MELLON REPRODUCTIVE BIOLOGY CENTERS MEETING

OMNI EUROPA HOTEL, CHAPEL HILL, NC
NOVEMBER 7-9, 1993

MEETING SUMMARY
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I. Executive Summary

This meeting of reproductive biology centers (RBCs), and contraceptive development and funding agencies was sponsored by the Andrew W. Mellon Foundation and Family Health International (FHI). Invited participants included the eight Mellon-supported RBCs: Baylor College of Medicine, Eastern Virginia Medical School, The Population Council, University of California at Davis, University of Connecticut Health Center, University of North Carolina, University of Virginia Health Sciences and the University of Washington. In addition, various contraceptive development and funding agencies were also invited: Centre for Reproductive Biology, Contraceptive Research and Development Program (CONRAD), National Institute of Child Health and Human Development (NICHD), The Population Council, Rockefeller Foundation, South to South, the United States Agency for International Development (USAID), and World Health Organization (WHO). The complete list of participants and agenda are attached (Appendices 1 and 2).

The meeting was opened by Dr. Theodore King, President of FHI and Dr. Roberto Rivera, Corporate Director for International Medical Affairs at FHI. Dr. Carolyn Makinson, Program Associate of the Mellon Foundation gave a brief overview of the purpose of the meeting: to report on the current program status of the eight Mellon-supported Reproductive Biology Centers, to initiate a process of communication and collaboration among the participating organizations, and to explore possibilities of developing new contraceptive products based on research findings from the centers.

On the first day, representatives from each RBC presented a short summary of their ongoing research. Following that, the invited contraceptive research and funding agencies discussed their current research program and funding priorities. Several guest speakers presented various topics on contraceptive product development. These topics included discovery of new contraceptives, phases of clinical trials, identification and evaluation of new contraceptive leads, and current policies for FDA approval of new contraceptive drugs, devices, and vaccines.

The morning of the second day consisted of working group meetings to review and assess some of the current issues and/or questions facing basic and applied research organizations in contraceptive development. There were four working groups, based on the research questions previously submitted by the participants. These interest areas were 1) HIV/STD Prevention and Contraceptive Development, 2) Immocontraception/Contraceptive Vaccine Development, 3) Male Contraceptive Development, and 4) Animal, Cell, and Molecular Models used in Contraceptive Development. Each group prepared a summary of its discussion and presented it in the afternoon session. In addition, Dr. Makinson explained Mellon’s Twinning Program, and plans were discussed for future meetings.
II. Research Summaries of Reproductive Biology Centers

A. Baylor College of Medicine, Department of Cell Biology

The Mellon Training Grant project at Baylor College of Medicine is comprised of two components which are directed towards the development of contraceptive methods. First, specific research projects are ongoing which support junior faculty in their programs to develop contraceptive methods which can be tested in animal models. Secondly, post-doctoral fellows and graduate students are being trained in contraceptive development research. The joint training of these young scientists in laboratories established in contraceptive development with those in state-of-the-art molecular biology will be critical for the advancement of techniques in this area.

Staff members are carrying out studies to demonstrate the feasibility of regulating hormone action in vivo using cholesterol-derived triplex-forming oligonucleotides which can be taken up by cells to inhibit transcription. Also, staff have been examining the effects of progesterone on uterine stromal cell gene expression using subtracted cDNA libraries.

Further research efforts have established new methods using injectable forms of nucleic acids designed to be incorporated into cells for limited or long term expression of specific proteins. In addition, it has become increasingly apparent that a limitation in contraceptive vaccine development has been the lack of immunogenicity of specific peptides and recombinant proteins, and the development of better expression systems designed for immunogenicity enhancement in contraceptive vaccines is crucial.

The Baylor College of Medicine has a twinning collaboration with the Institute of Primate Research (IPR) in Nairobi, Kenya. One of their staff members has been involved in the molecular cloning of cDNAs for zona pellucida proteins and the expression of these proteins in a variety of bacterial expression vectors. In addition, he has been involved in the purification of these proteins for testing in the primate model (cynomolgus monkeys).

B. Eastern Virginia Medical School, The Jones Institute for Reproductive Medicine

The Mellon Contraceptive Research and Training Center at The Jones Institute is taking a three pronged approach to Contraceptive Development with each avenue of study falling under the direction of one of the Mellon-supported investigators.

One area of study focuses on factors that effect sperm maturation. So far, efforts have been focused on developing the methodology for establishing primary cultures of epididymal epithelial cells and on gaining a better understanding of the normal
maturational process that occur within the epididymis. The relationship between maturational antigens present on epididymal spermatozoa and the androgen-dependent proteins secreted by the epididymal epithelium are being investigated. This study will involve the treatment of male cynomolgus monkeys with agents (5α-reductase inhibitors and GnRH antagonists) to abrogate the production of these androgens.

Another area of research looks at ways to enhance and extend the effectiveness of suckling-induced subfertility for lactating women. The physiological mechanisms responsible for the contraceptive effects of breast feeding are not completely understood. However, current thinking is that the neural stimulus provided by the infant sucking in some way reduces the pulsatile release of GnRH from the hypothalamus, thereby reducing tonic LH/FSH secretion and hence maintaining ovulation. When ovariectomies are performed in monkeys during the first month postpartum, the rise in serum gonadotropin concentrations is both delayed and less marked suggesting that the proximal signal provided by the sucking infant is able to attenuate the gonadotropin hypersecretion that normally follows ovariectomy. We have recently established that when ovariectomies are performed at five months postpartum, levels of gonadotropins rise rapidly even though suckling continues. We propose to utilize this model to predict the contraceptive effectiveness of the GnRH antagonist regimens to be tested.

Finally, a working non-human primate (cynomolgus) in vitro fertilization (IVF) system that can be used to directly assess the action of contraceptive approaches designed to act at the level of oocyte maturation and/or fertilization has been established. Studies were also performed in the development of an in vitro assay which evaluated human sperm penetration through the human zona pellucida. Referred to as the Zona Penetration Assay (ZPA), this test uses the zona pellucida of nonviable human oocytes. This assay can be used with the Hemizona Assay (HZA) and Sperm Penetration Assay (SPA) tests, which assess zona binding and plasma membrane penetration, to allow a sequential evaluation of gamete interaction and fertilization events. In the future, we will be using the ZPA to evaluate various contraceptive agents to determine at what level fertilization is inhibited.

C. The Population Council, Center for Biomedical Research

A large fraction of the Basic Research Program in Male Reproductive Physiology at the Center for Biomedical Research is focussed on the development and differentiation of the testes and on autocrine and paracrine regulation of testicular functions. Present research projects involve: (1) studies of the differentiation of Leydig cell precursors in vitro; (2) identification of Sertoli cell proteins that affect germ cell development; (3) characterization of a germ cell factor that regulates Sertoli cell function; (4) determination of the roles of inhibin and activin in intercellular signalling in the testes; and (5) analysis of the transmission of HIV in genital tract epithelial cells.
The experimental approach to define the mechanisms that control pubertal differentiation of Leydig cells involves characterizing changes in Leydig cell function during their developmental maturation in the testis. Understanding the mechanism by which Leydig cell progenitors achieve their capacity for steroidogenesis will mark a significant advance in the ability to regulate testicular function, and thus fertility, in animals and humans.

A comprehensive study of Sertoli protein secretion is being undertaken to determine physiological significance of these proteins in the regulation of germ cell development in the testis. Testins I and II, two structurally and immunologically related Sertoli cell proteins, were shown to be components of the junctional complexes between epithelial cells in the reproductive tract. More importantly, the secretion of testins by Sertoli cells appears to be inversely related to the number of germ cells both in vitro and in vivo. This finding suggests that germ cells can regulate specific Sertoli cell function which were also indicated by the identification of a factor released by germ cells that affects the secretion of testins I and II by Sertoli cells. These observations support the concept that newly identified proteins from Sertoli and germ cells will lead not only to a better understanding of specific cell interactions, but also to more general knowledge of testicular function.

Cytokines and opioids within the seminiferous tubule may act as mediators of cell-cell interactions. Studies indicated that germ cells produce an inhibitory factor that attenuates the response of Sertoli cells to FSH. This factor inhibits the Sertoli cell response by affecting the signal transduction system used by FSH at the level of the guanine nucleotide binding subunits of adenylyl cyclase. In contrast, Sertoli cell proenkephalin gene expression is increased in the presence of this germ cell factor, suggesting that opioids are involved in a regulatory loop between Sertoli and germ cells. Previous studies showed that the opioid-derived peptides are regulators of proliferation and differentiation, a finding consistent with the concept that a local germ cell-dependent opioid regulatory circuit regulates the size of the germ cell population and determines its growth in the tubule. Germ cells may also provide a microenvironment in which their secretory factors modulate the responsiveness of the Sertoli cell to extragonadal stimuli. Current experiments are aimed at establishing how these germ cell factors are regulated.

Gonadal inhibins and activins modulate physiological functions in the testis, in addition to the well-known feedback regulation of pituitary FSH secretion. These observations suggested that inhibins and activins, and their receptors, are co-expressed in gonadal tissues and play a role in the complex intercellular signaling that controls testicular function. To study the activin receptor and its function in the testis, cDNAs for two species of the Type II receptor (ActRII and ActRIIB) from rat testis were clones and characterized. The genes for these receptor subtypes are widely expressed in the reproductive tissues of male and female rats. While the ActRIIB gene is constitutively expressed in reproductive tissues, the expression of two different-sized ActRII mRNAs (6 and 3 kilobases) is tissue-specific and age-dependent in rat testis. The 6-kilobase mRNA is the predominant form in the immature testis, while the 3-kilobase mRNA
increased with age and became the major form in mature testis. Interestingly, germ cells express high levels of the 3-kilobase ActRII mRNA. The structure of the two activin receptor genes and the possible mechanisms involved in the regulation of their expression in Sertoli and germ cells are under investigation.

Development of a vaginal contraceptive that will also protect women and men against the sexual transmission of AIDS is a long-term goal of our Center. We have developed a culture system that mimics the sexual transmission of HIV, and it can be employed to test compounds for their effectiveness in inhibiting such transmission. Research has concentrated on identifying nontoxic compounds that may be good candidates for a vaginal formulation to inhibit HIV infection. Investigators identified a class of compounds that block attachment of HIV-infected blood cells to epithelial cells and inhibit HIV infection at very low doses. Research to determine which of the compounds in this class is the most effective will pave the way for clinical studies.

D. University of California - Davis, California Regional Primate Research Center

The research at the California Regional Primate Research Center (CRPRC) is focused on the non-human primate model. The objective of the Center is to train investigators for contraceptive research studies with this animal model and to develop the understanding of primate sperm biology which will be needed for new approaches to immunologic and barrier contraception.

One important area of Center research involves basic research on sperm transport and physiology in the primate female reproductive tract. This research area is highly relevant to contraceptive development because the female tract is the site of action for barrier contraceptives and most immunocontraceptives. Methodology has been developed at CRPRC for studies of sperm transport kinetics including methodology for sperm recovery from the female tracts, for evaluation of sperm motility and for testing of acrosomal function. Research is underway to develop in vitro assays for sperm interaction with uterine cells and oviductal cells to complement established tests of primate sperm-cervical mucus interaction and sperm-zona pellucida interaction. Methods for the culture of macaque oviduct cells have been developed and studies have revealed that these cells produce a protein which is similar to an oviduct-specific protein isolated from baboon oviducts.

Although macaques are widely used as primate models in contraceptive research, previous research at CRPRC has identified a number of potentially important differences between the physiology of macaque sperm and human sperm. Unlike human sperm which capacitate spontaneously in vitro, macaque sperm require the addition of "activators" (caffeine and dbcAMP) for capacitation. Our experiments suggest that a second messenger system other than cyclic AMP might also be involved in macaque sperm capacitation. Macaque sperm-zona pellucida interaction results in more rapid induction
of the acrosome reaction than is observed with human gametes, but macaque sperm appear to be less sensitive than human sperm to induction of the acrosome reaction with agents such as follicular fluid or progesterone. The capability to induce acrosome reactions in motile sperm will be needed for experiments on the mechanism of action of immunocontraceptives which interfere with fertilization, and efforts are underway to develop this capability. We are also developing an in vitro fertilization model (IVF) to test the ability of immunocontraceptives to inhibit sperm penetration of the zona pellucida and fertilization. The IVF model will be particularly useful to evaluate contraceptive actions which involve sperm fusion with the oolemma.

In the area of female reproductive endocrinology, the two principal issues for study have been early pregnancy signals and the development of improved assays for reproductive hormones in non-human primates. The endocrine profiles of ovarian steroids and relaxin have been compared in humans and macaques during the menstrual cycle, early pregnancy and spontaneous abortion. Overall, the profiles were similar and support the concept that the endocrinology of early pregnancy in the macaque and human are similar, further validating the macaque as a model for study of early pregnancy signals in humans.

In the area of immunocontraceptive development, cynomolgus macaques have been immunized with purified, clones rabbit zona pellucida proteins provided by Dr. Bonnie Dunbar of Baylor University and the immunized females have responded with increased serum titers of antibodies to two of the three proteins. Subsequent studies utilizing serum from immunized females indicate that antibodies to one of the zona proteins can prevent sperm-zona pellucida binding and acrosome reactions of bound sperm. Histology on tissue obtained at necropsy from these animals showed normal ovaries with developing follicles in numbers that were consistent with the animals’ advancing age. Analysis of estrogen and progesterone profiles after immunization also support the finding that immunization has not disrupted ovarian function.

Fertility studies are being initiated using female cynomolgus macaques immunized with recombinant macaque PH-20 protein provided by Drs. Paul Primakoff and Diana Myles of the University of Connecticut. Ultrastructural studies with a rabbit polyclonal antiserum to the PH-20 protein and a gold labeled second antibody have revealed the location of the cynomolgus PH-20 homolog on the plasma membrane and inneracrosomal membrane of the sperm head in locations where antibodies may interfere with fertilization.

To study the effect on contraceptives on HIV transmission, the rhesus macaque/SIV system has been used to develop a model of the heterosexual transmission of HIV. This system has demonstrated the ability of commercial spermicides containing nonoxynol-9 (N-9) to prevent the vaginal transmission of SIV. Despite the demonstrated antiviral efficacy of N-9 spermicides, it has been proposed that the vaginal irritation that results from chronic use of N-9 in women may increase the efficiency of HIV transmission. This hypothesis is currently being tested in the rhesus macaque/SIV system. Thus, rhesus
macaques are given an intravaginal dose of N-9 that produces vaginal irritation and then challenged vaginally with SIV. This model can be used to test the effect of experimental contraceptives on heterosexual transmission of HIV. It also characterizes the target cells involved in the genital transmission of these viruses. Both of these efforts have led us to define the cellular basis of the mucosal immune system in the lower female genital tract. This work has shown that the immune cell populations in the genital tract of rhesus macaques and women are very similar.

E. University of Connecticut Health Center, Contraceptive Development Research Center

The Mellon Center of the University of Connecticut Health Center is a multi-institutional Center whose research mission is to develop new contraceptives. The focus of our present research is immunocontraception in which the target is surface molecules of the sperm cell. Immunocontraception directed against the gamete surface is the most sophisticated barrier method of contraception, where the barrier is at the molecular level. The projects in the Center are at different stages of development in terms of a usable contraceptive product. The most advanced is the PH-20 vaccine for women. PH-20 is a sperm protein shown to give 100% effective contraception in immunized female animals, and it thus has a reasonable chance of being developed into a marketed contraceptive product. Other projects in the Center are focused on sperm antigens that might ultimately be used in a second generation, multi-antigen vaccine in which PH-20, peptides from PH-30 and p95 would be used together. Such a second generation vaccine might require few injections, give longer-lasting contraception, or have other unforeseen advantages. Another significant area of Center research is on novel strategies for male contraception. An extensive clinical literature shows that certain men, who are otherwise healthy, are infertile because they make anti-sperm antibodies. This "experiment of Nature" establishes that an immunocontraceptive approach for males is feasible.

F. University of North Carolina, The Laboratories for Reproductive Biology

The Laboratories for Reproductive Biology includes reproductive scientists at several institutions within the Research Triangle area of North Carolina. Programs include basic research leading to contraceptive vaccine development, and identification of unique regulatory targets in Sertoli cells and developing germ cells of the testis. Targeted oncogenesis is being utilized to develop much needed cell lines for studies on the regulation of Sertoli cells and granulosa cells. Extensive research is directed towards understanding molecular mechanisms of androgen, progestin and estrogen action in the male and female reproductive tracts.

The following are highlighted as promising targets for contraceptive development: human sperm autoantigens, which have been shown to be zona pellucida (ZP) binding proteins
essential for fertilization; a human plasma membrane protein, p95, a ZP3 binding protein, which is a tyrosine kinase that regulates the acrosome reaction; a newly discovered pituitary factor that is a specific inhibitor of FSH production; and an endometrial integrin that has a key role in embryo implantation and is inhibited by one or more factors produced by endometriosis cells.

G. University of Virginia Health Sciences, Center for Recombinant Gamete Contraceptive Vaccinogens

The long term mission of the Center for Recombinant Gamete Contraceptive Vaccinogens is to provide the essential organizational framework to allow convergence and assembly of the disparate technologies and personnel required to identify, formulate and test vaccine candidates and thus maximize the potential development of a contraceptive vaccine for humans. The Center currently emphasizes a vaccine for females, although research germane to a male vaccine is also underway. The vaccine will consist of one or several gamete associated immunogens which elicit immunological responses that function to prevent fertilization. The Center coordinates research and development activities encompassing seven stages of a recombinant contraceptive vaccine product development program: 1) fundamental discovery and evaluation of gamete specific molecules [vaccinogens] derived from the sperm, egg, egg investments or accessory reproductive organs; 2) genetic engineering of genes encoding specific vaccinogens into appropriate expression systems; 3) production and purification of recombinant vaccinogens under good laboratory practices; formulation of vaccine doses; 4) small animal and primate testing of vaccine formulations for immunogenicity, safety and efficacy; 5) evaluation of mechanisms of vaccine action; 6) human trials in association with industrial sponsorship; and, 7) development of diagnostics to monitor infertility status.

Research projects in the Center include: 1) evaluation of peptides derived from ZP3; 2) identification and cloning of a new human sperm surface antigen which functions in sperm/zona binding; 3) cloning and characterization of a human sperm antigen identified with infertile sera; 4) development and testing of a oral sperm vaccine for stimulating secretory immunity in the oviduct; 5) primate efficacy trials of injectable contraceptive vaccines based upon human sperm immunogens LDH-X; 6) SP-10; and, 7) studies of sperm autoantigens recognized by serum from vasectomized rats. Attention will be placed on development of multideterminant vaccine [combination formulations] if indicated.

H. University of Washington, Population Center for Research in Reproduction

A major practical aim of our work is the development of a new, safe, reversible human male contraceptive. We are actively exploring GnRH analogs and progestational agents, together with testosterone as contraceptive agents in normal men. Active studies at this time include use of the GnRH antagonist Nal-Glu, or the progestational agent
levonorgestrel, combined with testosterone injections to suppress spermatogenesis in normal men. We are also one of the sites for the ongoing World Health Organization multi-center trial of the contraceptive efficacy of testosterone. This trial is yielding very encouraging results in normal couples throughout the world. We are committed to the development of a contraceptive for men that would be used in the developing world as well as in the United States.

We also study the effects of hormones from the testes (testosterone, estradiol, dihydrotestosterone) on lipid and bone physiology, on human behavior, and on the expression of the human androgen receptor. For example, we have recently demonstrated the ability of physiological levels of testosterone in men to suppress high density lipoprotein levels, which has important implications for both male contraceptive development and for the etiology of the increased incidence of cardiovascular disease in men compared to women. In additional studies, we are collaborating with another Mellon-supported center (Population Council, New York) in studies of 7-MENT, an androgen steroid that is not capable of 5 α reduction. This agent, now being assessed in primates, could be useful in future contraceptive regimens.

We are conducting basic research to understand the molecular physiology of GnRH neurons, thereby providing understanding of the control of the brain peptides that regulate reproduction. We are also interested in the intracellular signaling pathways that control activities of anterior pituitary gonadotropes, with an emphasis on the short-term signals that couple GnRH to secretion of LH and FSH. These basic studies are giving clues to the mechanisms by which proposed GnRH analogs and steroid contraceptives would act on control of pituitary function and therefore on reproduction. Other basic research at our laboratories include the role of protein kinases in male germ cell development and the modulation of specific transcription factors involved in cAMP-regulated gene expression.

III. Contraceptive Development and Funding Agencies

A. Centre for Reproductive Biology, University of Edinburgh, Scotland

The Centre for Reproductive Biology of the University of Edinburgh forms the major focus within the UK for basic and applied research in the field of contraception and associated aspects of reproductive health. The Centre comprises the Medical Research Council (MRC) Reproductive Biology Unit and the University Department of Obstetrics and Gynaecology. As part of the recently-agreed Concordat between the UK Medical Research Council and the UK Overseas Development Administration, there have recently been meetings to establish research priorities for contraceptive development and to initiate collaborative ventures.

In the MRC Reproductive Biology Unit, studies are ongoing in neuroendocrine regulation of reproduction, peptide receptors in the pituitary gland, and in the pituitary-ovarian axis.
Studies are also being undertaken in gamete biology, cell biology of antigestagens, paracrine mechanisms regulating spermatogenesis, and the role of hormones and neurotransmitter mechanisms in the regulation of the sexuality and well-being of women. In the University Department of Obstetrics and Gynaecology, clinical and basic studies into the use and mechanisms of antigestagens are ongoing, as well as ovarian paracrinology and endocrinology studies. In the Lothian Family Planning Service, research in emergency contraception is being undertaken, particularly with antigestagens, and LNG-containing IUDs.

B. Contraceptive Research and Development Program (CONRAD)

The CONRAD Program has as its primary mission supporting preclinical research and clinical studies directed at developing improved and/or new methods of family planning for use in less developed countries. The primary focus of the CONRAD Program is on the early stages of contraceptive research and development, beginning with targeted or applied research studies and progressing through the first two phases of clinical testing in humans.

CONRAD has over 45 ongoing projects which are supported worldwide at universities, research institutes, and private companies. In addition, intramural research is conducted in the laboratories and clinics of Eastern Virginia Medical School in Norfolk, Virginia. Examples of some current clinical studies include intravaginal barrier devices and films, norethindrone-containing implants for women, progesterone suppositories to prolong lactational amenorrhea, and testosterone formulations and gonadotropin releasing hormone antagonists for male contraception. The CONRAD Program is also actively supporting research aimed at developing methods to prevent the heterosexual transmission of sexually transmitted diseases, including HIV.

C. Family Health International (FHI)

Family Health International is an international not-for-profit biomedical research and technical assistance organization dedicated to improving reproductive health, contraceptive safety and health service delivery. FHI is committed to improving all aspects of reproductive health, from increasing contraceptive choices to slowing the spread of sexually transmitted diseases. Since 1971, FHI has worked to broaden the range of safe, effective and affordable contraceptives and make them effective to families around the world. FHI has designed, implemented, and managed over 500 multi- and single center studies to evaluate the safety and efficacy of contraceptive methods. Currently, FHI’s Research and Development Department’s activities can be grouped into two main categories: 1) development and evaluation of new contraceptives and 2) clinical trials to provide information to family planning programs on available contraceptives.
Activities in the contraceptive development/clinical trials component are designed to provide sufficient data to the FDA and regulatory agencies in other countries to secure marketing approval of new products. During the past fiscal year, FHI filed three applications for marketing approval with the FDA: a 510(k) application for a thermoplastic male condom, the Filshie Clip for female sterilization, and support for Wisconsin Pharmacal’s application for the female plastic condom, Reality. Priorities for contraceptive development and clinical trials in the current year continue to emphasize the development of long-acting steroidal contraceptive systems, especially the NET products, and of iodine as a possible method of transcervical female sterilization, and continued improvements in the design of the plastic male condom leading to another 510(k) submission. Development efforts in barrier contraception with the Lea’s Shield and male sterilization continue in close cooperation with CONRAD and the Association of Voluntary Surgical Contraception (AVSC), respectively. Also during this year, we expect to work closely with the FDA while they review our PMA for the Filshie Clip, which was submitted during FY '92.

D. Andrew W. Mellon Foundation

The Mellon Foundation’s population program makes grants totalling roughly $8-$10 million a year in the following program areas: reproductive biology, applied contraceptive development, population dynamics of developing countries, family planning service delivery in developing countries and in New York City, and population policy. Grants are usually made for a three-year period and are usually made to U.S. institutions. Within the area of reproductive biology, eight centers receive support. The major purpose of these grants is to provide support for junior investigators whose research interests are relevant to the development of new contraceptives. However, within this area of reproductive biology, the Mellon Foundation has also made money available for centers in developing countries. These centers have coordinated their research efforts with a domestic institution in what Mellon refers to as a "twinning" arrangement.

E. National Institute of Child Health and Human Development, Contraceptive Development Branch

The mission of the Contraceptive Development Branch (CDB) is to support research on the development of new improved methods of fertility regulation for both women and men that can satisfy the needs of various population groups. In order to accomplish this mission CDB is currently supporting a number of projects designed to develop new physical and chemical barrier methods that in addition to preventing pregnancy, may also prevent heterosexual transmission of STDs, including HIV. The Branch is supporting research on long-acting biodegradable implants for women, and long-acting injectable progestin and androgen that have the potential for both female and male contraception. Synthesis of GnRH antagonists is part of an active program to develop new approaches.
to male contraception. Preclinical studies are ongoing to evaluate the use of antiprogestins for post-coital contraception and other contraceptive uses. The Branch is supporting three Contraceptive Development Centers, two of which are devoted to contraceptive vaccine development. The Branch has two chemical synthesis facilities and two biological testing facilities which provide a critical service for drug synthesis and evaluation. Plans are being developed to establish clinical trials centers that could provide for uniform evaluation of contraceptive products.

F. The Population Council, Center for Biomedical Research

The Population Council's Research and Development Program for Contraceptive Development encompasses the spectrum of scientific inquiry from pre-clinical testing at the Center for Biomedical Research in New York to introduction of new contraceptive methods worldwide. The Population Council's past achievements include the first contraceptive subdermal implant system (NORPLANT®), several Copper T IUDs, and the levonorgestrel IUD approved for use in Finland. At present, ongoing research at the Council includes spermicides/viricides, contraceptive vaginal rings, long-acting contraceptive methods for women (i.e., implants, IUDs, and vaccines), and long-acting contraceptives for men (i.e., implants and vaccines), medical abortifacients and transdermal systems.

G. Rockefeller Foundation

Within the Rockefeller Foundation, the division of the Population Sciences has identified a strategy for joining forces with other agencies and institutions to meet the unmet need for contraception in the world. The Foundation has defined one component of this strategy as "Mobilization of Resources to Launch a Second Contraceptive Technology Revolution". The central aim of this component is to lift the whole field of contraceptive research and development rather than run a Foundation-sponsored research program as a member of that field.

The Foundation has proposed a three pronged strategy: a woman-centered agenda for contraceptive research and development to provide the field with a mission and a focus; a Contraception-21 initiative to reinvigorate the science to provide the leads for new contraceptive approaches in the 21st century; and, a new program thrust to promote private/public sector collaboration. The Foundation is particularly interested in funding research on male contraception, effective control of STDs including HIV (especially female-controlled methods), and menses inducers (i.e., once-a-month pill). In addition, the Foundation is interested in seeing that their funds will be used to mobilize more funding from both the public and private sectors.
H. South to South Cooperation in Reproductive Health

The general objective for the South to South Cooperation, based in Salvador, Brazil, is mutual assistance and collaboration in reproductive health research and, building in the process, a network of experts who can advise the policy makers of developing countries about how reproductive health issues can be addressed through the application of research results to national policy decisions and health program design. The ultimate objective is the overall improvement of the reproductive health status in developing countries.

Current areas of research interest for the STS group are based on scientific work initiated and carried out by developing country scientists. Some of the ongoing research includes: development of a one capsule contraceptive implant (UNIPLANT); development of Vaginal Pill Contraception, and Development of a vaginal cream or gel with contraceptive, bactericidal and virucidal properties.

I. United States Agency for International Development (USAID)

The USAID Office of Population is committed to the development of effective family planning programs, which will in turn improve the status of mothers, children and families and slow population growth. The Research Division, housed within the Office of Population, serves as the funding source for scientific and technological work in the area of contraceptive development. The objectives of the research are to: 1) develop and introduce new and/or improved methods of contraception, 2) identify and test more acceptable and cost-effective methods of delivering family planning services, 3) improve understanding of both contraceptive technology and family planning service delivery, and 4) improve knowledge, availability and effectiveness of natural family planning, including breast feeding. The Division funds activities in contraceptive development and family planning service delivery based on such criteria as effectiveness, safety, side effects, convenience, programmatic issues, reversibility, as well as privacy, desirable attributes, and ethical considerations. USAID's research program is carried out primarily through grants and/or contracts with the CONRAD Program, FHI, the Population Council and Georgetown University.

J. World Health Organization, Special Programme of Research, Development and Research Training in Human Reproduction

The Special Programme of Research, Development and Research Training in Human Reproduction promotes reproductive health, particularly in the area of fertility regulation including infertility, by collaborating with Member States, with special regard to the needs of developing countries, in developing appropriate technologies and service approaches for the provision of reproductive health care. Present research areas include safety and effectiveness of current methods of fertility regulation, new methods of fertility regulation,
psychosocial and epidemiological aspects of reproductive health, introduction and transfer of technologies for fertility regulation, and prevention and treatment of infertility. In addition the HRP works to strengthen national resources for biomedical, epidemiological, psychosocial and health service research in human reproduction.

IV. Presentations - Discovery to Reality: How Does a Product Reach the Public?

A. Lead Development

Dr. Audrey Phillips of the R.W. Johnson Pharmaceutical Research Institute gave an overview of how a new contraceptive lead is identified and evaluated. In identifying new therapeutic agents for contraception, the pharmaceutical industry searches for compounds to mimic the actions of natural hormones. Initially, basic research is conducted to identify potential receptors, determine their structure, and develop cell lines. A target is chosen, determining class, such as progestin, estrogen, GnRH, FSH, LH, activin, inhibin, integrin, etc, and its type. The compound type is then determined: steroid, non-steroid, protein, peptide, non-peptide, and the type of production: lab chemistry, recombinant therapy, or natural product. Next, the synthesis approach is determined and in vitro screens developed. Various features of the compound are tested and improved: potency, efficacy, selectivity, solubility, and compatibility with delivery systems. The potential compound is screened many times, and a structure activity relationship is developed. After a lead compound is identified, its reproductive evaluation is expanded, the non-reproductive pharmacology evaluated, and metabolism and pharmacokinetics evaluated. Often during its development, further research is conducted to improve the compound’s solubility and other characteristics. Many compounds fail to make their way through the research process, and the costs of development are not included in successful therapeutic products. In vivo testing in animal models is essential to collect the necessary information on safety and efficacy before the compound can be recommended to management for development.

B. Preclinical Research

Dr. Rosemarie Thau of the Population Council gave a presentation detailing what items were required in preparation of a new contraceptive product for clinical testing in humans. After the idea and lead are created for a new product, preclinical trials are conducted in rats and mice to determine the acute toxicity of a single dose, and to determine the maximum feasible dose that produces observable toxic symptoms. Additional tests are performed over thirty days in rats and monkeys in control and three dose levels to determine repeat dose toxicity. High dose effects are tested in rats at 200 times the anticipated human dose and in monkeys at 50 times the anticipated human dose. The compound’s effects on body weight, food consumption, urinalysis, hematology, ophthalmology, blood chemistry, gross and microscopic pathology of 40 different tissues,
and blood pressure are measured in monkeys, as well as the blood level of the parent compound.

Preclinical requirements for Phase II trials include the areas of subchronic toxicity, pharmacology and return to fertility. The duration of the subchronic toxicity animal studies are flexible, but not less than the proposed duration of the clinical study. Rats and monkeys in a control and three dose level groups test the highest dose that will produce blood levels of the parent compound that are at least ten times higher than the effective human blood level. Study parameters include: body weight, food consumption, hematology, blood chemistry, histopathology, etc. The pharmacology studies test the various endocrine effects of the parent compound on rats, such as androgenic, estrogenic, progestogenic, receptor binding studies and antagonistic effects.

Preclinical requirements for Phase III trials include studies in genotoxicity or mutagenicity, and reproductive and developmental toxicity. Segment I of these toxicity trials study the potential of the drug to alter fertility and reproductive performance. Segment II determines the teratogenic potential of the drug, and should be done if the drug is to be used in women who are at risk of pregnancy. Segment III of the toxicity studies tests effects on the development of the fetus during the last third of gestation, as well as adverse effects on delivery, lactation, and post-parturition pup development in rats. Requirements for NDA and marketing trials include chronic toxicity: six months for rats, twelve months for monkeys, and a 2 year carcinogenicity study in mice and rats.

Dr. Thau concluded her presentation with a summary of present formulations and delivery systems of contraceptives. These include injectables, vaccines, implants, vaginal rings, intrauterine devices, transdermal systems, nasal sprays, and oral pills.

C. Clinical Research

Dr. Howard Miller of Family Health International presented an overview of the various steps in the clinical research phase of a new contraceptive product. Researchers need to provide trials with good science and good documentation to steer potential drugs through the approval process. A clinical plan must be developed to determine how studies interrelate, as well as what studies are sequential and which are concurrent.

Phase I studies determine the metabolic and pharmacological effects as well as adverse effects in less than thirty subjects protected from pregnancy. Phase II studies determine side effects, effectiveness and additional pharmacology in less than 100 subjects. Phase III trials study the effectiveness, tolerance and adverse effects in a broad subject population. Several hundred to several thousand individuals take part in controlled multicenter trials.
Dr. Miller gave practical guidelines on study design. A control group is advisable, and placebo control is most desirable for statistical purposes, but not always practical for ethical reasons. Randomized trials are good, but not always feasible. If a subject is randomized to device A but doesn’t like it, the subject will discontinue too early. In considering cross-over design versus parallel group design, the subject might get used to the first treatment and not want to change to the other treatment. The second half of the cross-over trial will become polluted by the subjects’ experience in the first half. Often this produces a higher drop-out rate, and if there are too many drop-outs, the study will not produce good results. Parallel groups require more subject, but there is no carry over effect. In this type of study, drop-outs are easier to handle than with cross-over studies. Double blinded studies are good, but one cannot always blind all contraceptive studies, especially when the difference in a device is apparent to the subjects.

In a discussion of various issues regarding clinical trials, Dr. Miller had a number of recommendations. Clinical trials should have adequate statistical power to detect differences between groups considered to have clinical interest. The recruitment of subjects is often as much art as science. Researchers should establish conservative recruitment goals, and plan for contingencies. Subjects should not be reused, as it will inject a bias that is unacceptable.

The researcher must randomly audit data to confirm that it was collected on the correct date, etc. Compliance is important. Did the subjects take the pills? Often 15% or less comply with the protocol, and the compliance with devices is often worse. We must take their word that they followed the procedure correctly. Coital logs and menstrual diaries are inaccurate if memory is bad.

In data analysis, we must analyze by "intent-to-treat." We cannot arbitrarily exclude subjects, however if the subject didn’t take the drug, we can eliminate their data from the set, but must document our actions. Statistical procedures can’t be determined after the study is complete. This leads to problems with the scientific community and "creative statistics." In addition, we must be aware of cultural differences in multicenter trials versus single center trials. It is important at the end of a multicenter trial to justify that we can merge the data to analyze the results.

D. FDA Perspective

Dr. Lisa Rarick of the Food and Drug Administration reviewed current policies for approval of new contraceptive drugs, devices, and vaccines. She reviewed the general process of IND and NDA approvals, and addressed several new issues in the pharmaceutical industry.

Dr. Rarick then discussed regulatory aspects of spermicides. These agents are considered drugs, and used to be an "Over the Counter" product. However, the FDA doesn’t believe
that the efficacy data on existing products is sound. In fact, they may ask that all currently marketed products be re-evaluated. Discussion with the industry on this topic are currently ongoing. We are used to long trials but we have to determine the number of subjects, concentration, and time to show efficacy. In vitro tests need to be correlated with in vivo action. The action of spermicides on HIV should be tested. Women’s groups are lobbying to have spermicides labeled for their efficacy of action against HIV. In addition, efficacy and labeling of condoms should be improved, especially in comparing different methods of contraception. Labeling should more strongly worded and more readable.

Some questions from the audience included:
What exclusions to user fees are possible for non-profit organizations?
A: The secretary has the authority to make a waver.

If you have a product composed of two therapeutic agents, how do you assemble the data?
A: The FDA hopes that it is just a combined product. Toxicology, safety and efficacy are done both individually and together. The combination must show that provides more benefits and is more effective, or acceptable.

Should interim analysis of data be allowed in clinical trials?
A: This should be part of your statistical plan. The FDA requires a penalty if interim analysis is performed. There should be an extremely good reason, as it can create a statistician’s nightmare.

V. Working Groups

Four categories of working groups were determined based on the research questions submitted by the participants. Each working group reviewed and assessed some of the current issues and/or questions facing basic and applied research organizations in contraceptive development. The ultimate goal of these working groups was to initiate a process of communication and collaboration among the participating organizations. Each working group was presented with an illustrative list of issues for discussion prior to the meeting.

The specific objectives of each working group were:

• to identify priority research areas, or types of methods/compounds;
• to identify technical problems, methodological issues, or specific research needs that require special attention with elaboration of the actions recommended; and
to identify general areas or more specific projects or activities for collaboration both among the reproductive biology centers and/or between the centers and the applied research organizations.

A. Group 1: HIV/STD Prevention and Contraceptive Development

Research Overview

Extensive research efforts are ongoing in the area of heterosexual transmission of HIV and other STDs. These are focused on understanding the mechanisms of HIV transmission as well as evaluating female-controlled methods to reduce transmission of both HIV and other STDs. Specific areas being studied within the Mellon centers related to HIV include an analysis of the transmission of HIV in genital tract epithelial cells; the physiological mechanisms of HIV transmission; the detection and quantification of HIV in reproductive tissues and secretions; and, the screening of compounds for anti-HIV activity.

Illustrative List of Issues for Discussion

1. What characteristics of chemical barriers are most effective and/or necessary in reducing transmission of STDs. Should they be virus neutralizing, bactericidal and/or spermicidal?

2. What options exist for vehicles and delivery of chemical barriers?

3. What type of delivery systems would be the most effective and acceptable?

4. What kinds of considerations and assessments should be conducted to determine the role of vaginal irritation in HIV/STD transmission?

5. What are the knowledge gaps in cervical and vaginal physiology related to contraception or STD transmission?

6. Do animal models exist to test new chemical barrier methods for toxicity and effectiveness?

Presentation/Findings

The role of chemical barriers in reducing STD/HIV transmission

Sexual transmission is the most common mechanism by which HIV infection occurs. Vaginal sex is not the only mode of transmission, and anal and oral sex may play a role. Since anal sex may be used by couples to prevent conception, and as a mode of sexual
expression without losing virginity, greater emphasis should be given to the role of anal sex in heterosexual HIV transmission.

Worldwide, there is a lack of information and education about HIV transmission and the role of various contraceptives and their relationship to HIV transmission. Spermicides kill HIV in the test tube but can cause irritation in the vagina. Does this irritation lead to increased viral transmission? Spermicidal foam comes in a 12.5 percent formulation and gels come in formulations with several different percentages of active ingredients, but it is not known what is optimal for HIV prevention. Irregular bleeding is a possibility with progestin contraceptive methods. Are women who are bleeding more infectious, or at greater risk of HIV infection? Do IUDs enhance transmission?

Should energy be put into the development of an agent that is only virucidal? Many people would like to be able to prevent the transmission of HIV, but still leave open the possibility of becoming pregnant. From a pragmatic perspective, it will be difficult to prove that these agents are effective but will not cause adverse effects on sperm. The group recommended that a vaginal microbicide is needed. Ideally both contraceptive and non-contraceptive formulations are needed. However, great attention must be paid to the issue of safety, including teratogenicity.

Effectiveness and acceptability of delivery systems
NICHD is funding a study to look at the duration of action of spermicide formulations: performing a vaginal lavage at varying times after spermicide insertion, measuring the amount of N-9 in the lavage, will allow a quantitative measure of the remaining spermicidal and possible anti-STD activity.

On April 6-8, 1994, NICHD will sponsor a meeting to define the clinical study design necessary to evaluate contraceptive efficacy of barrier methods. In designing studies, it is important to define rational endpoints which are practical to implement in reasonable periods of time. What is the ultimate or more important endpoint: A public health impact, or an individual impact?

The acceptable level of anti-viral and antimicrobial efficacy for a chemical barrier is not clear. Ideally, a very high efficacy (approaching 100%) for antiviral and antimicrobial activity is desired; however, practically, this may not be possible. The view of the FDA is unclear. Will the FDA allow approval and use of a product with 50% efficacy, for example? It seems unlikely even though such a product, if used, could have an important impact on sexual transmission.

Evaluation to demonstrate effectiveness of current formulations and new formulations is challenging. Given ethical issues, studies must be conducted in couples counseled to use condoms. This necessitates very large studies and probably will require conducting studies in the developing world, such as the NIAID Preparation for AIDS/HIV Vaccine Preparations (PAVE) sites.
The role of vaginal irritation in HIV/STD transmission
Information on potential effect of spermicides on HIV spread is unclear. In particular, vaginal irritation is an area that needs greater study, including the effect of frequent use of certain barrier methods and the relationship to cervical/vaginal erosion.

Knowledge gaps in cervical and vaginal physiology
More information is necessary on the potential for increased susceptibility at certain stages of the menstrual cycle, pregnancy, or with use of various exogenous hormone preparations. Studies on how to reduce infectiousness of seropositive individuals will be important. The group recommended studying the use of a systemic agent such as gossypol to reduce the transmission of HIV.

Vaginal physiology and how it is affected by exogenous agents must be defined. These include vaginal secretions, pH, cervical mucus and the intact surface epithelium. The immune response i.e., immunoglobulin vs. cell-mediated immunity and how vaccines might affect transmission is poorly defined. The effect of the vaginal flora and exogenous agents, e.g., lactobacillus, detergents, needs more study.

In addition, standardized terminology for colposcopy to define vaginal/cervical irritation is needed to better allow the cross-evaluation of data. It is critical that a working group to coordinate the planned and ongoing studies in this area be established.

Animal models for chemical barrier methods
Are studies in non-human primates needed before proceeding to human studies? These studies have provided crucial information to date, but there are a number of questions that cannot be clearly answered in the monkey model (e.g., the effects of vaginal intercourse). Such studies are not imperative to the development of vaginal products. The time and resources involved are not reasonable to make non-human primate studies a general requirement. Other animal models are usually employed for safety evaluation, and in vitro testing can be used to determine the effects of various products against HIV.

Conclusion
Better coordinated research to improve the definition of efficiency and outcomes, as well as defining the potential for collaboration between basic and applied centers needs to be undertaken. Nancy Alexander’s manuscript summarizing the state of understanding of HIV transmission and unanswered questions should be distributed widely when it is completed. This will help stimulate discussion on where successful collaborations among basic and/or applied research agencies may be possible. In addition, the group recommended post-graduate courses on STDs in the reproduction circles and on reproduction in the STD circles in order to stimulate cross disciplinary interest and work.
B. Group 2: Immunocontraception/Contraceptive Vaccine Development

Research Overview

Several of the centers or agencies are working on the development of immunocontraceptives. This research includes the development of molecular approaches to enhance immunogenicity of proteins for vaccine development. The basic goal is to develop and test safe, effective, reversible contraceptive vaccines for both women and men. A wide variety of antigens are being explored including hormones (hCG, GnRH, FSH), sperm proteins, zona pellucida proteins, and trophoblast proteins. The leads are in various stages of development ranging from early screening to Phase I clinical testing.

Illustrative List of Issues for Discussion

1. Which antigens are most promising at this time? What are the key concerns with the various approaches (such as autoimmune disease, irreversibility, etc.)?

2. Discuss the concept of using multiple antigens versus single antigens for vaccines.

3. Should resources be concentrated on the antigen(s) in the most advanced state of development to get at least one vaccine to the stage of wide scale testing as soon as possible? Should several promising antigens be selected and concentrated on? Should all the leads identified be pursued?

4. What are the leading adjuvants and conjugates being considered for contraceptive vaccines?

5. Specific issues/needs for the pre-clinical evaluation of the safety and effectiveness of contraceptive vaccines.

Presentation/Findings

The priority efforts of the research centers involved in immunocontraception are to develop methods with emphasis on pre-fertilization vaccines which can be reversible and which can be developed for either men or women. It is established that naturally occurring as well as induced autoantibodies to gametes do not have adverse effects on the immune system. The research in this area will provide information which can be used to study infertility as well as other reproductive diseases including ovarian cancer.

Current leads and approaches at all centers

University of Connecticut Health Center: The projects in the center are at different stages of development in terms of a usable contraceptive product. The most advanced is the PH-20 vaccine for women. With PH20, the sperm antigen is localized on the sperm
surface, and we have studied sperm differences between the guinea pig, humans and the
cynomolgus monkey. This antigen is known to have hyaluronidase activity. We have
found that the native protein is effective in guinea pigs and the recombinant form will be
tested in monkeys in 1994. Other antigens we are studying include P95 (tyrosine kinase)
and PH30, a sperm antigen which has been shown to reduce fertility in guinea pigs.
Presently the guinea pig form of the cDNA is cloned, and similar disintegrins have been
identified.

The Population Council: Various antigens are being tested at this center and are at
different stages of development. The hCG vaccine which is targeted towards females
only, has been studied for toxicology in primates for eight years and most likely inhibits
post- as well as pre-fertilization. Clinical trials for the hCGTT vaccine are completed for
Phase I, but there is no funding for Phase II.

A Phase I IND has been filed for LHRH Target Antigens with androgen replacement, and
clinical studies are underway in prostate cancer patients. This product is targeted toward
men, and has been found to inhibit spermatogenesis and reduce testosterone.

Testing in non-human primates has been initiated for FSH (native ovine FSHB). The
mechanism of action has been found to directly inhibit spermatogenesis without inhibiting
normal testosterone. This antigen induces only oligospermia and not complete inhibition,
and is targeted only towards males.

For the FSH receptor, testing of the C and N terminal peptides in the testing of the N
terminal has shown no effect on fertility in rats. More rat experiments with other peptides
are planned, and eventually this product will be targeted for both females and males.

The AS1 sperm antigen, or sperm head antigen, has been tested in rats against native
protein, and been found to be partially effective. This antigen, which is targeted towards
females, has also been successfully cloned by the center. Studies are also ongoing in rats
for the HSD1 Sperm head antigen, which is targeted towards females. In addition, the
center has cloned the antigen from rat sperm.

World Health Organization: Phase I trials for the antigen hCGB have been completed,
and Phase II clinical trials are ready to start in Sweden and Australia. This antigen does
not interfere with normal cycles. The prototype vaccine had problems with titer, but the
center is now using a new delivery system. The peptides have been defined in hCGB.
This antigen has been targeted towards females, and its action is exclusively post-
fertilization, probably before implantation.

National Institute of Immunology, New Delhi, India: At this center, the antigen hCGB
has been annealed to ovine LH alpha, and researchers have used both diphtheria or
tetanus toxoid as adjuvants. Phase II clinical trials have been completed, with conjugates
found to be more immunogenic. Seventy-five percent of the subjects injected responded
with effective titers, which were defined as 50ng/ml in serum. This antigen is targeted towards women, with its action occurring post-fertilization with impaired luteal function, but normal cycles in the women.

**University of Virginia Health Services Center:** In this research center, injections of recombinant vaccine immunogens in primates have shown strong and specific immune responses. The sperm peptide p10G on the sperm head (equatorial acrosomal border), a rabbit B cell epitope, has been isolated and tested in mice with 71% inhibition of fertility. Most men with antisperm antibodies have antibodies to this antigen. This antigen works during prefertilization, and is targeted towards men.

A recombinant rabbit sperm antigen, Sp17, is a testis and sperm-specific zona binding protein, and this protein is also found in the sperm head and tail in humans and mice. This antigen is targeted towards females, and works during prefertilization. Tests are now in progress with recombinant bacterially produced and synthetic peptides.

The LDHC4 peptide antigen, which has been targeted towards females, have been conjugated to diphtheria toxin, and studied in baboons. Although there was a 75% inhibition of fertility, this finding had no correlation with the serum antibody. Additional tests with a T cell epitope are underway. This prefertilization-acting antigen would be a likely candidate for a multi-determinant sperm vaccine.

The sperm specific antigen Sp10 has been cloned from human, baboon, and monkey cells. Acrosomal membranes, matrix and equatorial segment have been shown in all 3 species. The human antigen has been tested in baboons and showed an antifertility effect, but there was a 46% pregnancy rate. Antibodies to Sp10 have been shown to inhibit sperm in hemi-zona tests. No reversibility studies have been undertaken. Currently the center is conducting tests with baboon antigens into baboons, and *in vitro* tests. Current studies are with the WHO formulation using squalene, that is with no adjuvant. This antigen is targeted towards females and acts during the prefertilization period.

S71, a human sperm acrosomal antigen targeted towards females, is also being studied at the center. It has been shown that antibodies in mice to S71 inhibit fertilization *in vitro*. The center has successfully cloned cDNA for human cells. Researchers plan to continue mice fertility studies and further study the prefertilization action of this antigen.

ZP3 peptides, a prefertilization antigen targeted towards females have been tested in mice only. Some of the peptides give rise to ovarian oophoritis, and some don't. The fertility effects of this antigen have not yet been demonstrated in current studies.

**Baylor College of Medicine:** This center has been studying Rec 55, a prefertilization antigen targeted towards females. It is a rabbit zona pellucida antigen which has antigenic similarity to human, baboon, cynomolgus monkey, deer, cat, dog, pig, but not
to mice and rats. *In vitro* studies of this antigen show antibodies inhibit sperm binding in monkey.

Baylor College is also studying Rec 75, or rabbit zona pellucida antigen, a homologue of mouse ZP2. Primate studies in cynomolgus monkeys show ovarian oophoritis. The mode of action of this antigen is during preovulation and prefertilization, which makes it not acceptable for human but for animal sterilization. This antigen is targeted towards females.

**Priority research areas**

The working group suggested that the goal of immunocontraceptive vaccine research should be to develop a vaccine with comparable efficacy comparable to other currently available methods, that wouldn’t require frequent administrations or monitoring, and that would last for at least one year. They also felt that a prefertilization vaccine would be more acceptable.

Priorities for current research should be to continue testing individual candidates, and develop multideterminant compounds. Work with various adjuvants, immune enhancement, and delivery systems should be continued by identifying NIH centers in adjuvant and immune enhancement research, studying the efficacy of oral vs. injectable preparations, continuing to study slow release compounds (such as microspheres, polymers, hydragel, etc.), and encouraging center interaction.

The group stated that candidate gamete antigens have not been sufficiently tested to prioritize use, however, for hormone vaccines, it is a priority to develop a hCG vaccine for women and a GNRH vaccine and a FSH vaccine for men. The working group also suggested additional basic research in regions of plasma membranes of gametes which have not been evaluated, and in other antigens in reproductive tract.

**Conclusion**

The working group recommended funding for center support to provide services for antigen production, scale up purification and standardization under Good Laboratory Practices for animal testing, as well as specific funding for delivery systems. They also recommended a working group on adjuvants, emulsifiers, delivery systems, and identification of tested products and FDA approved delivery systems.

**C. Group 3: Male Contraceptive Development**

*Research Overview*

Several centers or agencies are working on some type of male contraception ranging from new sterilization methods to vaccines. Basic research is focused on spermatogenesis and
sperm maturation, the development and differentiation of testes, sperm transport, male vaccines, and on autocrine and paracrine regulation of testicular functions.

Illustrative List of Issues for Discussion

1. Discuss the new androgens which have been identified and the use of androgens as male contraceptives.

2. What is the outlook for new delivery systems for androgens as male contraceptives?

3. Are there agents being used for other treatment modalities, e.g. 5α-reductase and aromatase inhibitors, which may have potential value in male contraception?

4. What is the current status of GnRH agonists and antagonists in male contraception?

5. Which areas of basic research are most likely to help in the development of a male contraceptive?

6. What appear to be the most promising research areas which will lead to a potentially viable product in five years?

7. Are developing male contraceptives economically feasible?

8. What can be suggested as techniques to affect the function of the epididymis and be used as a male contraceptive?

Presentation/Findings

The discussion of the working group was organized to evaluate hormonal methods of contraception, contraceptive methods acting on the testes, contraceptive methods acting on the epididymis and constituents of barrier contraceptives acting on the sperm cells.

Hormonal Methods

These methods are aimed at turning off gonadotropic hormone production either by inhibiting the release of GnRH or blocking the effect of GnRH on the pituitary. A possible method would be to eliminate FSH secretion specifically and thereby inhibit spermatogenesis. Because LH and FSH are both involved in stimulating spermatogenesis, even the virtual elimination of FSH secretion may not be a viable approach as long as LH is present. Also, no method so far developed has had a capability to selectively inhibit FSH secretion. The most effective approach presently available is to inhibit the secretion of both FSH and LH. Current studies demonstrate that testosterone alone will reduce gonadotropin secretion sufficiently to inhibit spermatogenesis, but the amount of hormone
needed may cause unacceptable side effects. GHbR antagonists can also achieve this
effect, but side effects related to histamine release at the site of injection are a problem.
Improvements in delivery systems are needed for these methods. Progestational agents
such as levonorgestrel together with testosterone may be more effective in suppressing
spermatogenesis than testosterone alone and should allow use of a lower dose of
testosterone. The fertility data in normal men in the current WHO clinical trials with
testosterone injections are encouraging in that men whose sperm counts are suppressed
to less than 3 million/ml are nearly always infertile and nearly all men get to a sperm
count less than 3 million/ml. The overall contraceptive efficacy is therefore very high.

One of the problems with using the current forms of testosterone for contraception is the
need to administer the hormone frequently. Other longer-acting esters, such as
testosterone buciclate are under investigation. These hormones require only a single
injection each three to four months. Microencapsulated testosterone beads with early and
late release may provide the type of formulation which is needed. Other androgens such
as MENT may be advantageous because they are not metabolized by 5 α reductase.

Additional effort will be needed to identify other progestins which may be used for
contraception in males. Many of these hormones have already been tested in females.
Non-peptide GnRH antagonists should also be sought. The possibility of using GNRH
antagonists at higher doses than in previous studies is also worth consideration. However,
in past studies, such treatments have led to small increases in FSH over time with
consequent rise in sperm counts and higher risk of fertility.

Methods Acting on the Testes

More work is needed on contraceptive methods that act on Sertoli cell function. Efforts
are needed to identify gene products expressed during specific stages of spermatogenesis.
These products may be unique to germ cells and could be targets for immunocontraception, although delivery of antibodies across the blood testis barrier could
be problematic. If inhibiting substances from germ cells could be identified and
synthesized, these substances could be used as pharmacological agents acting on Sertoli
cells. The FSH receptor on Sertoli cells has been cloned and could be a target for
immunologic approaches, although the likelihood of undesirable side effects on the testes
must be recognized. Compounds could be screened for their capability to bind the FSH
receptor site and thus inhibit biological action without being biologically active
themselves.

Compounds which act on the testes should continue to be investigated. Recent research
indicates that the problem of hypokalemia as a side effect of gossypol administration may
be less serious than previously thought, and that the contraceptive dose of gossypol may
be lower than those used previously. The problem of irreversible infertility following
treatment with this drug has not been overcome. The possibility that devices which alter
testicular temperature could be used as a means to disrupt spermatogenesis should also
continue to receive attention.
Epididymis as a Target for Contraception
The epididymis is an attractive target for contraception. Some animal epididymal secretory genes have been cloned, and it is likely that some of these genes will have human homologs. Sperm coating proteins could be targets for immunocontraception. Because changes occur in intrinsic sperm surface proteins during transport through the epididymis, the sperm cells themselves may represent unique targets for contraceptive vaccines. Recent experiments have suggested that immunization against epididymal sperm antigens may lead to increased sperm removal from the epididymis. Very little is known about the biology of sperm removal from the epididymis under normal conditions, and this area should be investigated in the context of contraceptive development.

Contraceptive Methods that Target Sperm in the Ejaculate
The currently available constituents of barrier contraceptives are all spermicides. There is concern that prolonged use of spermicidal agents such as nonoxynol-9 may lead to alteration of vaginal flora, vaginal irritation, in increased susceptibility to STDs. It is desirable to develop contraceptive compounds that target specific sperm functions. The inhibitors of sperm acrosin are examples of these types of compound. More effort should be devoted to identifying other specific inhibitors of sperm function. Reevaluation of the contraceptive efficacy of hyaluronidase inhibitors may be warranted, in view of the demonstration that there are proteins on the sperm cell surface with hyaluronidase activity. Hyaluronidase activity may be important not only for interaction with the oocyte but also for penetration of the cervical mucus. Therefore, inhibitors of this enzyme could target two steps in the process of sperm transport and fertilization.

Recommendations
The most immediate, targeted clinical research needs to be in the area of hormonal methods since these are being demonstrated to have high efficacy (in the ongoing WHO multicenter study). A variety of other potential methods need more basic science investigation.

In view of the need for more activity in the area of male contraceptive development, the group recommends that a future meeting of the Mellon Centers have discussion of male contraceptive research as one of the major objectives.

Since there are relatively few basic or clinical scientists engaged in research on male reproductive biology who are also interested in contraception, consideration should be given to requesting applications for research proposals in this area. This would seem to be an excellent time to have a Request for Proposal (RFP) or Request for Application (RFA) from NICHD in the area of basic and clinical studies in male contraceptive development.

A working group should be convened to carefully evaluate whether the standards for acceptable side effects of contraceptives in males and females are equivalent.
D. Group 4: Animal, Cell, and Molecular Models Used in Contraceptive Development

Research Overview

Development of new contraceptive products is dependent upon appropriate molecular, cellular and animal models for identifying and evaluating potential leads. Within the Mellon Reproductive Biology Centers, research is being conducted using a wide variety of different animal, cell or molecular models for the identification and development of new contraceptives leads. Research activities include use of non-human primates to evaluate the efficacy of a variety of potential approaches, particularly immunocontraceptive leads; development of a non-human primate in vitro fertilization system that can be used to directly assess the actions of putative agents designed to act at the level of oocyte maturation and/or fertilization; use of a zona penetration assay (ZPA) to evaluate potential agents for the inhibition of early fertilization events and cleavage; use of several cell and animal models to evaluate the feasibility of regulating hormone action in vivo using triplex-forming oligonucleotides which inhibit transcription; use of primary cultures of epididymal epithelial cells to evaluate factors that affect sperm maturation; use of primary cultures of Leydig progenitor cells to evaluate effects of various hormones on cell function; and development of in vitro systems to evaluate sperm interaction with uterine and oviductal cells.

Illustrative List of Issues for Discussion

1. What are the most appropriate animal models to evaluate the effectiveness of various contraceptive leads (may need to address in a method-specific manner).

2. Are there animal models that are clearly inappropriate for evaluation of potential contraceptive approaches?

3. Which animal or cell models may be most appropriate for evaluating and predicting safety? (May need to address in a method-specific manner)

4. Is demonstration of effectiveness in monkeys important prior to human studies or are studies in other non-primate species sufficient to demonstrate contraceptive potential in humans?

5. What animal models might be feasible for the evaluation of triplex-forming oligonucleotides as contraceptives?

6. What are the merits of a non-human primate in vitro fertilization system to assess potential contraceptive leads?
Presentation/Findings

The working group proposed unification of model systems for identifying conserved principles e.g., spermatogenesis, oocyte meiosis and gamete interaction. They recommended discussions among scientists working in areas appropriate for unification recognizing that there are areas where unification may not be appropriate due to variation between species e.g., luteal function and implantation. Two particular systems that they considered inappropriate are the use of hamster and rat for gamete interaction studies due to non-selectivity of the oocyte membrane in the former and difficulties with IVF in the latter.

In addition, consideration should be given to appropriate product formulation and route of administration prior to animal trials (e.g., difficulties with solubility of GnRH antagonists).

In terms of vaccine development for gamete specific antigens, the group suggested that the initial step would be identification of homologues in multiple species, including human. *In vitro* and *in vivo* testing for mechanism of action should be conducted in at least two species (perhaps, but not necessarily including primates) in order to ensure the biological conservation of the principle before moving to human trials. However, primate studies will be essential for prototypic experiments (e.g., the use of salmonella as a delivery system).

Requirements for toxicology are likely to vary considerably and the group did not consider it appropriate to make a firm recommendation on this point.

For development of new barrier methods, *in vitro* testing with human semen as an initial screen is recommended. While it is recognized that the rabbit is not optimal, no more appropriate model has yet been identified for *in vivo* testing for effectiveness. The use of sheep is suggested for the study of vaginal irritation and the possibility of interactions with seminal plasma should be incorporated in study protocols.

There is a need for an appropriate animal system to test novel contraceptives for their potential to affect transmission of sexually transmitted diseases.

Studies in non-human primates have a vital importance in contraceptive development due to key physiological differences between primates and non-primates. The group strongly urged continued support for work in this area of great public sensitivity.
VI. Mellon’s Twinning Program and Group Recommendations

Mellon’s Twinning Program
At the Foundation’s December 1993 Trustees Meeting, a grant was approved in support of additional twinning arrangements between centers of reproductive biology in developing countries and the eight centers supported by Mellon in the U.S. The grant was awarded to CONRAD, which will responsible for reviewing proposals and making small grants. The average grant size will be about $25,000, but if the Foundation receives a very compelling large proposal, the grantee may receive more funds.

The Foundation anticipates two rounds for proposals--the first in June, 1994, the second--contingent on sufficient funds remaining after the first round--in the spring of 1995. At the first round, requests will be considered only for arrangements with developing-country centers which do not currently have a twinning arrangement with a Mellon center--i.e., the first six centers on the target list. If there is a second round, collaborations will be considered with any of the eleven centers listed below.

The Foundation will circulate the research summaries submitted by the eight U.S. Mellon centers to the six “non-twinned” centers. At the same time, the Foundation will request similar summaries from the six developing-country centers (if they were interested in participating in the program) for circulation to the U.S. centers.

Collaboration could be initiated by either the U.S. or the developing-country side, but proposals would be submitted to CONRAD by the Mellon centers in the U.S., and grants would be awarded to these centers. The twin in the developing world needs to be an equivalent tax-exempt corporation. Neither the Foundation nor CONRAD will play a role in negotiating twinning arrangements. It is hoped that circulating the summaries of all the centers eligible to take part in the program will help centers find an appropriate “match”.

Proposed "Target" Centers for the twinning program include:
• Institute for Planned Parenthood Research, Shanghai, China
• CEMICAMP, Campinas, Brazil
• Mahidol University, Bangkok, Thailand
• Maternidad Climerio de Oliveira, Bahia, Brazil
• National University of Singapore
• Assiut University, Egypt

The Centers that are currently twinned with a U.S. Mellon Center include:
• Chilean Institute of Reproductive Medicine (ICMER), Santiago, Chile
• National Institute of Nutrition Salvador Zubiran, Mexico City, Mexico
• Institute for Primate Research, Nairobi, Kenya
• National Research Institute for Family Planning, Beijing, China
• National Institute of Immunology, New Delhi, India
Group Recommendations
At the conclusion of the meeting, participants requested that the next meeting of the Mellon Reproductive Biology Centers be an expanded meeting in the format of the present meeting. This meeting would combine basic research with contraceptive development and testing, but include more information on the Food and Drug Administration (FDA), and the process of patenting, thereby becoming both an educational as well as a managerial meeting for contraceptive strategy. This meeting should be open for all post-doctorates in training at the Mellon Reproductive Biology centers to attend.

In addition, participants suggested that representatives from each of four workshop/interest groups interact and keep in touch with a key person, to keep up-to-date on the state of art, and to make a focus for the next meeting.

Since the study area of the Mellon centers is comprised of a hybrid group of biologics and contraception, participants wished to examine delivery systems for vaccines more closely, and to discuss lessons learned and prior pitfalls. Also, participants requested more details on the regulatory aspects on biologics, e.g., how do biologic approvals differ from drug approvals?

It was also pointed out that centers in developing countries want to keep abreast of the latest developments in science, too. Therefore, it was felt that, at upcoming meetings, guidelines for international drug development should be discussed to train scientists in these countries. In the future, the FDA might accept clinical trials from developing countries more easily if the trials were conducted using good clinical practices.
VII. Appendices
# MELLON REPRODUCTIVE BIOLOGY CENTERS MEETING

**OMNI EUROPA HOTEL, CHAPEL HILL, NC**  
**NOVEMBER 7-9, 1993**

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MELLON REPRODUCTIVE BIOLOGY CENTERS MEETING
OMNI EUROPA HOTEL, NC
NOVEMBER 7-9, 1993

AGENDA

Sunday, November 7

5:00-7:00  Registration  Lobby Foyer
6:00-7:30  Reception  Lobby Foyer

Monday, November 8

8:00-8:05  Welcome  Vienna-Brussels Room
Theodore King, Family Health International

8:05-8:15  Participant Introductions

8:15-8:20  Meeting Overview
Carolyn Makinson, Andrew W. Mellon Foundation

8:20-8:30  Introduction
Roberto Rivera, Family Health International

8:30-10:30  Basic Research Centers
Moderator: Carolyn Makinson, Andrew W. Mellon Foundation

Discussion of current program status at each of the eight Mellon-supported Reproductive Biology Centers. Each center will give a five minute presentation based on the research summary it provided followed by a ten minute discussion period.

Baylor College of Medicine
Department of Cell Biology

Eastern Virginia Medical School
The Jones Institute for Reproductive Medicine

The Population Council
Center for Biomedical Research
(Reproductive Physiology)

University of California - Davis
California Regional Primate Research Center
Monday, November 8 (con’t)

University of Connecticut Health Center
Contraceptive Development Research Center

University of North Carolina
The Laboratories for Reproductive Biology

University of Virginia Health Sciences
Center for Recombinant Gamete Contraceptive Vaccinogens

University of Washington
Population Center for Research Reproduction

10:30-10:50  Break

10:50-11:40  Applied Research and Funding Agencies
Moderator: Carolyn Makinson, Andrew W. Mellon Foundation

Discussion by contraceptive research and funding agencies based on summary submitted. Each agency will be allowed 10 minutes in which to present and discuss its current research program and/or funding priorities.

- Agency for International Development
- Contraceptive Research and Development Program
- Family Health International
- Andrew W. Mellon Foundation
- National Institute of Child Health and Human Development

12:00-1:00  Lunch

1:00-1:30  Applied Research and Funding Agencies (con’t)
Moderator: Michael Harper, Andrew W. Mellon Foundation

The Population Council - Center for Biomedical Research (Contraceptive Development)
Rockefeller Foundation
World Health Organization

1:30-4:20  Discovery to Reality: How Does a Product Reach the Public?
A series of presentations on how a new contraceptive is discovered, how it is tested in animals, and then how it is tested in human trials.
Monday, November 8 (con't)

1:30-1:50  **Lead Development**  
Overview of how a new contraceptive lead is identified and evaluated.

Audrey Phillips, R.W. Johnson Pharmaceutical Research Institute

1:50-2:00  **Discussion**

2:00-2:20  **Preclinical Research**  
Preparing a new contraceptive product for clinical testing in humans: what is required?

Rosemarie Thau, The Population Council

2:20-2:30  **Discussion**

2:30-2:50  **Break**

2:50-3:10  **Clinical Research**  
Overview of the various steps in the clinical research phase of a new contraceptive product.

Howard Miller, Family Health International

3:10-3:20  **Discussion**

3:20-3:40  **FDA Perspective**  
Current policies for approval of new contraceptive drugs, devices, and vaccines.

Lisa Rarick, Food and Drug Administration

3:40-3:50  **Discussion**

3:50-4:20  **Panel discussion**  
The four speakers on contraceptive development will respond to questions from the audience.

6:00-7:00  **Reception**

7:00-8:45  **Dinner**  
Keynote Speaker: Cynthia Lloyd, The Population Council
Topic: Population Policy and the Unmet Need for Contraception

Lobby Foyer

Paris I-II Rooms
Monday, November 9

8:30-8:45 Overview of Today’s Session
Moderator: Roberto Rivera, Family Health International

8:45-10:00 Working Groups
The four working groups were determined based on the research questions submitted by the participants. Each working group will review and assess current issues and/or questions facing basic and applied research organizations in contraceptive development. The ultimate goal is to initiate a process of communication and collaboration among the participating organizations.

Group #1:
HIV/STD prevention and contraceptive development

Group #2:
Immucontraception/contraceptive vaccine development

Group #3:
Male contraceptive development

Group #4:
Animal, cell, and molecular models used in contraceptive development

10:00-10:20 Break

10:20-12:00 Working Groups (con’t)

12:00-1:00 Lunch

1:00-2:30 Summary of Working Group Outcomes
A representative from each working group will give a ten minute presentation of the group’s results followed by ten minutes of discussion.

Moderator: Roberto Rivera, Family Health International

2:30-2:45 Break

2:45-3:00 Mellon’s Twinning Program
Carolyn Makinson, Andrew W. Mellon Foundation

3:00-3:30 Evaluation of the Meeting and Future Plans
Roberto Rivera, Family Health International