents. Still in preliminary stages of development, the concept of potential uses of angiogenesis inhibitors for reproductive health and/or contraceptive use will be given further consideration.

Other Research Efforts

- Molecular Endocrinology—The CRHB will continue to develop methods for testing potential new contraceptive agents, as appropriate, including employing a wide variety of cell lines to utilize new technologies for identification of tissue specificity, cytotoxicity, and metabolism.

- Cooperative Contraceptive Research Centers—The Centers will continue to explore specific development targets that may result in safe and effective new contraceptives.
- New methods for inhibiting ovulation, fertilization, and spermatogenesis—The Cooperative Contraceptive Research Centers will continue to study the mechanisms of spermatogenesis and fertilization in order to identify targets that offer a potential mechanism for contraception. A related effort, supported by the Reproductive Sciences Branch, is expected to generate recommendations for new avenues of research in the area of spermatogenesis. The CRHB will also continue to encourage research on novel methods of contraception through research and training.
- Lonidamine Analogs—The action of lonidamine analogs will be explored further to determine if they are a safe method of contraception for males.
- Acyline—This GnRH antagonist will continue to be made available to the research community and to industry.

CONTRACEPTIVE AND REPRODUCTIVE EVALUATION

The CRHB is planning a number of future activities in contraceptive and reproductive evaluation.

New Approaches to Hormone Therapy for Postmenopausal Women

The recent results on postmenopausal hormone therapy and risk of breast cancer and cardiovascular disease from the NIH WHI have alarmed and confused the public. In less than 12 months, approximately one-third of U.S. women on combined E+P regimens have discontinued this medication. Drug companies are introducing new drugs, changing doses of currently prescribed drugs, and introducing new routes of administration. This critical time represents an opportunity to start post-market surveillance studies to determine the safety profiles for new forms of treatment**.**

The Cochrane Collaboration

In addition to completing the publication of collective reviews to date, consideration will be given to supporting new reviews on additional subjects of particular relevance to contraception. More emphasis will be given to making these reviews accessible via the Internet. Gaps in knowledge identified through these reviews will help to generate future projects.

Hormonal contraception, weight gain and diabetes

There is great concern about the current problem of weight gain in U.S. adolescents. Anecdotal evidence suggests that steroidal contraceptives may play a role in weight gain in selected populations. The Branch will summarize research results in this area and plan ways to develop a research agenda.

Vaginal Epithelial Integrity

There is an increasing interest in developing new vaginal products, including contraceptives. The CRHB will encourage the exploration of alternative technologies for evaluating *in vivo* defects in vaginal epithelium. These efforts may include colposcopy and alternative means for defining vaginal lesions.

Other Research Efforts

- Sterilization—Possible future research activities include comparing the efficacy of different vasectomy procedures, measuring infertility after vasectomy, and studying the short-term, method-specific adverse effects of tubal sterilization.
- Condom effectiveness—The Branch will summarize the critical issues in the design of STD/condom effectiveness studies. Further development of research methods will be considered.
- Reproductive Epidemiology—The CRHB will sponsor a research workshop to review areas of emerging scientific and public health importance, and to provide guidance on future programmatic projects.
- Progestins and Uterine Bleeding—The Branch will continue its efforts to encourage research on abnormal uterine bleeding occurring with progestin-only contraceptives.

PREVENTION OF HIV AND OTHER STIS

The CRHB is planning a number of future activities in prevention of HIV and STIs.

Microbicide Development

A number of dual-activity (contraceptive and microbicidal) products are currently under development. Several are in Phase I trials. The Branch will consider doing Phase II clinical testing of selected candidate microbicides, as well as testing the efficacy and safety of new potential products.

The NICHD, in collaboration with the NIAID, will consider re-issuing the integrated preclinical/clinical program. Phase I/II and III clinical trials may be coordinated through the NIAID HIV Prevention Trials Network or through the NICHD CCTN. Additional support from both Institutes may be used to help the investigators in product development.

The CRHB will continue to encourage the development and evaluation of spermicidal microbicides. In addition, the Branch will encourage applications for studies of the differences between fusible and non-fusible membranes, in hopes of determining significance relative to preventing STIs.

Evaluation of Colposcopy

The CRHB will evaluate colposcopy's role in the development of safe microbicides. Colposcopy is of value in clinical evaluation of cervical lesions and carcinomas. Its usefulness in clinical trials of microbicides and contraceptives required for approval by FDA is unclear.

New and Emerging Technologies in Contraceptive and Microbicide Delivery

Advances in genomics, proteomics, and pharmacogenomics may help to support the development of new contraceptives and microbicides, which would include the pairing of existing technologies with emerging technologies, such as nanotechnology, in order to reduce the toxicity of drugs, increase their absorption, and improve their release profiles. It may also be

possible to use this new technology to stimulate research in the development of new formulations and delivery systems for optimally effective contraceptives and microbicides.

Contraceptive/Microbicide Discovery Utilizing Natural Products

The CRHB will continue to collaborate with the Fogarty International Center on the International Cooperative Biodiversity Groups (ICBG) Program. The ICBG Program consists of domestic awards with foreign components to identify and develop new natural product drug leads. In fiscal year 2003, the CRHB funded its first grant under this Program; the Branch will continue to collaborate in this area for the possible discovery of new microbicides and contraceptive agents.

Extension of the NICHD African HIV Incidence Cohort

The CRHB's prospective study of seroconversion among users of different steroidal contraceptives is clinically complete; data analysis is under way, and publication of its primary results is anticipated in fiscal year 2005. The seroincidence data by category of hormone use will be published first, while data from substudies of the roles of HSV, bacterial vaginosis, and HPV on risk of HIV infection relative to steroid use will follow.

Additional funding will increase the size of the NICHD's African HIV Incidence Cohort to approximately 250 women and will allow long-term follow up. This group is one of few female cohorts in the world with a known seroconversion date, thus providing knowledge of the duration of infection. Long-term follow up of this seroincidence cohort will provide important data on the role of hormonal contraceptives in progression and manifestation of HIV disease in women.

Other Research on HIV in Women

In spite of the increasing prevalence of HIV in women, relatively little research on women has been completed. To address this lack, the NICHD will consider extending the WHIN, with the primary emphasis likely to continue to focus on the interdisciplinary approach to research, with special emphasis on integrating family-planning researchers and HIV-infectious disease researchers. Consideration will be given to more international research and to comparisons between developing and developed country populations. Because it is likely that many countries will be initiating treatment programs for women during this period, it will be important to emphasize the gender-specific aspects of treatment and the interrelationships between treatment and family planning.

Cooperation and Collaboration across Institutes

As emphasis on collaboration between NIH Institutes in research on HIV/AIDS continues, the NICHD will continue to fund the CFAR Program in conjunction with the NIAID. Additionally, the NICHD will continue to co-fund the HIV Prevention Trials Network. As stated above, the CRHB will continue to collaborate with the Fogarty International Center to support discovery of natural products that might be viable microbicide candidates. In addition, the Branch will provide guidance and encourage further research efforts that relate to the efficacy of latex and non-latex condoms in the prevention of STIs in collaboration with the NIAID.

Alternative Test Models for Assessing Genital Irritation

Irritation of the epithelial surfaces of the vaginal tissue has been a source of concern in the microbicide product development process. The current preclinical model for assessment of irritation is the rabbit vaginal irritation model. *In vitro* models are needed that are cost effective and that are documented to be reliably predictive of activity in humans. Recent studies of vaginal and penile *ex vivo* culture and research using cell lines suggest that there may be cellular model alternatives to the rabbit vaginal irritation model. The CRHB will continue to encourage research on the discovery or validation of new test models for vaginal or penile irritation, which will more accurately and readily predict results in humans. To this end, the Branch is supporting the PA *Alternative Test Models for Assessing Genital Irritation of Microbicidal/Spermicidal Products* (PAS-03-081), issued in fiscal year 2003.

SELECTED REPRODUCTIVE AND GYNECOLOGIC HEALTH ISSUES

The CRHB is planning a number of future activities in selected reproductive and gynecological health issues.

Female Pelvic Floor Disorders

- The impact of the 1999 meeting convened by the CRHB to standardize terminology on female pelvic floor disorders will be assessed by examining a series of publications on the topic, to see how well their outcome measures conform to the recommendations made at the 1999 meeting. In preparation for a follow-up meeting, newly published results on standardization of terminology and outcomes measurements will be synthesized into a summary document for discussion and consensus building.
- The CRHB will maintain the cooperative agreement mechanism in the PFDN for further studies on the diagnosis, treatment, and prevention of pelvic floor disorders. Plans include adding more sites to expand the clinical base, enrolling subjects more quickly, and performing clinical trials more efficiently.
- Publication of the proceedings of the 2002 meeting, *Basic Science and Translational Research in Female Pelvic Floor Disorders,* will be instrumental in guiding the development of Branch initiatives in translational research. Emphasis may be given to establishing collaborative relationships between fields not typically involved in pelvic floor disorders, such as neurology, muscle physiology, vascular biology, biomechanics, and engineering.
- The National Children's Study will enroll about 100,000 children to study the effects of environmental exposures on children's growth and development and is expected to follow individuals from before birth through to age 21. This design provides a critically important opportunity to study mothers, along with their children, to address the role of childbirth events and subsequent life events in the development of pelvic floor disorders. The mothers will be already involved in the study on behalf of their children. The Branch is represented on the Pregnancy and the Infant Working Group, which will explore maternal pelvic floor disorders, as well as other issues.

Urinary Incontinence

As with the PFDN, the CRHB anticipates maintaining the cooperative agreement mechanism in the UITN. The Branch also plans to continue to collaborate with NIDDK for further studies on the diagnosis and treatment of urinary incontinence in women.

National Capital Consortium Fellowship in Female Pelvic Medicine and Reconstructive Surgery

The Department of Defense/Army maintains an active fellowship in Female Pelvic Medicine and Reconstructive Surgery. The NICHD has agreed to provide one year of basic laboratory experience with an NICHD intramural researcher in an area related to female pelvic floor disorders to one fellow in this program.

State-of-the-Science Conference on Elective Cesarean Delivery

Working with staff in the NICHD Pregnancy and Perinatology Branch, CRHB staff are planning a State-of-the-Science conference to address the growing debate on the risks and benefits of elective cesarean delivery. Proponents of the procedure claim protection for mothers from pelvic floor disorders; while opponents argue that the overall impact on public health is negative, given the risks to mother and baby of cesarean delivery. Panel members will use newly available research results to formulate evidence-based guidelines on the relative risks and benefits of elective cesarean delivery.

Treatment of Endometriosis and Uterine Fibroids

The CRHB plans a future study of CDB-2914 or its analogues for potential therapeutic uses in treating these diseases. Efforts are under way to examine the newer SPRMs, discovered by the Branch, to see if tissue specificity may identify candidate compounds whose selective action make them better than others for treating these diseases.

RESEARCH TRAINING

In the field of contraception and reproductive health there is a great need for training early and mid-career investigators. Many promising individuals in the field have difficulty in securing protected time, and in finding mentors for research activities. The Branch will consider extending and expanding support in this area wherever possible.

In addition, the Branch will collaborate with the Fogarty International Center to promote international training programs, especially in the area of HIV/STIs. More clinical trials and epidemiologic expertise are needed in developing countries, where incidence of these diseases is increasing.

FIGURES AND TABLES

FIGURE 1: CRHB CONTRACEPTIVE DEVELOPMENT MECHANISMS

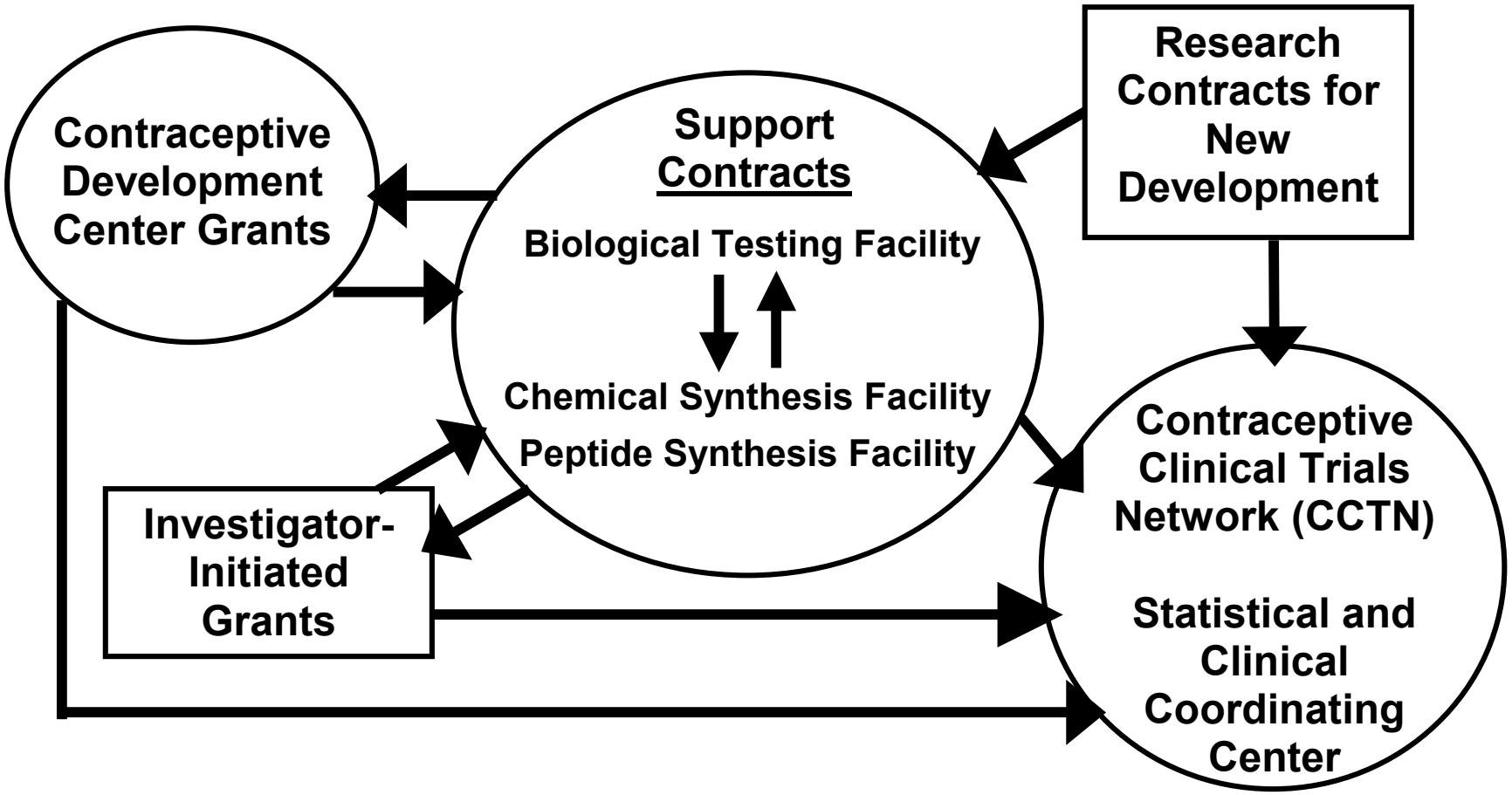

FIGURE 2: CRHB PORTFOLIO BY SUPPORT MECHANISM, FISCAL YEAR 1999 TO FISCAL YEAR 2002

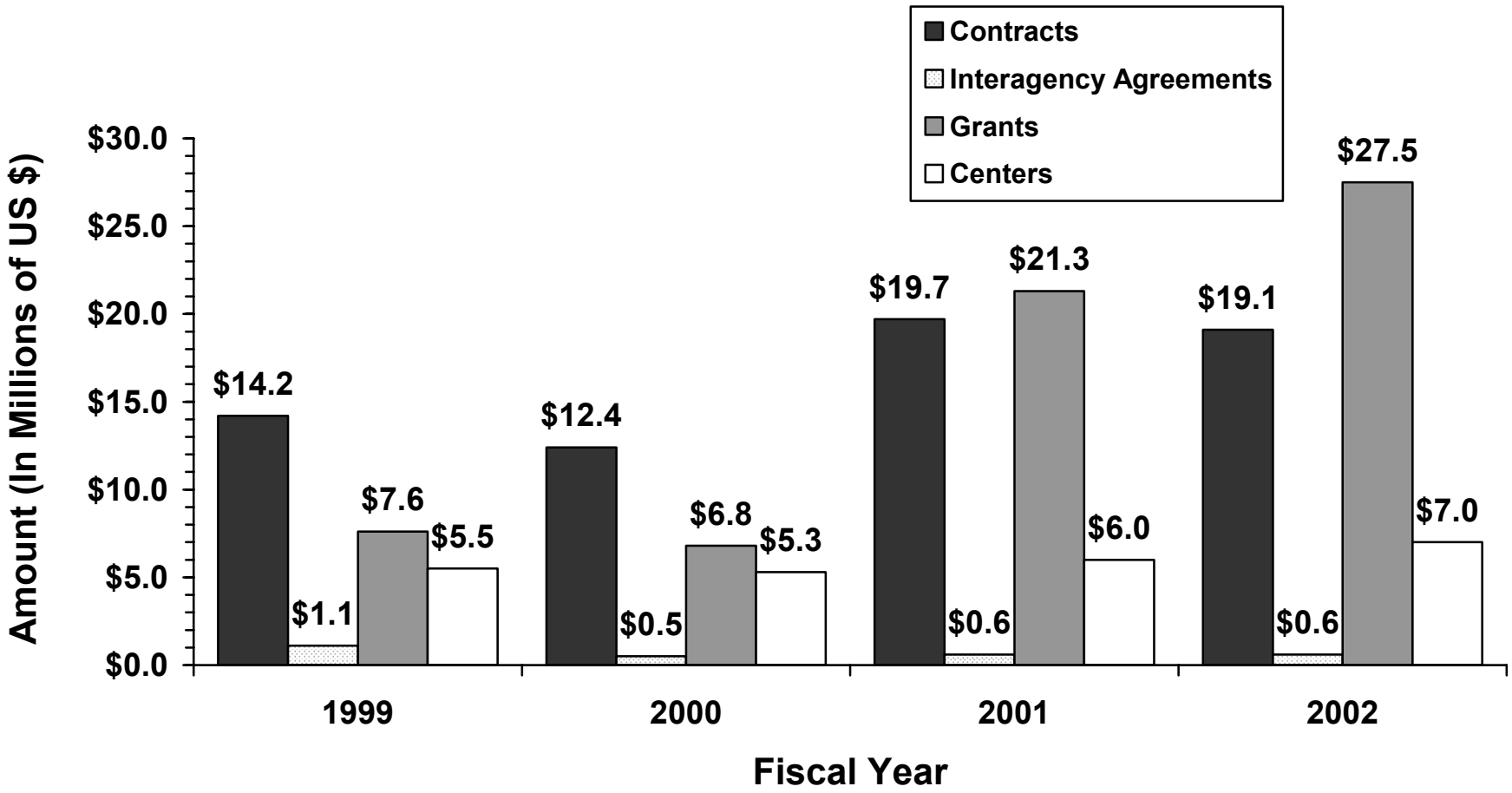

FIGURE 3: CRHB FUNDS IN CURRENT AND CONSTANT DOLLARS, FISCAL YEAR 1980 TO FISCAL YEAR 2002

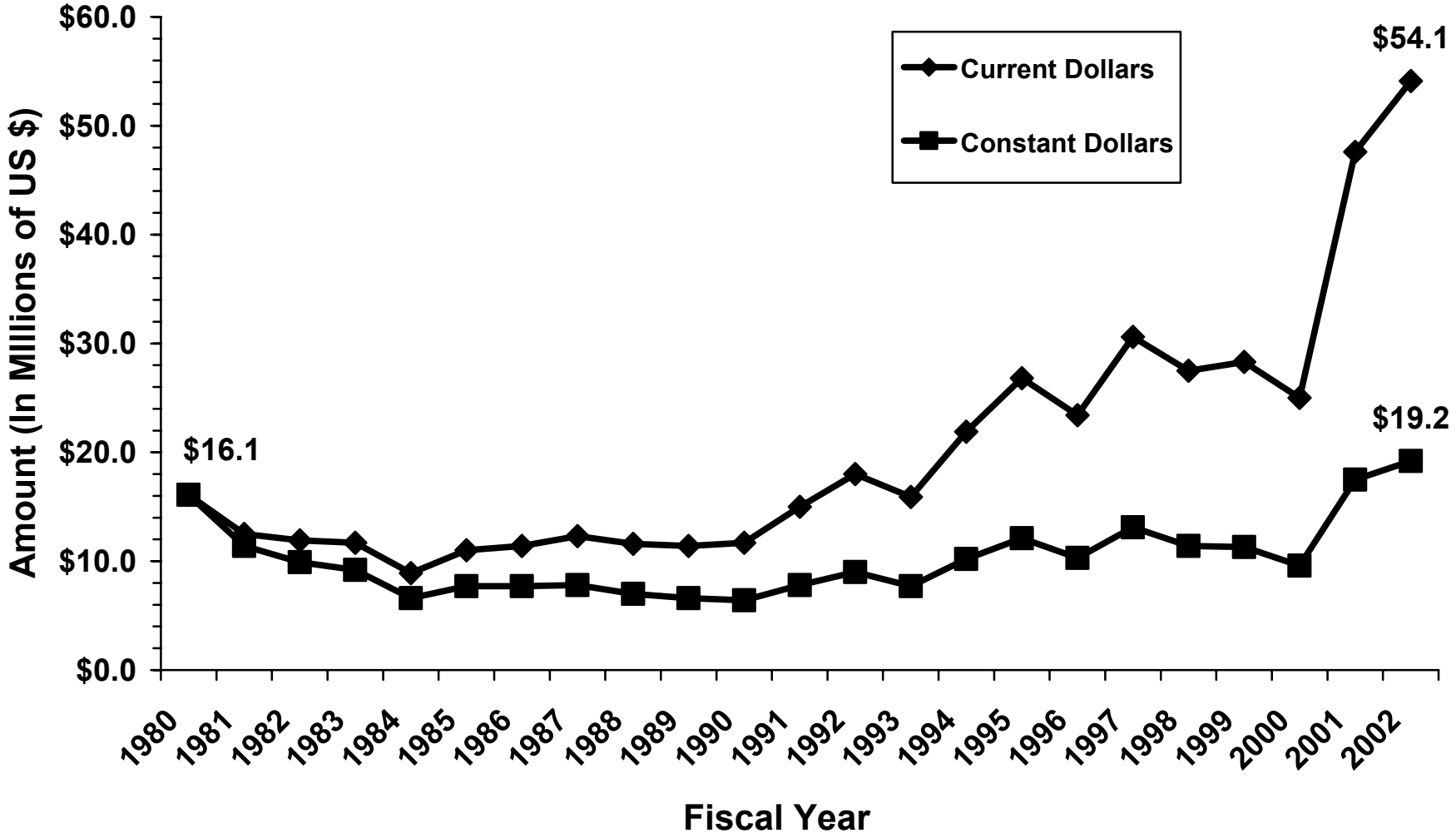

TABLE 1: CRHB PROJECTS BY PROGRAM AREAS, FISCAL YEAR 2002

PROGRAM AREA	NO. OF GRANTS	FUNDS
Contraceptive Research and Development		
Contraceptive Research	6	$2,205,876
Preclinical Contraceptive Development	9	$6,050,234
Contraceptive Clinical Studies	16	$4,803,320
Research and Development Support Facilities	5	$7,391,507
Subtotal	36	$20,450,937
Contraceptive Evaluation		
Contraceptive Epidemiology	11	$3,587,606
Reproductive Epidemiology	3	$6,110,820
Clinical Studies	9	$2,562,754
Subtotal	23	$12,261,180
Prevention of HIV and Other STIs		
Preclinical Product Development	19	$5,854,215
HIV/STI Pathogenesis	3	$1,788,309
Clinical Studies	13	$2,869,746
Subtotal	35	$10,512,270
Selected Reproductive and Gynecologic Health Topics		
Epidemiology	14	$3,406,381
Preclinical Studies	1	$809,797
Clinical Studies	11	$5,220,711
Subtotal	26	$9,436,889
Research Training		
Training Grants	10	$1,450,628
Subtotal	10	$1,450,628
TOTAL	**130**	**$54,111,904**

APPENDIX A: CRHB PERSONNEL AND ACTIVITIES

Robert Spirtas, Dr.P.H., joined the Contraceptive Evaluation Branch in 1988. The Branch later became the Contraceptive and Reproduction Evaluation Branch and, in 1997, when it merged with the Contraceptive Development Branch to become the CRHB, Dr. Spirtas was appointed Branch chief. As chief, he is responsible for a progressive, national program in reproductive epidemiology, contraceptive research and development, and reproductive health. In 2003, he received the Charles C. Shepard Science Award and the NIH Director's Award for his role in designing and coordinating the NICHD Women's CARE Study. In addition to his duties as Branch chief, he directs Branch efforts in the area of cancer epidemiology, where he has published extensively. Dr. Spirtas represents the NICHD in the following groups: WHO Human Reproduction Program, Epidemiological Research Committee; Family Health International, Technical Advisory Committee; and Contraceptive Research and Development Program, Technical Advisory Committee. Dr. Spirtas is certified as a fellow of the American College of Epidemiology and has served as a member of the board of Planned Parenthood, Inc.; as an adviser to the FDA, the U.S. Environmental Protection Agency, and the Consumer Product Safety Commission; and as a member of the Governing Council of the American Public Health Association. Dr. Spirtas has also served as reviewer for the *American Journal of Epidemiology, Fertility and Sterility*, and the *International Journal of Cancer*.

Diana Blithe, Ph.D., joined the Contraceptive Development Branch in 1996 from the NICHD's DIR. She has expertise in biochemistry, endocrinology, and glycobiology. Dr. Blithe is the research coordinator for the Cooperative Contraceptive Research Centers Program and director of the Male Contraceptive Development Program. She also serves as co-director of the CCTN. Dr. Blithe is a PI on a Collaborative Research and Development Agreement with HRA Pharma to develop CDB-2914 as a SPRM for contraceptive and therapeutic applications. Her additional responsibilities in the Branch include reviewing technology transfer arrangements with commercial partners. Dr. Blithe also contributes to developing new spermicidal microbicides and serves as the project officer for development and evaluation of C31G as a new spermicide. She is a member of the Endocrine Society and the American Society for Cell Biology and currently serves on the editorial board of *Endocrine,* and as an ad hoc reviewer for other journals.

Richard Blye, Ph.D., joined the Contraceptive Development Branch in 1971 to develop the Biological Testing Facility, which has become a mainstay of the Branch's operations in demonstrating biological activity for a broad spectrum of new drugs. The Facility has the capacity to perform more than 150 different tests and assay procedures. Dr. Blye is also responsible for a wide variety of tests of new compounds in primates following studies in rodents and rabbits, including long-term pharmacokinetic studies of injectable steroids and contraceptive delivery systems. Dr. Blye maintains contacts with numerous scientists in both academic and industrial research laboratories and has contributed to collaborative studies with these individuals. Dr. Blye also participates in the preparation of manuscripts and patent applications describing research to which he has made substantial contributions.

Ms. Diane Eagle joined the Contraceptive Development Branch in 1995. Her responsibilities include managing files, correspondence, travel, and conference planning. Prior to joining the CRHB, she worked for the National Center for Medical Rehabilitation Research at the NICHD.

Steven C. Kaufman, M.D., M.S., came to the Contraceptive and Reproductive Evaluation Branch from the FDA's Office of Epidemiology and Biostatistics in 1992. His recent duties include serving as project officer for contracts dealing with male condoms, vasectomy, tubal sterilization, infertility, and peri/postmenopausal gonadotropin data collected by the National Health and Nutrition Examination Survey, and as medical officer for a joint NICHD/NIAID cooperative agreement dealing with microbicide development. He has coordinated the CRHB grant portfolio since 1992, including serving as health scientist administrator for all of the Branch's investigator-initiated grants, providing guidance to grant applicants and CRHB staff about funding opportunities and the grant application process, and advising Branch members concerning their RFAs and PAs. Dr. Kaufman has made presentations at national scientific meetings on such topics as: *The NICHD and Pre-doctoral Training,* and *Epidemiology Research Opportunities at the NICHD*. He has published recently on regret after vasectomy and tubal sterilization. He also represented the NICHD at the 2001 and 2003 Expert Consultation on Vasectomy Effectiveness, initiated the CRHB Web site (which he has managed since its inception), and served on NICHD's Web Site Coordinating Committee.

Hyun K. Kim, Ph.D., has been with the Contraceptive Development Branch since 1972. As a medicinal chemist, he is responsible for contracts that deal with operation and maintenance of Synthetic Chemical and Synthetic Peptide Facilities that conduct syntheses of male contraceptives, such as hexahydro-indenopyridines, ketoconazole analogs, and bioisosteres of lonidamine, and a variety of steroids, including orally active estrogen, long-acting androgens, and orally active anti-progestins. Dr. Kim's 3D-Molecular Modeling including Comparative Molecular Field Analysis (CoMFA)-Quantitative Structure Activity Relationships (QSAR) module has been used successfully for the design of more potent, second generation anti-progestins with reduction in anti-glucocorticoid activity. Compounds produced for biological testing include CDB-2914, dimethandrolone undecanoate, and CDB-4124. Dr. Kim serves as reviewer for *Organic Letters*, the *Journal of Organic Chemistry*, and *Medicinal Chemistry,* and also participates in the preparation of manuscripts and patent applications describing research and process development.

June Lee, M.D., Ph.D., joined the CRHB in 1999 from the National Eye Institute. She is a pharmacologist whose responsibilities include: oversight of screening novel compounds for spermicidal and anti-HIV activity; oversight of carcinogenicity testing procurement for C31G Gel and Buffergel; collaborations with Dr. Blye on testing of compounds at the Biological Testing Facility; initiation of an RFA for alternative test models for genital irritation; and creating, developing, and managing the CRHB database. Dr. Lee is actively involved in the National Emerging Technologies Committee, the NIH Drug Discovery Interest Group, and the NIH Clinical Pharmacology Interest Group. She is a member of the editorial board of *Modern Drug Discovery* and has served as a reviewer for the *Clinical Pharmacology* and *Therapeutics and Journal of Drug Delivery*. Dr. Lee currently serves on the NICHD Workplace Improvement and Diversity Advisory Committee and represents the NICHD on the NIH Asian American/Pacific Islanders Employee Committee.

Joanne Luoto, M.D., M.P.H., joined the Contraceptive and Reproductive Evaluation Branch in 1995 from the Office of the Assistant Secretary for Health, DHHS. Dr. Luoto is board certified in preventive medicine and received her M.P.H. in public health administration from Johns

Hopkins University School of Hygiene and Public Health. She focuses on research evaluation of contraceptive methods, including responsibility for spermicide contraceptive efficacy trials, evaluation of colposcopy, the steroidal contraception and risk of HIV study and substudies, research on intrauterine devices and acquired tubal infertility research, and the studies of hormones, cervical ectopy, and STI acquisition. She frequently represents the Branch with other organizations dealing with barrier contraceptives, is actively involved with condom relabelling activities at the FDA, and sponsored a workshop on critical issues in condom study design in 2002. Dr. Luoto received the NIH Director's Award in 2003 for her work establishing a network of interrelated studies of women's HIV risk and steroidal contraceptive use in Africa.

H. Trent MacKay, M.D., M.P.H., joined the CRHB in 1998 from the CDC, where he was a medical epidemiologist at the Division of Sexually Transmitted Disease Prevention. He is board certified in obstetrics and gynecology. He is responsible for the recompetition of the CCTN as well as for the SCCC of the CCTN. Dr. MacKay oversees the Phase II trial of Buffergel and serves as medical officer for the CDB-2914 trial. He developed the Progestin Contraception and Endometrial Bleeding Grant Program and solicited grants for Training in Epidemiology and Clinical Trials for Obstetricians and Gynecologists. He participated in the NIH-wide meeting on Menopausal Hormone Therapy in October 2002 and contributed to the development of the 2002 American College of Obstetricians and Gynecologists statement on hormone replacement therapy. He also attends the annual NICHD Aspen conferences. Dr. MacKay spends part of his time as the chief of the Obstetrics and Gynecology Service at the National Naval Medical Center (since 2001) and is also an associate professor of obstetrics and gynecology at the Uniformed Services University of the Health Sciences. Dr. MacKay recently completed two years as the board chairman of the Association of Reproductive Health Professionals. Dr. MacKay has been a reviewer for the *American Journal of Obstetrics and Gynecology, Obstetrics and Gynecology*, the *Journal of the American Medical Association*, *Contraception*, and others.

Patricia Reichelderfer, Ph.D., joined the CRHB in 1998 from the NIAID Division of AIDS, where she was program virologist. She represents the CRHB in HIV research, in microbicide research, and in research on HIV in women and girls and is responsible for the NICHD's portion of the CFAR. She is the NICHD representative on three HIV committees at the OAR, including therapeutics, microbicides, and women and girls. Dr. Reichelderfer was the primary organizer for the international meetings on microbicides for *Microbicides 2000, Microbicides 2002*, and *Microbicides 2004*. She is on the editorial board for the *Journal of Clinical Microbiology* and the *Journal of Women's Health*. In addition, she regularly reviews for *AIDS* and the *Journal of Infectious Diseases*. She is also responsible for microbicide development in grants supported by the intramural program for bio-weapons defense from the DHHS.

Ms. Lois Thomas joined the Contraceptive Evaluation Branch in 1983. Her responsibilities include travel, correspondence, preparation and maintenance of the Branch's administrative budget, and conference planning. Prior to joining the Branch, she worked in the Office of the Director at the CPR.

Anne M. Weber, M.D., M.S., has represented the CRHB since 1999 in female pelvic floor disorders on an Intergovernmental Personnel Act appointment. She remains an associate professor in the Department of Obstetrics, Gynecology, and Reproductive Sciences at the

University of Pittsburgh Medical Center and at Magee-Womens Hospital. She is board certified in obstetrics and gynecology, with subspecialty training in urogynecology and pelvic reconstructive surgery, and received her M.S. degree in clinical research design and statistical analysis. Dr. Weber established the PFDN, works with the NIDDK on the UITN, and has initiated several training RFAs. She is working to integrate basic science and translational research in the field of female pelvic floor disorders, to promote more collaborative, multidisciplinary efforts. She directs the NIH component of the newly established National Capital Consortium Fellowship in Female Pelvic Medicine and Reconstructive Surgery. She organized three NICHD conferences in support of the female pelvic floor disorders program. Dr. Weber is an active reviewer for the *American Journal of Obstetrics and Gynecology, Obstetrics and Gynecology, Journal of Women's Health*, and others. She was a member of the board of directors and the research committee for the American Urogynecologic Society and was on the subspecialty writing committee of the Council of Resident Education in Obstetrics and Gynecology.

APPENDIX B: CRHB -SPONSORED CONFERENCES/WORKSHOPS, 2000-2003

- Workshop: *Potential Clinical Applications for GnRH Antagonists*, January 2001
- Conference: *Natural Products as Microbicides and Contraceptives*, September 2001
- Workshop: *Relevance of Experimental Models to HIV Disease*, November 2001
- Workshop: *Grant Fundamentals for Researchers in Urogynecology*, October 2002
- Workshop: *Basic Science and Translational Research in Female Pelvic Floor Disorders*, November 2002
- Workshop: *Critical Issues in Study Design of Research on Condoms and the Prevention of STIs*, December 2002
- Conference: *Fertility Regulation and Systemic Hormones in HIV-Infected and At-Risk Women*, January 2003
- Workshop: *DMPA, Weight Gain, and Diabetes: Is There a Relationship?* November 2003