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## I. EXECUTIVE SUMMARY

Within the National Institute of Child Health and Human Development (NICHD), research on the efficacy, safety, and mechanisms of action of various methods of contraception and on reproductive epidemiology has traditionally been part of the mission of the Center for Population Research (CPR). The two branches within the CPR that were historically responsible for supporting research dealing with all aspects of contraceptive research and development and with epidemiology and certain issues in reproductive health were the Contraceptive Development Branch (CDB) and the Contraceptive and Reproductive Evaluation Branch (CAREB), respectively. During the past several years, research on transmission of sexually transmitted diseases (STDs), and especially HIV, has significantly expanded, as have other areas of the program. Therefore, the activities of the two Branches were integrated into a single entity, called the Contraception and Reproductive Health Branch (CRHB). This Branch is in the unique position of being a new entity that not only combines the research foci of the two previous Branches but is better positioned to develop a broader program, to explore new reproductive health and contraceptive technologies, to undertake complex studies related to STD/HIV transmission, and to design multicenter clinical trials.

Challenges of combining the interests, activities, and staff of these two diverse groups have included how to best utilize their knowledge and skills while integrating their differing emphases on research. The overall effect has been to create a more dynamic, focused group whose combined talents have allowed the Branch to expand into new areas of research, such as prevention of STDs, including AIDS; gynecologic/urologic concerns related to reproduction; and a more women-oriented agenda. Once the management and logistical changes attendant to the merger were made, however, it was imperative to focus on how well the current programs were meeting the CRHB mission. To that end, eight experts in contraception and reproductive health reviewed CRHB's activities and programs and met as a Program Advisory Committee (PAC) to discuss with CRHB and other NICHD staff new directions for the Branch.

The PAC meeting was held in July 1999, and the results were very positive. The discussion, as well as the PAC recommendations, energized Branch staff to review programs and activities with a new vision and to more clearly define Branch goals and objectives. For example, the Branch agreed with the PAC's recommendation that a more abbreviated, focused mission be adopted and a framework of goals be developed that would best serve to successfully accomplish the CRHB mission.

The revised mission statement is *to advance research in contraception and reproductive health*. In support of this mission, the Branch has defined five major program areas, based upon broad goals. Within these program areas, specific objectives were defined to delineate areas of emphasis. Therefore, although this report discusses the scientific activities and achievements of CRHB (including CDB and CAREB) since their respective 1995 Council Reports, it focuses on these five program areas and goals and the projected future directions foreseen for the Branch.

## II. OVERVIEW OF PROGRAM AREAS AND GOALS

### PROGRAM AREA 1: Contraceptive Research and Development

**GOAL:** *Promote contraceptive research and development to prevent or reduce unintended pregnancies*

Specific objectives include: 1) develop new male contraceptive methods, primarily nonhormonal agents and vaccines; 2) develop new hormonal methods for emergency contraception; 3) support basic research and development that may lead to new methods for inhibiting ovulation, fertilization, or spermatogenesis; and 4) develop experimental studies in animals and clinical trials in humans to determine optimal formulations and dosages of contraceptive agents.

In a world with an ever-expanding population, contraceptive research and development is critical for providing safer, more efficacious methods of preventing unintended pregnancies--both mistimed and unwanted. Despite the availability of a range of contraceptive methods, over 50% of pregnancies in the United States are unintended. Thus, there is a critical need for contraception that better fits the diverse needs of women and men throughout their reproductive lives. It is unclear whether dissatisfaction with available methods leads to misuse or abandonment of effective methods or whether these methods are too inconvenient, too expensive or too complicated. Optimally, a variety of contraceptive methods would be available to address the needs of people with different ethnic, cultural, and religious values, those with inadequate access to services, and those with changing needs related to age. The CRHB program is designed to expedite the development of new methods to regulate fertility. Encouragement and support for this mission comes from a number of sources:

- **Congressional Support.** The Center for Population Research was established in 1968 by the Secretary of the Department of Health, Education, and Welfare. One of the goals was the development of new contraceptives through the use of contracts and grants. This goal was reemphasized in the 1996 amendment to the Public Health Service Act (Title X). Each year in its appropriations bill, Congress has reiterated its support for this goal by highlighting contraceptive research and development as important parts of NICHD's mission. In addition, in 1993, Congress passed legislation directing that NICHD establish three extramural centers devoted to contraceptive research and development.
- **The Institute of Medicine (IOM)** conducted a study on contraceptive research and development and concluded that the public need for continued efforts was overwhelming (*Contraceptive Research and Development: Looking to the Future*, PF Harrison and A Rosenfield, editors; National Academy Press, Washington, DC, 1996). Among their recommendations were the development of barriers to sperm and to STD pathogens, once-a-month methods, and male contraceptives. They recommended strengthening efforts to identify gamete-specific targets either for inhibition of development (i.e., spermatogenesis) or for inhibition of fertilization (i.e., contraceptive vaccines, ovulation suppressors).

- **The United Nations International Conference on Population and Development**, held in Cairo in 1994, also emphasized the urgent need for new methods of contraception to meet the variety of needs in the international community. Highlighted was the need for woman-controlled methods that could be used either in cooperation with, or independently of, a partner.

Development of effective, safe, and acceptable male contraceptive drugs is a major component of the women's health agenda. Male contraceptive drugs must have little or no effect on libido and potency, which complicates using hormonal methods that compromise the gametogenic and endocrine function of the testis. The development of male contraceptive drugs has historically lagged substantially behind development of female contraceptives due to the complexity of the male reproductive system, social/behavioral aspects, and economic considerations. The last is based on the suppositions that due to the availability of safe and effective female contraceptives, male methods are unnecessary; that men are unwilling to take contraceptive pills or injections, and that men will not adhere to contraceptive drug regimens as carefully as do women. Perceptions of the need for male contraceptive drugs may be changing, since two large pharmaceutical companies and two large private foundations have begun to provide financial support for the development of male contraceptive drugs. Recent market research by the pharmaceutical industry suggests that significant numbers of men are willing to use contraceptive drugs.

## **PROGRAM AREA 2. Contraceptive Evaluation and Reproductive Epidemiology**

**GOAL:** *Expand evaluation of contraceptive methods and reproductive epidemiology*

Specific objectives: 1) conduct epidemiologic, statistical, and clinical studies for post marketing surveillance of drugs, devices, and procedures utilized for contraception and reproductive health; and 2) collect and analyze data from diverse sources to assess the effect of drugs, devices, and procedures utilized for contraception and reproductive health.

This program area includes evaluation of contraceptive methods currently marketed in the United States through clinical trials and epidemiologic studies. Whereas contraceptive discovery and development activities allow determination of short-term or acute side effects they do not offer maximal opportunity to examine possible longer-term or infrequent associations between contraceptive methods and other medical conditions. The clinical trials required for FDA approval involve samples that are too small and studied for too short a time to be able to detect relatively infrequent, but important, side effects that may emerge only after new methods are marketed. Therefore, CRHB also supports Phase IV studies which include selective studies of available methods, devices, or drugs. These include studies that allow examination of associations between contraceptive methods and reproductive or other outcomes that require either larger

populations, special populations, or longer time periods than those needed for FDA approval.

The former CARE Branch brought a portfolio of research grants (primarily R01s) to the merger that formed the CRHB. These grants include areas of research that reflect the reproductive health mission of the old branches and the new consolidated branch. The Institute welcomes investigator-initiated grant applications on various topics and periodically solicits proposals focused on a particular area by issuing a Request for Applications (RFA) for research grants or a Request for Proposals (RFP) for research contracts.

The importance of these activities to contraceptive utilization decisions is illustrated by the public concerns regarding oral contraceptives and subsequent cancers of the reproductive system, including breast, cervical, and endometrial cancers. Another example of the relevance of such research can be found in the Dalkon Shield controversy, where studies of relatively large populations using these IUDs revealed dangers of septic abortion and death and resulted in their removal from the marketplace.

### **PROGRAM AREA 3. Prevention of HIV/AIDS/STDs**

**GOAL:** *Promote research on the prevention of HIV/AIDS/STDs through development and evaluation of spermicidal microbicides and research on gender-specific HIV issues for women*

Specific objectives: 1) establish a priority research agenda linking contraceptive technology to AIDS prevention; 2) develop new microbicides with spermicidal activity; 3) conduct experimental studies in animals and clinical trials in humans to determine optimal formulations and dosages of spermicidal microbicides; 4) review current and develop new animal models useful for investigating HIV heterosexual infection mechanisms and prevention of transmission; and 5) test specific contraceptive methods for their effect on preventing or enhancing the heterosexual transmission of HIV. These objectives were partially taken from the NICHD HIV agenda, derived from recommendations made at a 1989 conference, Heterosexual Transmission of AIDS, co-sponsored by NICHD.

There is a lack of knowledge regarding the effect of steroidal hormones on HIV acquisition and disease progression. Steroidal contraceptives and hormone replacement therapy (HRT) are widely used throughout the world. Oral contraceptives (OCs) are used by at least 72 million women worldwide and by 18 million women in the United States. An estimated 80% of U.S. women will use OCs at some point during their reproductive years. In 1990, about 10 million women worldwide used injectable depot medroxy-progesterone acetate (Depo-Provera or DMPA) and, since then, its use has increased rapidly. Because HIV infection primarily affects women of reproductive age, understanding the impact of steroidal contraception on HIV transmission is a critical public health issue. In addition, many HIV-positive women continue to use steroidal contraceptives. Thus, it is important to understand the role of steroidal hormones in HIV

progression as well as to address the effect of HRT on disease progression in postmenopausal HIV-infected women. In the future, it will be important to define the role of hormones on the efficacy of HIV vaccines.

In the United States and worldwide, HIV infection rates in women are increasing. Given the preponderant role of heterosexual transmission globally, it is apparent that HIV acquisition and progression must be considered in the context of sexual activities and fertility regulation methods, including spermicides and steroid hormones. Additionally, data are continuing to emerge that support the hypothesis that some aspects of HIV disease in women differ markedly from men, such as more rapid disease progression with lower viral loads. There are also gender-specific complications of HIV disease such as cervical dysplasia. As the transmission from mother to child has decreased, the interest in prevention of heterosexual transmission has increased concurrently with research interest on HIV infection in women.

The NICHD HIV/AIDS/STD research program includes activities central to the NIH HIV prevention research endeavors. The NICHD's HIV Prevention Research agenda focuses on preventing heterosexual and perinatal transmission of HIV/AIDS. Microbicides could offer a female-controlled alternative for prevention of transmission of HIV and other STDs.

Encouragement and support for the NICHD program comes from two sources:

- **The U.S. Congress**, which encouraged the NICHD's activities in this area; committee language accompanying the FY99 House Appropriations Bill states:

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

- **The NIH Office of AIDS Research (OAR)**, which has stated that microbicide development should be an area of prevention science developed with as much attention as that placed on vaccine prevention strategies.

#### **PROGRAM AREA 4. Selected Reproductive and Gynecologic Health Issues**

**GOAL:** *Advance research into selected reproductive and gynecologic health issues.*

Specific objectives: 1) sponsor research and development efforts on reproductive health issues that have been either overlooked or underfunded; and 2) focus research efforts on reproductive health issues considered important to women's health, gender studies,

and issues of minorities and aging as these relate to reproductive health within the purview of CRHB.

NICHD is a major source of NIH funding for research in obstetrics and gynecology. However, while research in perinatology and reproductive endocrinology has received adequate funding from NICHD and research in gynecologic oncology is well-funded by NCI, research in the area of gynecology has been underfunded. For example, very little NIH funding has been provided for research on female pelvic floor disorders. Pelvic floor disorders include pelvic prolapse, urinary and fecal incontinence, and other sensory and emptying abnormalities of the lower urinary and gastrointestinal tract. Up to one-third of adult women may suffer from one or more of these disorders, and almost 10% of women in the United States will undergo a major surgical procedure to correct urinary incontinence or pelvic 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. This is a new area of research funding for CRHB with little relationship to other Branch activities discussed under Research Highlights.

Other research areas in gynecology of interest to CRHB include new hormonal treatment of endometriosis and leiomyomata and the elucidation of mechanisms and treatment of abnormal uterine bleeding. These disorders are among the most common reasons for women to seek gynecologic care, and the proposed research in these areas represent extensions of current research in contraceptive methods funded by CRHB.

In 1992, the Institute of Medicine published *Strengthening Research in Academic OB/GYN Departments*, in which they recommended that Institutes at NIH whose missions include areas of science to which OB/GYN contributes should affirm their commitment to reproductive health and insure its appropriate priority in their programs. The report specifically mentioned the need for research on the treatment of endometriosis. More recently, both House and Senate Appropriations Committees have included report language that encouraged the collaboration of the National Institute of Diabetes, Digestive and Kidney Disease (NIDDK) and NICHD in funding research in urinary incontinence in women as well as NICHD support of research in the area of pelvic floor disorders.

## **PROGRAM AREA 5. Research Training**

**GOAL:** *Promote training in areas of contraception and reproductive health to attract new investigators to the field*

Specific objectives: 1) support training of obstetricians and gynecologists in epidemiology and clinical research to ensure future cadres of investigators in

contraception and reproductive health; and 2) provide training for pharmacologists, organic chemists, engineers, biologists, and epidemiologist to promote future research in this field.

While academic departments of obstetrics and gynecology are a logical venue for much of the research in contraception and reproductive health, few academic obstetricians and gynecologists have received formal research training. The 1992 IOM report, *Strengthening Research in Academic OB/GYN Departments*, identified a lack of academic obstetricians and gynecologists with formal research training as an important obstacle to obtaining research funding. The IOM recommended 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."

Another IOM report, *Careers in Clinical Research*, recommended encouragement of selected centers to develop programs of interdisciplinary studies which lead to advanced degrees in evaluative sciences related to clinical research. This same report emphasized the differences between laboratory research and clinical research. In addition, language in the FY98 report of the House Appropriations Committee encouraged support of research training for obstetricians and gynecologists. While the Reproductive Sciences Branch of the CPR funds training for academic obstetricians and gynecologists with an interest in basic science research, NIH support for training of obstetricians and gynecologists in epidemiology and clinical research is minimal.

### **III. RESEARCH HIGHLIGHTS**

#### **Male Contraception**

In addition to its efforts in new condom development, the CRHB has long supported research and development of pharmacological approaches to male contraception, including hormonal and antispermato-genic methods. In the future, we expect to expand research in this area. Based on the recommendations of the PAC, future research will be directed toward nonhormonal methods.

#### **Male Condoms**

Condoms made of latex are not comfortable or appropriate for all consumers, including those who are allergic to latex. Although the first polyurethane condom has been approved for use in the United States, no clinical trial had compared its performance to the latex condom until the results of a CRHB-supported study appeared in 1998. In this crossover study, 360 couples were randomly assigned to use three Avanti™ condoms (polyester polyurethane) either before or after using three latex condoms. Although the breakage rate of the polyurethane condom was found to be significantly higher than that of the latex condom, nearly half of the users preferred the polyurethane condom. This demonstrated that the polyurethane condom provides an option for couples who cannot



or will not use latex condoms, although it may not protect against STDs as well as do latex condoms.

To follow up on these results, another trial now underway compares the performance of another nonlatex Tactylon™ condom (styrene ethylene butylene styrene) to two different latex condoms. Couples enrolled in the study are randomly assigned to use either the Tactylon™ condom or one of two brands of commercially available male latex condoms. Comparisons on efficacy, safety, and product acceptability will be made between couples using the nonlatex condom and the latex condoms. It is notable that even in the select group participating in a clinical trial, couples reported that in nearly one-third of uses that they failed to follow one or more of the study instructions for correct condom use. Complete data on the differences between the condom types will be available after the follow-up ends in September 1999.

### ***Hormonal Methods***

The CRHB has sponsored three important developments in the use of hormonal steroids for male contraception:

***Testosterone Bucyclate.*** The Branch has actively pursued the development of a new long-acting androgen, testosterone bucyclate, for many years. Originally prepared under a WHO-sponsored steroid synthesis program, this ester was evaluated for duration of androgenic activity. The Branch's Biological Testing Facilities have played a role in developing this compound through extensive testing of testosterone bucyclate, including subchronic toxicology that would support Phase I/II clinical studies. Preliminary clinical studies have been supported by the World Health Organization (WHO). The duration of action following a single intramuscular injection appears to be greater than that of testosterone enanthate, the most widely employed injectable androgen preparation. NIH and WHO jointly share the patent for this drug. A licensing agreement is currently being negotiated with a large pharmaceutical company to commercialize this drug as a replacement or supplemental androgen for hypogonadal men, including those receiving gonadotropin releasing hormone (GnRH) analogs or progestational agents for male contraception.

***MENT™ (7 $\alpha$ -methyl-19-nortestosterone).*** The development of MENT™ for male contraception and for HRT holds promise. This synthetic androgen is being developed by The Population Council under Center grant support from CRHB. It is considerably more potent than testosterone in its effects on muscle and the pituitary, even though its stimulatory effect on the prostate is less than that of other testosterone derivatives. MENT™ can be administered to men without overstimulation of the prostate, which can occur with testosterone. MENT™ has a high binding affinity to androgen receptors, but does not undergo enzymatic 5 $\alpha$ -reduction in the prostate. In contrast, testosterone is 5 $\alpha$ -reduced to dihydro-testosterone (DHT), an androgen with higher affinity for androgen receptors and greater potency in stimulating growth of the prostate.

***Levonorgestrel Butanoate.*** This ester of levonorgestrel, a synthetic progestational agent widely employed in progestin-only and combination (with estrogen oral contraceptives, also originated from a WHO-sponsored synthesis program. Its potent long-acting progestational activity was discovered at the Branch's Biological Testing Facility. This drug has been extensively studied in rodents and primates by the CRHB, including a one-year toxicology study and a pharmacokinetic study to support Phase I/II clinical investigation as a long-acting injectable contraceptive for women, and a hormonal contraceptive for men when used in combination with androgen supplementation. The free alcohol moiety, levonorgestrel, has been successfully employed in oral form in combination with a supplemental androgen by intramuscular injection, often testosterone enanthate, in experimental studies to induce azoospermia or oligospermia in normal men. Thus the foundation for the use of levonorgestrel butanoate in aqueous microcrystalline suspension as a sustained source of active steroid is established. Formulation studies are in progress to develop a stable and clinically acceptable aqueous suspension.

### ***Antispermatic Agents***

The antispermatic activity of a series of indenopyridines (nitrogen heterocycles) continues to be studied. A single oral dose of 2.5 mg/kg of indenopyridine is sufficient to produce irreversible infertility in rats. Research is in progress that could provide for reversibility of the action of this drug via pretreatment with GnRH antagonists. Present pharmacological studies are directed at identifying the mechanism of action which could lead to achieving reversal of the effect on the germinal epithelium. These include studies of Sertoli cell function in the production of inhibin and histocytological studies of Sertoli cells, as well as examining the effects of pretreatment with GnRH agonists and antagonists. Leydig cell function does not seem to be impaired; thus, no supplemental androgen therapy is required.

### **Immunocontraceptives**

CRHB funds three extramural centers to do research on contraceptive development. Much of the focus to date has been on immunocontraceptive research. The concept behind this approach to contraception is to identify gamete-specific antigens, to engineer the genes encoding these antigens into appropriate expression systems, to formulate vaccine doses and to test the vaccines in animal models, primates, and human volunteers. Antisperm contraception can target either sperm function or sperm development. Inhibition of sperm function could be achieved in either men or women, while inhibition of sperm development would be specific to men.

The productivity of the investigators in the contraceptive development centers program has been impressive, resulting in many publications, patents, and clinical trials. A commercial product for measuring sperm concentration in semen has been developed,

which will be a useful adjunct in determining efficacy of hormonal, vaccine, or surgical contraception in men.

## **Basic Research**

Angiogenesis is the process of formation of new blood vessels in a variety of biological systems in which vascularization plays an important role. Some of the molecules that play a role in angiogenesis may also be important for aspects of follicular development and ovulation and endometrial development and differentiation. The role of angiogenesis inhibitors is under intensive study as it relates to cancer therapeutics. However, these molecules are also potential candidates as contraceptive agents, utilizing their action to inhibit formation of blood vessels. The concept is still in preliminary stages of development, but more efforts are being made to learn about the functions of angiogenesis inhibitors in the reproductive process.

## **Contraceptive Clinical Trials Network**

The Contraceptive Clinical Trials Network (CCTN) is comprised of nine field centers, as well as a Statistical and Clinical Coordinating Center (SCCC). The CCTN also makes use of the CRHB Scientific Advisory Committee (SAC) which is composed of outside experts in the fields of basic and clinical contraceptive research, pharmacology, and epidemiology. The nine 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 site has, at a minimum, a qualified obstetrician-gynecologist, study coordinator, data/research manager, and access to clinical facilities that are capable of recruiting at least 50 women per year for Phase I trials and at least 200 couples per year for phase II/III trials.

There are currently three active clinical protocols in the CCTN: the Phase I trials of four spermicides; a Phase II/III trial, limited to one center, involving testing of efficacy and breakage/slippage of a nonlatex condom; and a Phase II/III trial of CDB-2914, a selective progesterone receptor modulator (SPRM), for emergency contraception.

## **Sterilization**

### ***The Collaborative Review of Sterilization (CREST)***

The CREST study was the first major longitudinal study of women undergoing tubal ligation. Papers resulting from this study (both published and submitted) present the following findings:

- Women who have undergone tubal sterilization are more likely to undergo hysterectomy within 5 years after sterilization (regardless of age at sterilization or method of tubal occlusion) than are women whose husbands have had a vasectomy.

- The 10-year cumulative probability of ectopic pregnancy for all methods of tubal sterilization combined was 7.3 per 1,000 procedures and varied by age and sterilization procedure. The annual rate of ectopic pregnancy after all methods of sterilization combined was no less in the fourth through tenth years after sterilization than it was in the first 3 years. The highest risks were seen among women who were sterilized under age 30 and among women sterilized by bipolar tubal coagulation.
- The risk of sterilization failure (nonectopic and ectopic pregnancies combined) was higher than generally reported in medical textbooks and was found to persist for years after the procedure and to vary by method of tubal occlusion and age.
- Fourteen years after having undergone sterilization, the risk of regret is higher for those who were 30 years old or younger at the time of sterilization (20.3%) than it is for older women (5.9%) and is lowest for those having no previous births (6.3%).

### ***NICHD Conference on Sterilization***

In 1998, the CRHB organized a 2-day conference on "Male and Female Sterilization: Medical Effects and Behavioral Issues." Three review articles were commissioned for presentation at the conference and have been submitted for publication to *Fertility and Sterility*. The following research topics were among those identified as needing to be resolved:

- **Contraceptive decision-making regarding sterilization.** This area is largely unexplored. Topics needing further study include couple vs. individual decision-making, the influence of provider attitudes, insurance coverage for and costs of contraceptive alternatives, ethnic variations in contraceptive methods used, and the influence of people's understanding of safety and efficacy. This issue has been referred to the Demographic and Behavioral Sciences Branch.
- **Vasectomy.** Long-term studies of efficacy, separately by type of vasectomy, have never been done and are long overdue. Short-term studies to help define the extent of follow-up needed to provide sufficient evidence of infertility are also needed to develop evidence-based guidelines on recommended numbers and timing of postvasectomy visits and the use of alternative contraceptive methods until infertility is demonstrated. The postvasectomy chronic pain syndrome needs to be characterized with respect to its prevalence, predictability, preventability, severity, and prognosis. Study of the effect on urolithiasis may be warranted.
- **Female Sterilization.** Due to the major changes that have occurred in procedures and equipment for tubal sterilization since the CREST data were collected, a large, short-term study of the effects of the most common current methods of sterilization may be warranted.

### **Postmenopausal Estrogen and Progestin Intervention (PEPI) Study**

The CARE Branch partially funded and provided scientific collaboration on the National Heart, Lung and Blood Institute's (NHLBI) PEPI study. This was a double-masked randomized placebo-controlled clinical trial in which four postmenopausal hormone regimens were studied for their effects on High Density Lipoprotein-cholesterol, systolic blood pressure, fibrinogen, and plasma insulin. All active treatments increased HDL-cholesterol, while women taking the placebo experienced a decline over 3 years. Similarly, compared with the placebo, active treatments decreased Low Density lipoprotein-cholesterol and raised triglycerides. Fibrinogen levels did not differ between active treatment and placebo. Unopposed estrogen increased the HDL-cholesterol value more than any of the regimens including progestins.

### **Cardiovascular Disease and Steroid Hormone Contraception**

Research on cardiovascular disease and steroid contraception was funded in collaboration with the Human Reproduction Program at WHO. The entire WHO case-control study involved 21 field centers worldwide and included acute myocardial infarctions, strokes, and venous thromboembolisms as outcome variables. CRHB funded one field site and two data coordinating centers for this study; it also funded two related projects in the United States. The primary results of these studies confirmed the belief that the second generation of oral contraceptives had less elevated cardiovascular risk compared with the first generation. These studies and a related scientific meeting in 1997 at WHO helped to form the basis for the American College of Obstetricians and Gynecologists' current guidelines on OCs and cardiovascular disease.

### **DMPA Use and Bone Mineral Density in Young Women**

Published studies to date suggest that DMPA use decreases bone density, which possibly leads to an increased risk of osteoporosis in later life. There is, however, a need to define the complex relationship of DMPA in relation to age at use and duration of use. A CRHB supported study documents long-term data on bone mineral density (BMD) in DMPA users (ages 18-35), assesses the effect of discontinuation of DMPA, and assesses the effect on BMD in adolescents. A supplement has been submitted for examination of adolescents as a special group; they will be followed for 24 to 36 months, with BMD measured by dual energy x-ray absorptiometry every 6 months. The preliminary data support the hypothesis that DMPA use reduces bone mineral density, but suggest that this effect is reversible following discontinuance.

### **Weight, Obesity and Oral Contraceptive Failure**

Among women using reversible birth control methods in the United States, 50% use OCs. Among OC users, 500,000 pregnancies occur annually. These pregnancies are routinely attributed to method noncompliance (user failures) rather than method failure. There is, however, no provision for dosage considerations in routine clinical prescription

of OCs. This 4-year population-based case-control study among reproductive age women in an HMO will determine if obesity leads to a higher risk of OC failure, if there are differences in failure rates of OCs among obese women by type or dose of OC used, and whether typical use versus perfect use of OCs plays a role in unexpected pregnancy.

### **Contraceptive Hormones and Risk of Breast Cancer**

The relationship between OCs and breast cancer has been investigated extensively for more than two decades, but complications to a definitive conclusion exist (e.g., changes have occurred over time in pill formulations, in pill prescribing and compliance patterns, in cancer screening guidelines, in histologic cancer classification, and in reproductive choices such as age at first birth or use of pills, among others). Research to date has not attempted to measure the association between oral contraceptive use and lifetime risk of breast cancer, including hormonal use for other than contraceptive purposes (e.g., therapy for other conditions, postmenopausal HRT). Women now in the highest risk ages 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.

The NICHD's Women's Contraceptive and Reproductive Experiences (Women's CARE) Study, a retrospective case-control study of approximately 5,000 women, ages 35-64, was designed to study these issues. The primary objectives were to: 1) compare breast cancer risk of OC users to never-users; 2) evaluate the impact of various patterns of OC use to breast cancer risk; 3) assess the impact of time of life for use of OCs on breast cancer risk; 4) elucidate the role of formulation, intensity, and identity of estrogens/progestins; and 5) assess the role of HRT 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 conduct of appropriate laboratory studies on biologic specimens (blood and tumor tissue). The study consists of contracts with five academic clinical sites and an Interagency Agreement for data coordination support with the Centers for Disease Control and Prevention (CDC).

### **The Cochrane Collaboration**

The Cochrane Collaboration is an international network of organizations and individuals that perform ongoing systematic reviews of randomized, controlled clinical trials on specific medical interventions. It was developed to provide clinicians with access to up-to-date and valid information for decision-making, since dissemination of information frequently lags far behind what is scientifically known from randomized trials. The approximately 50 Cochrane Review Groups encompass most of the major areas of medicine. The systematic reviews are made widely accessible through publication in the Cochrane Library, which is distributed at low cost on disk, CD-ROM, and via the Internet.

Through an Interagency Agreement with USAID, CRHB provides funding for publication of a book with a compilation of all the Cochrane Collaboration fertility regulation reviews. It is expected that the collaboration will produce approximately three to four reviews annually and that the reviews will be made available on the Internet. A book with a compilation of the reviews performed by the collaboration as well as the reviews produced by the other members of the Fertility Regulation Review Group is scheduled to be published by the end of the 5-year project. The availability and wide dissemination of such reviews will markedly enhance decision-making by practitioners in the field. In addition, the development of this database will assist the CRHB in the identification of gaps in knowledge and contribute to defining our research agenda.

### **Progestins and Endometrial Bleeding**

“Endometrial Vascular Endothelial Growth Factor: Endocrine Regulation of Angiogenesis” is the topic of a CRHB-supported grant which seeks to understand the molecular and cellular mechanisms that underlie irregular bleeding commonly associated with DMPA injections and levonorgestrel-containing silastic capsules (Norplant™). Unlike the initiation of normal menses, which is triggered by spiral artery constriction, irregular bleeding associated with parenteral progestins is thought to originate from the subepithelial capillary plexus. Regulation of the endometrial microvasculature is understood poorly, but its growth and development are coordinated by ovarian hormones. The investigators have hypothesized that vascular endothelial growth factor (VEGF) mediates the effects of ovarian steroids on the growth and function of the endometrial microvasculature. Progestational agents alter endometrial VEGF action, disrupting normal angiogenesis and regulation of endometrial microvessels. This disruption of endometrial vasculature, glands, and stroma ultimately leads to unpredictable, irregular uterine bleeding. An integrated, multidisciplinary team of investigators with expertise in clinical contraception and basic laboratory investigation will address the following objectives: 1) to examine the ultrasonographic, hysteroscopic, microscopic and biochemical characteristics of the endometrium (including expression of VEGF and estrogen and progesterone receptors) in women using parenteral progestin contraceptives and in normal, ovulatory controls; 2) to study the *in vivo* regulation of VEGF by ovarian steroids and the role of VEGF in endometrial angiogenesis; and 3) to study the molecular regulation of ovarian steroids and their receptors by VEGF. An understanding of the cellular expression of VEGF and the endocrine regulation of endometrial angiogenesis should provide new targets to improve the acceptability of these effective contraceptive methods.

### **Prevention of HIV/AIDS/STDs**

The CRHB currently maintains grant portfolios on vaginal physiology and vaginal immunology. This research focuses on the interrelationship between hormones, coitus, and intra-vaginal products and their effect on systemic and local immune systems, as well as the impact of these and other factors on the shedding of HIV in the female genital tract. Protective immunologic mechanisms of the vagina and the interplay of

these factors with HIV and other pathogens are at the heart of the prevention of HIV transmission. Female-to-male, male-to-female, and mother-to-newborn transmissions of HIV are likely to be heavily mediated by vaginal and cervical factors. A better understanding of virologic, immunologic and disease factors at play in the uninfected, at-risk woman are key to the prevention of heterosexual HIV transmission. NICHD also funded studies on: 1) factors influencing detection of HIV in semen; 2) 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 3) 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 nonspermicidal compounds.

CRHB funds a multisite, international, prospective study of possible effects of contraceptive steroids (both oral and injectable) on the risk of HIV acquisition in high incidence areas, i.e., Africa and Asia. This study utilizes the NIAID's HIVNET infrastructure. The protocol has received final approval and the 5-year study is initiating recruitment of the 6,400-woman cohort. Additional studies will be nested within this protocol.

The only FDA-approved active ingredient in most marketed spermicides is nonoxynol-9 (N-9), which was monograph-approved by the FDA as safe and effective in the early 1980s along with closely related octoxynol-9 (O-9). In 1995, the FDA expressed concerns about the conflicting evidence available on both the safety and efficacy of vaginal N-9 and proposed to require stringent new clinical evidence for such products. The CRHB is undertaking a Phase III trial of five N-9 vaginal spermicide products for contraceptive efficacy (through detection of both clinical and preclinical pregnancies) and, secondarily, for a comparison of product safety (through colposcopy, effects on vaginal microflora, and reports of adverse reactions). The trial is taking place at 11 clinical sites in the United States and has a target accrual of 1,800 women, ages 18-35, to be followed for 39 weeks. The five vaginal spermicide products chosen for the trial will allow for comparison of contraceptive efficacy of products with the same formulation but different doses of N-9 (all gels), as well as a comparison of the efficacy of different formulations with the same dose of N-9 (gel, suppository and film at 100 mg.).

NIAID and NICHD have cosponsored important clinical studies on viral shedding in the genital tract of HIV-infected women. Several institutes (NICHD, National Institute of Dental and Craniofacial Research {NIDCR}, and NIAID) funded studies on various questions concerning the etiology and pathogenesis of HIV infection and its manifestations in women, including studies on parameters affecting genital tract and oral cavity shedding of HIV-1 and the effect of the menstrual cycle on virologic and immunologic parameters in HIV-infected women.

In 1997, the NIAID opened their Centers for AIDS Research (CFAR) Program to other institutes for participation. The NICHD agreed to cosponsor and be primary on one CFAR and CRHB is the sponsoring Branch. This CFAR has a strong interest in both



genital HIV and microbicide/STD prevention research as well as behavioral prevention research.

In FY 1991, the CARE Branch funded a proposal to conduct a prospective follow-up study of the efficacy of the male latex condom in preventing transmission of STDs (specifically, gonorrhea, chlamydia, and herpes virus) in a cohort of 2,615 women at high risk of STDs. In FY 1995, in response to a request to NIH from the Commissioner of the FDA, this contract was modified to include a similar but separate study cohort of 1,159 women among whom the protective effect of the female condom (REALITY™) relative to STDs was evaluated. CDC funded a behavioral add-on study with objectives to evaluate the effect of sociodemographic, psychosocial, and behavioral characteristics on use of the female condom. Preliminary analysis of the data finds that participants reported a high degree of consistent use of condoms, and that both the male and female condoms are effective in preventing gonorrhea and chlamydia.

Funding has been provided for a grant to develop a N-9 vaginal contraceptive with hydrogen-peroxide for possible enhanced antimicrobial properties (Buffergel, Johns Hopkins University). Research on this formulation has demonstrated that the carbopol gel base is stable in the presence of 1% hydrogen peroxide, that lactobacilli remain viable, and that the compound does not affect condom integrity. Support is provided for evaluation of multiple formulations for *in vitro* antimicrobial activity, spermicidal activity, antiviral activity, and antilactobacillus activity. A single formulation will be selected for Phase II testing, and for spermicidal activity *in vivo*.

CRHB staff have been instrumental in organizing an international conference on microbicides in FY2000.

One obstacle to predicting the clinical efficacy of microbicides has been the lack of a validated measure of their activity in HIV-positive women who are shedding virus. NICHD, along with NIAID and NIDCR, has supported a series of studies to understand the factors influencing shedding of HIV-1 in the genital tract and oral cavity of HIV-1-infected women as a first step towards initiating microbicidal activity studies in HIV-1-infected women.

### **Selected Reproductive & Gynecologic Health Issues**

In response to a perceived need and Congressional language, the CRHB has undertaken a number of activities in the area of pelvic floor disorders, including: 1) hiring an academic urogynecologist on a part-time basis; 2) cosponsoring and cofunding an RFA from NIDDK on urinary incontinence in women; 3) planning a workshop in December 1999 to standardize terminology and outcomes measurement; and 4) developing separate RFAs to fund epidemiologic research and a clinical trials network. In addition to pelvic floor disorders, activities in other areas of gynecology are also being planned: chronic toxicity studies of a selective progesterone receptor modulator (SPRM);

and clinical trials in the Contraceptive Clinical Trials Network of a SPRM to ascertain its efficacy for the treatment of endometriosis.

### ***Pelvic Floor Disorders***

The CPR has assumed the task of developing a research program in pelvic floor disorders. The OB/GYN community and, in particular, the urogynecologic community, have expressed concerns about the lack of funding for research in this area. A planning meeting was held in March 1998 with representatives from NICHD, the NIH Office of Research on Women's Health (ORWH), and the American Urogynecologic Society. A subsequent meeting, which also included the NIDDK and the National Institute on Aging (NIA), was held in September 1998 to address the current knowledge and needs in the areas of basic science, epidemiology, and clinical research. A number of topics for research in each of the areas were identified, and RFAs were planned for each of the three research areas. Also identified was the need for standardization of terminology, definitions, and outcomes. After the September meeting, language in Congressional reports from both the House and Senate encouraged the continued cooperation of NICHD, NIDDK, and the ORWH in the development of a research agenda on pelvic floor disorders.

As a direct result of the September 1998 planning meeting, an RFA for basic research in pelvic floor disorders was issued in February 1999 by the Reproductive Sciences Branch, NICHD for awards in FY2000. RFAs for research in epidemiologic and clinical aspects of pelvic floor disorders are planned for funding by the CRHB in FY2001. A related RFA from NIDDK focuses on the development of treatment centers that would enroll subjects in a prospective cohort study to examine the long-term outcomes of the commonly used surgical interventions for urinary incontinence in women. The first year of the study will involve the development of standardized diagnostic and outcome measures. CRHB will support one of the centers funded by this RFA.

### **Research Training**

#### ***Reproductive Epidemiology Training Grant***

Nationally, there is a shortage of obstetrician-gynecologists who are experienced or capable of vigorous, independent academic investigation. One currently funded grant addresses that shortage, including training in etiology, prognosis, treatment, and economics. In FY 1996, NICHD funded the establishment of a 2 to 3 year formal postgraduate training program, including: 1) core curriculum in clinical epidemiology, research methods and biostatistics; 2) elective courses in reproductive biology and basic science; 3) independent research and symposia; and 4) independent research in reproductive clinical epidemiology. To date, two postgraduate M.D.s. have been in training: one for 2 years (1996-98); one for 1 year (1997-98). The senior fellow has obtained funding from outside sources for several studies (12 publications in peer-reviewed journals). In collaboration with the Fogarty International Center, NICHD

is also co-funding training of foreign scientists in contraceptive vaccinology as well as in male reproduction/contraception.

#### IV. COLLABORATIVE EFFORTS

The CRHB PAC noted the need to improve communication and collaboration with pharmaceutical companies to optimize technology transfer and with other programs, institutes and agencies involved in similar research to decrease duplication of efforts and funds and to increase productivity. 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 involves the efforts of government agencies, academic institutions, non-governmental organizations, and private industry and cuts across national borders. The CRHB has found it necessary and useful to collaborate with other Institutes within NIH and with the following organizations:

- WHO Special Programme of Research, Development and Research Training on Human Reproduction
- Centers for Disease Control and Prevention
- Institute of Medicine, National Academy of Sciences (NAS)
- USAID and its cooperating nongovernmental organizations: the Contraceptive Research and Development Organization (CONRAD), the Family Health International, and the Population Council
- Activist groups: Alliance for Microbicide Development, American Society for Emergency Contraception
- The Deputy Assistant Secretary for Population Affairs, DHHS
- Alan Guttmacher Institute
- Planned Parenthood
- Association of Reproductive Health Professionals
- American Public Health Association
- American College of Obstetricians and Gynecologists (ACOG)
- Private Industry
- Government of India

#### V. FUTURE DIRECTIONS

The CRHB looks forward to an exciting future. Based on our ongoing internal planning efforts, recommendations from our PAC, and discussions with colleagues and collaborators, we are pleased to set forth our ideas for future research. Planned and potential specific research ideas include:

***Continue to develop new methods of male contraception, focusing on nonhormonal methods and vaccines.*** CRHB, in collaboration with WHO, has developed a long-acting androgen and long-acting progestin that will have practical use

as a male contraceptive. We will complete this work through our collaborations with the WHO and with industry to bring these promising products to the market for use as safe, effective male contraceptives. The action of indenopyridines will be explored further to determine if they are a safe method of contraception for males. An RFA/RFP will be issued to stimulate research in the development of new nonhormonal methods. The Contraceptive Centers will continue to explore the specific development targets that may result in safe and effective contraceptive vaccines.

***Continue to stimulate and support research and development that may lead to new methods for inhibiting ovulation, fertilization, and spermatogenesis.*** The Contraceptive Centers will continue to study the mechanisms of fertilization and spermatogenesis in order to identify targets that offer a potential mechanism for contraception. A workshop organized by the Reproductive Sciences Branch will generate recommendations for new avenues of research in the area of spermatogenesis. We will also continue to encourage research on novel methods of contraception through future RFAs and new training programs.

***Recompete the Contraceptive Clinical Trials Network.*** We anticipate moving from a contract to cooperative agreement for further studies of contraceptives and spermicidal microbicides. Expansion is being considered to include sites that can conduct studies on male contraceptives.

***Recompete support services contracts for chemical synthesis and biological testing.***

***Issue new contracts for a formulation facility and a metabolic facility.***

***Enhance collaboration with the research community and with industry.*** We will make acyline, a GnRH antagonist, available to the research community and will work with industry to bring promising male and female contraceptive products, including reproductive health-related products, to the market.

***Publish results of the NICHD Women's CARE Study.*** Twenty manuscripts have been identified for publication by the CARE Study Steering Committee based on the questionnaire database.

***Initiate one or more RFAs, RFPs, or PAs related to sterilization.*** Options include vasectomy efficacy, the type of follow-up needed to provide sufficient evidence of infertility after vasectomy, the epidemiology of post-vasectomy chronic pain syndrome, and the short-term method-specific adverse effects of tubal sterilization.

***Continue funding of the Cochrane Collaboration, including making the results available.*** This will be done through our Interagency Agreement with USAID.

**Develop a new research plan in the area of reproductive epidemiology.** Hold a workshop to review areas of emerging scientific and public health importance and provide guidance to the Branch on future RFAs.

**Increase HIV/AIDS cooperation and collaboration across Institutes.** Many changes have occurred within the last year in the NICHD and OAR HIV/AIDS agenda. Greater emphasis is being placed on inter-Institute collaboration, especially in the area of HIV prevention. NICHD is funding one Center For AIDS Research (CFAR) for 5 years. Additionally, NICHD is committed to co-funding the next generation of NIAID's HIVNET (HIV Network), being re-competed as the HIV Prevention Trials Network (PTN). CRHB is the primary NICHD Branch on the PTN Memorandum of Understanding (MOU) with NIAID.

**Continue efforts to develop new microbicides with spermicidal activity.** We will be providing the preclinical support necessary to move the first two non-N9 spermicidal microbicides, C31G and BufferGel from Phase I to Phase II/III clinical trials. OAR funding is planned to cover the cost of FDA-required long-term toxicology testing. These tests are beyond the capital investment of small biotech companies. Additional funds are being sought to assess the possible use of BufferGel, alone or in conjunction with a lactobacillus suppository, as a therapeutic agent for treatment of bacterial vaginosis.

A number of other dual activity products are also under development. Several are in Phase I trials; pending successful outcomes, they will be tested in Phase II trials. New, potential products will be tested for safety to determine if they are suitable for Phase I studies.

We will continue to advertise the availability of compound screening for contraceptive efficacy and anti-HIV activity to attract new products into the pipeline. In addition, we plan to further encourage the development and evaluation of spermicidal microbicides through the formation of "National Cooperative Microbicide Discovery Groups." This endeavor is modeled after the National Cancer Institute's drug development process and will be achieved through an RFA issued in FY2001. An RFA/PA will be issued to study the differences between fusible and nonfusible membranes.

**Fund two additional, closely related prospective studies building on the existing HIVNET-based study on the effects of hormones on HIV infection.** Initial substudies will examine the influence of different hormonal contraceptives on factors influencing early HIV infection in women; another substudy will follow the clinical course of disease progression among women using steroidal hormones compared to women not using steroidal hormones.

**Issue an RFA designed to answer questions on the effects of gender on disease acquisition, transmission, and manifestation.** This will be done jointly with the

Pediatric and Maternal AIDS Branch in FY2000. We anticipate that the results from these studies will be immediately applicable to public health practice regarding current understanding of pathogenesis and treatment of HIV in women. NICHD funds have also been awarded to continue analysis and future work on a cross-sectional study of HIV in the genital tract and oral cavity (sponsored by NIDCR).

**Define the role of both male and female condoms in STD prevention.** The role of condoms in the prevention of STDs is not as clearly defined as in the case of HIV. Some studies have reported on reduction in STDs with use of both the female and male condom, while others have not shown a significant decrease. Much of the controversy is probably due to which STDs are being used as an endpoint, as well as issues of study design. CRHB proposes to hold a workshop to better define the needs of the field.

**Conduct a workshop on the standardization of terminology and outcome measures for research in pelvic floor disorders by the end of calendar year 1999.**

**Issue RFAs in FY2000 for research in epidemiologic and clinical aspects of pelvic floor disorders.** Work is underway on the development of two RFAs for research in epidemiologic and clinical aspects of pelvic floor disorders, respectively. It is hoped that these RFAs will be published in late 1999 or early 2000 with funding to start in FY2001.

**Issue RFAs in FY 2001 for small grants (R03s) and midcareer investigator awards in patient oriented research.**

**Expand research into treatment of endometriosis and uterine fibroids.** CRHB plans to further study CDB-2914. Efforts are underway to examine the newer selective progesterone receptor modulators discovered by CRHB to see if tissue specificity may indicate selective candidates that are better suited for one therapy than to another.

**Expand support of epidemiologic and clinical research training.** An RFA to expand such training to include additional centers will be issued in FY2000.

## VI. CRHB PERSONNEL AND STAFF ACTIVITIES

### CRHB Professional Staff

Robert Spirtas, Dr.P.H., Chief, CRHB, joined the Contraceptive Evaluation Branch (CEB) in 1988. He directed the Contraceptive and Reproductive Evaluation Branch (CAREB) from 1992 until its merger with the Contraceptive Development Branch in 1997. As Branch Chief of the new Contraception and Reproductive Health Branch (CRHB), he is responsible for a progressive, national program in reproductive epidemiology, contraceptive development, and reproductive health. In addition to his duties as Branch Chief, he directs Branch efforts in the area of cancer epidemiology, where he has published extensively. He represents NICHD as a Collaborating Agency

Representative to the following groups: World Health Organization, Human Reproduction Program, Epidemiological Research Committee; Family Health International, Technical Advisory Committee; and Contraceptive Research and Development Program, Technical Advisory Committee. Dr. Spirtas holds the rank of Captain in the United States Public Health Service. He is certified as a Fellow of the American College of Epidemiology; has served as a Member of the Board of Planned Parenthood, Inc.; as an adviser to the FDA, EPA, CPSC; 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 CDB in 1995. She has expertise in bio-chemistry, endocrinology, and glycobiology. Her responsibilities in the Branch include serving as Scientific Officer for the three Contraceptive Development Centers and Project Officer for the Phase II clinical trial comparing CDB-2914 and levonorgestrel for emergency contraceptive efficacy. Dr. Blithe is the contact person for the technology transfer arrangements with commercial partners. These activities include licensing of patented compounds, clinical trials agreements, material transfer agreements, and collaborative research and development agreements. Along with other members of the CRHB, Dr. Blithe is actively involved in developing and characterizing novel classes of selective progesterone receptor modulators for new therapeutic uses in gynecologic medicine. Dr. Blithe also contributes to the Branch goals of developing new spermicidal microbicides. She is the Project Officer on a contract to develop C31G as a new spermicidal microbicide and serves as the contact person for the Branch program which screens novel compounds for spermicidal and anti-HIV activity through an interagency agreement with USAID and CONRAD. Dr. Blithe is a member of the Editorial Boards of *The Journal of Biological Chemistry*, *Archives of Biochemistry and Biophysics*, and *Endocrine*.

Richard Blye, Ph.D. joined the Contraceptive Development Branch in 1971 to develop a Biological Testing Facility, which has become a mainstay of many of the Branch's operations. Dr. Blye oversees the biological testing facility, which has been responsible for the demonstration of biological activity for a broad spectrum of new drugs and currently performs over 150 different tests and assay procedures. Dr. Blye was also responsible for the development of a Primate Testing Facility which maintains a colony of male and female cynomolgus monkeys for the exclusive use of the Branch. These animals are used in a wide variety of tests to extend findings 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 made substantial contributions.

Hyun K. Kim, Ph.D. has been with the CDB since 1972. As a medicinal chemist, he is responsible for the contracts dealing with synthesis of male contraceptives, such as indenopyridines, and a variety of steroids including orally active estrogens, long-acting

androgens and orally active antiprogestins. Dr. Kim is also responsible for the operation and maintenance of synthetic chemical and synthetic peptide facilities, the latter of which produced a clinical batch of acyline. He serves as reviewer for the *Journal of Organic Chemistry and Medicinal Chemistry*.

Steven C. Kaufman, M.D., M.S. joined the CARE Branch in 1992. He manages the Branch's contract dealing with infertility and surgical sterilization as well as its contracts supporting a clinical trial of a non-latex male condom and the National Health and Nutrition Examination Survey. He also manages all of the grants assigned to CRHB (other than the grants for the Center for AIDS Research and the Contraceptive Development Centers). Dr. Kaufman organized two NICHD conferences, "Conference on Vasectomy and Prostate Cancer" (1995) and "Male and Female Sterilization: Medical Effects and Behavioral Issues" (1998). Since joining the Branch, his publications have dealt with the possible role fertility drug exposure may play in ovarian cancer, the safety of vasectomy (particularly with regard to prostate cancer), HRT usage patterns in the United States, urinary pregnanediol measurement methodology, and the evidence concerning the so-called "post-tubal ligation" syndrome. He has served as a reviewer for the *Journal of Women's Health*, the *Online Journal of Current Clinical Trials*, and ECRI's *Health Technology Assessment Service*. Dr. Kaufman was a member of the NICHD External Communications Task Force, currently serves on the NICHD's World Wide Web Home Page Committee and Workforce Improvement and Diversity Advisory Committee, and represents NICHD on the NIH Clinical Trials Database Working Group.

Joanne Luoto, M.D., M.P.H., joined the CARE Branch in 1995 from the Office of the Assistant Secretary for Health, DHHS. Dr. Luoto is Board Certified in Preventive Medicine and received her Masters of Public Health 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 the spermicide contraceptive efficacy trial, the hormones and HIV acquisition study and substudies, IUDs and acquired tubal infertility, and the study of hormones, cervical ectopy, and STD acquisition. She is a member of the NIH AIDS Epidemiology Committee, and presented the NICHD's AIDS research program to the OAR's Prevention Sciences Task Force. Dr. Luoto represents the Branch at the World Health Organization's Subcommittee on Regulation of Male Fertility and on the Joint Working Group of the bilateral Indo-US Contraceptive and Reproductive Health Research Program. Dr. Luoto conducted a workshop in October of 1998, on "Endometrial Ablation: Emerging Technology and Research Needs."

H. Trent MacKay, M.D., M.P.H. joined the CRHB in 1998. He represents the Branch in the areas of contraceptive clinical trials and clinical and epidemiologic aspects of obstetrics and gynecology. He recently transferred from CDC where he was a medical epidemiologist in the Division of STD Prevention. He is the project officer for the Contraceptive Clinical Trials Network (CCTN) as well as for the Statistical and Clinical Coordinating Center for the CCTN. He is the project officer and medical officer for the clinical trials of four new spermicide in the CCTN as well as the medical officer for the clinical trial of CDB-2914. He has taken an important role in the new NICHD initiative in the area of pelvic floor disorders and is developing an RFA for Epidemiologic and



Clinical Research Training for Obstetricians and Gynecologists. He is developing a joint conference with the Association of Reproductive Health Professionals (ARHP) on Contraception in the Perimenopause, and he is the branch representative to the annual NICHD Aspen Conference. Dr. MacKay has been a reviewer for the *American Journal of Obstetrics and Gynecology*, *Obstetrics and Gynecology*, *JAMA*, and others. He is an Associate Professor of Obstetrics and Gynecology at the Uniformed Services University of the Health Sciences, an active staff member at the National Naval Medical Center, and a Clinical Professor of Obstetrics and Gynecology at the University of California, Davis. Dr. MacKay is the treasurer and board chairperson-elect of ARHP and a member of the National Medical Committee of Planned Parenthood Federation of America.

Patricia Reichelderfer, Ph.D., represents the Branch in the area of HIV research. In 1998, she moved to the CRHB from NIAID's Division of AIDS, where she was Program Virologist for seven years. She has assumed the NICHD AIDS responsibilities for the Center for AIDS Research (CFAR) program and the Prevention Trials Network (PTN). She worked with staff to coordinate the spermicidal microbicide agenda for the Office of AIDS Research (OAR). In cooperation with the Pediatric Adolescent and Maternal AIDS (PAMA) Branch, she oversees several large-scale projects involving HIV in women. She is on both the NIAID HIV Network perinatal transmission and microbicide working groups, as well as Pediatric Virology working group for the AIDS Clinical Trials Group (ACTG). She was part of the organizing committee for the CDC-sponsored symposium on Laboratory Science of HIV. She is the NICHD extramural liaison to the OAR-sponsored HIV Interest Group seminar series. She has been a regular reviewer for the *Journal of Clinical Microbiology* and the *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* and more recently a reviewer for the *Journal of Alternative and Complementary Medicine*, and *Fertility and Sterility*. She is the project coordinator responsible for an International/Department of Defense/NICHD effort to commercialize a panel of HIV subtypes for use in the clinical laboratory as global standards.

Anne M. Weber, M.D., M.S., is working in the Branch on an Intergovernmental Personnel Act appointment while remaining on staff in the Department of Gynecology and Obstetrics at the Cleveland Clinic. Her background includes Board Certification in obstetrics and gynecology, subspecialty training in urogynecology and pelvic reconstructive surgery, and a Master of Science degree in Clinical Research Design and Statistical Analysis. Dr. Weber is developing the research agenda on female pelvic floor disorders, including planning for upcoming RFAs on the epidemiologic and clinical aspects of pelvic floor disorders. In addition, she is working with other organizations such as NIDDK and the NIH Office of Research on Women's Health to facilitate collaborative, multidisciplinary research on pelvic floor disorders. This will include a jointly sponsored workshop to define standard terminology for use in research on pelvic floor disorders.

## VII. CONFERENCES/WORKSHOPS, 1995-1999

Conference: **Research on Long-Acting Contraception**, Bethesda, MD, August 24-25, 1995.

Conference: **IUDs-State of the Art** with Synermed, Bethesda, MD, February 15-16, 1996.

Conference: **Enhancing Vaginal Defense Mechanisms-Immunology and Physiology**, Bethesda, MD, April 9-10, 1996.

Conference: **Steroid Contraceptives and HIV Transmission: Planning for Research**, Bethesda, MD, June 6-7, 1996.

Conference: **Androgen Receptors: Exploiting Differences in Hormone Action**, Bethesda, MD, July 23-24, 1996.

Conference: **New Models for Preclinical Evaluation of Vaginal Contraceptives**, Bethesda, MD, October 7-8, 1996.

Workshop: **Vaginal Microbicide Formulations**, Bethesda, MD, November 7, 1997.

Workshop: **Cell-Based Anti-HIV Screening Assays for Topical Spermicide/Microbicides**, Bethesda, MD, July 31, 1998.

Workshop: **Endometrial Ablation and Abnormal Uterine Bleeding**, Rockville, MD, October 21, 1998.

Conference: **Male and Female Sterilization: Medical Effects and Behavioral Issues**, Bethesda, MD, June 11-12, 1998.

Symposium: **WHO/NICHD Steroids and Breakthrough Bleeding**, Clayton, Australia, May 27, 1999.

The information in this document is no longer current. It is intended for reference only.

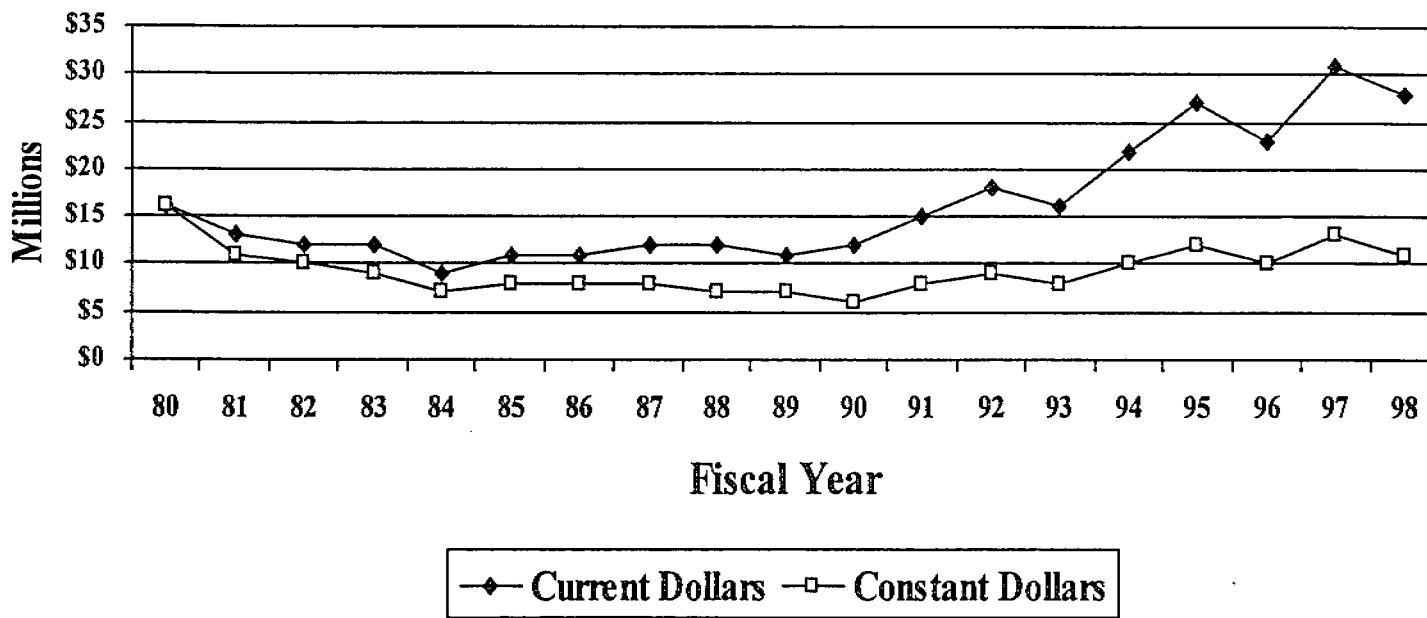
## VIII. BUDGET

<b>CRHB PROJECTS BY PROGRAM AREAS, Fiscal Year 1998</b>	<b>#</b>	<b>FUNDS</b>
<b>CONTRACEPTIVE RESEARCH AND DEVELOPMENT</b>		
Devices	1	\$287,571
Hormones	1	\$268,609
Immunocontraception	5	\$4,793,128
Support Contracts	3	\$2,752,876
Subtotal	10	\$8,102,184
<b>CONTRACEPTIVE EVALUATION AND REPRODUCTIVE EPIDEMIOLOGY</b>		
Sterilization	1	\$185,509
Infertility	4	\$676,872
Oral Contraceptive Side Effects	8	\$6,463,145
Progestins and Uterine Bleeding	3	\$779,714
General	10	\$2,536,984
Subtotal	26	\$10,642,224
<b>PREVENTION OF HIV/AIDS/STDs</b>		
Spermicidal Microbicides*	4	\$2,211,468
Hormones and HIV Transmission/Progression	2	\$2,185,777
Vaginal Immunology/Physiology	5	\$1,460,875
Contraceptive Clinical Trials Network (CCTN)**	5	\$979,357
General	4	\$1,665,937
Subtotal	20	\$8,503,414
<b>SELECTED REPRODUCTIVE AND GYNECOLOGIC HEALTH ISSUES</b>		
Therapeutic Hormones	1	\$68,092
Subtotal	1	\$68,092
<b>RESEARCH TRAINING</b>		
Training Grant	1	\$222,334
Subtotal	1	\$222,334
<b>TOTAL</b>	<b>58</b>	<b>\$27,538,248</b>

\*This estimate differs from other estimates where attempts were made to estimate percentage of each project attributable to microbicide research.

\*\*In FY98, studies in the CCTN involved Phase I tests of spermicidal microbicides and condoms. In FY 99, CCTN studies include hormonal contraception.

# Consolidated Budget CD/CARE/CRH Fiscal Year 1980 - 1998



# Consolidated Budget by Category for FY96-98 (\$M)

## CDB/CAREB/CRHB

