



F R O M   C E L L S   T O   S E L V E S



# Reproductive Health for the 21st Century



National Institute of Child Health and Human Development



## **Contents**

<b>The NICHD Mission .....</b>	<b>1</b>
<b>The Strategic Planning Process .....</b>	<b>2</b>
<b>Introduction .....</b>	<b>3</b>
Overall Goals and Objectives .....	3
<b>Scientific Goals of the Strategic Plan .....</b>	<b>6</b>
Pursue Research Leading to Improved Outcomes in ART .....	6
Use Genetic Advances To Identify Factors Leading to Infertility .....	7
Use Genetic Advances To Identify Novel Contraceptive Leads .....	8
Increase Efforts To Develop Acceptable Male Contraceptives .....	9
Identify New Treatments for Common Reproductive Problems .....	10
Conduct Research on Male Reproductive Behaviors .....	11
Identify New Strategies for Improving Contraceptive Use .....	13
Study the Behavioral Factors Relating to Infertility, the Use of Infertility Services, the Ethics of Infertility Treatment, and the Status of Children Born as a Result of ART .....	14
Increase Knowledge About Healthy Sexuality .....	15
<b>Research Technologies and Resources .....</b>	<b>17</b>
<b>Training and Education .....</b>	<b>19</b>
<b>Appendix—Roster of Advisors .....</b>	<b>21</b>



## **The NICHD Mission**

The National Institute of Child Health and Human Development (NICHD) seeks to ensure that every individual is born healthy, is born wanted, and has the opportunity to fulfill his or her potential for a productive life unhampered by disease or disability. The Institute further strives to help parents have the children they want, at the times they want them, and to ensure that every mother experiences a pregnancy free of adverse complications. Key to the success of this mission is answering the fundamental questions of how a single fertilized cell eventually develops into a fully functional adult human being and how a multitude of genetic and environmental factors influence that process for good or ill.

Programs at the NICHD are based on the concepts that adult health and well-being are determined in large part by episodes early in life, sometimes before birth; that human development is continuous throughout life; and that optimal outcomes of development are important not only to the individual but to society. NICHD research is also directed toward restoring or maximizing individual potential and functional capacity when disease, injury, or a chronic disorder intervenes in the developmental process. Thus, the NICHD mission truly spans the life cycle, and much of the health and well-being of our population depends on the success of the Institute's research.

## The Strategic Planning Process

During 1998 and 1999, the NICHD staff engaged the scientific community in jointly developing a strategic plan to facilitate achieving its mission. The initial framework document for this plan, *From Cells to Selves*, highlighted four areas for immediate strategic development and described a series of scientific goals under each area. These four areas were as follows:

- *Genetics and Fetal Antecedents of Disease Susceptibility* includes the interaction of the genotype with socioeconomic, environmental, and psychological factors in the fetal and postnatal environment that contribute to health or the pathophysiology of diseases.
- *Reproductive Health for the 21st Century* comprises the biological and behavioral factors that allow couples to have healthy children when they want them and the reproduction-related conditions that may affect women during and after their reproductive years.
- *Developmental Biology: Understanding Normal and Abnormal Development* consists of the basic biological science necessary to understand early development *in utero* and through the time when many organ systems form.
- *Biobehavioral Development* includes research to better understand the developmental processes involved in forming cognitive, learning, emotional, social, and physical behaviors, and the biological and environmental factors that make infants, children, and adolescents more susceptible to behavioral disorders or to adopting risk-taking and violent behaviors.

This document refines the goals and objectives outlined under the area titled “Reproductive Health for the 21st Century.”

To help establish the more detailed research agenda that follows, the NICHD convened a working group comprising distinguished scientists (see Appendix) from around the country and asked them to collaborate with Institute staff to identify and prioritize research goals and to suggest appropriate strategies to meet those goals. The working group drew upon ongoing planning efforts, previous emphasis areas, recent forums, workshops, conferences, and research findings to develop a draft of the strategic plan that would guide the Institute’s research agenda in reproductive health for the next 5 years.

The draft plan was posted on the NICHD Web site to allow members of advocacy groups, nonprofit organizations, the scientific community, and the general public to comment. In addition, the Institute shared the plan with members of the National Advisory Child Health and Human Development Council and with the Friends of the NICHD, a coalition of more than 100 professional and patient organizations committed to the Institute’s scientific mission. After consolidating and reviewing all comments, the NICHD revised and finalized the plan. This document is intended as a targeted, but flexible, blueprint that can be modified as new scientific findings, research opportunities, or resources become available.

## Introduction

The ability to control one's own reproduction encompasses the desire not only to have children but also to have them at a time and in a manner that best ensures their future health, both physical and mental. Reproductive health significantly influences the overall health of individuals and society and has been the subject of increased attention from a health and economic viewpoint. The economic burden imposed on infertile couples attempting to achieve pregnancy is difficult to estimate accurately because the cost of treatment is not always reported as infertility related. The projected direct cost of assisted reproductive technologies (ART) together with the cost of multiple-gestation pregnancies is estimated to be \$1.1 billion for the year 2000. The direct cost of unintended adolescent pregnancies alone is more than \$1.5 billion. Thus, the overall costs of infertility treatment and those of all unintended pregnancies would substantially exceed \$3 billion annually. These direct costs are in addition to the considerable indirect costs associated with the immediate and long-term psychological and other consequences that accompany both conditions. In addition, the direct and indirect costs associated with uncontrolled population growth worldwide are difficult to comprehend, let alone quantify. Consequently, it is critical to address these problems from the broadest possible perspective.

During the past decade, major advances have been made in both the biomedical and behavioral sciences that can be applied to the important issues of infertility treatment, to the development of improved methods of family planning, and to the identification of behavioral factors that affect both fertility and infertility. The Institute's strategic plan builds on this solid research



base, much of which was developed with funding from the NICHD. While leaving intact the NICHD's existing areas of research emphasis, the plan also builds on the goals listed below, allowing the Institute to advance the technologies that are indispensable to achieving reproductive health without neglecting other research areas that are within its broad mandate. Finally, this plan clearly emphasizes the need for the biomedical and behavioral sciences to collaborate closely to successfully accomplish these goals.

### Overall Goals and Objectives

To help establish the research agenda for reproductive health, the NICHD asked the working group, in collaboration with Institute staff, to identify strategies that will best achieve the following goals:

- Pursue research leading to improved outcomes in ART
- Use genetic advances to identify factors leading to infertility
- Use genetic advances to identify novel contraceptive leads
- Increase efforts to develop acceptable male contraceptives
- Identify new treatments for common reproductive problems
- Conduct research on male reproductive behaviors
- Identify new strategies for improving contraceptive use

- Study the behavioral factors leading to infertility, the use of infertility services, the ethics of infertility treatment, as well as outcomes of children born as the result of ART
- Increase knowledge about healthy sexuality

The working group based its concept of reproductive health on the World Health Organization (WHO) definition:

Reproductive health is not merely the absence of disease or disorders of the reproductive process, but rather it is a condition in which the reproductive process is accomplished in a state of complete physical, mental, and social well-being. This implies that people have the ability to reproduce, that women can go through pregnancy and childbirth safely, and that reproduction is carried to a successful outcome, i.e., infants survive and grow up healthy. It implies further that people are able to regulate their fertility without risks to their health and they are safe in having sex.

This positive definition has several advantages. First, it emphasizes that biomedical and behavioral research relating to reproductive health should proceed within an interdisciplinary context that can accommodate economic, political, sociocultural, and psychological factors, while considering other somatic factors—such as systemic disease or the biological changes associated with aging—that affect sexual and reproductive function. The definition also reinforces a key aspect of the Institute’s core mission, which is to foster collaborative approaches to problems of reproductive health within the context of human development.

In addition, the working group felt that the WHO definition implies that progress in improving the reproductive health of the world’s population depends on the attainment of three broad objectives:

- Reducing the incidence of unwanted pregnancy
- Progressing towards desired levels of fertility
- Reducing morbidity from diseases and disorders of the reproductive system

These objectives, without displacing existing priorities of the NICHD, provide an important structure within which the Institute’s more focused research goals and agenda items can be analyzed and ordered:

- The objective of **reducing the incidence of unwanted pregnancy** unites the NICHD goals of using genetic advances to identify novel contraceptive leads, increasing efforts to develop acceptable male contraceptives, conducting research on male reproductive behaviors, identifying new strategies for improving contraceptive use, and increasing knowledge of healthy sexuality.
- The objective of **progressing toward desired levels of fertility** unites the goals of improving outcomes in ART, using genetic advances to identify factors leading to infertility, identifying new treatments for common reproductive problems, addressing behavioral and ethical issues in infertility and infertility treatment, and increasing knowledge of healthy sexuality.
- The objective of **reducing morbidity from diseases and disorders of the reproductive system** unites the goals of improving outcomes in ART, using genetic advances to identify factors leading to infertility, identifying new treatments for common reproductive problems, identifying new strategies for improving contraceptive use, studying the behavioral and ethical issues in infertility and infertility treatment, and increasing knowledge of healthy sexuality.

This classification demonstrates that the Institute’s nine scientific goals in reproductive health represent a



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## FROM CELLS TO SELVES

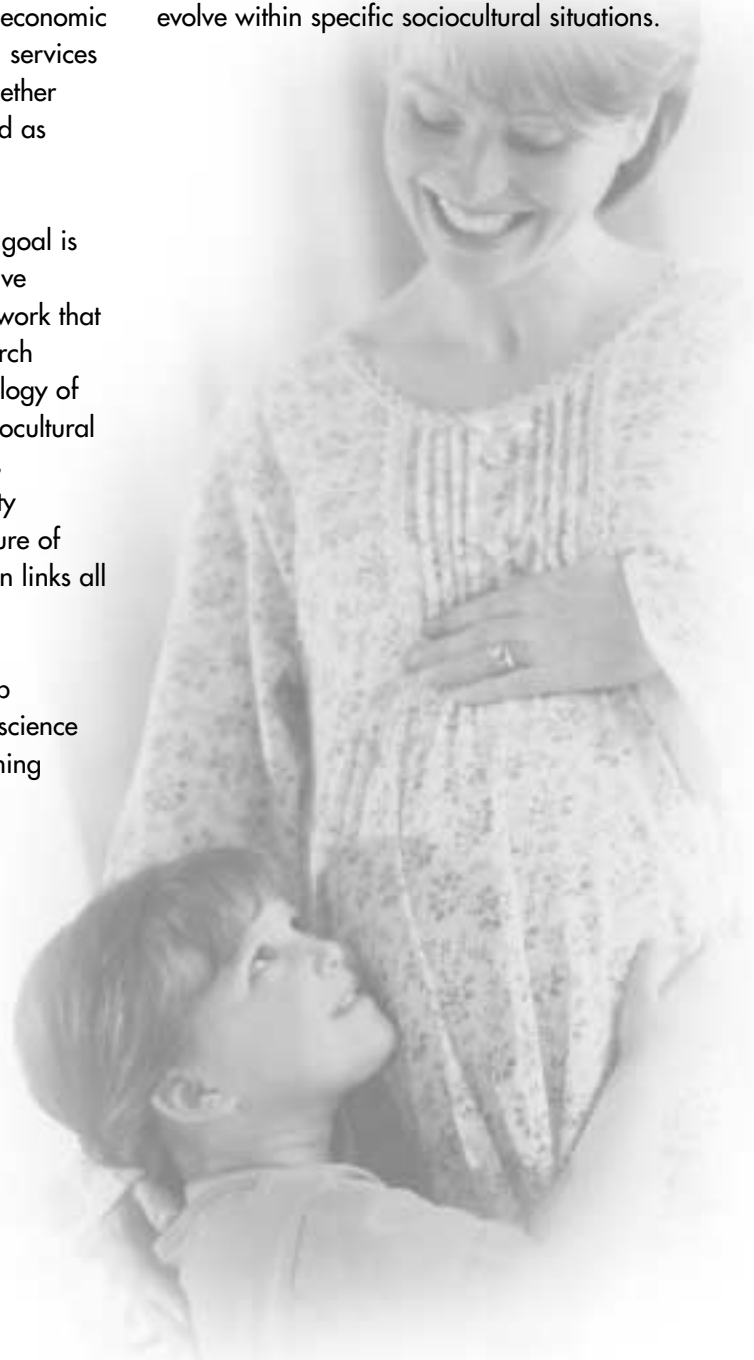
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continuum rather than discrete areas of research, justifying collaboration not only within the NICHD but also with other NIH Institutes, Centers, and Offices and with other Federal agencies. The goals also encourage collaboration among specialists in biomedical sciences, behavioral sciences, and social sciences. Sharing expertise, information, and methodological approaches is crucial for understanding issues such as how economic factors affect accessibility to reproductive health services and how cultural attitudes help to determine whether specific contraceptive technologies are perceived as acceptable by various social groups.

The inclusion of healthy sexuality as a scientific goal is strongly motivated by this emphasis on integrative research: it reflects a desire to develop a framework that unifies what could easily be two separate research agendas involving both the biology and psychology of individuals, as well as research concerning sociocultural issues. In addition, because healthy sexuality is predicated on effective contraception and fertility management, as well as on the prevention or cure of reproductive disorders and diseases, its inclusion links all of the scientific goals identified in this section.

Finally, in view of the Institute's desire to develop combined approaches to the nine reproductive science goals, the working group recommended combining

research focused on male reproductive physiology and behavior into a single topic. The issue of contraceptive acceptability is one good reason why these are being combined because contraceptive acceptability is predicated not only on physiological criteria (i.e., the physical side effects of hormonal contraceptives) but also on individual perceptions, values, and beliefs, which evolve within specific sociocultural situations.



## Scientific Goals of the Strategic Plan

### Pursue Research Leading to Improved Outcomes in ART

ART encompasses any method beyond natural intercourse intended to help produce a child. These methods range from the simple and well-tested to the complex and controversial. The number of ART practices has grown faster than the science needed to make evidence-based decisions in patient care. This has led to the empirical choice of treatments at significant cost, often with loss of time, and in some cases with morbidity.

Although overall age-specific infertility rates have remained stable as measured by surveys such as the National Survey of Family Growth (NSFG), the number of visits for infertility-related services has skyrocketed. This increased demand is due primarily to the aging of the general population and to the delay of childbearing for economic or professional reasons by a growing number of women.



Before developing strategic steps to improve ART outcomes, several key scientific considerations must be addressed. These include understanding the sequelae of treatment and developing a definition of “success” for clinical interventions. This is a highly controversial issue among clinicians using ART because pregnancy rates are higher than delivery rates. Therefore, although many research topics will yield important information about improved ART outcomes, the main issues are how to improve pregnancy and delivery rates while reducing the multiple pregnancies associated with the technology. A global database using consistent diagnostic and followup criteria, coupled with the inclusion of a DNA bank, could yield helpful information. Yet, to fully understand the nuances of ART outcomes and to answer the many questions about ART raised by science and society, it is also critical to support rigorous epidemiological and basic science research projects.

#### Research Areas

- Differentiate between successful (e.g., full-term deliveries), less favorable (e.g., multiple gestations, preterm births), and adverse ART outcomes, using large-scale statistical research, standardized criteria, and unified assessments. Develop standardized definitions of “success” and “adverse outcomes.” Adverse outcomes, in particular, lack standard definition and tend to be underreported because they may become apparent only over time.
- Increase scientists’ understanding of the development of primordial germ cells to mature oocytes and sperm through differentiation, meiosis, and maturation in an effort to evaluate the “quality” of eggs and sperm.





## FROM CELLS TO SELVES

- Enhance detection of abnormalities in preimplantation embryos; advance the technology of preimplantation genetic diagnosis.
- Understand what constitutes a receptive uterine environment and how receptivity can be enhanced. Understand how a healthy blastocyst-maternal tissue interaction during implantation leads to a healthy pregnancy and to the well-being of children born as a result of ART.
- Elucidate the multifactorial causes that lead to subfertility or infertility in couples and how these factors, both male and female, interact. Develop effective methods with minimal side effects to treat these causes.
- Understand the nature of the abnormalities either parent brings into the treatment setting, and identify those that may constitute risks to the offspring. Understand age-related fertility factors. These issues require basic science research to help differentiate normal from abnormal gametes and to make epidemiological risk-factor assessments.
- Understand the effects of gynecologic disorders, such as tubal disease or polycystic ovarian syndrome (PCOS), on fertility rates and the prevention of infertility. Understand how these disorders may affect the choice of infertility treatments.
- Understand the long-term effects of ART interventions on parental and child health. For example, in women, this includes the possible connection between ovulation induction and ovarian cancer; in men, the transmission of impaired fertility.
- Improve the culturing of immature sperm and ova. Conduct basic research into cryopreservation and subsequent maturation of oocytes.
- Utilize knowledge gained from basic stem cell research for understanding reproductive processes and for novel therapeutics.

### **Use Genetic Advances To Identify Factors Leading to Infertility**

Little is known about the pathophysiology of infertility, and many cases remain “unexplained.” However, as the power of human genetic analysis has increased, the evaluation of infertile couples has begun to uncover mutations involving essential factors or processes in reproductive health. For example, when a mutation occurs in a critical hormone receptor, the individual may become infertile because the effect of related hormones is decreased, even though adequate amounts of the chemical substances are produced. Likewise, a mutation in the machinery of the sperm tail movement prevents these sperm from normally fertilizing eggs and leaves a man infertile, even though he may produce adequate numbers of sperm.

It is possible that many instances of infertility may be attributable to genetic mutations because reproductive functions are probably controlled by a very large number of genes. Thus it is possible that the genetics of infertility may turn out to be at least as complex as the genetics of psychiatric illness. As yet, scientists lack a clear understanding of the overall contribution of genetic and nongenetic factors to much of female infertility and almost all of male infertility. Moreover, scientists know very little about the pathophysiology of germ cell defects.

The creation of new models is an essential first step in unlocking the genetics of infertility. This was made apparent by recent studies identifying numerous genes in mice and humans that are important during male and female meiosis, the formation of eggs and sperm, the process of fertilization, preimplantation development, implantation, and the complex processes involved in the origins and differentiation of germ cells. When

these genes are defective or absent, a variety of pathophysiological effects will occur, any of which could lead to infertility. Recent studies in mice have also shown how gene expression patterns in oocytes, sperm, and preimplantation embryos may vary under different experimental conditions, including variations in culture conditions that clearly influence the patterns of gene expression. Therefore, researchers can use the full power of mouse genetics to understand which genes are normally expressed at each stage of egg and embryo development, as well as during implantation and germ cell formation. This in turn will help determine which genes are abnormally expressed or silent under conditions of genetic alterations or environmental stress. Thousands of new mutant mouse strains will soon be produced through chemical mutagenesis, providing a vast number of reproductively impaired mouse strains to aid these studies.

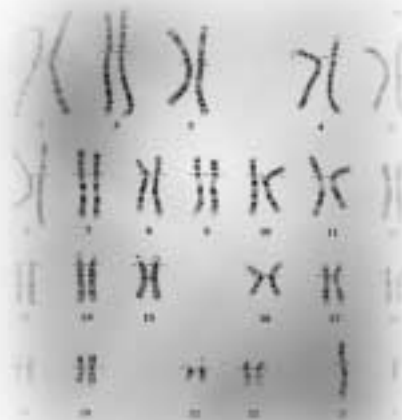
#### Research Areas

- Expand basic research on germ cell genetics as a foundation for understanding impaired reproduction as well as contraceptive leads.
- Devise a conceptual framework for the relationship between epidemiology and basic genetics.
- Combine genetic/epidemiological approaches to infertility in human populations, including investigation into the incidence of familial patterns of subfertility and infertility and possible modes of inheritance.
- Differentiate the genetic mutations that actually cause infertility from mutations that do not.
- Identify candidate genes in the general population, using both classical human genetics and pedigree analysis with new technologies of genomics and proteomics.

## Use Genetic Advances To Identify Novel Contraceptive Leads

Many steps are involved in normal human reproduction, including production and maturation of gametes; cell proliferation and programmed cell death; synthesis, secretion, and action of hormones; fertilization; preimplantation embryonic development; implantation; and sex determination. Genetic research involving reproductive processes, such as meiosis, could reveal molecular targets that could be the focus of novel contraceptive leads for both sexes. Potential targets include coding sequences for proteins or receptors or regulatory sites that control gene expression.

To identify the most promising molecular targets for contraceptive intervention requires understanding the genetic regulation of reproductive processes, a subject that scientists are just beginning to explore. The primary goal of genetically based contraceptive research should be to develop interventions that do not cause widespread somatic effects. The steps in the reproductive process that appear most likely to lead to effective and acceptable approaches are gamete production and maturation and the fertilization processes.



The past few decades have seen a dramatic increase in understanding the genetic control of male reproduction. In particular, the identification of genes involved in various aspects of testicular steroidogenesis, spermatogenesis, and sperm maturation has provided novel targets for fertility regulation. Coupled with the increased interest from the pharmaceutical industry in developing tissue-specific delivery approaches for drugs and genes, the time appears ripe to capitalize on this new knowledge about male reproduction to develop novel contraceptives.

#### Research Areas

- Discover associations of gene expression using discovery strategies and bioinformatics, such as expression profiling by means of microarrays and libraries, genomewide mutagenesis, and quantitative trait loci (QTL) analysis.
- Explore gene functioning at the cellular level using conditional targeted mutagenesis, RNA targets, and QTL analysis.
- Study the effects of these molecules at the level of the organism by using knockouts and transgenesis.
- Develop targeted interventions with minimal side effects.

### Increase Efforts To Develop Acceptable Male Contraceptives

To develop acceptable male contraceptives from a biological perspective, scientists must identify processes that regulate male germ cells without negatively affecting extragonadal systems. Basic and applied research during the past decade has uncovered a number of steps in the gametogenic process in the testes, as well as steps in epididymal sperm maturation, that may be amenable to therapeutic intervention. Studies have also shown that suppressing the hypothalamic-pituitary axis with a

variety of hormonal agents yields severe oligozoospermia, then azoospermia. Both of these conditions result in effective contraception. Much of this clinical research, however, was conducted on a small number of male volunteers, making it very difficult to select the more effective and acceptable regimens.

From a behavioral and sociocultural perspective, males must also be willing to use these novel contraceptives. Current data suggest that they may be willing to do just that: approximately 30 percent of all contraception in the United States is male based, despite the fact that abstinence, withdrawal, condoms, and vasectomy are now the only contraceptive alternatives widely available to men. Further evidence is supplied by several recent studies indicating that men will utilize effective, reversible male contraceptive methods when they become available; one recent poll has found that up to 70 percent of men are willing to use a contraceptive.

The lack of progress in developing affordable, safe, effective, and reversible male contraceptives is due not to the biological complexity involved in suppressing spermatogenesis, but rather to social and economic/commercial constraints. During the past decade, reasonably safe and effective methods for reversibly suppressing spermatogenesis have been developed. Most are hormonally based, but some immunocontraceptives are now in clinical trials. However, making these new contraceptives widely available on the market will require collaborative efforts that bring together the full spectrum of biological, epidemiological, and biobehavioral research and their political interfaces with the public. In the end, all of these factors must be addressed to help resolve sociocultural impediments to using these techniques as well as industry fears of litigation should they choose to market these novel products.

Because this topic represents intersecting priorities of all three branches of the NICHD Center for Population Research (CPR), it has particular merit, providing an

excellent opportunity for the CPR branches to collaborate in developing the initiatives.

*Research Areas*

- Identify specific hormonal agents and target their delivery; support research to design formulations and methods of delivery that are convenient and acceptable to men.
- Design new approaches based on the molecular biology of the epididymis and testis, including signal transduction pathways in seminiferous tubules, somatic-germ cell interactions, and factors that regulate germ cell differentiation and/or apoptosis. Increase knowledge about the factors that control spermatogenesis to facilitate the design of more specific compounds for male contraception. Identify new targets that can be explored in animal models and translated to clinical research and clinical trials.
- Study behavioral issues surrounding use of new male contraceptives. This includes the acceptability of such technologies to men and women and the possible behavioral issues relating to each of the new techniques.
- Support epidemiological assessments and analysis of cost-effectiveness for the various methods of male contraception.
- Conduct postmarketing surveillance of the benefits and potential adverse effects of any new agents introduced to the market.
- Analyze the long-term health effects, e.g., beneficial or adverse effects on the prostate and the effects of androgens on bone mass of these new agents, particularly synthetic hormones and receptor modulators. Collaborate with other NIH Institutes, where appropriate.

**Identify New Treatments for Common Reproductive Problems**

A number of conditions have an impact on fertility and quality of life for women as they progress through the reproductive years and the postmenopausal period. These conditions, which can span the reproductive life of women and include postmenopausal women on hormone therapy, can result in considerable morbidity, lowered fertility, and substantial economic burden. Treatments, however, are frequently empirical and not based on solid scientific evidence.

Scientists do not understand the etiologies of some of the most common reproductive problems, including varicocele in men and PCOS, uterine fibroids, endometriosis, and abnormal uterine bleeding in women. Without this knowledge, researchers and clinicians cannot begin to prevent these problems. In addition, little is known about the most effective treatments. For instance, many gynecological conditions are treated with hormonal manipulation, which may have unintended consequences. Additional research must be conducted to identify the etiology and proper treatment for these conditions.



New scientific advances promise to speed research in this area. Knowledge of the roles of sex steroids in reproductive tissues and nonreproductive tissues (bone, brain, and cardiovascular) has led to the development of hormone replacement therapies for postmenopausal women and aging men. Researchers have also developed novel selective hormone receptor modulators known as SERMs (estrogen), SPRMs (progesterone), and SARMs (androgen). Originally designed to help target treatment of breast cancer, these agents hold promise for treating reproductive problems and many other hormone-regulated conditions in men and women. It is also clear that specific co-regulators interact with hormone receptors, resulting in marked tissue-specific effects for many compounds. This understanding can lead to new drug development. Conversely, some conditions are not susceptible to hormonal manipulation, making the development of nonhormonal therapeutic strategies also vital.

#### Research Areas

- Study gynecological issues that are important to women in their later reproductive years.
- Understand the effects of new specific receptor modulators (SPRMs, SERMs) on reproductive tissues and their utility for treating dysfunctional uterine bleeding, uterine fibroids, endometriosis, and so forth.
- Study the impact (negative or positive) of existing hormonal treatments and new receptor modulators on tissues other than the one targeted for therapy.
- Study the basic biology of the endometrium, including the factors involved in initiating pathological bleeding.
- Understand the initial phases of these disorders to discover their etiologies and to develop strategies for prevention or early intervention.

- Study the secondary effects of these disorders on other organ systems.
- Better understand the effects of contraception, hormone replacement therapy, and infertility treatment on these disorders.

### Conduct Research on Male Reproductive Behaviors

For years, males have been the forgotten partners in reproductive health. Research into male reproductive behaviors has largely been neglected because reproductive issues such as infertility have been perceived as female related. Similarly, reproductive health services have been defined around women's health needs; moreover, behavioral studies of fertility, infertility, and contraceptive use have focused largely on women. The 1994 Cairo Population Conference identified the development of contraceptives for men as a component of its women's health agenda. The longstanding belief that men would not accept the responsibility for contraception has been one of the many barriers to gaining support for worldwide efforts in developing male contraceptives.



Interestingly, however, it is estimated that up to one-third of all contraception in the United States is, in fact, accomplished with male methods. Recent polls also indicate that a sizeable majority of men may be willing to use a contraceptive. However, to identify and develop the most acceptable methods will take improved research. For example, to date, male participation in surveys has been limited, and as a result, there is a conspicuous lack of data obtained directly from males. In addition, researchers tend to use paradigms drawn from studies of female reproductive disorders to discuss male issues.

Therefore, when studying and developing male contraceptive techniques, it is important to (1) engage men as individuals to address their reproductive health, (2) involve men in larger issues of reproduction and sexuality that involve women, couples, and society, and (3) link these issues to the enhancement of children's life prospects. In terms of the latter, understanding how men choose to become fathers and the circumstances in which they do so is critical to improving the well-being of families and children. In the end, opportunities to improve knowledge about men's access to, attitudes towards, and use of contraceptive methods will pave the way for developing new male methods that respond to men's needs.

#### Research Areas

- Study men and couples with regard to perspectives on gender roles, sexual access and function, fertility management, and parenting responsibilities to advance the understanding of fathers and fathering.
- Understand male influences on the timing of pregnancy, not only in regard to first births but also in regard to subsequent pregnancies. Conduct behavioral research on male contraceptive practice and on the acceptability of novel approaches to male contraception, to complement biomedical approaches to the development of new male methods.
- Study (1) factors influencing male relationships with the children of first, second, and later families, (2) male investment in childbearing and child rearing, and (3) the influence of male participation in the decision to conceive. Study the impact of changing family and fertility patterns (delayed marriage, cohabitation, nonmarital childbearing, marital instability, and remarriage) on male sexual behaviors, fertility, and fathering.
- Study male sexuality as a spectrum from basic biology to health care delivery. Examine men's attitudes, values, and beliefs about sexual behavior, sexual relationships, pregnancy, human immunodeficiency virus (HIV) and sexually transmitted disease (STD) prevention, and fathering.
- Study the reproductive behaviors and attitudes of adolescent males in order to better inform health providers' efforts to engage young men in improving reproductive health.
- Examine males' influence on females' access to and use of reproductive services. Examine male and female behaviors related to sex, fertility, and parenting in the context of dynamic relationships. Study couple interaction as an important facet of relationship studies.
- Study the effects of larger cultural factors—economics and the media, especially advertising—on males' self-perceptions and perceptions of their own responsibilities and behaviors. This research may prove relevant to health disparity studies. Conduct research on gender ideologies and gender norms, their antecedents, and their impact on male behaviors related to fertility, STD risk, union formation, and parenting.

- Examine the extent to which pregnancies either are, or are not, wanted by men: most of the data now available record women’s reactions.
- Study the incidence of STDs and infertility among males.

## Identify New Strategies for Improving Contraceptive Use

One of every two pregnancies in U.S. women is unintended. About one-half of these unintended pregnancies result from contraceptive nonuse, and the other half from the ineffective use of contraception or contraceptive failure. Rates of unintended pregnancy are highest among women who are young, poor, of African American or Hispanic origin, or a combination of these factors. The NICHD has supported substantial research on individual, family, and societal factors that are associated with higher risks of unintended pregnancy. This body of research has contributed greatly to our basic understanding of these issues but

relatively little to the goal of improving the use of contraception. Changes in the delivery of health services and the increasing diversity of our population have prompted the need to reexamine individual, institutional, and cultural barriers to accessing and effectively using contraceptive methods. Recent national surveys conducted both in the United States and in developing countries have demonstrated behavioral changes, including increased acceptance of contraceptive use, based on the availability of newly introduced contraceptive technologies.

### Research Areas

- Examine the effects on contraceptive experience of individual risk-taking, partner relationships, STD risk, and male involvement in pregnancy prevention, across the reproductive lifespan.
- Research the delivery of family planning services, including observational studies, clinical trials for new intervention approaches, and operations research for integrating and ensuring the sustainability of “proven” approaches in clinical settings.
- Study the microbehaviors of contraceptive use and misuse by men and women, contraceptive continuation, and the factors that influence these.
- Research the sustained use of contraceptives and the reasons behind the discontinuation, inconsistent use, or switching of a specific technique, especially the role of side effects and health concerns in such behaviors.
- Study patterns of contraceptive use by individuals in postabortion and postpartum contexts, as well as patterns of contraceptive use by individuals after they have started using a particular method of birth control.
- Better understand the impact of access to services and quality of services on effective contraceptive use, from



the perspective of the potential client. This includes the organization and content of services, the continuity of services and followup, and the structure of the delivery systems in which contraception is provided.

- Examine methods to integrate contraceptive services into STD care, male-oriented services, and youth-oriented services.

### **Study the Behavioral Factors Relating to Infertility, the Use of Infertility Services, the Ethics of Infertility Treatment, and the Status of Children Born as a Result of ART**

Infertility exerts a substantial emotional and financial toll on affected couples because available techniques have high failure rates. At the same time, many couples are denied access to ART services because they lack insurance coverage or because these treatments are not provided by public clinics. Ethical considerations governing who should be given infertility treatment may also limit access for some individuals, despite the paucity of research on such ethical issues. In addition, although little attention has been given to the etiology and prevention of infertility, two key behavioral factors are known to contribute to its cause—exposure to STDs and the trend toward delayed childbearing.

With delayed childbearing being the norm for many groups of American women, infertility and infertility treatment have become critical issues in reproductive health. In 1995, 1 in 10 U.S. women of reproductive age had a fecundity impairment, and an additional 3 percent were sterile for reasons other than contraceptive sterilization. About 15 percent of women had received some kind of infertility service, with the proportions sharply higher among high-income women than low-income women.

Knowledge is needed about the prevalence of infertility and its antecedent risk factors, decisions made by infertile individuals and couples concerning the use of infertility services, the impact of economic and other barriers to services, and the effects of ART on the health and development of children born as a result of ART.

#### *Research Areas*

- Conduct behavioral, population-based, and clinical research on ART coupled with biological measures of reproductive function and child outcomes.
- Study the decisionmaking processes of patients in seeking and using infertility services, and of providers in recommending services to patients.
- Examine whether preserving fertility potential might provide a positive motivational force leading to STD prevention.
- Examine the effects of oocyte cryopreservation on delayed childbearing and whether the technology can influence processes of decisionmaking as to timing of childbirth.
- Study the obstacles to access to infertility services. This would include unequal access due to the financial burden of treatment, as well as sociocultural barriers to access.
- Study the ethical issues involved in the delivery of infertility services, including the adequacy of informed consents and availability of infertility services to same-sex couples, unmarried women, or HIV-positive individuals.
- Discover the disparities in the use of various treatment modalities, outcomes, and levels of satisfaction among different sociocultural groups.



- Study the relationship between insurance coverage and choices of treatment.
- Study the effect of levels of motivation on the choice of treatment modalities and long-term satisfaction with outcomes.
- Examine the effects of stress on the success of infertility treatment and treatment outcomes, and identify appropriate treatments for different couples.
- Study the psychological outcomes of children born as a result of infertility treatment.

### Increase Knowledge About Healthy Sexuality

Sexuality is an integral part of human functioning. The healthy expression of sexuality is central to individual well-being, but under certain circumstances, sexual behavior also carries potential risks, including unintended pregnancy, STDs (including HIV), and emotional or physical harm resulting from unwanted or coerced sex.

Despite its significance, healthy sexuality has not been well studied partly because of the subject's highly politicized nature and also because healthy development is not suited to the problem-oriented model of most biomedical research. Healthy sexuality, which spans the life course, must be studied within multiple contexts and from different perspectives. Important topics include the emergence of sexuality; sexuality in marriage; sexuality and aging; sexuality in special populations, including institutionalized groups, children in foster homes, and the imprisoned; the intersection of sexuality with disease and disability; and the aftermath of a nonvoluntary sexual experience.

Current NICHD-supported work in sexual behavior consists of a substantial body of research on adolescents (historically, mainly females) and a few studies of adults (males and females). Most of these studies examine individual, familial, social, and community factors that influence sexual behaviors. There are only a few projects on the neurology and endocrinology of sexual behavior in animal models. Likewise, there has been little research into issues of sexual function and dysfunction, in either sex, beyond erectile dysfunction in males.

#### Research Areas

- Conduct studies to extend knowledge of human sexual development and the precursors in childhood of healthy sexuality across the lifespan; research the role of the family in promoting healthy sexual development.
- Research adult sexuality and sexual behavior. Study the influence of multiple contexts on the expression of sexuality in collaboration with other NIH components; for example, questions of sexuality and aging can be investigated jointly with the National Institute on Aging (NIA).



- Study the relationships between illness or disabling conditions and sexual practice, including the effect of reproductive cancers on sexuality and the effect of infection with an STD (including HIV) on sexual function and sexual and contraceptive behavior.
- Study societies' management of sexual behavior. Examine approaches that promote positive sexual functioning and prevent negative outcomes of sexual activity in adults; examine effects of individual, social, relational, and cultural factors.
- Examine the effects of unintended pregnancy and unintended sex on expressions of sexuality.
- Examine acceptability issues relating to contraception and ARTs and how various methods or treatments influence sexuality.
- Comprehend the basic biology and physiology of normal and abnormal sexual function in males and females.
- Expand research concerning the prevention, diagnosis, and treatment of sexual dysfunction in males and females.

### ***Multidisciplinary Approaches to the Scientific Goals***

Understanding the complexity of factors affecting reproductive health and sexual function requires integrating sociocultural sciences with traditionally biomedical research disciplines. Integrative approaches are especially crucial for addressing issues such as equality in access to health services and disparities

among different sociocultural groups, formulating innovative methods of care, and analyzing the impact of economic issues on individual treatment choices and on industry decisions concerning product development and marketing. Collaborative approaches are also critical in designing interventions to prevent reproductive morbidities resulting from STD transmission or contraceptive failure.

The Institute's research agenda on reproductive health requires collaboration not only among investigators and program officials within the NICHD but also between the Institute and other parts of the NIH. For example, interactions with the National Institute of Allergy and Infectious Diseases (NIAID) will benefit research on HIV/AIDS, STDs, and gynecological disorders resulting from infection, while researchers affiliated with the NIA can join NICHD investigators in conducting research on sexuality and reproductive issues within the context of the aging American population. The NICHD already has shared interests and collaborations with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in the area of urinary incontinence and pelvic floor disorders, the National Institute of Mental Health (NIMH) in behavioral aspects of risk for STDs (including HIV), and the National Institute of Environmental Health Sciences (NIEHS) in environmental effects on reproductive function and fertility. The NICHD investigators can also benefit from establishing collaborative relationships with experts in fields such as political science, sociology, psychology, economics, and demographics: these fields are especially important for investigating the complex behavioral, cultural, and economic factors that affect reproductive health and perceptions of sexuality. Collaboration with industry would also be productive.

## Research Technologies and Resources

Complementing the scientific goals, the research agenda must include developing the necessary resources to accomplish these goals. These resources include tools, databases, services, technologies, and methodologies that investigators will need to conduct their studies.

- Collaborative groups of investigators and clinicians to collect very large numbers of subjects and data, which generally cannot be provided by individual clinics.
- Informatics in conjunction with molecular biology and genetics.
- Genetically engineered animals to study the pathophysiology of infertility and to determine the validity of such models to human pathophysiology.
- New animal models to translate mouse data into knowledge of other important model systems, especially large domestic species and nonhuman primates. These essential models must be further developed to help identify promising targets for further investigation into the causes of human infertility and for conducting infertility studies that cannot be done on humans.
- Identification of familial gene deletions resulting in infertility.
- Molecular genetic technology and chromosome technology to perform diagnostic screening tests of most infertility patients. This will be used to establish an extensive database and identify known deleterious genes and abnormalities of chromosomes.
- Cataloging known reproductive phenotypes in transgenic mice, nonhuman primates, and other species.
- Generation of expression sequence tags (ESTs) for reproductive tissues.
- Plans for using data from the human genome project, which so far has not focused on reproduction, including ESTs.
- Identification of genetic defects that result in azoospermia that could be exploited to identify new contraceptive targets. This would provide a means of avoiding problems involved in attempting to translate animal models to human reproductive function.
- Advances in genomics and proteomics of reproductive tissues as the basis for transgenic animal models and gene array technology.
- Techniques of gene targeting and of gene array technology used to define networks of gene expression in various parts of the female and male reproductive tracts that can be explored for fertility regulation.





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## FROM CELLS TO SELVES

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- Collaborations between public- and foundation-supported research and private industry research to connect basic science with more applied contraceptive development work.
- Databases to examine demographic and biobehavioral information about women's decisions regarding the management of reproductive diseases and disorders.
- New technologies to screen for the benefits and risks of new compounds without the need for human subjects to test each candidate (microarray technology for each tissue).
- Databases to examine demographic and biobehavioral information about patients' decisions regarding the management of reproductive diseases and disorders.
- Improved methods for measuring and studying male fertility and family behaviors, dyadic processes and behaviors, and the inclusion of men in surveys.



## **Training and Education**

There is a need for investigators with interest and skills in a wide spectrum of disciplines and methodological approaches to conduct research on the broad range of research agendas relating to reproductive health and sexuality. An emphasis on training in the following areas will build a cadre of expert researchers and enhance progress in meeting our scientific goals:

- Molecular research on reproduction
- Genetic epidemiology
- Steroid biology
- Developmental biology
- Translation of bench research on contraception to clinical and social marketing research
- Family planning operations research: contraceptive use and the improvement of contraceptive service delivery
- Outcomes research and cost-effectiveness analyses
- Longitudinal behavioral surveys and research on couples
- Continued encouragement of multidisciplinary research



## Appendix—Roster of Advisors

Although this document has benefited from the input of many scientists within and outside the NICHD, and from the general public, we wish to particularly note the advice of the following members of the strategic plan working group:

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