Strengthening Research in Academic OB/GYN Departments

Jessica Townsend, Editor; Committee on Research Capabilities of AcademicDepartments of Obstetrics and Gynecology, Institute of Medicine

ISBN: 0-309-58442-6, 320 pages, 6 x 9, (1992)

STRENGTHENING RESEARCH IN ACADEMIC OB/GYN DEPARTMENTS

Jessica Townsend, Editor

Committee on Research Capabilities of Academic Departments of Obstetrics and Gynecology
Division of Health Sciences Policy
INSTITUTE OF MEDICINE

NATIONAL ACADEMY PRESS
Washington, D.C. 1992

NATIONAL ACADEMY PRESS 2101 Constitution Avenue, N.W. Washington, D.C. 20418

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The Institute of Medicine was chartered in 1970 by the National Academy of Sciences to enlist distinguished members of the appropriate professions in the examination of policy matters pertaining to the health of the public. In this, the Institute acts under both the Academy's 1863 congressional charter responsibility to be an advisor to the federal government and its own initiative in identifying issues of medical care, research, and education.

This project was supported in part by funds from the National Institutes of Health, National Institute of Child Health and Human Development, Contract Number NO1-HD-0-2905. The Johnson and Johnson Foundation, the Burroughs Wellcome Fund, Syntex (U.S.A.), Inc., the Institute of Medicine, the Andrew W. Mellon Foundation, and the Richard King Mellon Foundation also supported this project.

Library of Congress Catalog Card No. 92-70987
International Standard Book Number 0-309-04697-1
Additional copies of this report are available from: National Academy Press 2101 Constitution Avenue, N.W. Washington, D.C. 20418

S557
Printed in the United States of America

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held at the Staatlichemuseen in Berlin.

First Printing, April 1992
Second Printing, June 1992
Third Printing, December 1992

COMMITTEE ON THE RESEARCH CAPABILITIES OF ACADEMIC DEPARTMENTS OF OBSTETRICS AND GYNECOLOGY

RICHARD E. BEHRMAN (Chairman),* Executive Director, Packard Foundation—Center for the Future of Children, Los Altos, California

EVERETT ANDERSON,** Professor of Anatomy and Cellular Biology, and Associate Director, Laboratory of Human Reproduction and Reproductive Biology, Harvard School of Medicine, Boston, Massachusetts

C. WAYNE BARDIN,* Vice President, The Population Council, and Director, Center for Biomedical Research, New York, New York

GERARD N. BURROW,* Dean, School of Medicine, University of California, San Diego, La Jolla, California

SHIRLEY S. CHATER,* President, Texas Woman's University, Denton

ARTHUR L. HERBST, Professor and Chairman, Department of Obstetrics and Gynecology, University of Chicago, Chicago, Illinois

ERNST KNOBIL,** Director, Laboratory for Neuroendocrinology, University of Texas Medical School, Houston

PAUL C. MACDONALD,* Professor, Department of Obstetrics-Gynecology and Biochemistry, and Director, Cecil H. and Ida Green Center for Reproductive Biology Sciences, University of Texas, Southwestern Medical Center, Dallas

DORIS H. MERRITT, Associate Dean, Indiana University Medical Center, Indianapolis

RODRIGUE MORTEL, Professor and Chairman, Department of Obstetrics and Gynecology, Pennsylvania State University, Hershey

MARY LAKE POLAN, Professor and Chairman, Department of Obstetrics and Gynecology, Stanford University School of Medicine, Palo Alto, California

GLORIA E. SARTO, Professor and Chairman, Department of Obstetrics and Gynecology, University of New Mexico School of Medicine, Albuquerque

PAUL D. STOLLEY,* Professor and Chairman, Department of Epidemiology and Preventive Medicine, University of Maryland Medical School, Baltimore

JOSEPH B. WARSHAW, Chairman, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut

* Member, Institute of Medicine
** Member, National Academy of Sciences

Institute of Medicine Staff

RUTH ELLEN BULGER, Director, Division of Health Sciences Policy
JESSICA TOWNSEND, Study Director
DEE SUTTON, Administrative Assistant

PREFACE

The work of this committee could not have been accomplished without the contributions of many people and organizations who provided assistance and information. The staff of the National Institutes of Health were especially generous with their time and expertise. Many individuals contributed, including Duane F. Alexander, Sumner J. Yaffe, Charlotte Catz, Michael E. McClure, Donald McNellis, Darlene D. Levenson, George E. Lewerenz, and many others at the National Institute of Child Health and Human Development who spent considerable time with us. A particular debt is also owed to Jerome G. Green and his staff at the Division of Research Grants who provided data that were crucial to the work of the committee. Our project officers were Pamela Wolf and Jeffrey A. Perlman.

Important help with data was also provided by Paul J. Friedman of the University of California, San Diego, who supplied special analyses of data on physician age distribution, and Warren H. Pearse of the American College of Obstetricians and Gynecologists (ACOG), who kindly allowed us to participate in a survey sponsored by ACOG and the Association of Professors of Gynecology and Obstetrics.

Individuals who participated at meetings of the committee include Florence Haseltine (who provided the inspiration for this study), Daniel R. Mishell, Lawrence D. Longo (who also contributed a background paper), Harold Pincus, and Frederick Naftolin.

We also wish to acknowledge the help of many members of departments of obstetrics and gynecology who welcomed staff and gave generously of their time and experience. Sites visited include the University of California at San Francisco, San Diego, and Irvine; the University of Pennsylvania; and Yale University.

The committee solicited input from chairs of departments of OB/GYN and others members of the profession. Their thoughtful responses gave us perspectives and information that provided important groundwork for our deliberations.

The research agenda, which constitutes Chapter 6, could not have been completed without the contributions of those who wrote background papers. Their names are listed in Appendix C, and our thanks go to each of them.

Finally I would like to thank my fellow committee members whose deliberations provided the basis for this report. On their behalf, I wish to express our gratitude to the Institute of Medicine staff. Jessica Townsend as study director managed all aspects of the study activities and report preparation. Dee Sutton provided secretarial support, and Paul B. Phelps edited the manuscript.

Richard E. Behrman
Chairman

Contents

EXECUTIVE SUMMARY

Many people in the biomedical research community, including those who fund research and those who conduct it, have detected what they believe to be signs of weakness in the research capabilities of academic departments of obstetrics and gynecology (OB/GYN).

If weakness, indeed, exists, its implications would be extensive, both for present and future generations: research that might be undertaken in these departments has great potential for improving the health of women of all ages and the outcomes of pregnancy, and for reducing health care expenditures for such conditions as the sequelae of low birth weight. This gives a sense of urgency to questions about OB/GYN research capabilities. Below are a few examples of large-scale problems that could be ameliorated by a strengthened OB/GYN research capability:

- the percentage of infants who are born weighing less than 2,000 grams, which has remained at about 7 percent throughout the 1980s;
- pregnancy-induced hypertension, which complicates about 2.6 percent of all deliveries and increases the risk of poor outcomes for both mother and child;
- ectopic pregnancies, which have increased every year since 1970 and have a fatality rate of 42 per 1,000 cases;
- infertility, which affects about 10 percent of married couples who want children; and
- an epidemic of sexually transmitted diseases that include 4 million cases annually of chlamydial infection and 24 million people in the United States infected with human papillomavirus, many types of which are associated with cervical carcinomas and severe dysplasia.

To address the question of whether the field of OB/GYN lacks a sufficiently vigorous research capability, the National Institute of Child Health and Human

Development asked the Institute of Medicine to convene a study committee. The committee took OB/GYN research to mean research that would be most advantageously conducted in academic departments of OB/GYN, whether for reasons of patient availability, locus of expertise, or because of the particular concerns of the physicians in the specialty. At the heart of this activity are investigators who are trained in the specialty of OB/GYN but who often work alongside physicians from other specialties and investigators trained in basic science.

An integral part of the background to the study is widespread distress about the general state of clinical investigation and the diminishing interest and participation of physicians in research. Thus, other clinical specialties confront many of the difficulties that OB/GYN departments face in generating and sustaining research manpower. Although the committee's charge was confined to finding ways of advancing and strengthening OB/GYN research, to the extent that the solutions recommended here are helpful to other disciplines, there may be additional benefits from this study.

The committee viewed its charge as encompassing three major tasks:

- developing indicators of the research strengths of academic departments of OB/GYN to assess whether a problem exists;
- examining the causes of problems or the barriers to improvement and identifying possible solutions; and
- developing a research agenda for OB/GYN that would both contribute to the resolution of the question of whether a problem in OB/GYN research exists and provide priorities for future research.

The committee used several mechanisms to gather the information necessary to fulfill its charge. It held four meetings of the full committee and established two task forces, one on NIH and the other on the research agenda. To learn about the concerns of the OB/GYN academic research community, the committee sent letters to all chairs of academic OB/GYN departments in the United States and Canada; it received replies from 50 individuals, some of whom responded as representatives of leading OB/GYN professional societies. The committee also commissioned background papers and authorized interviews of a wide array of knowledgeable individuals.

THE CURRENT SITUATION

Data on total federal support of research or research training in academic departments of OB/GYN were not available, but the committee was able to examine detailed data on NIH support:

- NIH funding of research in academic departments of OB/GYN increased from $16.1 million in 1978 to $46.5 million in 1989, representing an increase of 180 percent in current dollars and 43 percent in constant dollars. However, the increase in the proportion of total NIH resources going to OB/GYN departments was very small. More importantly, departments of OB/GYN continued to receive a small share (7.5 percent in 1989) of the funds of the National Institute of Child Health and Human Development (NICHD)—the institute that provides the majority of funds from NIH to departments of OB/GYN and that has a mandate to improve reproductive health.
- Between 1980 and 1989, OB/GYN had a low success rate, compared with other departments, in securing funding for its NIH grant applications. Success rates were 37.6 percent for internal medicine, 33.4 percent for radiology, 31.0 percent for pediatrics, and 28.5 percent for surgery—but only 26.5 percent for OB/GYN.
- Physicians in departments of OB/GYN made a particularly poor showing. Not only did they submit relatively few applications, but their success rate was lower than that of Ph.D.s from OB/GYN departments and of M.D.s in the four comparison departments noted above.
- There were relatively few applications for or awards of NIH training and career development awards to departments of OB/GYN, particularly for physicians. It is estimated that only 50 physicians in departments of OB/GYN received NIH research training or career development support between 1980 and 1989—a finding that bodes ill for the future of OB/GYN research manpower.
- Initiation of the Reproductive Scientist Development Program is a promising sign. This program provides postresidency or postsubspecialty fellowship support for two or three years of training in a basic science laboratory. Grantees thereafter spend three years, with at least 75 percent of that time in research, as junior faculty in the sponsoring department of OB/GYN. The program, which generally accepts three individuals per year, is funded jointly by NIH, OB/GYN professional groups, and industry.

Information on support of research and research training by the private sector provides a less complete but equally disturbing picture, particularly with

regard to training future generations of investigators. Industry contributed $19.3 million to research in departments of OB/GYN in 1990. It is not known how this level of funding compares with that of past years. In earlier decades. organizations such as the Josiah Macy, Jr., Rockefeller, Ford, and Mellon foundations played an important role both in supporting research and training and in providing early support for the careers of many of today's most prominent investigators in OB/GYN. Today, however, these foundations have withdraw or radically reduced their support of research in reproduction and of the training of young investigators who intend to pursue careers in reproductive research. Private-sector support of training for young investigators now comes mainly from industry and from OB/GYN professional associations and their foundations. It is estimated that six to eight physician/scientists each year are recipients of major training support from these sources.

The pattern of NIH and private funding confirms what knowledgeable individuals have known for a long time: only a handful of the nation's academic departments of OB/GYN host the kind of research enterprise that provides a truly vibrant environment for research training. There are several specific grounds for this statement. Only me departments reported receiving more than $2 million in federal funds in 1990. The involvement in research by faculty of departments of OB/GYN is low by two measures: the percentage of M.D.s and M.D./Ph.D.s who are principal investigators on NIH or Alcohol, Drug Abuse, and Mental Health Administration grants, compared with other clinical departments; and the proportion of M.D.s and M.D./Ph.D.s who spent more than 20 percent of their time in research activities in 1990 compared with departments of internal medicine in 1983. (This last is admittedly a poor comparison both because of the different time periods and because the procedural demands of OB/GYN make it more like a department of surgery than a department of medicine; however, it is the only department for which comparison data are available.) Finally, there are large numbers of women at the lower academic levels of departments of OB/GYN whose full participation and productivity in research is not likely to occur unless attention is paid to their special requirements, which may include flexible work arrangements and extended time to tenure.

COMMITTEE FINDINGS

All pertinent data, as well as the impressions gathered by the committee in interviews and from responses by OB/GYN department chairs to a request for

information, indicate present as well as potential future weakness in the research capabilities of academic departments of OB/GYN. In particular, there is cause for acute concern about the research capabilities of physicians in such departments: too few are entering research, and those who do are often not competitive with their Ph.D. colleagues or with physicians in other disciplines. More ominously, the future is compromised because there are too few centers of excellence in OB/GYN research that can serve as research training grounds, and because the level of support for the next generation of investigators is not sufficient to sustain, let alone expand, existing research capabilities. Although it is appropriate for many departments of OB/GYN to preserve their clinical focus, it is also important to expand the number of departments that are competitive players in the research arena, so that OB/GYN can fulfill its potential for improving the health of women.

Findings Related to Career Choices

It is vital for the health of the OB/GYN research enterprise that individuals with the talent and inclination for research be identified early and that obstacles to their growth as investigators be diminished. In particular, since women represent nearly half of all OB/GYN residents and are therefore a very significant component of the pool from which investigators are drawn, it is important that they not be lost to research because of the particular obstacles they face. These include coping with pregnancy and childcare during crucial early faculty years; isolation from traditional information and support networks that guide young investigators; and a dearth of women role models and mentors.

- OB/GYNs who intend to pursue a career in research must complete a four-year residency, usually followed by two to three years of subspecialty fellowships. It is difficult, however, to interleave research training with clinical training; as a result, these physicians are not equipped with the methodological tools for research nor with the basic science knowledge that would allow them to undertake investigation in the molecular aspects of biology—if that is where their interests lie. Acquiring this knowledge requires at least two to three years. Many in the field have noted that much of the education of the generalist OB/GYN is wasted when an individual selects a subspecialty. Some specialties have made arrangements that allow those destined for an academic career to reduce the time needed to complete clinical and research training. The committee found that the extended duration of training for a physician

investigator in OB/GYN and the difficulties of interleaving clinical and research training deter some individuals who would otherwise enter a research career. As a result, there is an urgent need to reexamine OB/GYN residency and subspecialty training requirements to decrease the total time needed to tram academicians.

- OB/GYN, like other clinical departments, loses investigators because of the discrepancy between practice and academic income. Data show little difference in this income discrepancy between OB/GYN and other specialties, but a young academician (under the age of 36) earns only approximately 80 percent of the earnings of his or her peers in practice. The experience of many academicians is that this gap (particularly if combined with high debt) deters some potential investigators. A heartening note for OB/GYN is that the specialty choices of women physicians may be driven less by income than by other considerations, suggesting that they may be less deterred from investigation by the difference between academic and practice income if their other needs are met.
- Debt, when combined with the many other deterrents to an investigative career, does result in the loss of talented individuals from the pool of OB/GYN investigators. Although there is little information on the role of debt in the decision to enter a career in investigation, analysis of the income needed to repay various levels of debt shows that entry-level academic salaries—let alone training and fellowship stipends—do not allow for comfortable repayment of the average debt accrued by the time an individual enters OB/GYN residency. Furthermore, anecdotes abound of individuals in OB/GYN who are unable to pursue an inclination for research because of the burden of debt. The income that OB/GYNs can expect from practice would make debt repayment less burdensome and practice an attractive alternative.

Findings Related to NIH and Other External Support

Although the weakness of OB/GYN research stems in part from factors within the discipline, external factors also play a role. The committee therefore deliberated over what might have caused foundations to decrease their support of research and training in reproductive science, and whether there might be factors at NIH that work against OB/GYN research.

- In the past, foundation support (e.g., from the Mary R. Markle, Josiah Macy Jr., Rockefeller, Ford, Mellon foundations), was an important factor in the OB/GYN research enterprise and in the training and development of today's

OB/GYN investigators and academic leaders. These foundations have either withdraw from or substantially diminished such support. The committee found cause for alarm in this decline—which appeared to be the result of changes in foundation leadership, changes in the magnitude of government support, and a sense that the interests of OB/GYN investigators do not sufficiently meld with the interests of the foundations.

- The absence of an OB/GYN intramural program at NIH places OB/GYN at a disadvantage in several ways. In particular, an outstanding training and research environment is lost. Efforts by individuals in the OB/GYN community and by Congress have resulted in welcome moves to establish intramural programs in OB/GYN at NICHD and the National Cancer Institute (NCI). The effectiveness of these efforts points to the importance of leaders of the discipline engaging themselves in endeavors to advance OB/GYN research.
- OB/GYN is funded primarily by NICHD, whose principal focus is not OB/GYN and whose staffing reflects this lack of emphasis on the reproductive sciences. As a result, OB/GYN lacks the strength that a focal point within the NIH provides, and it also lacks NIH leaders for whom enhancing the field is a high priority. This, too, puts the discipline at a disadvantage.
- OB/GYN is sparsely represented on NIH study sections—in 1989, only 3 members of NIH initial review groups listed OB/GYN as their area of expertise, compared with 21 in surgery, 19 in pediatrics, 124 in dentistry, and 117 in internal medicine. Despite this lack of representation, however, there is no evidence that applications from OB/GYN receive unbalanced reviews. Scientific Review Administrators possess valuable knowledge that could enable investigators to improve their grant applications.

Findings Relating to Departments of OB/GYN

There is a pervasive sense among chairs of departments of OB/GYN that they operate in an environment in which it is particularly difficult to conduct research. For example, high salaries must be paid to recruit OB/GYNs into academia. In 1990, average salaries for M.D. assistant professors in OB/GYN departments were $121,500, and them are reports that today $150,000 is needed to recruit newly qualified subspecialists. These salaries can only be supported if practice income is substantial; faculty must therefore spend significant time in clinical activities—often at the expense of investigation. The need to generate income to support high salaries also makes it difficult to protect the time of young faculty to allow them to gain the experience necessary to become independent investigators. Added to this financial burden is the fact that many

OB/GYN departments provide large amounts of uncompensated care. The committee thus concluded the following:

- Academic departments of OB/GYN face particular difficulties in establishing the infrastructure for research and expanding their research capability.
- Two central problems are the need for clinical income to support salaries and the difficulty of sustaining young investigators until they become independent.
- Most importantly, chairs of OB/GYN departments play a pivotal role in establishing the importance of research in a department, securing external support and providing internal leadership. Three critical areas for their leadership are ensuring a cross-subsidy of research by clinical income, recruitment of promising investigators, and establishing research collaboration with other departments.

Findings Related to Professional Organizations

The professional organizations of a discipline play a role in informing members of the discipline, and others, of the priorities and values of the discipline and in enlisting members in efforts to further those priorities. Thus, OB/GYN professional organizations have considerable opportunities to encourage young people who may be considering research careers, to assert to the discipline the importance of supporting research, and to ensure that influential groups and decision makers are apprised of the potential social and financial return on investment in OB/GYN research.

- The ethos of a discipline determines its direction. In the case of OB/GYN, the discipline has not developed a critical mass of leaders for whom the advancement of research within the specialty is a high priority. This lack reflects the small number of academic departments of major research status: 38 departments receive no federal research funds; 10 departments receive 50 percent of the NIH funds that are directed to departments of OB/GYN; and there is substantial agreement among knowledgeable people that between 6 and 12 departments can be counted as serious research centers.
- There has been a recent surge of interest in research to improve the health of women. This is reflected in a major new research initiative proposed by Bernadine Healy, director of NIH, the establishment at NIH of the Office of Research on Women's Health, and an array of legislative proposals from

Congress. The emerging realization of a need to foster research on issues related to women's health offers an unprecedented opportunity to make the case for the role of OB/GYN research in women's health and the need to support OB/GYN research. However, this opportunity will be missed unless vocal OB/GYN leaders emerge.

- Despite what appears to be a generally gloomy picture, several encouraging events have occurred in the area of OB/GYN research. Organizations are supporting the training of investigators through such programs as the Reproductive Scientist Development Program and the James Kennedy Fellowship Award. In addition, the American College of Obstetricians and Gynecologists (ACOG) and other OB/GYN groups have become engaged with groups concerned about strengthening women's health research. Interest in stimulating research has also been expressed by the Council of University Chairs of the Association of Professors of Gynecology.
- There are lessons to be learned from activities undertaken by other specialties that are attempting to stimulate interest in research. One such example is the Office of Research of the American Psychiatric Association, which undertakes numerous activities to promote research.

COMMITTEE RECOMMENDATIONS

The committee concluded that, in order to accomplish the proposed agenda of important research it is necessary to strengthen the OB/GYN research enterprise. The highest priority should be the building of physician research manpower so that more departments of OB/GYN would be able to successfully compete for research support. The committee therefore focused its recommendations on ways of recruiting and sustaining OB/GYNs in investigative careers, and on developing research capabilities in departments that have the potential to become first-rank centers of OB/GYN research.

The committee was also acutely aware of the interaction between research manpower and the research funding needed to strengthen investigation. First-rate investigators must be given time to develop, but this cannot occur in the absence of adequate funds to support their work. Similarly, funds will be forthcoming only if first-rate investigators are available to use them. Therefore, in addition to recommendations to strengthen physician research manpower, the committee considered strategies that would result in increased funding for OB/GYN research. Investigation in a particular field will thrive only if those who fund research are knowledgeable about its importance. The research agenda that constitutes Chapter 6 of this report therefore emphasizes the

significance of the proposed research to the prevention, cure, or amelioration of major health problems. In addition, the committee encourages OB/GYN leaders to educate decision makers and to stimulate support for OB/GYN research.

The committee was aware that many of the problems being confronted by the discipline are also faced by other clinical departments that are trying to develop or sustain clinical investigation. This does not lessen the problems for OB/GYN. Moreover, each clinical discipline has unique characteristics that must be accommodated in arriving at solutions to its problems.

No one entity bears total responsibility for this effort. Rather, the following recommendations are directed toward those in positions of leadership at NIH and in foundations, in the departments of OB/GYN, and, most importantly, in the profession of OB/GYN itself. This is the main source from which must flow the leadership that is the prerequisite for development of a strong research community. The committee's conviction that members of the discipline of OB/GYN must play leading roles in strengthening support for research in the profession itself and in the organizations that fund training and research underlies many of the following recommendations.

Recommendations for NIH and NICHD

- NICHD program staff should exercise to the fullest extent possible their ability to target training support to expand the number of research training opportunities for physicians in OB/GYN. The committee also recommends that NICHD tailor another career development award to OB/GYN physicians. Because of the importance of the program, NICHD should continue to sustain the Reproductive Scientist Development Program.
- Institutes at NIH whose missions include areas of science to which OB/GYN contributes should affirm their commitment to reproductive health and ensure its appropriate priority in their programs. The committee believes that there is an urgent need for changes that emphasize the importance of OB/GYN research. Actions that would help overcome some of the problems OB/GYN research now confronts might include the National Institute of Child Health and Human Development's changing its name to signal to the public and institute staff its commitment to and responsibility for reproductive health. NICHD could also recognize the importance of programs in reproductive health by establishing the position of deputy director for reproductive health or by appointing a board-certified OB/GYN to the position of deputy director. Further actions that might be considered by NICHD include increased representation of

OB/GYN on its staff, and the development of requests for applications (RFAs) on high-priority OB/GYN research topics identified in institute plans.

- NIH should develop a system to track OB/GYNs who are receiving federal training and career development support.

Recommendations for Other External Support

- Congress should ensure the success of recent initiatives to establish intramural programs in OB/GYN by appropriating the necessary funds. Leaders of the profession of OB/GYN have the responsibility to educate and inform those in decision-making positions about the importance and promise of an intramural program of OB/GYN research.
- Decision makers in foundations that are concerned with the development of scientific personnel—or with population problems, women's health, cancer, pregnancy outcomes, and other topics that OB/GYN is well positioned to address—should be aware of the role that their support of training and research could play at this crucial time in the development of OB/GYN research.
- A foundation should set up a program to assist the advancement of potential research leaders. The Markle Scholars Program and other efforts to develop academic leaders should be examined to determine which of their characteristics should be replicated.

Recommendations for Which Multiple Groups Have Responsibility

- The committee recommends that a program to alleviate the burden of debt (e.g., loan forgiveness, deferral of repayment, targeted fellowships or awards that eliminate the need to recur further debt, etc.) be established for physicians qualified in the specialty of OB/GYN who have demonstrated a serious intention to pursue a career in research. Program costs will not be large and should be home by a consortium of OB/GYN professional associations, the pharmaceutical industry, academic departments of OB/GYN, and the Public Health Service.
- Professional groups and other private-sector organizations that support the Reproductive Scientist Development Program should ensure its stability through a long-term commitment of resources.

Recommendations for Departments of OB/GYN

- Chairs of departments of OB/GYN should make a serious commitment to augment their research capabilities and to vigorously engage in informing medical school leaders and OB/GYN faculty of the potential of investment in research and research training. This commitment should also extend to accommodating the nonfinancial working needs of investigators, to facilitate and ensure their continued involvement in research.
- In particular, OB/GYN department leaders should pursue ways to ameliorate the stresses that attend the life of women in science. Every effort should be made to find women mentors and role models for women investigators. In addition, chairs in institutions in which no provisions exist for extending time to tenure for individuals with pressing personal commitments should engage the institution's decision-making groups in an effort to initiate such a policy.
- The committee recommends three specific strategies for increasing research activities: (1) increase the clinical income used to support research; (2) conduct important epidemiological and behavioral research that is relevant to OB/GYN; and (3) create interdepartmental research linkages.
- To ensure the dissemination of knowledge about NIH grant processes, and to enable applicants to improve their applications and make full use of the many NIH funding mechanisms, members of academic departments of OB/GYN and members of professional societies concerned with OB/GYN research should explore all avenues of communication with NIH staff.
- Chairs of departments of OB/GYN should work with NIH staff to improve the success rate of applicants for FIRST (First Independent Research Support and Transition) awards.

Recommendations for Professional Organizations

- The American Board of Obstetrics and Gynecology should immediately reexamine training requirements for generalists and subspecialists in OB/GYN to ascertain whether the training programs are unnecessarily long. A reduction in the time needed to obtain subspecialist status would allow those interested in pursuing a career in research and academic OB/GYN to achieve their goal more quickly than is possible today.
- OB/GYN professional organizations should create opportunities for expanding research and for stimulating young members of the profession to view investigation as an exciting and valued activity. Useful mechanisms include

special sessions at annual meetings and providing funds for interested residents to attend such meetings. These organizations should combine resources to establish an office whose mission would be the encouragement of OB/GYN research.

- OB/GYN professional organizations should expand their efforts to educate decision makers about the potential of OB/GYN research and the importance of accomplishing the research agenda laid out in this report.
- The American College of Obstetricians and Gynecologists and the Association of Professors of Gynecology and Obstetrics should continue to include in their manpower survey questions on sources of research support received by departments of OB/GYN. This information will for the first time allow tracking of the level of research activity in departments of OB/GYN.

Recommendations for Leadership

- Individuals with a strong interest in research should be represented in decision-making positions in leading OB/GYN professional organizations.
- OB/GYN leaders should take the initiative in demonstrating to foundation and voluntary health agency trustees and other representatives, to leaders of professional associations, and to relevant foundations of industrial corporations, ways in which expanded support of training for OB/GYN investigators would be a worthwhile investment.
- OB/GYN leaders should also seek additional research support from the types of organizations mentioned above.
- Leaders of the profession of OB/GYN have the responsibility to educate and inform those in decision-making positions about the importance and promise of OB/GYN research.
- OB/GYN leaders should also work with NIH staff to identify key issues and otherwise encourage OB/GYN research.

A RESEARCH AGENDA FOR OB/GYN

The committee developed an agenda of OB/GYN research using the following criteria:

- The research should contribute to the resolution of an important health problem.

- The research approach suggested should have promise.
- The research should be conducted in departments of OB/GYN or in collaboration with members of such departments.

The research agenda serves two purposes: (1) its depth and breadth underscore the need to strengthen OB/GYN research capabilities so that the suggested research can be undertaken, and (2) it can be used as a guide to prospective funders. The implementation of this important research agenda will require more resources than are currently being used by OB/GYN researchers, and the shifting of resources to OB/GYN research.

During the period of this study, NIH initiated three activities that will result in research agendas that overlap many areas of the committee's work: the Pregnancy, Birth, and Infant Research Plan of the National Institute of Child Health and Human Development, a research agenda being developed by the Task Force on Opportunities for Research on Women's Health, and the development of a strategic plan that brought together a panel on reproductive biology and development and one on infant health and mortality. In light of these large-scale efforts, the committee felt that it would be duplicative to produce a comprehensive, detailed research agenda. Instead, individual committee members were asked to highlight areas of investigation that meet the criteria listed above and that exemplify the range of questions that might fruitfully be investigated. Because there were no committee members with expertise in the behavioral sciences, technology assessment, or outcomes analysis, the agenda outlined in the following sections does not sufficiently emphasize those areas. The committee therefore wishes to stress its opinion that **departments of OB/GYN, in conjunction with individuals with relevant expertise, are well suited to undertake investigation of many topics related to behavior that affects reproductive health, the technologies used by the field of OB/GYN, and the outcomes of care provided by OB/GYNs. The large number of patients who receive care in the OB/GYN clinics of academic centers represents an opportunity for clinically relevant epidemiological research—including research on the efficacy of treatment, on the natural history of disease, and on the prevention of disease. Faculty of departments of OB/GYN, in collaboration with epidemiologists, sociologists, statisticians, and health services researchers, have the patient base and the discipline-specific interests needed to investigate questions that other disciplines are not likely to undertake. The committee also believes that the advantages of the patient base and knowledge that resides in departments of OB/GYN suggest that these departments should organize**

and conduct clinical/epidemiological trials that are often now initiated by other departments.

OOCYTE AND FOLLICULAR DEVELOPMENT IN THE OVARY

Follicular Formation

- Elucidation of the events responsible for the transformation of endodermal cells into germ cell elements.
- Understanding of the forces responsible for guiding the germ cell toward the proper location in the future ovary.
- Clarification of the cellular origins of the somatic follicular cells.
- Analysis of the cellular mechanism or mechanisms responsible for the initiation of meiosis and for its arrest at the prophase stage of the first division.
- Improved understanding of the role of putative intraovarian paracrine and autocrine regulators.

Follicular Atresia

- Understanding of the molecular events responsible for determining follicular fate.
- Development of a reliable, reproducible experimental model for improved understanding of the atretic process.
- Understanding of the apoptotic nature of the atretic process and, in particular, of the ionic events that appear to trigger the molecular enzymatic events.
- Focused investigation of potential putative intraovarian regulators concerned with the atretic process.

Follicular Recruitment, Selection, and Dominance

- Development of more specific markers capable of predicting the general well-being of the follicle in question and most importantly the quality of the resident oocyte.

- Improved understanding of existing known cytokine and growth factor regulators and the elucidation of the potential role of as yet unrecognized peptides.

Corpus Luteum Function

• It would be interesting to determine if the block to cell proliferation involves known genes associated with suppression of cell growth (perhaps one or more of the recently discovered tumor-suppressor genes, such as the retinoblastoma, or RB) or new examples of similarly functional genes.

Leukocytes, Cytokines, and Ovarian Function

• Determine the physiological role of immune system-derived products on ovarian function.

FERTILIZATION

- Continued investigation of the role of maturation-promoting factor(s) in the reinitiation of meiosis and the continuation of egg maturation.
- Continued investigation of the molecular biology of sperm chromatin processes.
- Continued investigation of the biochemical composition of cortical granules and the significance of cortical granule dehiscence prior to sperm-egg fusion, as well as their general role in the fertilization process.
- Determination of the physiology and biochemistry of germinal vesicle breakdown.
- Further investigation of the molecular events and physiology of the formation of maternal and paternal pronuclei.
- Determination of the physiology and biochemistry of male and female pronuclei (envelopes) breakdown and the re-condensation of their chromosomes.
- Continued investigation of the molecular biology of the zona proteins and their significance to sperm binding. Particular questions include how zona proteins are related to the slow block to polyspermy, and how sperm receptors are inactivated.

- Continued investigation of the fast block to polyspermy following the sperm-egg fusion.
- Investigation of the biophysics of sperm-egg-cortical granule fusion.
- Continued investigation of the molecular biology of sperm capacitation.
- Continued investigation of the molecular biology of the acrosome reaction with an emphasis on understanding the significance of the hydrolytic enzymes and their role in the general process of fertilization.
- Definition of the molecular events of the first cleavage, focusing on the involvement of cyclins. Continued focus on each of the fertilization events, keeping in mind a possible means of interruption as a contraceptive tactic.

FETAL GROWTH AND DEVELOPMENT

Embryology and Congenital Malformations

- Investigation of the basis of genetic regulation of early embryogenic events, including the role of homeotic genes in both normal embryogenesis and in congenital malformations.
- Characterization and study of embryologic mechanisms, including cell-cell interactions, cell migration, cell matrix interactions, and programmed cell death, all of which are important in normal and abnormal development. Development and exploitation of tissue and embryo culture techniques to examine developmental mechanisms and teratogenic influences on development including a study of drug-induced malformations as well as those resulting from conditions such as maternal diabetes or abnormal immune states.
- Investigation of endocrine and growth factor signaling that modulates fetal growth and organ maturation—for example, the basis of actions of muellerian inhibitory factor (MIF) and androgens in regulating sex differentiation.

Fetal Growth and Placental Transport

- Placental transport during normal development and under conditions in which nutrient flow is compromised.
- The mechanisms by which specific disease states alter transport processes and the basic signaling mechanisms that regulate fetal growth and organ maturation. For example, infants of diabetic mothers with excessive

substrate delivery and of large fetal size show a delay in organ maturation, whereas those with intrauterine growth restriction secondary to fetal malnutrition exhibit accelerated lung and brain maturation. The mechanisms underlying such changes are largely unknown.

- Metabolic regulation during development.

Congenital Infection and Substance Abuse

- Studies of mechanisms of maternal to fetal transmission of viruses.
- Development of strategies to alter high-risk behaviors.
- Investigation of pathogenesis of defects resulting from congenital infection.
- Development of drug surveillance and treatment programs.

Perinatal Research

- Investigation of what controls the signaling that induces lung maturation in preparation for the extrauterine environment.
- Development of new therapies to induce maturation.
- Investigation of the influences of maternal disease states and environmental insults on maturational events.
- Refinement of techniques for fetal surveillance and the development of better indices for normal and abnormal function.
- Development of new systems to deliver drugs, replacement hormone therapy, or nutrients to the fetus.

Epidemiological Research

- How does prenatal care reduce perinatal morbidity?
- How can we measure the effectiveness of social and behavioral interventions in changing high-risk behaviors that impair and limit fetal development?
- How do specific obstetric interventions—for example, cesarian section and maternal nutritional supplementation—affect newborn outcomes?

PRETERM LABOR

Preterm, Premature Rupture of the Fetal Membranes

- Research must be directed to understanding the regulation of synthesis and degradation of the extracellular matrix of the fetal membranes and contiguous decidua parietalis.
- It is suspected, but not established, that infection by way of the action of bacterial toxins (lipopolysaccharide, or LPS) may serve to initiate the formation of metalloproteinases that act upon the extracellular matrix of chorion laeve and amnion. We must ascertain if this is a mechanism by which fetal membrane rupture is commenced because if this is indeed the case, the condition is theoretically preventable.

Complications of Pregnancy That Compromise Fetal or Maternal Well-Being Independent of the Onset of Labor

- Research is needed on the pathogenesis of pregnancy-associated hypertension.
- Research must be directed toward defining the pathophysiology of the processes that mandate delivery prematurely even though independent of labor. Commonly, the obstetrician is faced with choosing between a deteriorating intrauterine environment for the fetus and the neonatal intensive care nursery for a sick newborn.

Preterm Onset of Labor

- Information must be assembled to understand the fundamentals of the maintenance of pregnancy and the spontaneous initiation of parturition at term.
- What are the physiological processes that effect such a stronghold on uterine contraction during human pregnancy?
- How are these processes translated at the biomolecular level?
- What is the role of the fetus in the maintenance of pregnancy and in the retreat from pregnancy maintenance at the end of normal gestation? It now seems very likely that retreat from pregnancy maintenance is the most likely choice of potential mechanisms for the initiation of spontaneous labor at term.

Therefore, we must define in great detail the processes that bring this remarkable situation about.

- An understanding of the contractile properties of the uterus before and during pregnancy must be gained.
- The role of Ca^{2+} channels and Ca^{2+} sequestration must be understood as these apply to the uterus of pregnancy.
- The contribution of the unusual hormonal milieu of human pregnancy to the maintenance of uterine quiescence must be investigated. Before we can realistically address the causes of preterm labor, an understanding of these processes operative in normal human parturition at term must be acquired.

Preterm Labor and Infection

- Research must be conducted to establish the role, if any, of infection in the preterm onset of labor.
- An understanding of the cause or muses of preterm cervical dilatation is urgently needed.
- The nature of the pathophysiology of the association with preterm labor and extrauterine infections also must be defined.

CONTRACEPTION

- Develop contraceptives that protect women against breast and cervical cancer.
- Increase user satisfaction by offering contraceptors a wider array of choices.
- Provide contraception for some underserved groups including men, lactating mothers, teenagers, and premenopausal women.
- Develop contraceptives that protect women against sexually transmitted diseases (STDs).

Contraceptive Implants

- Develop new drag delivery systems for steroids that would improve the pharmacokinetic profile to eliminate long-term tail-off of drug release once implants were sufficiently depleted of steroid as to be ineffective.

- Assess the carcinogenic and other long-term effects of progestins on the breast, cardiovascular system, and other organs.
- Conduct and evaluate implants in clinical trials.
- Conduct long-term studies on NORPLANT to determine the health benefits and risks of long-term, low-dose, progestin-only contraception compared with combined oral contraceptives.
- Develop biodegradable implants that can be removed at any time and that do not have a long period of drug tail-off.
- Conduct studies in lactating women with ST 1435.

Contraceptive Rings (CRs)

- Determine the optimal steroid for use in different CRs.
- Determine how much the hormone dose can be decreased without compromising effectiveness and safety.
- Perform specialized phase 2 studies on CRs to determine whether vaginally administered steroids are different from orally administered steroids with respect to ovarian function; lipoprotein levels; metabolism; effects on cervical, uterine, and vaginal pathology; and carbohydrate metabolism.
- Determine the long-term effects of CR use.

Transdermal Delivery

- Determine what type of transdermal delivery will be most acceptable to women: high-tech patches vs. low-tech creams.
- Conduct optimization of studies to select appropriate contraceptive steroids and their proper doses.
- Determine subject-to-subject variability in absorption using pharmacokinetic studies.
- Conduct local dermal irritation and toxicity studies. Conduct clinical studies for effectiveness.

Intrauterine Devices (IUDs)

- Conduct behavioral studies to determine why women do not wish to use IUDs and why many health care workers will not insert them.

- Develop effective methods to identify, those women who are not good candidates for IUD use, that is, those who will have to discontinue IUD use because of bleeding and pain.
- Develop IUDs that act as barriers to infection of the upper reproductive tract.
- Develop hormone-releasing IUDs that will further reduce IUD side effects.

Oral Contraception

- Study the long-term consequences of OCs, and determine the mechanism of action of mellatonin in women.

Barrier Methods

- Select candidate compounds from results of previous screening tests on sperm and sexually transmitted diseases (STDs).
- Test candidate compounds for evidence of antifertility effects and effectiveness against selected STDs in vitro. Prepare formulations (suitable for human use) of individual multiple compounds for animal tests. Test formulations in vitro.
- Test selected formulations for evidence of effectiveness in animal model systems.
- Prepare selected candidates for tests of effectiveness in humans.
- Conduct comparative trials in humans.

Male Contraception

- Determine whether luteinizing hormone-releasing hormone (LHRH) agonists or antagonists are the optimal component of a male method.
- Develop long-term delivery systems for LHRH analogs.
- Select an appropriate androgen for long-term administration, and develop an appropriate delivery system.
- Conduct phase 1 and 2 clinical studies of the androgen and the LHRH analog.

- Investigate new approaches by developing methods that will interfere with the autocrine/paracrine control of germ cell maturation in the testis (a long-term objective).

Antifertility Vaccines

Sperm Antigens

- Isolate a full-length cDNA that encodes promising sperm proteins, and determine their nucleotide sequences.
- Identify the nucleotide segment encoding the extracellular domain of membrane proteins and the entire sequence of secreted proteins; express such proteins in the baculovirus or similar expression system; and isolate expressed proteins for biological testing.
- Study the effect of immunization with the recombinant proteins and/or synthetic polypeptides.
- Produce a human dosage form, and test it in animals.
- Perform trials in humans.

LHRH-Vaccine Used With or Without a Vaccine to the Luteinizing Hormone or FSH (Follicle Stimulating Hormone) Receptor

- Conduct trials of the LHRH vaccine in animals and humans.
- Prepare recombinant polypeptides of the luteinizing hormone (LH) and follicle stimulating hormone (FSH) receptors, and study their immunogenicity.
- Prepare synthetic peptide segments of LH and FSH receptors corresponding to the hormone-binding and adenylate cyclase-stimulating domains, and conjugate the peptides with a carrier protein.
- Establish immunogenicity of the LH and FSH receptor peptide segments by determining the interaction of antibodies developed against specific receptor peptide segments with the recombinant extracellular domain of the respective receptor, and with isolated ovarian and testicular membranes containing the LH and FSH receptors, respectively.
- Immunize male and female rats with various combinations of LHRH-antigen and specific LH/FSH receptor peptide segments, and determine their effects on sex steroid production, gonadotropin secretion, spermatogenesis, ovulation, and fertility.

Medical Abortifacients

- Identify an antiprogestin that can be used as a substitute for RU 486 in a new medical abortifacient.
- Test combinations of an antiprogestin, anordrin analogs, progesterone synthesis inhibitors, and prostaglandins in pregnant animals to determine the lowest effective dosages in terminating pregnancy.
- Determine the window of effectiveness during the postcoital period when the combined drugs could be most effectively administered.
- Select the most promising combination of drugs for small-scale clinical trials, and perform the appropriate toxicology.
- Develop an appropriate delivery system so that the drug combination could be administered in only one clinical visit.
- Investigate the acceptability of new delivery systems to users and providers.

INFERTILITY

- A structured, comprehensive research program, including an epidemiologic description of the etiologies of infertility and basic research in cervical, tubal, and sperm development and function, would both expand our knowledge and the therapies available for infertile couples.
- Specific disease processes associated with infertility, such as endometriosis and tubal adhesions, need investigation.
- The new reproductive technologies of in vitro fertilization and gamete intrafallopian transfer (GIFT) offer a tremendous opportunity for understanding the specific cellular processes of human reproduction.

Epidemiology

- Research is needed on the effect of chemical contaminants on sperm and oocyte function. In addition, more research on the effect of such substances as alcohol, tobacco, and drags on gametogenesis and fertilization is necessary.
- Firm, normative data on normal fecundity and fertility, and a multitude of other reproductive issues, are needed for comparative data as the newer reproductive technologies continue to expand.
- There is a need to ascertain the relationship between age and human (both male and female) fertility.

Cervical Physiology and Function

- Research is needed to understand the physical and chemical properties of cervical mucus that facilitate sperm motility and to develop solid criteria for diagnostic tests of mucus function.
- Study is needed of the relationship of cellular and antibody mediated immunologic function to normal sperm motility, as well as to the prevention of pelvic infection.
- More research is needed to define normal cervical function and immunology with the goal of improved therapies for cervical factor infertility.

Fallopian Tube Function

- New techniques must be developed to evaluate tubal function and to describe the specific etiologies of abnormal tubal function.
- Studies are required to assess ciliary function and the role of muscular contractions in transporting the embryo into the uterus.
- The area of steroid and growth factor interactions with tubal epithelium requires a major research commitment.
- Normal implantation in the endometrium is modulated by a number of growth factors, and research into the role of growth factors in tubal function may provide important answers on the etiology and genesis of tubal ectopic pregnancies.

Endometriosis

- Research is needed on the relationship of endometriosis to infertility.
- Basic and clinical research into questions of who needs treatment and what is the best modality could yield an excellent societal return on investment.

Male Infertility

- Research at the basic science level must be initiated before a true understanding of the causes and possible treatments of male infertility can be proposed.

- Research is needed into sperm-oocyte interaction, including details of fertilization and chromosome exchange, sperm acrosome reaction, sperm maturation, sperm metabolism, and detailed sperm morphology.

In Vitro Fertilization and New Reproductive Technologies

- Research using appropriate animal model systems in the primate and research utilizing human follicular fluid, corona, and cumulus cells should investigate the molecular biology of human fertilization and early cell division.
- Research should be conducted on the involvement of growth factors, activation of the embryonic genome, and metabolism in the very early embryo.

PREMENSTRUAL SYNDROME

- The metabolism and bioactions of progesterone and its metabolites are fruitful areas for research to define the biological muses of symptoms referred to as the premenstrual syndrome.

THE BRAIN AND REPRODUCTION

- The nature, specific localization, and mode of operation of the gonadtrophin-releasing hormone (GnRH) pulse generator must remain a critically important subject for intensive investigation at the systems, cellular, and subcellular levels.
- While estradiol can initiate the preovulatory gonadotropin surge in the absence of changes in GnRH production, what actually happens during the normal menstrual cycle is not known and should be investigated.
- The quantitative role of neuroendocrine deficits in the causation of infertility in women must be defined.
- The mechanisms whereby "stress" inhibits the GnRH pulse generator and consequent ovarian function must be elucidated.
- The mechanisms whereby lactation, severe exercise, and caloric deficits lead to amenorrhea and infertility must be characterized.
- The mechanisms of action of a variety of modulators of GnRH pulse generator activity must be elucidated.

- It is now clear that the control of LH and FSH secretion by the pituitary gland is not the same. The role of activins and inhibins and other factors in the control of FSH secretion must be investigated in a physiological context.
- The mechanisms that cause the inhibition of the GnRH pulse generator shortly after birth and its reawakening at the time of puberty remain a complete mystery. The initiation of puberty continues to be a central, unsolved problem in human biology.
- The functional relationship between the hourly activation of the GnRH pulse generator and "hot flashes," synchronous events in postmenopausal women, should be a subject of concerted study with the aim of discovering the physiological basis of the phenomenon and its potential alleviation by alternatives to estrogen therapy.

MENOPAUSE

- Long-term, prospective studies to evaluate the effects and side effects of combinations of estrogen and progestins in the treatment of postmenopausal women should be conducted.
- Studies are needed to explain why very few postmenopausal women are treated with estrogen.
- Studies are needed to discover and assess the risks of adding progestin to estrogen treatment.

ONCOLOGY

Ovarian Cancer

- What are the factors that predispose the development of ovarian cancer?
- What preventive measures can be identified that could be implemented on a wide scale?
- Is there a cost-effective method for early detection, such as the development and refinement of sensitive vaginal ultrasound, that would greatly improve survival?
- Which genetic alterations, if any, play a causative role in neoplastic transformation merits further investigation.

- Are there methods, including human minor clonogenic assay, which can provide useful information and important clues to guide therapists to the optimal form of chemotherapy for specific patients?
- What new agents or new approaches can be developed to kill the cancer cell—for example, novel delivery systems or specialized treatment approaches such as the improved use of intraperitoneal therapy as well as the immunologic development of new biological response modifiers?

Uterine Neoplasms

- Can transvaginal ultrasonography become a cost-effective tool for early uterine cancer detection, similar to the project described in the discussion on ovarian cancer?
- Specialized treatment trials are needed to determine optimal methods for combining chemotherapy and radiation therapy, as well as chemotherapy and hormone manipulation, to enhance responses in survival.
- What is the safety and risk of estrogen replacement therapy in those who have been successfully treated for uterine cancer?

Cervical Cancers

- What is the influence of human immunodeficiency virus (HIV)-related immunosuppression upon the risk of cervical human papillomavirus (HPV) infection, cervical dysplasia and cervical neoplasia? This requires population studies.
- Do HPV infections require therapy and if so, which types are needed to reduce the frequency of cervical cancer?
- Can a methodology be developed to identify which "premalignant" cervical neoplastic conditions are at risk for progression?
- What are the optimal intervals for cervical cytologic screening?
- What are the optimal methods of treating various degrees of cervical intraepithelialaeoplasia, and which are most cost-effective?
- What is the role of HPV in the genesis and progression of cervical neoplasia?
- What characteristics (oncogene amplification, for example) can be identified that will reliably predict aggressive tumor behavior and thus provide the basis for improved initial treatment strategies?

- How can the standard therapies of radiation or operation for cervical cancer be combined with newer modalities of chemotherapy or immunotherapy to improve survival?
- What new strategies can be developed to improve the therapy of recurrent cervical cancer, which currently is almost uniformly fatal?

Vulvar Malignancies

- Clinical trials are needed to establish efficacy and safety of new treatments.
- What is the optimal method of therapy of premalignant lesions of the vulva, and can one identify which of these lesions actually require therapy? This should include investigation of rates of progression and regression, identification of lesions that require therapy, and determination of optimal screening intervals. Understanding the molecular biology of premalignant vulvar disease should help in this area of research.

Breast Cancer

- What is the potential effect of oral contraceptives on pre- and postmenopausal breast cancer?
- Does prolonged oral contraceptive use or early initiation of use (prior to age 20) alter the risk of the development of breast cancer?
- Does prolonged estrogen replacement therapy alter the risk of breast cancer?
- Does the addition of a progestin (protective for endometrial carcinoma) alter breast cancer risks?
- Can estrogen replacement therapy be safely used in patients who have been successfully treated for breast cancer to avoid the morbidity of estrogen deprivation?
- Does tamoxifen therapy for breast cancer alter the risk of endometrial neoplasia?
- Can groups of high-risk and low-risk women be identified through metabolic hormonal investigation or through molecular studies such as those involving proto-oncogenes?

Trophoblastic Disease

- What are the effects on future fertility of successful chemotherapy of trophoblastic diseases?
- What are the effects of chemotherapy in the mother on future genetic abnormalities in the offspring?
- What improved treatment strategies can be developed to help patients who currently succumb to the disease?
- What are the genetic or other muses that lead to the development of gestational trophoblastic diseases?

SEXUALLY TRANSMITTED DISEASES

Prevent Sexually Transmitted Diseases by Developing Clinically Effective and Safe Vaccines

- Basic research on the microbiology, immunology, and pathogenesis of STDs is essential to the eventual design and development of effective vaccines against them.
- Development of prototypes of vaccines for use in the prevention of N. gonorrhoeae, C. trachomatis, HIV, and herpes simplex virus (HSV), is under way and should be intensified with additional resources.
- The mucosal immune response to organisms that cause STDs is critical for the development of successful vaccines, which may stimulate both B- and T-cell limbs of the immune response. Consequently, detailed mapping and analysis of the epitomes of the proteins associated with STD organisms in eliciting immune response are necessary.
- The mucosal immune system of the human female genital tract and its role in the prevention of infection and/or susceptibility to infection should be studied more intensely.
- The function of the mucosal immune system, specifically antigen-processing, humoral, and cellular immune responses and the effects of hormones on these responses, should be studied.

Develop Cost-Effective Tests for Early Diagnosis of STDs

- Develop simple, inexpensive, rapid STD detection methods that are accurate in both symptomatic and asymptomatic women. Highest priority in this area is the development of a test for chlamydial infections. Development of a similar test for vital STDs, such as HSV, HPV, and HIV, is also critical.
- Investigate the safety and efficacy of experimental drugs antiviral against HIV and treatment of opportunistic infections in both pregnant and nonpregnant women.
- Evaluate the efficacy of treatment regimens for pelvic inflammatory disease in relation to preservation of normal reproductive function. This will require a long-term multicenter trial to adequately assess long-term outcomes.
- Develop improved methods to diagnose pelvic inflammatory disease (PID) and to identify women at high risk for reproductive sequelae. Accurate, noninvasive approaches must be developed, particularly to address the challenges posed by atypical infections. Virulence factors and immunologic markers should be sought that are predictive of postinfectious infertility or ectopic pregnancy.

Develop New Therapies Where Needed and New Cost-Effective Antibiotics That are Easily Administered and Sufficiently Acceptable to Maximize Compliance

- Develop curative antiviral agents for infections with HPV, HSV, and HIV. Studies are also needed to better define the effect of existing palliative therapies on transmission and progression of their infections.
- Evaluate PID treatment regimens for efficacy in preserving normal reproductive function, as well as for ability to achieve clinical and microbiological resolution of acute infection. This will require a multicenter clinical trial, with support for a minimum of 7 to 10 years, to permit adequate assessment of relevant long-term outcomes. The role of adjunctive PID therapy using anti-inflammatory or immunomodulating agents to reduce long-term sequelae should also be examined.
- Conduct further studies to document the safety and efficacy of STD/HIV regimens during pregnancy.
- Evaluate the safety and efficacy of experimental antiviral drugs against HIV and treatment of opportunistic infections in both pregnant and nonpregnant women.

- Expand community research programs for treatment of HIV, and identify mechanisms to increase access to care, particularly for low-income women.
- Develop an understanding of the nature of pathogen-cell interactions, especially virus attachment and entry, in order to formulate effective strategies for interruption of transmission. Natural history studies of HPV infection and the influence of the immune system are critically important in attempts to prevent the development of cervical cancer.
- Encourage therapeutic studies of STDs that specifically address efficacy and safety as well as compliance and cost.
- Develop inexpensive, accessible therapeutics that can be used reliably by women who must frequently manage multiple responsibilities (e.g., family, job) despite declining health.
- Evaluate and develop clinical trial recruitment and retention procedures to facilitate enrollment and follow-up of women (e.g., access to primary medical care, child care, transportation to clinic sites, as well as other support services).
- Review clinical trial eligibility criteria in ongoing studies, specifically, inclusion/exclusion criteria that may be too restrictive and thus prohibit the participation of women (e.g., definitions of active drug use, pregnancy, anemia, elevated liver enzymes, etc.).
- Study and develop better barrier/contraceptive methods (e.g., condoms vs. female-controlled methods) and viricides that are effective, safe, and acceptable to women; especially needed are methods that can be controlled by women and that may be used without detection by their sexual partners.

Clarify the Natural History of Genital Infections

- Describe the full spectrum of HIV-related illnesses and malignancies in women to fully evaluate current AIDS case definitions and standards of medical care for women.
- Establish prospective cohorts of women to determine the natural history and clinical presentation of HIV infection in women. Factors that affect the progression to AIDS among HIV-infected women should be identified, and the types of opportunistic infections that occur in women should be studied more intensively. Clinical, virologic, and immunologic markers of disease progression should be evaluated to the female-specific endpoints of disease progression,
- To better understand, prevent, and treat HI infection in women, conduct studies to address the frequency and factors responsible for transmission

of HIV to women with specific focus on STDs, stage of disease, hormonal influence, and age.

- Continue studies on the frequency and factors responsible for transmission of HIV from mother to child, and evaluate the use of therapy that prevents transmission.
- Initiate detailed studies on the impact of STD infections on HIV transmission and the impact of HIV on STD infections. For example, detailed studies on HPV infection in HIV-infected women should be conducted to determine the impact of HIV on HPV in the subsequent development of cervical cancer.
- Define the factors and mechanisms that alter risk of disease progression, such as HPV infection and its association with premalignant and malignant lesions of the genital tract. Epidemiologic studies are necessary to further define the factors required for initiation versus potentiation of typical cell growth.
- Conduct epidemiological and basic studies to better define the risk factors and biological mechanisms that influence progression of HPV infection to anogenital neoplasia. Urgently needed are HPV natural history studies that examine the roles of vital type and immune status.
- Examine the mucosal immune system of the human female genital tract, its relationship to other mucosal immune systems, and its role in the prevention of STDs and HIV infection. Specifically, antigen-processing, humoral, and cellular immune responses and the effects of hormones on the responses should be studied.
- Define the chronology and the host and pathogen factors involved in ascent of lower tract organisms into the endometrium and fallopian tubes, and subsequent tubal scarring. Development of improved animal models for PID would greatly facilitate this research.
- Determine the clinical and microbiological spectrum, the frequency, and the natural history of atypical PID. Seroepidemiological studies of infertile women and women with tubal pregnancies strongly suggest that atypical or subclinical PID is responsible for a substantial proportion of these disorders.

Define Behaviors Associated with the Acquisition and Spread of STDs

- Investigate determinants of health care-seeking behavior in women, including the role of social networks and support systems in facilitating women's access to services.

- Develop a specific behavioral research agenda in STD prevention. Epidemiologic studies are needed to identify the type and prevalence of behaviors that put individuals at risk for transmission or progression of an STD.
- Identify behavioral risk factors; this work would be facilitated by a national survey of sexual behavior.
- Determine population rates for STDs, and conduct natural history studies for disease progression in specific, well-characterized populations.
- Study the psychosocial needs of HIV-positive women and their family systems (traditional and nontraditional, including lesbian women) as they cope with the chronic, crisis-oriented, and usually fatal nature of HIV disease. Give special attention to adolescent psychosocial needs with emphasis on suicide prevention and support strategies.

Characterize the Role of STDs in Adverse Pregnancy Outcomes

- Study factors such as the infecting pathogen, the stage of gestation during which infection occurs, chronicity of infection, and behavioral patterns such as drug abuse. Organisms should be specifically examined for virulence factors and for other markers associated with specific patterns of fetal or neonatal morbidity.
- Conduct further studies to demonstrate whether drugs such as acyclovir and zidovudine are safe and effective for use during pregnancy.
- Direct immunologic studies toward the protective immune responses during breastfeeding to identify the components in breast milk that axe primarily responsible for inhibition of specific pathogens.
- Similarly, identify the role that breastfeeding plays in the transmission of certain infections such as HIV.
- Examine such factors as chronicity of infection and stage of gestation during which infection occurs to identify specific pathogens. Improved understanding of the immunobiology of pregnancy and the use of both natural and artificial animal models of STDs in pregnancy are likely to be important to productive research in this area. In addition, organisms should be examined for virulence factors or other markers associated with specific patterns of fetal or neonatal morbidity.

1

INTRODUCTION

This study addresses a concern, expressed inside and outside the discipline of obstetrics and gynecology (OB/GYN), that women's health is suffering because of weakness in the research capabilities of academic departments of OB/GYN. This concern often focuses on three indicators of weakness:

1. the relatively low level of funds that flow from the National Institutes of Health (NIH) to departments of OB/GYN;
2. the dearth of departments that possess a sufficient cadre of investigators to generate a vital research environment; and
3. some special characteristics of the discipline, and of the environment in which it operates, that are thought to make it particularly difficult to attract talented individuals into res h careers or to stimulate and sustain research.

There is also a larger fear that important health problems, some of which could potentially be solved with an intensified research effort, are not receiving the research attention they need and deserve. If this were true, it would be reason for concern since research that might be undertaken in these departments has great potential for improving the health of women of all ages and for improving the outcomes of pregnancy. Indeed, this work might have an enormous social impact on present and future generations. A few examples of large-scale problems that could be ameliorated by increased OB/GYN research include the following:

- the percentage of infants born weighing less than 2,000 grams, which has remained at about 7 percent through the 1980s;
- pregnancy-reduced hypertension that complicates about 2.6 percent of deliveries and increases the risk of poor outcomes for the mother and child;

- ectopic pregnancies that have increased every year since 1970 and have a fatality rate of 42 per 1,000 cases;
- infertility that affects about 10 percent of married couples who want children; and
- an epidemic of sexually transmitted diseases, including 4 million cases annually of chlamydial infection and 24 million people in the United States infected with human papillomavirus, many types of which axe associated with cervical carcinomas and severe dysplasia.

Research that provides solutions or partial solutions to some of these problems has the potential to generate significant reductions in health expenditures. For example, an Institute of Medicine committee[1] conservatively estimated that, based on the costs of care in the early 1980s, a reduction in the rate of low birthweight from 11.5 percent to 9 percent just in women aged 15 to 39 years who receive public assistance and who have less than 12 years of education would save $188.2 million in the first year alone. Subsequent heavy health care, education, and other expenditures are incurred to care for the frequent long-term morbidity and disability sequelae of low-birthweight babies.

ORIGINS OF THE STUDY

IOM Planning Committee

Questions about the state of research in obstetrics and gynecology (OB/GYN) departments arise in a troubling context: epidemics of sexually transmitted diseases and teenage pregnancy, lagging improvement of infant mortality, and the advent of new reproductive technologies such as in vitro fertilization. This context demands that serious attention be paid to OB/GYN research capabilities.

In 1988, the Center for Population Research of the National Institute of Child Health and Human Development asked the Institute of Medicine (IOM) to convene a committee to assess whether women's reproductive health would be better served if a stronger research base were developed in OB/GYN departments and whether IOM might usefully undertake a study to determine how to strengthen that research base. The planning committee convened by IOM noted the interdependence of several relevant factors: accomplishing needed research depends on the availability of human resources and funding, but generating a cadre of investigators depends on training programs, the quality of

mentors, the alternatives available to potential researchers, and, perhaps most importantly, the funding available to support research careers.

The planning committee examined the problems of a career in academic research, which include the impact of debt accumulated during medical school and specialty training, the financial cost of choosing an academic life, and the difficulties OB/GYN departments experience in finding protected time to allow the transition to independent investigator status. It also found that clinical investigators in OB/GYN must compete for funds with full-time investigators in basic science departments, as well as with clinical investigators in other medical departments. On the topic of funding, the planning committee surmised that the "relatively sparse" support OB/GYN receives from NIH might stem from the lack of an institute devoted to OB/GYN research, as well as from the ethical issues raised by some reproductive research.

Finally, the planning committee decided that an important research agenda in OB/GYN exists that is not receiving sufficient attention, and that academic departments of OB/GYN are the appropriate locus of this research. In the current funding climate, however, and with only the existing cadre of OB/GYN investigators, this research agenda is unlikely to receive the attention it deserves. Moreover, the planning committee found strong and widespread disquiet about the state of OB/GYN research, sufficient to conclude that further investigation of the causes and possible ways to improve the situation was justified. Thus, it recommended a full study by IOM.[2]

THE CHARGE TO THE COMMITTEE

The Committee on Research Capabilities of Academic Departments of OB/GYN was charged with studying the perceived weakness in research and the related shortage of investigators who can build on the successes of the past and contribute to the reproductive sciences in the future. In particular, the committee was asked to determine whether there is an actual as well as a perceived weakness and if so, to identify its causes and potential remedies. To respond to the first part of the charge—determining whether a weakness exists—the committee was also asked to judge whether there was an important research agenda, suited to the unique capabilities of departments specializing in OB/GYN, that currently was not being undertaken. If there was such an agenda, the committee was to describe it. This research agenda would then serve two purposes: (1) to demonstrate that there are promising areas of research whose pursuit is likely to have a beneficial impact on the health of

women and their children and (2) to provide decision makers with guidance for setting priorities for research investments. If the committee found cause for concern about research conducted in departments of OB/GYN, it was to examine factors that could affect the state of research conducted by obstetrician/gynecologists, including

- the role of NIH and other funding sources in supporting academic departments of OB/GYN, facilitating research in those departments, and developing high-caliber research personnel;
- the career paths of OB/GYN physician investigators; and
- the roles of major actors in academic health centers.

This examination was expected to reveal barriers to improvements in research and to result in recommendations by the committee of ways to enhance the research capabilities of departments of OB/GYN.

THE COMMITTEE'S INTERPRETATION OF ITS CHARGE

The broadest interpretation of this charge would encompass not only the many areas of research likely to promote women's reproductive health but also those areas relevant to related conditions—for example, postmenopausal neoplasia, which is possibly related to estrogen deprivation—regardless of the academic department in which such work is conducted. At the other extreme, the committee could confine its examination to research performed by physicians certified in the specialty of OB/GYN and conducted in academic departments of OB/GYN. The committee took a middle position, based on the notion that departments of OB/GYN represent the primary locus of research intended to improve women's reproductive health and ameliorate the impact of the many diseases and conditions that affect reproductive organs and that are related to different stages of a woman's reproductive life cycle. Investigators in many academic departments outside of OB/GYN are involved in work that pertains to these topics, but attempting to encompass those investigators and their work in the scope of this study would require careful definition of the research areas to be included, lacking generally accepted, clear-cut boundaries of responsibility, the results of this effort would generate controversy among specialties without clarifying their roles in specific research areas in which overlap appropriately occurs. Many research topics could reasonably be undertaken in departments of OB/GYN or in other departments, but factors such as the greater availability

of particular expertise or of a particular patient population often decree that one department is preferable to another. **In this report, "OB/GYN research" means research most advantageously conducted in academic departments of OB/GYN.** At the heart of this activity are investigators trained in the specialty of OB/GYN, who often collaborate with investigators from other disciplines and with nonphysician investigators, who bring essential knowledge and techniques to bear on questions that belong in OB/GYN departments.

The committee viewed its charge as encompassing three major tasks:

1. developing indicators of the research strengths of academic departments of OB/GYN to assess whether a problem exists (Chapter 2);
2. examining the causes of problems or the barriers to improvement and identifying possible solutions (Chapters 3, 4, and 5); and
3. developing a research agenda for OB/GYN that would both contribute to the resolution of the question of whether a problem in OB/GYN research exists and provide priorities for future research (Chapter 6).

OB/GYN research confronts some difficulties that spring from the particular characteristics of the specialty (such as its surgical and procedural orientation) and its environment. But many of the difficulties are similar or identical to those confronted by any medical discipline that endeavors to generate or sustain a serious clinical research effort. Thus, although the committee did not set out to solve the broader problems of clinical research, its deliberations were illuminated by information about the experience of clinical research in general, and to some extent its analyses and recommendations apply also to other disciplines. In making its recommendations, the committee has tried to take an approach that will help departments of OB/GYN nourish a strong research environment for the future, recognizing that the development of the necessary infrastructure and personnel requires a long-term commitment and cannot be rapidly achieved.

LIMITS ON THE SCOPE OF THE STUDY

Many factors impinge on the ability of a discipline such as OB/GYN to develop a research base, including private and federal arrangements for payment for health care, structural issues in the provision of health care, factors relating to the funding of medical schools and their constituent departments, and the content of undergraduate and graduate medical education. The committee

concluded that consideration of such broad factors was far beyond the task with which it had been charged. Similarly, the committee as constituted was not suited to examine structural change at NIH, such as the establishment of a women's center or institute, which would have repercussions beyond the scope of this study. In 1990, NIH instituted the Office of Research on Women's Health, with responsibility for monitoring progress in research on topics pertaining to the health of women. With NIH policies and structure relating to women's issues in a state of flux, recommendations for major structural change would be ill-timed. And because of a lack of adequate evaluations of past and present programs for the training of investigators, the committee was unable to answer important questions on this topic (such as how best to combine clinical skills and basic science training to ensure the maintenance and currency of both areas, or how to prepare investigators to take their place in a modern research environment).

The committee also recognized that a policy study in one area of biomedical research must be conducted with full awareness of the current climate of funding for biomedical research overall, since increased funding for one area may occur at the expense of other areas. However, although the committee's research agenda for OB/GYN stresses the importance of the recommended research advances to solutions of social and health problems and to the health care system, the committee was not in a position to evaluate the potential contributions of one research area compared with another. It therefore determined that such an evaluation was beyond the scope of this study.

There is widespread agreement that current policy, which in effect prohibits the use of federal funds for research on human embryos and fetal tissue, has inhibited advances in OB/GYN research. This has occurred because the major source of investigator-initiated research funding—NIH—is barred from supporting some specific areas of research that would be likely to contribute to the understanding and treatment of infertility, pregnancy loss, developmental disorders, and advances in contraception. To the extent that the policy represents a barrier to progress in OB/GYN research, it is pertinent to this study. For example, funding problems in these research areas are likely to discourage individuals who would otherwise have embarked on a research career in the reproductive sciences. This committee was not constituted, however, for an examination of the complex ethical and social issues related to embryo research, and the topic was therefore determined by the committee to be beyond its brief, apart from noting the negative effect of the policy on OB/GYN research. The significant societal benefits that would result from a resolution of the divisive issues that surround questions of embryo research and use of fetal tissue are laid out in three other Institute of Medicine (IOM) publications.[3] ,[4] ,[5]

CONDUCT OF THE STUDY

During the course of the study, the committee held four meetings to address the questions posed in its charge. To facilitate its work and make good use of the range of expertise on the committee, the group established two task forces: the Task Force on NIH and the Task Force on the Research Agenda.

To learn about the concerns of the OB/GYN academic research community, the committee sent a letter to the chair of each academic OB/GYN department in the United States and Canada. The chairs were invited to indicate their priority items for an OB/GYN research agenda, to describe difficulties they confront in attempts to develop research activities, and to comment on any other factors they wanted to bring to the attention of the committee. Replies were received from 50 individuals, some of whom responded as representatives of the leading OB/GYN professional societies.

The committee also commissioned background papers to provide analyses of topics of particular interest, two of which are published as appendixes to this report. To add breadth to the material available to the committee, IOM staff undertook a wide range of interviews with individuals in academic departments, funding agencies, and elsewhere. NIH was a major source of data, providing extensive information on applications and awards for research and training support. In addition, interviews with NIH staff contributed to the committee's understanding of structural issues at NIH.

In pursuing these approaches, the committee found that they illuminated not only specific aspects of research in OB/GYN departments but also general concerns about clinical investigation. Such concerns form an integral part of the background of the study and are discussed in the section below.

GENERAL CONCERNS ABOUT CLINICAL INVESTIGATION

Several commentators have expressed concern about diminishing interest and participation of physicians in biomedical research.[6] ,[7] ,[8] Over a decade ago, one such report opened by saying, "Clear evidence now at hand demonstrates that there has been and continues to be a marked decline in the number of medical students and postdoctoral physician trainees intent upon pursuing careers in investigative medicine."[9] This dismay evolved from the joint perception that clinical research is important and that support for such research (and the human resources to conduct it) may not in the future be sufficient, due to problems in recruitment, training, retention, and support of clinical investigators.

Clinical research continues to be important, especially at a time when molecular biology is making impressive advances in understanding biological processes, precisely because clinical research provides the critical link between the new biology and patient care.[10],[11] Indeed, interdependence of all stages, from untargeted basic research through preclinical to clinical research and the development of medical technologies, makes each part of the process vitally important.[12]

Because the National Institutes of Health (NIH) is a major source of funds for investigation and training, and because it is the principal source of relevant data, discussion has often focused on the NIH role in support of clinical investigation and how physicians fare in the grant process at NIH.* In 1989, approximately 6.9 percent of the total NIH budget went to clinical trials, up from 5.5 percent in 1981. (These data do not include all clinical research, which can be more broadly defined to include, for example, studies using tissue from human subjects.) This amounted to $487 million in 1989, of which an estimated 14 percent of the total was spent in the NIH intramural program.[13] Much of the growth was experienced by the National Institute of Allergy and Infectious Diseases, whose spending on clinical trials rose from $8 million m 1981 to almost $102 million in 1989. Most of this growth occurred after 1985, indicating the large impact of AIDS. Spending on clinical investigation by the National Institute of Child Health and Human Development (NICHD), the principal supporter of OB/GYN research, also grew rapidly—almost fivefold between 1981 and 1989—but started from a low level; by 1989, NICHD was spending $31 million on clinical trials.[14]

Some but not all studies corroborate the prevailing sense that clinical research grants are less likely than basic research to be funded.[15] For instance, a study found comparable award rates for clinical and basic science applications for research project grants submitted between 1980 and 1989.[16] It is suggested that investigators are deterred from submitting clinical research applications by their belief that funding is unlikely. Data illustrate a growing discrepancy between the volume of research activity of M.D. and M.D./Ph.D. investigators compared with Ph.D. investigators as measured by RO1 applications (an

* Problems in attracting, training, and retaining clinical investigators should be distinguished from problems in getting clinical research studies funded, although the two are related. An appreciation of both the lengthy training and low probability of funding can deter those who consider embarking on clinical investigation.

imperfect surrogate measure since clinical trials are often funded by other NIH mechanisms).* For instance:

- Between 1979 and 1989, the number of RO1 applications from M.D.s and M.D./Ph.D.s increased by 1.5 percent, compared with an increase of 16.3 percent in applications by Ph.D.s.[17]
- The proportion of new rant applications from M.D.s dropped from 27.6 percent of total RO1 applications in 1979 to 25.9 percent in 1989.[18] The supply of clinical investigators is also determined in part by the availability of training opportunities and by the ability of the investigator to gain support for subsequent research. The following data indicate relevant trends:
- The number of physicians in research training programs sponsored by NIH decreased between 1969 and 1980. Despite growth in the 1980s the number of physicians NIH is able to support either partially or fully is still below the level of the late 1960s and early 1970s.[19] ,[20] However, many trainees of the early period did not opt for investigative careers. Because of changes in the programs, such as the introduction of a payback requirement for trainees who do not subsequently engage in research, the retention in research may be higher today.
- Ph.D.s supported by NIH fellowship programs or NIH training grants are more likely than M.D.s to apply for research awards. According to a 1986 study, 62 percent of former NIH Ph.D. fellows applied for NIH or ADAMHA (Alcohol, Drug Abuse, and Mental Health Administration) research grants, compared with 43 percent of M.D.s. For former NIH Ph.D. trainees the figure was 52 percent, compared with 17 percent for M.D. trainees.[21]
- However, for the physicians who entered the competition for NIH funds the picture was relatively encouraging—at least compared with Ph.D. scientists. The success rate for research project grants submitted to NIH by M.D.s and M.D./Ph.D.s was slightly higher than the success rate for Ph.D.s in each year

* Equating physician investigators with clinical research and Ph.D. investigators with basic research can be misleading. Some physician investigators conduct basic research, and some Ph.D. investigators are involved in clinical research. In the 1980s, Ph.D.s comprised roughly half the applicants for NIH research project awards that included human subjects [Judith L. Vaitukaitis, "The Future of Clinical Research," *Clinical Research* 1991; 39(2): 145–156].

between 1980 and 1989.* Although the success rate for both groups declined over the decade, the decline for M.D.s and M.D./Ph.D.s was only 5 percent, compared with 6.7 percent for Ph.D.s.[22]

Other data, however, indicate a decreasing, or at best flat, interest in research on behalf of physicians:

- After rising from 11,929 in 1970 to 18,535 in 1983, the number of physicians reporting research activity fell to 16,941 in 1989; this represents a decline in the proportion of the U.S. physician population who report that they are engaged in research of from 3.6 percent to 2.8 percent.[23] ,[24]
- Despite possible flaws in data, a 1990 IOM committee concluded that there has been no growth in the number of physicians participating in research in recent years.[25] Many factors are proposed as accounting for the diminished interest of physicians in clinical investigation:
- the length of training and uncertainties about how best to tram a successful clinical investigator;
- the level of debt with which physicians graduate from medical school;
- a perceived decrease in the funding of investigation of clinical problems;
- perceived instability in funding, which makes a career in research seem an uncertain undertaking;
- the lure of more highly paid clinical practice;
- pressures on academic departments to produce clinical practice revenues;
- the inability of academic departments to nurture clinical investigators;
- multiple demands on academic health center resources, which make it difficult to obtain the funds needed to protect the time of clinical investigators; and

* Moreover, although Ph.D.s average slightly better priority scores than M.D.s on competing and renewal RO1s, the mean score differences usually have been only 8 points or less on scores that range between approximately 200 and 280 (National Institutes of Health, "DRG Peer Review Trends: Workload and Actions of DRG Study Sections, 1979–1989," NIH Division of Research Grants, Bethesda, Md., p. 71.)

- the reluctance of third-party payers to pay the costs of care for patients participating in clinical research protocols.

Many of these factors have become more acute in recent years. The training of today's clinical investigator has of necessity become intense and extended, as vividly described below:

> Without substantial postgraduate training in the biological sciences, the modern physician cannot readily enter the arena of sophisticated and competitive biological research. Since the clinical training of a physician is so intense, developing the skills that are necessary for an investigational career in biomedical research has also become very difficult. A fear of the laboratory often arises in young physicians who are long removed from working in a research laboratory or who have never been exposed to such work. Threatened with the loss of highly polished clinical skills and the prospect of isolation from the familiar clinical environment, these physicians are reluctant to enter laboratory research. Subspecialty fellowship training ought to provide an opportunity for research, but unfortunately the laboratory experience in most fellowships tends to be narrow, is usually focused on a single technique, and does not offer the broad-based kind of training in biomedical research that is necessary to encourage physicians to pursue a research career. Those who are willing to obtain in-depth training in the biomedical sciences must therefore turn to basic science departments. This in itself poses a threat and acts as a deterrent to most physicians considering a career in investigation.[26]

In the face of such obstacles, it is surprising that a large and increasing proportion of medical school seniors have indicated that their first choice of career would be as full-time academic faculty, teaching and conducting clinical research. The proportion indicating such interest has risen from 21.5 percent of respondents in 1981 to 28.8 percent in 1990.[27] ,[28] Unless attitudes to research and to financial rewards are changing, these data suggest that many of the deterrents to an investigative career take hold at a later stage. Perhaps the full impact of repaying educational debt does not come until after medical school is completed. Or perhaps a physician does not face the opportunity cost of an academic research career until confronted with the reality of supporting a family.

In addition to the years of clinical training, most physicians will require additional years of research training and education in basic science to enable them to compete for funds with Ph.D. Investigators.

> It is imperative that the serious physician/scientist receive training in depth m a scientific discipline relevant to medicine. It is both inaccurate and arrogant to assume that the intensive professional training of a physician prepares him or her to compete in modern science with a scientist who has undertaken the rigorous discipline of a Ph.D. degree.[29]

Programs that have been established to prepare physician/scientists include the Physician-Investigator Fellowship Training Program in the Department of Medicine at the University of Pittsburgh School of Medicine and many similar programs; the Reproductive Scientist Development Program supported by NIH and private funds; federal and nonfederal M.D./Ph.D. programs; and NIH intramural positions and extramural training awards—particularly the Physician Scientist Award. However, there is no consensus on the best model for training physician/scientists, either in terms of preparing them to become competitive or in terms of efficiency—that is, maximizing the proportion of trainees who go on to productive careers in investigation. James Wyngaarden, former director of NIH, has acknowledged the problem in relation to NIH-sponsored training programs, which have variable success rates.[30]

Even after completing the formal training period, the potential investigator still needs support. To develop from research trainee to independent investigator requires time "protected" from the demands of teaching or clinical obligations. The academic department must in effect invest in the young investigator to ensure sufficient protected time. In a survey of young physician investigators, however, clinical and administrative activities were second only to lack of funding as factors that interfere with the performance of research, and lack of institutional support was felt to be a greater problem than the distraction of teaching duties.[31] The importance of this support in allowing the investigator time to mature is revealed by NIH grant data: in the 1980s, the success rate for first-time applicants was relatively stable at just under 30 percent, but with repeated applications, 50 percent of applicants won awards.[32] A department chair can thus expect that protecting the time of two new investigators to allow them to submit repeated applications will bring in, on average, one award.

Funding this protected time is increasingly difficult, however. Medical schools have become more dependent on service income, which in 1988–1989 repented 43 percent of revenues, compared with 12 percent in 1970–1971.[33] But without sufficient protected time, the investigator finds it difficult to write

grant applications and pursue serious investigation, a situation that can discourage even those physicians who have completed research training and started on the road of investigation. As current NIH director Bernadine Healy has noted:

> Teaching, research and practice are in aggregate the triple mission of the medical school, but the demands on the individual to be all three, the "triple threat," must be questioned. As science grows more complex and practice more demanding, the individuals should be allowed to choose which of the three missions to uphold and should be appropriately secured and rewarded for doing that one mission well.[34]

BELIEFS ABOUT RESEARCH AND ACADEMIC DEPARTMENTS OF OB/GYN

Departments of OB/GYN share many of the problems in generating research that confront most clinical departments, but there is also a sense that many of these problems are more acute in OB/GYN than in other specialties and that certain barriers unique to OB/GYN research compound these problems. Letters to the committee from chairs of OB/GYN departments reveal that they feel that they operate in an environment that is particularly discouraging to research. For example, several chairs felt that OB/GYN faculty must contribute relatively large amounts of time to clinical work to generate the income needed to sustain department and faculty salaries. This load is believed to be especially heavy in OB/GYN for several reasons:

- the need to generate sufficient service income to cover the high salaries needed to attract to academia individuals whose earning potential in practice is large;
- the high uncompensated care load borne by obstetrics; and
- high malpractice premiums.

When the earning capacity of each faculty member is important, these factors hinder the ability of a department to develop young investigators and to support mature investigators between grants or during fallow periods, when writing grant applications takes priority.

Departmental chairs also mentioned some special problems faced by OB/GYN in competing for NIH funds. Without an NIH institute whose primary mission is the furtherance of OB/GYN research, OB/GYN lacks an institutional

focus at NIH. And within NICHD, the prime funder for OB/GYN research, there are few individuals who are specialists in the discipline. This fosters a feeling that OB/GYN research lacks supporters at NIH and, until recent months, in the Congress, too—the latter being a very significant body in determining NIH priorities. In addition, many believe that NIH study sections (which review grant applications) are not only biased against clinical research in general, but lack sufficient OB/GYN representation. OB/GYN representatives are also care on the councils that advise the various institutes.

In short, there is a feeling that it is particularly difficult to generate interest in a career in OB/GYN research and that individuals who desire such a career confront special problems. Few role models are available to stimulate interest in research; only a small number of the nation's academic departments of OB/GYN have the critical mass of researchers needed to engender a lively research ethos. The prolonged, clinically focused residency and subspecialty training periods are thought to deter the would-be investigator and impede the acquisition of scientific knowledge and research skills. Finally, the lack of federal funding for fetal research is thought to both curtail OB/GYN research activities and act as a deterrent to the pursuit of investigative careers in this area. This report will assess the reality of some of these perceptions, which are listed here to indicate the prevailing thoughts and perceptions that lie behind this study.

REFERENCES

1. Institute of Medicine. Preventing Low Birthweight, Washington, D.C.: National Academy Press, 1985.
2. Institute of Medicine. Research Capabilities of Obstetrics and Gynecology. Report of a Planning Committee of the Institute of Medicine. Washington, D.C.: National Academy of Sciences, 1989.
3. Institute of Medicine. Medically Assisted Conception: An Agenda for Research. Washington, D.C.: National Academy Press, 1989.
4. Institute of Medicine. Science and Babies: Private Decisions, Public Dilemmas. Washington, D.C.: National Academy Press, 1990.
5. Institute of Medicine. Biomedical Politics, ed., Kathi E. Hanna. Washington, D.C.: National Academy Press, 1991.
6. Wyngaarden, James B. The Clinical Investigator as an Endangered Species. New England Journal of Medicine 1979; 301:1254–59 .
7. Association of American Medical Colleges. Clinical Research Manpower. The Report of the Ad Hoc Committee on Clinical Research Training. Washington, D.C.: Association of American Medical Colleges, 1980.

8. Healy, B. Innovators for the 21st Century: Will We Face a Crisis in Biomedical-Research Brain Power? New England Journal of Medicine 1988; 319:1058–64 .
9. Association of American Medical Colleges. Clinical Research Manpower. The Report of the *Ad Hoc* Committee on Clinical Research Training. Washington, D.C.: Association of American Medical Colleges, 1980.
10. Kelley, William N. Are We About to Eater the Golden Era of Clinical Investigation? Presidential Address before the Sixtieth Annual Meeting of the Central Society for Clinical Research. Chicago, Illinois, November 13, 1987. The Journal of Laboratory and Clinical Medicine 1988; 111(4):365–370 .
11. Thier, Samuel O. Clinical Investigation in the 1980s: Perspective from the Medical School. Clinical Research 1980; 28:248–251 .
12. U.S. Congress, Office of Technology Assessment. Impact of Randomized Clinical Trials on Health Policy and Medical Practice . OTA-BP-H-22. Washington, D.C.: Government Printing Office, August 1983, p.4 .
13. Kahan, James P., et al. The Decision to Initiate Clinical Trials of Current Medical Practice. Prepared for the National Center for Health Services Research and Health Care Technology Assessment; R-3289-NCHSR. Santa Monica, Calif.: The RAND Corporation, September 1985, p. 14 .
14. National Institutes of Health. NIH Data Book 1990. NIH Publication No. 90-1261. Bethesda, Md.: National Institutes of Health, September 1990 .
15. Cuca, J. A. Scientific, Social, end Other Factors in the Evaluation of Applications for NIH Research Grants. Unpublished doctoral dissertation, The Catholic University of America, Washington, D.C., 1990, pp. 36–37 .
16. Vaitukaitis, Judith L. The Future of Clinical Research. Clinical Research 1991; 39(2):145–156 .
17. National Institutes of Health. DRG Peer Review Trends. Workload and Actions of DRG Study Sections 1979–1989. Bethesda, Md.: Statistics and Analysis Branch, Division of Research Grants, p. 65 .
18. Ibid., p. 67 .
19. National Research Council/Institute of Medicine. Biomedical and Behavioral Research Scientists: Their Training and Supply. Vol. 1 : Findings. Washington D.C.: National Academy Press, 1989, p. 43 .
20. National Institutes of Health. NIH Data Book 1990. NIH Publication No. 90-1261. Bethesda, Md.: National Institutes of Health, September 1990.
21. National Research Council/Institute of Medicine. Biomedical and Behavioral Research Scientists: Their Training and Supply. Vol. 1 : Findings. Washington, D.C.: National Academy Press, 1989, p. 72–73 .
22. National Institutes of Health. Extramural Trends FY 1980–1989. Bethesda, Md.: Information Systems Branch, Division of Research Grants, 1990, p. 51 .
23. Institute of Medicine. Funding Health Sciences Research: A Strategy to Restore Balance, ed. Floyd Bloom and Mark Randolph. Washington, D.C.: National Academy Press, 1990.
24. Roback, Gene, et al. Physician Characteristics and Distribution in the U.S. Department of Physician Data Services, Division of Survey and Data Resources. Chicago, Ill.: American Medical Association, 1990.
25. Institute of Medicine. Funding Health Sciences Research: A Strategy to Restore Balance, ed. Floyd E. Bloom and Mark A. Randolph. Washington, D.C.: National Academy Press, 1990.

26. Levey, Gerald S., Lehotay, Denis C., and Dugas, Marcus. The Development of a Physician-Investigator Training Program. Sounding Board. New England Journal of Medicine 1981: 305(15):887–889 .
27. Association of American Medical Colleges. AAMC Data Book. Statistical Information Related to Medical Education. Washington, D.C.: Association of American Medical Colleges, January 1990.
28. Association of American Medical Colleges. 1990 Graduation Questionnaire Results. Washington, D.C.: Association of American Medical Colleges, 1991.
29. Smith, Lloyd H., Jr. Training of Physician Scientists. In Biomedical and Behavioral Research Scientists: Their Training and Supply. Vol. 3 : Commissioned Papers. National Research Council/Institute of Medicine. Washington, D.C.: National Academy Press, 1989.
30. National Research Council/Institute of Medicine. Biomedical and Behavioral Research Scientists: Their Training and Supply. Vol. 1 : Findings. Washington, D.C.: National Academy Press, 1989, p. 76 .
31. Cohen, Richard A. Ensuring the Future for Physician Investigators. Presented at the Association of American Medical Colleges Spring Meeting, March 26, 1991, Savannah, Georgia.
32. The Scientist. Rejected NIH Applicants Should Keep Trying. The Scientist, October 17, 1988.
33. Association of American Medical Colleges. U.S. Medical School Finances 1988–89. Section for Operational Studies. Washington, D.C.: Association of American Medical Colleges, July 1990.
34. Healy, Bernadine. The Human Factor at the Endless Frontier. Circulation 1989; 79(4):965–959 .

2

IS THERE A PROBLEM?

The previous chapter noted perceived difficulties in supporting research and in training research personnel in obstetrics and gynecology (OB/GYN). This chapter moves from perception to more solid ground by examining objective indicators to establish whether a problem exists. There are three ways to answer the question. The first measure is the level of external support for research and research training in academic departments of OB/GYN, primarily from the National Institutes of Health (NIH) but also from the private sector. The second involves the structural characteristics of departments of OB/GYN, specifically, whether OB/GYN departments differ from other clinical departments in ways that might indicate that problems exist or that might constitute a cause for alarm. The final measure is a research agenda for OB/GYN, the size and depth of which indicate unmet needs for research and promising avenues of investigation with great potential for repaying increased investment in OB/GYN research.

SUPPORT OF RESEARCH AND TRAINING IN DEPARTMENTS OF OB/GYN

Sources of funding for research in departments of OB/GYN include the federal government, foundations, the academic institutions within which the departments exist, the departments themselves, and industry. The Institute of Medicine (IOM) was fortunate in that the American College of Obstetricians and Gynecologists (ACOG) and the Association of Professors of Gynecology and Obstetrics (APGO) include questions in their joint survey of academic manpower that enabled the committee to gain an understanding of the overall level of research support in departments of OB/GYN and the relative contribution of each of the above sectors. Responses from all 136 approved U.S. medical schools indicated a total of $142.2 million in research funds from all sources m 1990. The principal source of research support was the federal government ($77.5 million, or 54.5 percent), followed by institutional support ($26.4 million, or 18.6 percent), industry ($19.3 million, or 13.5 percent), and foundations and other sources ($19.1 million, or 13.4 percent).[1] No data axe

available to indicate either past levels of support or changes in distribution, but some OB/GYN department chairs feel that the pharmaceutical industry has become a more significant source.[2] There are also indications that private foundation support, which played an important role in stimulating research in departments of OB/GYN in the past, has diminished in recent years.

The Role of Foundations

According to an inventory of private agencies that contribute to population research,[*] a small number of foundations—the Ford, Rockefeller, and Andrew W. Mellon foundations—have for years dominated the private funding scene. The Hewlett Foundation, created in 1966, entered the inventory in 1985. The Population Council, which is included in the inventory, is itself a research organization that solicits funds to support its work. However, it also supports investigators—mainly overseas—who collaborate with the council in fertility and contraception work.[**]

Between 1976 and 1985, several trends in foundation support were notable. Reproductive processes and contraceptive development both lost ground, losing 34 percent and 6 percent in funds, respectively. There was also a large shift of funds to the social and behavioral sciences (a gain of 224 percent) and smaller but nevertheless substantial gains for contraceptive evaluation (184 percent) and population research centers (98 percent).[3] These trends suggest that OB/GYN departments may have been losers, since the largest gains appear in areas in

[*] The term *population research* is not synonymous with the research activities appropriate to departments of OB/GYN. In the following discussion it is defined as "studies of the nature, determinants, and consequences of population characteristics and dynamics and the development of basic data and methods for such population analysis. Physical, biological, psychological, cultural, social, economic, geographic, historical and political factors may all be included in population studies" (U.S. Department of Health and Human Services, National Institutes of Health, Public Health Service, *Inventory and Analysis of Federal Population Research, Fiscal Year 1988*, Washington, D.C., 1990). Many population research projects are conducted in departments other than OB/GYN. Moreover, OB/GYN departments receive research support from foundations that are not included in the inventory. Nevertheless, this inventory is the best available indicator of trends in foundation support for the areas of science undertaken by departments of OB/GYN.

[**] The Population Council was a major grant-giving organization in the 1950s and early 1960s. There tier it became mainly a research organization funded by foundations, NIH, and other government agencies in the same way that other research organizations and universities are funded.

which other departments have a major stake. The area most specific to OB/GYN —that is, reproductive processes—experienced the greatest loss.

Private foundations have also made significant contributions to the training, development, and support of OB/GYN academic manpower. The principal foundations involved have been the Mary R. Markle Foundation; the Josiah Macy, Jr. Foundation; the Rockefeller, Ford, and Mellon foundations; and, more recently, foundations formed by OB/GYN professional groups. The history of the contributions of these organizations is detailed in Appendix A. The foundations played an important role in stimulating the research careers and bringing to prominence many of today's leaders in academic OB/GYN. It is particularly useful to note the contributions of the Macy and Mellon foundations, which provide good examples of the impact of foundation giving and of the factors that may cause a change in the programs these foundations support.

The program of the Josiah Macy, Jr. Foundation focused specifically on the furtherance of reproductive biology through faculty development, conferences and seminars, and support of research time for medical students. In the 1950s and 1960s, funds flowed into selected medical schools and to individuals in residency programs. There were also funds for interdisciplinary research. The program supported faculty fellows and postdoctoral fellows, many of whom later became distinguished contributors to their discipline. When the program ended in 1966, about 50 people had received training support; by 1979, 15 of the 50 were department chairs. Also of importance were the Macy-sponsored conferences, at which new directions for reproductive science were presented, discussed, and refined. It is estimated that between 1955–1970 the Macy Foundation allocated $6.[4] million to the development of academic OB/GYN research.4 Its heavy involvement in OB/GYN came to an end with a change in leadership within the foundation.[5]

Another foundation that formerly made important contributions but that has today diminished its involvement is the Andrew W. Mellon Foundation. Beginning in 1977, the foundation attacked the problem of world population growth through research aimed at contraceptive development. It helped support talented investigators entering the reproductive sciences and brought a number of young molecular biologists into the field. Major grants were awarded to 17 reproductive biology centers, supporting the development of more than 200 young M.D. and Ph.D. investigators and untenured faculty. A 1986 review of the program noted that Mellon funds were particularly valued by departments because of their flexibility—the money could be used to support individuals at crucial early phases of their careers, to bring into the centers people of various backgrounds to create multidisciplinary research teams, or to undertake areas of contraceptive investigation that NIH could not fund.[6] These young investigators

were starting to make important contributions to the field when the decision was made in 1989 to wind down the program. It is currently funded at $1 million per year, down from the former level of $2.5 million.

In 1980, the Mellon Foundation also started providing reproductive research project grants, often to institutions with Mellon reproductive biology center grants. Roughly $1.2 million per year was allocated to these grants, which were discontinued in 1989. It is estimated that between 1977 and 1988 the Mellon Foundation contributed a total of $27.5 million to reproductive biology, including support of young investigators.[7] Reasons for the reduction in Mellon support of the field of reproductive research are complex, but interviews with foundation staff indicate that contributing factors include a sense that few of the investigators who were supported have continued working in areas related to contraceptive development and that the project money was an add-on to NIH funds for work similar to NIH-supported research. In general, the foundation concluded that its greater strength lay in the humanities rather than in the biomedical field, a view reinforced by new leadership at the foundation. Moreover, discussions between scientists and foundation staff did not yield a focus that closely matched the foundation's goals, so it decided to transfer funds to applied research and other areas in the population research field.[8]

Islands of strength in OB/GYN research and leadership exist today in part because of the efforts of these foundations. They invested in OB/GYN research and the development of research personnel, and the flexibility of that money was particularly valuable as an adjunct to more regulated government support. The withdraw of the support that was so important in developing OB/GYN research leaders has generated fears that, as the generation of leaders whose development was assisted by the foundation programs approaches retirement, a vacuum in research leadership will become apparent. Whether it was within the power of those in OB/GYN to persuade the foundations to maintain their investment in reproductive sciences is uncertain. To some extent foundation policies are driven by external events, and to some extent by factors internal to the foundations such as a change in leadership. Moreover, foundations choose priority areas in many different ways: through internal priorities, personal contacts, and advisory committees.[9] Some foundations seek underfunded areas in which their support can make a difference, which may today represent an opportunity for OB/GYN.

In addition to awards specifically for reproductive sciences or to support individuals trained in OB/GYN, which have suffered a major decline in number and in level of funding, foundations today offer awards for which eligibility is less constrained and for which young OB/GYN investigators may be eligible. For example, the Searle Scholars Program awards three-year grants of $180,000

to individuals in the first or second year of their first appointments as assistant professors. The idea is to identify promising investigators at an early and crucial stage in their careers. Since its inception in 1980, the program has made 191 awards—mainly to basic science investigators, according to the program director, who notes that the selection committee seeks evidence of a departmental commitment to the candidate. This, he believes, is more often found for basic than for clinical scientists. Other foundations that give substantial awards to young biomedical investigators in many fields include the Lucille P. Markey Charitable Trust, which supports 16 individuals per year, and the David and Lucille Packard Foundation and the Pew Charitable Trusts, each of which supports 20 individuals per year.[10]

Other Private-Sector Training Support

Today, much private-sector support of OB/GYN training comes from industry, although OB/GYN professional associations and their foundations also contribute. ACOG has identified a total of 14 awards currently being made by the private sector, including some substantial fellowships:

- The James Kennedy Fellowship Award of the American Association of Obstetricians and Gynecologists Foundation (the funding arm of the American Gynecological and Obstetrical Society) provides $40,000 per year for two years for fellows and requires a $15,000-per-year institutional commitment. This postdoctoral award targets individuals who need research training to move toward an investigative career. The program began in 1984 and had awarded a total of 17 fellowships by July 1990. Thirteen of these fellows attended a retreat in June 1990 at which an impressive summation of their research activities was presented.[11]
- The Berlex Foundation offers one or two scholarships per year with a stipend of $50,000 plus $10,000 for laboratory support for an individual who already has a record of independent research.
- ACOG has joined with Ortho Pharmaceutical Corporation to provide two $30,000 fellowships annually, to be awarded to an ACOG fellow or junior fellow identified as progressing toward academic OB/GYN. The award is meant to allow the recipient to undertake an investigative project and basic research training.
- There are in addition a number of smaller professional association/industry grants that provide start-up funds for research projects, as well as some monies for training support.[12]

It is estimated that approximately six to eight physician/scientists are being trained annually in these major programs supported by the private sector.[13]

Many of these programs have their roots in assessments from inside the discipline that academic research needs enhancement and that a vitalized research effort would upgrade the status of OB/GYN.[14] The initiatives have resulted in a small but significant body of awards to further the development of investigators. The future magnitude of professional and industry support of OB/GYN research training will depend on a continuing sense in the discipline that an enhanced research capability would benefit it generally, both in terms of the status of academic OB/GYN and in the quality of clinical practice.

Voluntary Health Agencies

Voluntary health agencies—often founded by the friends and families of individuals with a particular disease—sometimes use their funds for disease-related research and training. They can make important contributions to the careers of scientists by supporting fellowships, initial research, and other career development awards. Voluntary health agencies do not, however, usually make long-term commitments to research.[15] OB/GYN departments are well positioned to tap into the resources available from these agencies since OB/GYN interests overlap to some extent with the interests of three of the largest—the American Cancer Society, the March of Dimes-Birth Defects Foundation, and the National Easter Seal Society. Data on the level of OB/GYN funding by such voluntary health agencies are not available; however, each of the three agencies mentioned above was included in lists of sources of support received by the committee from chairs of departments of OB/GYN.

FINDINGS: The committee found cause for alarm in the diminution of foundation support for the development of OB/GYN research personnel and for OB/GYN research. Foundations played a vital role in preparing many of the current leaders of the field, and without this support there may not be enough well-prepared individuals to step into leadership positions when the current generation reaches retirement age. Today only approximately 11 young investigators each year benefit from major private-sector training awards, including those supported by the joint public/private Reproductive Scientist Development Program but excluding those who are awarded other NIH training

support. Increasing the number of available awards by at least another six would return significant benefits to OB/GYN research.

RECOMMENDATIONS: OB/GYN leaders should take the initiative in demonstrating to foundation and voluntary health agency trustees and other representatives, to leaders of professional associations, and to relevant foundations of industrial corporations, ways in which expanded support of training for OB/GYN investigators would be a worthwhile investment. The purpose of such investments would be to ensure that sufficient research personnel are available to allow OB/GYN to fulfill its promise of improving women's health, contraception, and pregnancy outcomes. The committee encourages foundations to develop programs for OB/GYN, such as the former Josiah Macy, Jr. Foundation program, the current Searle Scholars Program, or other foundation efforts that can be regarded as models with characteristics that may be worth emulating.

OB/GYN leaders should seek additional research support from the types of organizations mentioned above. The promise of the research, together with a willingness to adapt research programs to correspond to foundation priorities, will provide powerful arguments that have a chance of salvaging some lost foundation support. By the same token, **decision makers in foundations that are concerned with the development of scientific personnel—or with population problems, women's health, cancer, pregnancy outcomes, and other topics that OB/GYN is well positioned to address—should be aware of the role that their support of training and research could play at this crucial time in the development of OB/GYN research.**

The committee also recommends that the American College of Obstetricians and Gynecologists and the Association of Professors of Gynecology and Obstetrics continue to include in their manpower survey questions on sources of research support received by departments of OB/GYN. This information will for the first time allow tracking of the level of research activity in departments of OB/GYN.

Federal Support

A 1980 report on the status of academic obstetrics noted that "federal funding of research in academic departments of obstetrics and gynecology in the

United States has never been substantial, and the situation is not different today."[16] That sentiment might be echoed in 1992.

The discussion below focuses on NIH support of departments of OB/GYN.[*] Other federal agencies also contribute, but their support is difficult to identify and is not thought to be sizable.[17] A survey of departments of OB/GYN in 1990 revealed a total of $77.5 million in federal research funds.[18] NIH data indicate that, of this amount, $45.7 million (59 percent) came from NIH, and there are reasons to believe that the NIH contribution exceeds 59 percent. (For example, the figure omits awards that flow to academic departments but that are awarded to other entities, such as hospitals.) Staff at federal agencies outside of NIH agree that their funding of research in departments of OB/GYN is limited. In 1989, the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) provided $1.6 million in research funds.

Trends in NIH Support of Departments of OB/GYN NIH funds flowing to departments of OB/GYN increased from $6.9 million in 1968 to $16.1 million m 1978 and to $45.7 million in 1990 (this latter figure represents a slight decline from the $46.5 million awarded in 1989). In constant dollars, however, the increase over the 1968–1989 period was 74 percent; it was 43 percent between 1978 and 1989 (Figure 2-1). Since the average amount of money per award increased over time, the number of awards has not grown at the same rate as dollar support. Thus between 1980 and 1989, the dollars going to departments of OB/GYN more than doubled, while the number of awards increased by less than 5 percent, more closely reflecting the real-dollar increase.

Departments of OB/GYN very slightly increased their share of the overall NIH budget. Their share of the NIH funds going to departments of medical schools has remained virtually unchanged. During the 1980s the NIH budget increased by 150 percent, while OB/GYN departments gained 190 percent. OB/GYN departments maintained their share of NIH medical school support at 1.4 to 1.5 percent between 1968 and 1989, although they received less than might be expected on the basis of faculty size: 3.8 percent of all medical school faculty are in departments of OB/GYN, but they were awarded only 1.5 percent of the NIH funds going to medical schools.

[*] The following discussion of the NIH role is, unless noted otherwise, based on a background paper by Robert A. Walkington, which is published as Appendix B of this report and to which the reader is referred for additional information. The data for this paper were extracted from the NIH data systems specifically for this study.

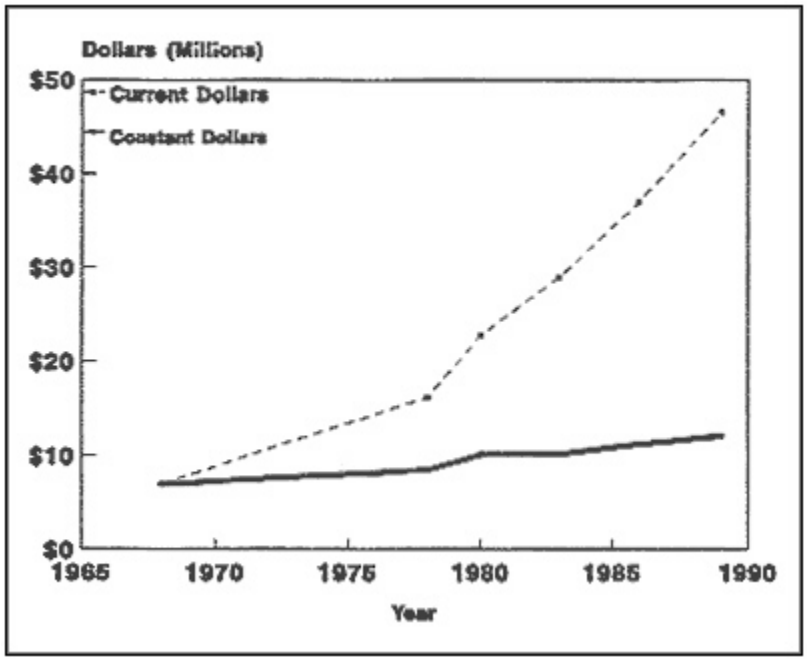

Figure 2-1: NIH support of departments of OB/GYN, current and constant (1968) dollars
SOURCE: Special tabulation by NIH.

An important element in the extent of support, at any given time, of specific areas of science or of specific disciplines relates to the fortunes of the NIH institute that provides the funds. Because public and congressional perceptions of the importance of the health or science issues undertaken by each institute have varied over time, budget appropriations for individual institutes do not always parallel overall NIH budget growth.

Historically, the National Institute of Child Health and Human Development (NICHD) has been the major NIH supporter of departments or OB/GYN, providing between 55 percent and 70 percent of NIH support since 1968. NICHD has received approximately 6 percent of total NIH funds since 1978, and departments of OB/GYN have increased their share of NICHD funds from 5.4 percent in 1978 to 7.5 percent in 1989.

The National Cancer Institute (NCI) has been the second largest NIH supporter of OB/GYN departments. However, the NCI contribution fell from 31 percent of total NIH funds going to departments of OB/GYN in 1978 to 9 percent ($4.6 million) in 1989. Although NCI's share of the total NIH appropriation has itself fallen substantially, NCI is still by far the largest institute, accounting for more than 20 percent of NIH's 1989 funds.

NIH offers many types of research and research training awards. Research grants absorb the largest proportion of NIH funds, a proportion that has risen from 77 percent of total NIH support awarded in 1980 to 84 percent in 1989. Awards to departments of OB/GYN followed a similar trend: research grants increased from 90 percent to 92 percent of OB/GYN awards over the same period. The largest component of this group of awards is the category of investigator-initiated awards (RO1s). Also included in the group of awards are First Independent Research Support and Transition (FIRST) and New Investigator Research awards, both of which can be pivotal support for young investigators; Research Program Project grants; and research center grants, which play a role in solidifying the research efforts of a department and ensuring the presence of a new generation of investigators. NIH also supports research training at both the pre- and postdoctoral levels. This aspect of NIH activities has experienced a relative decline, falling from 6.6 percent of the NIH extramural budget in 1980 to 4.3 percent in 1989. Again, the trend for departments of OB/GYN is similar, with training support falling from 3 percent of NIH support of departments of OB/GYN in 1980 to 1.3 percent in 1989.

In sum, departments of OB/GYN have made a very small gain in terms of share of NIH resources, but the funds they receive remain an extremely small component not only of the NIH budget as a whole—which is to be expected—but also of the budget of NICHD, the institute that has the mandate to improve reproductive health. Closer examination of the data causes a greater sense of alarm about how OB/GYN departments are faring. The following sections take such a look, viewing the state of NIH support of departments of OB/GYN from three perspectives: the types of awards applied for and received by departments of OB/GYN, the academic degrees of investigators, and how OB/GYN departments compare with some other clinical departments.

Competition for NIH Funds

To assess how OB/GYN departments are doing in gaining NIH support, the committee compared their applications with applications from departments of internal medicine, pediatrics, surgery, and radiology. Departments of internal

medicine were chosen for this purpose because they are the largest of all the clinical departments and are widely considered to be leaders in research capabilities. Pediatric departments were selected because pediatrics is a major focus of interest for NICHD; thus those departments share with OB/GYN some dependence on that institute. Surgery was chosen because it shares a technical orientation with OB/GYN—a characteristic that is also thought to affect the likelihood of success in NIH funding. Finally, departments of radiology were chosen because they are similar to OB/GYN in research intensity as measured by the percentage of faculty who are principal investigators (PIs) on NIH and ADAMHA grants. Although radiology faculty are more numerous than OB/GYN faculty, the two departments are nevertheless closer in size than the other departments chosen. Internal medicine had nearly six times as many full-time faculty as OB/GYN in 1988, while pediatrics and surgery had more than twice as many. Other departments or subspecialties might provide more appropriate comparisons, but data problems prohibited analysis.

All Competing Applications In the decade 1980–1989, the five clinical departments submitted a total of 46,148 competing applications to NIH (Table 2-1). Fifty-nine percent were submitted from departments of internal medicine (which have 44 percent of the full-time faculty in the five departments), 15 percent by departments of pediatrics (with 19 percent of faculty), 13 percent by departments of surgery (with 17 percent of faculty), 7 percent by departments of radiology (with 13 percent of faculty) and 6 percent by departments of OB/GYN (with 7 percent of faculty). Thus departments of internal medicine submitted a disproportionately large number of applications in relation to faculty size; OB/GYN, pediatrics, and surgery submitted a roughly proportional number; and radiology was slightly underrepresented. However, on a per capita basis, physicians in departments of OB/GYN submitted fewer applications than M.D.s from three of the other four departments (Table 2-2).

The success rate (percentage of applications funded) varied from 37.6 percent for internal medicine to 26.5 percent for OB/GYN. The differences in success rates among OB/GYN and the other departments, except for surgery, are statistically significant. The low relative success rate of OB/GYN departments became more acute toward the end of the decade.

Analysis by degree reveals that the success rate of applications from Ph.D.s in departments of OB/GYN was significantly lower than the success rates of Ph.D.s in departments of medicine and radiology. The differences in success rates for Ph.D.s among departments of OB/GYN, pediatrics, and surgery were

TABLE 2-1: Success Rates of Competing Applications Submitted to NIH by Departments of Obstetrics and Gynecology, Internal Medicine, Pediatrics, Radiology, and Surgery, 1980–1989

Department	Number of Applications	Number of Awards	Success Rate (%)
All Applicants			
Obstetrics/ Gynecology	2,669	706	26.5
Medicine	27,240	10,242	37.6*
Pediatrics	6,801	2,105	31.0*
Radiology	3,335	1,111	33.4*
Surgery	6,117	1,742	28.5
Total	46,162	15,866	34.4
M.D.s			
Obstetrics/ Gynecology	1,013	245	24.2
Medicine	17,684	6,962	39.4
Pediatrics	4,327	1,134	32.7*
Radiology	920	278	30.2*
Surgery	3,522	1,059	30.1*
Total	27,466	9,956	36.3
Ph.D.s			
Obstetrics/ Gynecology	1,473	416	28.2
Medicine	7,126	2,428	34.1*
Pediatrics	1,794	478	26.7
Radiology	2,127	745	35.0*
Surgery	2,038	547	26.9
Total	14,558	4,614	31.7

* Significant at 95% confidence level when compared with OB/GYN.
SOURCE: Special tabulation from NIH.

not significant; indeed, OB/GYN departments, with a 28.2 success rate, were not far off the average of 31.7 for all five departments. However, in the latter years of the decade, the success rate of Ph.D.s in OB/GYN departments fell below that of the other departments.

TABLE 2-2: Per Capita Competing Applications Submitted to NIH by Selected Departments, 1989

Department	Total Faculty	M.D.s and M.D./Ph.D.s
OB/GYN	1.1	0.5
Internal Medicine	1.9	1.4
Pediatrics	1.1	0.8
Radiology	0.8	0.3
Surgery	1.2	0.7

SOURCES: Calculated from *U.S. Medical School Faculty, "The Numbers Book,"* 1989 Washington, D.C., Association of American Medical Colleges, 1989; special tabulation from NIH.

Applications submitted by M.D.s from departments of OB/GYN fared significantly worse than those from any of the comparison departments. Compared with an average success rate of 36.3 percent for the five departments, OB/GYN's 24.2 percent success rate was significantly lower than each of the other four departments, including surgery, which was the next lowest at 30.1 percent. Thus it is apparent that the major portion of the weakness observed in the overall success rate of departments of OB/GYN is attributable to applications from M.D.s.

But success rates only tell part of the story. To win awards, applications must be submitted, and physicians in departments of OB/GYN submit relatively small numbers of applications per capita.

Investigator-Initiated Research The RO1 grant is the heart of the NIH extramural program. It is the traditional award for investigator-initiated research and in 1989 represented almost two-thirds of all NIH research grants.

The pattern observed above for all awards is repeated for RO1s: Ph.D.s from departments of OB/GYN have better success rates than their M.D. colleagues; M.D.s in departments of OB/GYN have a significantly lower success rate than each of the comparison departments. Thus research proposals from

M.D.s in particular, and to a lesser extent from Ph.D.s in departments of OB/GYN, are relatively unsuccessful in the competition for the important RO I research grants.

There are distinctive differences among the five departments in the proportion of RO1s submitted by M.D.s, despite similar proportions of M.D.s and Ph.D.s on their faculties. During the 1980s, almost two-thirds of RO1 applications from internal medicine and pediatrics came from M.D.s; for surgery, roughly one-half were from M.D.s, for OB/GYN, one-third, and for radiology, one-quarter. Thus access to RO1 funds for departments of OB/GYN was enhanced by the number of submissions from the more successful basic scientists.

Beginning Research Awards NIH offers research grants that are designed to help beginning researchers move from trainee status to independence. These First Independent Research Support and Transition (FIRST) awards support an investigator's initial independent effort and help in the transition to attaining an RO1. Departments of OB/GYN submitted few applications—a total of 165—for FIRST awards between 1980 and 1989; only 51 of the applications were from M.D.s. Since the success rate was significantly worse than that of each of the comparison departments, OB/GYN also received only a small number of FIRST awards—29 in total, 4 for M.D.s. Only radiology had a similarly low number of applications.

FIRST awards are small—for five years, with no more than $350,000 in total—but they help the investigator who must prove his or her worth before winning traditional types of NIH support.[*] The poor showing of departments of OB/GYN in general and of their M.D. applications in particular is disconcerting —the inability of M.D. investigators in departments of OB/GYN to win these awards may indicate weakness in younger es hers that bodes ill for the future. The low number of applications may indicate a lack of research interest in the younger generation that also has serious implications for the future.

NIH makes other awards that provide useful support for young investigators. For example, small grants (RO3s), often in the $20,000–$25,000 range, are well suited to investigators who are developing the preliminary data

[*] The level of support on an NIH FIRST award does not fully cover the salary of a physician/investigator, nor does it cover the total cost of the research. The department chair must therefore make a significant additional investment of departmental funds in the investigator.

needed for an RO1 application. Between 1987 and 1989, departments of OB/GYN submitted seven applications for RO3s—four from M.D.s and three from Ph.D.s. One M.D. was awarded an RO3. Thus it appears that another award of potential, if limited, use is not receiving much attention from OB/GYN.

Research Training NIH offers training support in two forms: fellowship awards to individuals and training grants to institutions, which then make awards of traineeships to individuals they select. Differences in success rates for these awards among the five comparison departments axe small and not statistically significant. Again, however, OB/GYN departments submit few applications and therefore win few awards. During the 1980s, OB/GYN submitted a total of 194 applications, 56 of them from physicians. This translated into only 84 awards, of which 24 went to physicians. Of the comparison departments, only radiology had comparably small numbers. Research training is the precursor of careers in investigation, and the paucity of awards does not bode well for future OB/GYN research manpower.

Career Development NIH offers several types of career development awards to support the training of scientists with clear potential who require additional training to reach independence. Some of these awards are for physicians only, some target individuals at particular stages of their development, and others target specific areas of work. The total number of investigators winning career development awards has not changed much over the past decade; however, there has been a shift away from Ph.D.s. toward M.D.s through an expansion of clinical investigator awards, which provide opportunities for medical scientists who will pursue research in areas of interest to the awarding institute. In addition, there axe two new programs for physician/scientists: one provides individual support and the other offers an institutional award for newly trained physicians to train in multidisciplinary programs.

As with research training awards, departments of OB/GYN, between 1980 and 1989, experienced success rates for career development awards similar to the rates of the four comparison departments. But, like radiology, OB/GYN submitted few applications; thus only 21 career development awards (18 to physicians) went to departments of OB/GYN during the decade. However, the number of individuals whose training has been supported exceeds the number of awards because the Reproductive Scientist Development Program (RSDP),

previously called the Reproductive Scientist Training Program, which takes in three physician trainees each year, is counted as one award.

The RSDP was developed in response to a perceived shortage of OB/GYNs with research expertise. Designed to give outstanding clinically trained individuals the basic research training in cell and molecular biology that would allow them to become competitive for research grants, the award was modeled after one developed in pediatrics. An individual is eligible for an RSDP award after completing residency training or a clinical fellowship. An awardee enters a laboratory to work with an outstanding mentor and to learn basic science skills, as well as to participate in research. This phase of the training program was originally expected to last two years; however, some trainees have requested and received support for a third year in the laboratory. Following the years of basic research, trainees spend three years as junior faculty members in the department of OB/GYN that originally sponsored them, with a guarantee of at least 75 percent time spent in research under a preceptor. The RSDP is funded by NIH and by $25,000 per year each from the American College of Obstetricians and Gynecologists, the American Fertility Society, the American Gynecological and Obstetrical Society, the Association of Professors of Gynecology and Obstetrics, Ethicon Incorporated, and GynoPharma Incorporated.

The first three trainees entered the RSDP in 1988 and presented their work in 1990 at a meeting of the Society for Gynecologic Investigation. The quality of the trainees is impressive, and the number of outstanding candidates has grown each year. Many members of the OB/GYN community believe that the RSDP represents the most hopeful endeavor for training new investigators that the discipline has seen for many years.

Although NIH data do not document the number of physicians in departments of OB/GYN who received research training and career development support from NIH in the past decade, according to one estimate the total for the decade is only 50 people.[19]

During the past year NICHD has changed the terms under which it grants the Clinical Investigator Award, an award for physicians who have completed clinical training and have had between three and seven years of postdoctoral training. Providing salary support of up to $50,000 per year, plus $10,000 for supplies, the award is designed to help an investigator work on a defined problem under the auspices of a sponsor and to assist in the investigator's transition to independence.[20] Previously NICHD granted the Clinical Investigator Award for only three years; now up to five years of support may be awarded. This extension can make a significant difference for young

investigators struggling to prepare themselves to compete on their own for grant support.

The ability to adapt awards to respond to changing needs or other circumstances is a strength of the NIH system. Thus, for example, the Physician Investigator Award was established in response to a perceived need to enhance the supply of physicians engaged in research. This year the National Heart, Lung, and Blood Institute initiated a new award to replace its Physician Scientist and Clinical Investigator awards. The change was made "to allow greater flexibility in developing a program suited to the experience and capabilities of the candidate." Thus the holder of the award may integrate research and subspecialty clinical training, interrupt the grant to continue clinical training, or develop a program that is suited to his or her level of research experience.[21] The ability of NIH institutes to creatively tailor awards to try to accomplish specific outcomes, not only for career development awards but also for training and research grants, should not be underestimated.

"Umbrella" Grants These multiproject grants include research centers, such as the General Clinical Research Centers (GCRCs) and Specialized Centers, as well as Program Project Grants. They involve large numbers of researchers, are often targeted to interdisciplinary areas of work, and can support both core and ancillary activities such as animal facilities, epidemiology units, or hospital beds used for the research—depending on the type of award. They provide funding mechanisms for the development of junior staff, for specialized research nurses and dieticians, and for research facilities for inpatient and outpatient studies. Many have laboratories with advanced technologies.[22] GCRCs are valued for the resource brought together that facilitate clinical research for investigators and subjects.

"Umbrella" grants are sometimes initiated when NIH—often at the behest of Congress—makes an announcement of the research area in which an institute wants to fund a center; generally NIH staff work closely with the applicant institution's staff during the development of applications. Once granted, the award is closely monitored by NIH staff. In general, these grants are awarded to institutions that have a proven track record in research (most of the investigators on center grants are also RO1 awardees) and are therefore thought to be able to sustain these large-scale efforts.

There is tension between the level of funding for RO1s and the number of centers funded by NIH, partly because the funding of one decreases the funding of the other. On the other hand, academic departments value the flexibility of

center grants; investigators between RO1s may be supported on such grants; interdisciplinary synergy between basic and clinical scientists is easier to generate; and center funds usually prove to be more stable, longer term support than other types of NIH funds. There are also differences between center grants and RO1s in terms of the work that can be accomplished. One observer noted that more clinical, innovative, and risky research is accomplished with center grants. In particular, research requiring three to four years to obtain data is more likely to be undertaken in the more stable context of a research center. Finally, the prestige attached to having a center can be used to stimulate contributions from nonfederal sources and to attract distinguished scientists to the departments.

Several awards of this umbrella type that pertain to OB/GYN research topics have been made. An example is the Specialized Centers (P50) awards for perinatal research centers, which include centers that focus on, for example, diabetes and pregnancy or premature labor. The Pregnancy and Perinatology Branch of NICHD supports six current P50 grants, of which two axe m departments of OB/GYN and four in departments of pediatrics. Other awards axe Research Project Cooperative Agreements, under which a maternal fetal medicine unit network and a neonatal intensive care unit network are supported. These networks were established in response to the notion that much obstetric and neonatal clinical management were not based on strong evidence of efficacy; groups were asked to design clinical trials to compare various clinical management approaches.

Departments of OB/GYN have fared differently depending on the type of umbrella grant they sought. The number of Program Project Grants awarded by NIH has increased over the past decade, but OB/GYN departments have not shared in this expansion. OB/GYN departments submitted only 28 Program Project Grant applications during the decade (one-quarter the number submitted by radiology, the department with the next fewest number of applications) and were awarded 13 grants. However, of the 33 applications for research center grants that were submitted by OB/GYN departments, 24 gained awards, for a success rate of nearly 72 percent—the highest among the five comparison departments. The high success rate for these awards (compared with many other NIH awards) is partly due to the understanding of departments that it is futile to apply unless a critical mass of investigation is already being conducted, and partly due to the consultation that takes place between NIH staff and applicants before the application is submitted.

FINDINGS: The committee finds cause for acute concern about the research capabilities of physicians in departments of OB/GYN. Ph.D.s in departments of OB/GYN who apply for NIH funding have success rates comparable to the rates of Ph.D.s from some other clinical departments, but the submissions from physicians in departments of OB/GYN are sparse and fare poorly in the competition for NIH funds. In response to this weakness, the committee focused its recommendations on ways of developing and strengthening physician investigators in departments of OB/GYN, enabling them to compete more successfully for NIH funds in the future.

RECOMMENDATIONS: NICHD program staff should exercise to the fullest extent possible their ability to target training support to expand the number of research training opportunities for physicians in OB/GYN.

Chairs of departments of OB/GYN should work with NIH staff to improve the success rate of applicants for FIRST awards. FIRST awards are particularly useful mechanisms in this regard, since their average length exceeds that of RO1s and applicants under 36 years of age have the best success rate.

The committee believes that survival of the Reproductive Scientist Development Program is essential for the future health of OB/GYN research. **Professional groups and the private-sector organizations that support the Reproductive Scientist Development Program should ensure its stability through a long-term commitment of resources. Because of the importance of the program NICHD should continue support of the Reproductive Scientist Development Program.**

The committee also recommends that NICHD tailor another career development award to OB/GYN physicians. This award should be flexible in terms of the type of training it provides and the timing of training, as is the Clinical Investigator Development Award of the National Heart, Lung, and Blood Institute. And because the supply of research manpower in OB/GYN is of great concern, **the committee also recommends that NIH develop a system to track OB/GYNs who are receiving federal training and career development support.**

STRUCTURAL CHARACTERISTICS OF DEPARTMENTS OF OB/GYN

Data on the relative success of departments of OB/GYN in competing for NIH funds are one indicator of a possible problem in their research capabilities.

A different set of indicators pertains to the departments themselves: how they differ from other clinical departments, the relative intensiveness of their research efforts, the composition of the departments in terms of the academic degrees of faculty members, and theft ability to provide a healthy research environment.

Overview of Faculty in Clinical Departments of Medical Schools

The number of faculty members in the clinical departments of U.S. medical schools grew by 69.5 percent between 1978 and 1989, from almost 29,000 to a little over 49,000 (see Table 2-3). However, not all departments shared equally in this expansion. Departments of internal medicine led the way with a growth rate of 86.1 percent, widening the gap in size between internal medicine and all other clinical departments. At the other end of the spectrum are the departments of physical medicine, which are small (only 561, or 1 percent of clinical faculty members in 1989) and which experienced a relatively meager growth of 24.4 percent between 1978 and 1989. Departments of OB/GYN are relatively small and slow-growing: their 1989 total faculty size of 2,383* was below the 3,167 average and represented only 5 percent of total clinical faculty. Theft growth of 58.3 percent between 1978–1989 was below the 69.5 percent average.

Composition of Faculty by Degree The principal factors driving faculty size are teaching load and clinical duties—research is usually secondary. The number of Ph.D.s in a department is considered an indicator, albeit an imperfect one, of research activity. In 1986, Herman and Singer remarked that "the major efforts of clinical investigation have moved from the bedside, where patient contact and research were closely linked, toward the basic science laboratory and its emphasis on cell culture, enzyme systems, and animal models." This, they posited, accounted for the growth in the number of full-time Ph.D. faculty appointments in clinical departments—up from 3,500 in 1972 to 5,900 in 1982. The authors suggested that Ph.D.s may have been recruited to compensate for the failure of M.D.s to maintain their share of the total research effort.[23]

* According to a survey conducted by ACOG, there were a total of 2,952 full-time faculty members in departments of OB/GYN in July 1990. This survey of all OB/GYN departments has been repeated at intervals since 1977. It documents an increase in faculty of 90 percent since 1977 and 22 percent between 1986 and 1990—a higher rate of growth than that shown by data from the Association of American Medical Colleges (AAMC) discussed in the text. The committee used AAMC data in this section because they allow comparison with other departments.

TABLE 2-3: Change in Number of Faculty Members in Clinical Department, 1978–1989

Department	1978	1989	Percent Change
Anesthesiology	1,579	2,777	75.9
Dermatology	262	379	44.7
Family Practice	1,098	1,581	44.0
Internal Medicine	7,558	14,065	86.1
Neurology	1,088	1,706	57.0
OB/GYN	**1,505**	**2,383**	**58.3**
Ophthalmology	594	1,093	84.0
Orth. Surgery	477	772	61.8
Otolaryngology	419	572	36.5
Pediatrics	3,327	6,009	80.6
Physical Medicine	451	561	24.4
Psychiatry	3,661	5,405	47.6
Public Health	712	1,187	66.7
Radiology	2,524	4,003	58.6
Surgery	2,893	5,270	82.2
Other	791	1,305	65.0
Total	28,939	49,068	69.5

SOURCES: C. R. Sherman et al., *On the Status of Medical School Faculty and Clinical Research Manpower 1968–1990*, NIH Publication No. 82-2458. Bethesda, Md., National Institutes of Health, 1981; Association of American Medical Colleges, *U.S. Medical School Faculty, "The Numbers Book*," Washington, D.C., Association of American Medical Colleges, 1989.

Table 2-4 shows changes in the type of degree held by faculty of clinical departments between 1978 and 1989. The proportion of faculty with the Ph.D. or M.D./Ph.D. degree grew from 18.1 percent to 21.2 percent; because of substantial overall growth in faculty, this translates into significant numerical growth—from 3,859 in 1978 to 10,436 in 1989. There is wide variation in the presence of Ph.D.s and M.D./Ph.D.s in clinical departments, from only 13 percent of anesthesiology faculty to 45 percent of departments of public health. OB/GYN departments, with faculty rosters that are 14.3 percent Ph.D. and 5.4 percent M.D./Ph.D., were not far off the average for clinical departments of 15.7 percent and 5.5 percent, respectively. Departments of OB/GYN are close

to the average clinical department in both the direction of change and the makeup of their faculty. Therefore, to the extent that the presence of faculty with basic science degrees indicates that departments are structured to undertake research, departments of OB/GYN are positioned to compete in the research arena.

TABLE 2-4: Change in Degrees of Full-Time Faculty, 1978 and 1989, as Percentage of Department Faculty

	M.D.		M.D./ Ph.D.		Ph.D./ O.H.D.*		Other	
Department	1978	1989	1978	1989	1978	1989	1978	1989
Anesthesiology	88.9	82.5	4.6	7.0	4.2	6.0	2.3	4.4
Dermatology	71.6	78.6	6.1	7.1	17.5	11.9	4.8	2.4
Family Practice	66.5	73.7	1.6	1.5	13.5	17.8	17.4	7.0
Internal Med.	85.4	80.8	4.7	6.5	7.1	9.5	2.8	3.1
Neurology	73.3	67.8	6.4	9.4	14.6	18.5	5.7	4.3
OB/GYN	**78.1**	**74.1**	**5.0**	**5.4**	**12.2**	**14.3**	**4.7**	**6.2**
Ophthalmology	65.5	63.0	6.6	6.3	22.1	23.9	5.8	6.8
Orth. Surgery	84.7	78.1	4.4	3.1	7.5	11.0	3.4	7.8
Otolaryngology	53.3	53.3	2.5	4.9	28.5	32.2	15.7	9.8
Pediatrics	80.4	78.4	3.3	4.8	10.0	10.6	6.0	6.0
Physical Med.	51.0	62.2	2.4	3.0	17.6	18.5	29.0	16.2
Psychiatry	55.5	54.2	2.5	3.8	29.5	33.1	12.5	9.0
Public Health	36.7	40.8	2.8	3.9	38.4	41.4	22.1	13.9
Radiology	72.8	71.1	3.7	4.5	15.7	18.2	7.8	6.1
Surgery	82.2	80.1	5.7	5.2	8.4	11.1	3.7	3.6
Other	59.6	31.0	1.8	3.8	19.3	59.1	19.3	7.0
Total	74.8	73.2	4.1	5.5	14.0	15.7	7.1	5.6

* Other health doctorate.

SOURCES: *Comparison of Characteristics of U.S. Medical School Salaried Faculty in the Past Decade, 1968–1978*, Publication No. NO1-OD-8-2116, Washington, D.C., U.S. Department of Health, Education, and Welfare, Public Health Service, 1979; Association of American Medical Colleges, *U.S. Medical School Faculty, "The Numbers Book*," Washington, D.C., Association of American Medical Colleges, 1989.

Age and Gender Composition of Faculties A body of empirical work, mainly pertaining to nonphysician scientists, suggests that there is at least a weak relationship between age and research productivity, as measured by publications.[24] The best available data on physician investigators come from a 1980 survey by the Association of American Medical Colleges (AAMC), which queried physician faculty listed in its Faculty Roster System. The data were analyzed to determine variations in time spent in research and in numbers of publications as they relate to age.[25] These data indicate that research productivity as measured by time spent in research does not peak at the same time as productivity measured by volume of publications. By both measures the latest peaks are at about 45 years of age.

Analysis of 1988 data from the AAMC Faculty Roster System (Table 2-5) indicates that the age distribution of physicians in departments of OB/GYN is similar to that of all physician clinical faculty. Indeed, the age distribution of the physician faculty of each of the five clinical departments analyzed is remarkably similar, suggesting that any differences in the research productivity of departments are not due to the age of physician faculty.

The relationship between gender and research activity is also unclear. Over the past decade, extensive note has been taken of the underrepresentation of women in the scientific work force and of differences in career trajectories for women in science compared with men.[26] Women scientists in general publish roughly 50 percent fewer papers than male scientists of the same age, and differences in publication rates increase with age.[27] This study, however, is concerned with academic scientists in general, and with physicians in particular —a segment of the scientific work force about which only a little is known.

During medical school, differences between men and women in their interest in research are slight. One study revealed that in 1987, the only activity during medical school in which men participated more than women was the authorship of published research—24 percent of men and 19 percent of women.[28] Women lag only slightly in expressing an interest in having research as part of their career—of 1989 graduating medical students, 23.6 percent of the men and 21.2 percent of the women intended to take a research fellowship; 16.1 percent of the men and 13.5 percent of the women expected to be significantly involved in research.[29] Evidently the discrepancies between men and women in this area appear after medical school.

TABLE 2-5: Age Distribution of Physician Faculty (as Percentage of Departmental Faculty) of Selected Clinical Departments

	Age				
	< 36	36–45	46–55	56–65	> 65
All Clinical Departments	13.8	41.4	25.7	15.1	4.0
OB/GYN	15.8	38.5	26.5	14.6	4.6
Internal Medicine	12.9	45.0	25.3	13.2	3.5
Psychiatry	13.8	38.5	25.0	18.0	4.7
Surgery	12.7	41.1	26.5	15.2	4.6
Pediatrics	13.1	47.0	24.6	12.6	2.7
Radiology	15.7	38.4	27.9	14.3	3.8

NOTE: Columns may not add to 100 due to rounding.
SOURCE: Special tabulation by Paul. J. Friedman, M.D., Professor of Radiology and Dean for Academic Affairs, University of California, San Diego; data taken from the Faculty Roster System, Association of American Medical Colleges.

Data on the advancement of women in academic medicine indicate that they have increased their representation in medical school faculty—from 13 percent in 1967 to 21 percent in 1990—and that female medical school graduates are more likely than their male equivalents to join medical school faculties. However, women advance more slowly through the faculty ranks: of the cohort of people who became faculty members in 1976, 25 percent of the men and 19 percent of the women were tenured or on a tenure track in 1987; 12 percent of the men were professors, as opposed to only 3 percent of the women.[30]

Clearly something is halting the progress of women through the academic ranks. One possibility is that, to the extent that academic advancement is based on research productivity, women are not equalling men. An analysis of internal medicine faculty members—the only available analysis of gender difference—indicated that in 1982 and 1983, 19 percent of men and 29 percent of women reported no research involvement; women were also less likely than men to have outside research funding and assigned research space.[31] Moreover, 16 percent of the men and 29 percent of the women had not had research training, and 44 percent of the men and 55 percent of the women had not been the first author of an original article.[32]

However, a 1989 survey of physicians by the American Medical Association does not substantiate the notion of lesser research involvement by women: 2.8 percent of both male and female physicians in 1989 reported research as a major professional activity.[33] Similarly, women who complete research training and apply for RO1 grants from NIH appear to be almost as accomplished as the men. Since 1980 women have averaged slightly poorer priority scores than men, but the difference in any one year was only from one to eight points, and in 1990 men and women had comparable success rates.[34] On balance, however, the weight of the evidence suggests that women in science are generally less involved in research than are men (reasons for this axe discussed later in this report).

Table 2-6 substantiates the finding that women are clustered in lower level faculty positions. More importantly for this study, departments of OB/GYN have a substantially higher representation of women (23.7 percent)* than the average clinical department (19.6 percent). The only departments with a higher proportion of women faculty than OB/GYN are pediatrics, public health, and physical medicine; the proportion of women faculty in family medicine is similar to that of OB/GYN. In addition, nearly 55 percent of instructors in departments of OB/GYN are women; thus the future ranks of senior faculty will be pulled from a pool in which women axe in the majority.** The gender distribution in departments of OB/GYN is not likely to contribute in a major way to the current competitive weakness in OB/GYN research identified earlier in this chapter. However, this characteristic of OB/GYN departments suggests that attention to the needs of women seeking research careers would be an investment with a substantial return.

Research Intensiveness

How Much Time Do Faculty Members Spend Doing Research? A more direct indicator of the research strength of a department is the time faculty members spend in research activities. Unfortunately, data that would allow comparisons

* ACOG survey data note that 29 percent of OB/GYN faculty are women. Again, the committee uses AAMC data since they allow comparisons with other departments.

** The pattern of NIH funding of women also indicates their increasing future role in research. Women hold about 18 percent of RO1 funds, 28 percent of FIRST awards, and 31 percent of NIH training grant funds (National Institutes of Health, *Women in NIH Extramural Grant Program. Fiscal Years 1981 to 1990*, Division of Research Grams, Bethesda, Md., 1991).

TABLE 2-6: Distribution of Medical School Faculty (as percentage of faculty at each level that are women) in Clinical Departments by Gender and Rank, 1989.

Department	Professor	Associate Professor	Assistant Professor	Instructor	Total
Anesthesiology	7.6%	17.9%	27.7%	26.0%	22.6%
Dermatology	7.9	16.3	35.5	36.8	21.5
Family Medicine	6.4	15.7	27.0	44.3	23.8
Internal Medicine	4.6	10.6	22.1	30.4	15.7
Neurology	5.0	16.3	19.7	34.5	15.8
OB/GYN	**7.2**	**13.6**	**30.1**	**54.8**	**23.7**
Ophthalmology	5.7	11.2	19.9	21.0	13.8
Orth. Surgery	0.9	7.5	10.2	21.2	8.1
Otolaryngology	2.2	14.8	22.4	49.1	17.1
Pathology (clinical)	8.9	19.6	30.0	43.9	21.6
Pediatrics	14.6	26.5	39.5	55.1	32.4
Phys. Medicine	12.1	30.6	36.9	49.5	34.1
Psychiatry	8.3	18.3	29.2	44.5	16.6
Public Health	12.1	20.7	40.0	55.1	30.1
Radiology	5.4	14.5	22.8	23.0	16.3
Surgery	1.6	5.9	12.6	20.5	8.1
Other Clinical	10.5	31.6	24.1	—	21.4
Total	6.3	15.0	25.7	37.0	19.6

SOURCES: Association of American Medical Colleges, *U.S. Medical School Faculty, "The Numbers Book,"* Washington, D.C., Association of American Medical Colleges, 1989.

among clinical departments are sparse. AAMC collects data on the activities of medical faculty, but only activities that consume more than 10 percent of a faculty member's time and without distinguishing between activities that consume, for example, 11 percent or 90 percent of time.

In 1983, to gain a better picture of medical faculty involvement in research, the Association of Professors of Medicine, in cooperation with AAMC, asked full-time faculty members in departments of internal medicine what percentage of time they spent in research.* In 1990, ACOG, at the request of this committee, added to its academic manpower survey a question asking whether faculty members spent 20 percent or more of their time in research. The results revealed that 34.5 percent of physician faculty (M.D. and M.D./Ph.D.) spent at least 20 percent of their time in research in 1990, compared with 45 percent of M.D. and 67 percent of M.D./Ph.D. internal medicine faculty, as recorded in the AAMC data for 1983. Ph.D. faculty in both internal medicine and OB/GYN departments are more involved in research than their M.D. colleagues6—90 percent of the internal medicine Ph.D faculty and 92 percent of the OB/GYN Ph.D. faculty spend at least 20 percent of theft time in research.[35] ,[36] Data from these two sources are not strictly comparable because of differences in sources of information and time of data collection and the difference between a specialty oriented toward surgical procedures and one oriented toward medicine. Nevertheless, the disparity between the two departments in research activity of physicians is suggestive. Departments of internal medicine, acknowledged leaders in research activity among clinical departments, appear to engage their physician faculty more heavily in research, which also reflects their relatively high success rate in competing for NIH funds (see above). The lesser involvement of OB/GYN in se h may also support the notion, current among OB/GYN leaders, that OB/GYN faculty maintain unusually large clinical practices.

Which Clinical Departments Are Research Intensive? The final characteristic examined here that may bear on the research capabilities of departments is the percentage of full-time faculty who are principal investigators on NIH or ADAMHA awards. This indicator functions as a proxy measure for the research intensity of departments. A 1988 AAMC study ranked departments of OB/GYN eleventh out of 17 clinical departments, with 9.8 percent of faculty as PIs, compared with an average of 14 percent for all clinical departments.

* That study defined the following as active researchers: individuals who spend at least 20 percent of their time in research, who have authored or co-authored an original article or other significant research publication, and who have either external funding or assigned research space.

Ophthalmology ranked first with 36.5 percent; family medicine was at the low end with 1.2 percent (Table 2-7).

As might be expected, research involvement varies by degree—11.1 percent of M.D.s, 24.3 percent of M.D./Ph.D.s, and 26.9 percent of Ph.D.s are PIs. Thus, M.D./Ph.D.s are generally more like Ph.D.s in their involvement in research. However, this generalization does not hold for OB/GYN. Both M.D. and M.D./Ph.D. faculty in departments of OB/GYN are below the average for clinical departments in the proportion of faculty that are Pis. On the other hand, Ph.D.s in departments of OB/GYN rank sixth of the 17 departments in the proportion that are PIs (32.2 percent) and are well above the 26.9 percent average.[37] Clearly, to the extent that these data measure research intensity, departments of OB/GYN are among the less research-intensive departments, and their relative weakness in research capabilities can be attributed to the performance of their physicians.[*]

The research intensiveness of specialties can be analyzed on a different axis—the proportion of departments with significant outside research funding. There are two sources of data on this topic. The 1990 ACOG manpower survey revealed that only 9 of the nation's 136 academic departments of OB/GYN received more than $2 million in federal research funds. At the other end of the spectrum, 38 departments had no federal funds, and this number is larger for other sources of research funding.[38]

Data from NIH also indicate that research funding is clustered in a small number of departments. Between 1980 and 1989, approximately 70 departments of OB/GYN per year were recipients of NIH support. However, 10 departments received approximately 50 percent of the funds, and in 1989 only 4 departments had more than ten awards, while 15 had only one award. This concentration of funds in a small number of departments is somewhat more acute than generally occurs for NIH funds going to medical schools, where 20 schools received 50 percent of NIH funds in 1989.[39]

These indicators of research intensity suggest a weakness in departments of OB/GYN compared with other clinical departments, both in terms of the proportion of faculty that are PIs and in the concentration of research activity in a small number of departments. The existence of a critical mass of investigators is thought to be necessary to provide an environment in which science can thrive, and in which new investigators can be trained and exposed to role models in an atmosphere of scientific endeavor. These findings suggest

[*] It should, however, be remembered that although NIH and ADAMHA are major sources of research funding, they are not the only sources. Data indicating the relative ability of departments to gamer other research support are not available, but departments of OB/GYN are thought to have relatively good access to pharmaceutical company research funds

that only a small number of departments of OB/GYN support a vital research effort or provide the necessary environment for the generation of new investigators.

TABLE 2-7: Ranking of Clinical Departments by Percentage of Full-Time Faculty Who Are PIs on NIH/ADAMHA Awards (1988).

	Total Full-Time Faculty		M.D.	
Department	No.	%PIs	No.	%PIs
Ophthalmology	1,014	36.5	650	25.7
Neurology	1,637	23.9	1,101	18.4
Dermatology	365	22.5	291	20.0
Internal Medicine	13,448	19.9	10,894	17.7
Pathology	1,152	17.0	656	13.9
Public Health	1,127	15.7	445	10.6
Other Clinical	69	14.5	21	19.0
Otolaryngology	543	14.2	296	6.4
Pediatrics	5,724	13.4	4,503	11.9
Psychiatry	5,244	12.1	2,858	8.1
OB/GYN	**2,265**	**9.8**	**1,687**	**5.9**
Surgery	5,031	9.5	4,038	7.0
Radiology	3,884	8.3	2,786	3.2
Orthopedic Surgery	730	7.8	569	4.4
Anesthesiology	2,649	3.5	2,186	1.6
Phys. Med/Rehab.	548	1.2	341	0.9
Family Medicine	1,539	1.2	1,127	0.7
Total/Average	45,969	14.0	34,449	11.1

	M.D./Ph.D.		Ph.D.	
Department	No.	%PIs	No.	%PIs
Ophthalmology	61	39.3	245	69.4
Neurology	148	37.8	315	35.6
Dermatology	22	40.9	43	34.9
Internal Medicine	875	31.1	1,261	33.9
Pathology	122	25.4	280	22.1
Public Health	48	14.3	472	25.0
Other Clinical	2	0.0	41	12.2
Otolaryngology	28	25.0	171	27.5
Pediatrics	275	28.4	614	21.8
Psychiatry	197	18.8	1,728	20.2
OB/GYN	**126**	**13.5**	**320**	**32.2**
Surgery	268	17.9	540	25.9
Radiology	169	13.6	696	29.0
Orthopedic Surgery	23	13.0	81	34.6
Anesthesiology	181	8.8	157	22.3
Phys. Med/Rehab.	18	5.6	97	6.2
Family Medicine	25	0.0	265	6.8
Total/Average	2,589	24.3	7,327	26.9

SOURCE: American Association of Medical Colleges, Medical School Faculty Roster (1988), linked with Information Management Planning, Analysis and Coordination records of research grants (NIH and ADAMHA) and contracts (NIH) that received funds during fiscal year 1987.

FINDING: Data pertinent to the present as well as the future research capabilities of OB/GYN departments indicate weakness. Time devoted to research by physicians is low, the proportion of faculty who are full-time investigators on NIH or ADAMHA grants is below average, and the number of departments with sizable research funding is small. The latter point indicates the small number of departments able to provide a suitable environment for training investigators. The strong and growing presence of women indicates that attention to differences among men and women in recruitment and retention in research will be important to the future health of the OB/GYN research enterprise. The committee's recommendations on these topics are found later in this report.

A RESEARCH AGENDA FOR DEPARTMENTS OF OB/GYN

The research agenda (which is fully discussed in Chapter 6) provides a different sort of evidence of the need for expanded research efforts in OB/GYN, because it identifies areas of investigation likely to repay investment with improvements in the reproductive health of women and in the results of pregnancy.[*] To ensure that the research agenda fulfills its purposes, the following criteria were applied:

- *The research should contribute to the resolution of an important health problem.* Importance can be defined in terms of high prevalence or incidence of a problem, in terms of the serious effect of the problem on individuals who experience it, or in terms of impact on the health care system where the costs of caring for the problem are incurred.
- *The research approach should be promising*. That is to say, there is reason to think that following the selected avenue of investigation would provide solutions or that answering the question posed by the research is an essential step in finding a solution.
- *The research should be done in a department of OB/GYN or in collaboration with members of such departments*. The mere fact that patients with OB/GYN should be a necessary element. Lack of interest by other specialties the problem are seen in OB/GYN departments is not sufficient justification. Rather, OB/GYN must be the discipline with the knowledge or skill needed to accomplish the research. If the research is interdisciplinary, would also be sufficient justification, since the work would not be accomplished if OB/GYN did not undertake it.

The committee followed several steps n developing the research agenda:

- A letter was written to the chair of every U.S. and Canadian academic department of OB/GYN, asking for an opinion on priority areas for future research. Letters were also sent to leading OB/GYN professional associations. All committee members received copies of the replies, as well as a summary of the contents.

[*] The research agenda developed by the committee does not stress the social, health care, and other cost savings that would be generated by research that eliminates or diminishes some of the problems listed. For instance, the high hospital costs of caring for low birthweight babies are only the tip of the iceberg of expenditures incurred as a result of the long-term morbidity and disability that are frequent sequelae.

- A subgroup of the committee met to develop an initial list of research agenda topics, which was then reviewed, discussed, and revised by the full committee.
- Taking into consideration the criteria listed above, committee members allocated priorities to each item on the research agenda, and items that received low priority scores were eliminated from the list.
- Experts were asked to contribute background papers reviewing the current state of knowledge and identifying useful research approaches (see Appendix C for authors of background papers).
- Using the background papers and their own expertise, committee members developed a research agenda. Readers are referred to Chapter 6 for the agenda, which covers the following topics:

-Oocyte and follicular development in the ovary, including follicular formation; follicular atresia; follicular recruitment, selection, and dominance; corpus luteum function; and leukocytes, cytokines, and ovarian function.
-Fertilization.
-Fetal growth and development including embryology and congenital malformations; fetal growth and placental transport; congenital infection and substance abuse; perinatal research; and epidemiological research.
-Preterm labor including preterm, premature rupture of the fetal membranes, complications of pregnancy that compromise fetal or maternal well-being independent of the onset of labor, preterm onset of labor, and preterm labor and infection.
-Contraception including contraceptive implants, contraceptive rings, transdermal delivery, intrauterine devices (IUDs), oral conception, barrier methods, male contraception, antifertility vaccines, and medical abortifacients.
-Infertility including epidemiology, cervical physiology and function, fallopian tube function, endometriosis, male infertility, and in vitro fertilization and new reproductive technologies.
-Premenstrual syndrome.
-The brain and reproduction.
-Menopause.
-Oncology including ovarian cancer, uterine neoplasms, cervical cancers, vulvar malignancies, breast cancer, and trophoblastic disease.
-Sexually transmitted diseases including preventing sexually transmitted diseases by developing clinically effective and safe vaccines: developing cost-effective tests for early diagnosis of STDs; developing new therapies where needed and new cost-effective antibiotics that are easily administered and sufficiently acceptable to maximize compliance; clarifying the natural history of genital infections; defining behaviors associated with the acquisition and spread of STDs; and characterizing the role of STDs in adverse pregnancy outcomes.

CONCLUSION

From its review of the evidence in this chapter, the committee concluded that there is cause for concern about both the current and the future state of research in departments of OB/GYN. While it is appropriate that many departments of OB/GYN have, and preserve, a clinical focus, it is important to expand the number of departments that can succeed in the competitive research arena. In that way the committee's research agenda can be accomplished, and departments of OB/GYN can fulfill their potential for improving the health of women. **The committee concluded that the highest priority is to build physician research manpower so that more departments of OB/GYN can successfully compete for, and effectively use, increased research support. The committee therefore focused its recommendations on ways of recruiting and sustaining OB/GYNs in investigative careers and on developing research capabilities in departments that, with some additional help, have the potential to equal the first-rank research departments of OB/GYN.** Recommendations are found earlier in this chapter and in subsequent chapters of this report.

No one entity bears the responsibility for this effort; rather, players to implement the committee's recommendations are to be found at NIH, in the departments of OB/GYN, in other loci in the medical schools, in foundations, and, importantly, in the profession of OB/GYN itself from which must flow the leadership that is a prerequisite to the development of a strong research community in OB/GYN.

REFERENCES

1. Pearse, Warren H., and Graham, Kathleen K. Trends in Obstetric-Gynecologic Academic Manpower and Research. Obstetrics and Gynecology July 1991; 78(1):141–143 .
2. Letters to the committee from chairmen of departments of obstetrics and gynecology.
3. Center for Population Research, National Institute of Child Health and Human Development, Bethesda, Md., Inventory and Analysis of Private Agency Population Research, 1984–1985. June 1988.
4. Longo, Lawrence D. Preparing for the Twenty-first Century in the Reproductive Sciences. Appendix A, this volume.
5. Telephone interview with Thomas H. Meikle, Jr., President, Josiah Macy Jr. Foundation, New York, New York, May 1991.
6. Haseltine, Florence P., and Campbell, Arthur A. The Impact of Fellowships Supported by the Andrew W. Mellon Foundation. Center for Population Research, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Md., March 26, 1986.

7. Longo, Lawrence D. Preparing for the Twenty-First Century in the Reproductive Sciences. Appendix A, this volume.
8. Telephone interviews with Carolyn Makinson. Program Associate for Population, The Andrew W. Melton Foundation, New York, New York, 1990–1991.
9. Institute of Medicine. Funding Health Sciences Research. A Strategy to Restore Balance, ed. Floyd Bloom and Mark Randolph. Washington, D.C.: National Academy Press, 1990.
10. Barinaga, Marcia. The Foundations of Research. Science 1991; 235:1200–1202 .
11. Robert F. Creasy, Professor and Chairman, Department of Obstetrics and Gynecology and Reproductive Sciences, University of Texas Health Sciences Center at Houston, personal communication, July 1990.
12. American College of Obstetricians and Gynecologists. Fellowships and Awards. Wallin, D.C.: American College of Obstetricians and Gynecologists. January, 1991.
13. Longo, Lawrence D. Preparing for the Twenty-First Century in the Reproductive Sciences. Appendix A, this volume.
14. Ibid.
15. Institute of Medicine. Funding Health Sciences Research: A Strategy to Restore Balance, ed. Floyd Bloom and Mark Randolph. Washington, D.C.: National Academy Press, 1990, p. 57 .
16. Kretchmer, Norman. Support of Academic Obstetrics: The Public Sector. In: The Current Status and Future of Academic Obstetrics. Report of a Conference Supported Jointly by the National Institute of Child Health and Human Development and the Josiah Macy, Jr. Foundation. ed. John Z. Bowers and Elizabeth F. Purcell. New York, New York: Josiah Macy Jr. Foundation, 1980.
17. Ibid.
18. Pearse, Warren H., and Graham, Kathleen K. Trends in Obstetric-Gynecologic Academic Manpower and Research. Obstetrics and Gynecology July 1991; 78(1) 141–143 .
19. Walkington, Robert A. National Institutes of Health Support of Research in Departments of Obstetrics and Gynecology. Appendix B, this volume.
20. National Institutes of Health. The K Awards. Division of Research Grants, Bethesda, Md., undated, p. 59 .
21. National Institutes of Health. Clinical Investigator Development Award. NIH Guide July 19, 1991; 20(28):6–10 .
22. Vaitukaitis, Judith L. The Future of Clinical Research. Clinical Research 1991; 39(2):145–1561 .
23. Herman, Samuel S., and Singer, Allen M. Basic Scientists in Clinical Departments of Medical Schools. Clinical Research 1986; 34:149–158 .
24. See, for example, Levin, Sharon, G., and Stephan, Paula E. Age and Research Productivity of Academic Scientists. Research in Higher Education 1989; 30(5):531–549 .
25. Sherman, C. R. et al. On the Status of Medical School Faculty and Clinical Research Manpower: 1968–1998. A report to the Clinical Sciences Panel of the Committee on a Study of National Needs for Biomedical and Behavioral Research Personnel, National Academy of Sciences, National Research Council. NIH Publication No. 82-2458. 1981, Bethesda, Md.: 1981. National Institutes of Health, Office of Program Planning and Evaluation, 1981.
26. National Research Council. Women: Their Underrepresentation and Career Differentials in Science and Engineering: Proceedings of a Conference, ed. Linda S. Dix. Washington, D.C.: National Academy Press, 1987.

27. Zuckerman, H. Persistence and Change in the Careers of Men and Women Scientists and Engineers: A Review of Current Research. In: Dix, L. S. ed., Women: Their Underrepresentation and Career Differentials in Science and Engineering: Proceedings of a Conference. Washington, D.C.: National Academy Press, 1987.
28. Bickel, Janet. Women in Medical Education. A Status Report. New England Journal of Medicine 1988; 319:1579–1584 .
29. Bickel, Janet. Unpublished tabulation from 1989 Medical Student Graduation Questionnaire. Association of American Medical Colleges, Washington, D.C.
30. Bickel, Janet. Women in Medical Education. A Status Report. New England Journal of Medicine 1988; 319:1579–1584 .
31. Ibid.
32. Ibid.
33. Roback, Gene, et al. Physician Characteristics and Distribution in the U.S. Chicago, Illinois: American Medical Association, 1990.
34. National Institutes of Health. DRG Peer Review Trends Workload and Actions of DRG Study Sections, 1980–1990. Bethesda, Md.: Division of Research Grants, p. 81.
35. Pearse, Warren H., and Graham, Kathleen K. Trends in Obstetric-Gynecologic Academic Manpower and Research. Obstetrics and Gynecology 1991; 78(1):141–143 .
36. Gentile, Nancy O., et al. Research Activity of Full-Time Faculty in Departments of Medicine. Washington, D.C.: Association of Professors of Medicine and Association of American Medical Colleges, 1987.
37. Sherman, Charies R. Summary of 1987 NIH and ADAMHA Research Support to U.S. Medical Schools, by Academic Department and Degree of Principal Investigator. Bethesda, Md.: National Institutes of Health, Office of the Director, May 1. 1989.
38. Pearse, Warren H., and Graham, Kathleen K. Trends in Obstetric-Gynecologic Academic Manpower and Research. Obstetrics and Gynecology 1991; 78(1):141–143 .
39. National Institutes of Health. Extramural Trends, FY 1980–1989. Bethesda, Md.: Division of Research Grants, Information Systems Branch, August 1990.

3

CAREER CHOICES

Chapter 2 narrowed the focus of concern from investigative capabilities in general to physician investigators in obstetrics and gynecology (OB/GYN). Basic scientists in OB/GYN departments are heavily involved in research and are quite successful in the competition for research funds, although there are indications of a decline in their success rate toward the end of the 1980s. Physicians are far less involved in research, as might be expected, given their clinical responsibilities. However, the number of physicians who successfully compete for research support is small, as is the number of physicians in the training pipeline who are likely to be able to compete in today's and tomorrow's research environment. There is no denying the importance of basic scientists to the biomedical research endeavor generally, as well as for OB/GYN. Many models can be cited of the relationship between basic and clinical scientists in clinical departments—individuals with complementary expertise who work together synergistically. Such models may include ones in which basic scientists provide the underpinnings on which clinical scientists build, basic scientists bring research expertise to the department that the physician investigators lack, or clinical and basic scientists conduct investigations in the same department but with little or no communication. Moreover, there are physician/scientists whose interest and training have extended so far into basic science that theft work is indistinguishable from the work of the Ph.D. scientist.* Attracting and retaining excellent basic scientists require a clinical department to overcome the fear of the basic scientist that he or she will be considered second-class by his or her

* The importance of the interaction between basic and clinical research in reproductive medicine is stressed in a paper by Lawrence D. Longo, "Fundamental and Clinical Research and Patient Care: A Triad for Progress in Reproductive Medicine," *American Journal of Obstetrics and Gynecology* 1988; 59(1):6–12.

peers. Suggestions for overcoming problems include the creation of joint appointments between basic and clinical departments and tenure-track appointments for basic scientists in clinical departments; there have also been calls for education of basic scientists in pathobiology.[1]

However, since the identified weakness in OB/GYN relates to physician/scientists rather than basic scientists, this chapter focuses on factors related to the decision of physicians to enter and sustain an investigative career in OB/GYN. Many of the problems and barriers confronted by physician/scientists in departments of OB/GYN axe common to most clinical departments—for example, the decision to forgo a higher income in order to focus on research. For these factors, this chapter explores whether there is a quantitative difference between OB/GYN and other specialties. Other factors, such as the impact of federal research policy or NIH structure, are unique to OB/GYN.

CAREER PATHWAYS

The roots of an individual's career choice may be found at an early age, but the question of early science education has wider implications than this study, Similarly, research experiences during medical school are strongly associated with postgraduate research involvement.[2] A group that examined ways of expanding the supply of clinical investigators made the following statement:

> During medical school, the first critical career decisions are made that determine whether an individual may become a clinical investigator. If interest in research is stimulated and sufficiently nurtured in medical school, it is likely that a student will select postgraduate training that is academically oriented and offers the opportunity to continue the research experience.[3]

This committee is convinced that the medical school years are crucial for generating scientific curiosity and the enthusiasm that will carry an individual through training to a career of independent investigation. However, because these years come before the physician chooses a specialty, this report emphasizes them only lightly.

The majority of physicians enter medical education intending to become full-time practitioners. Academia employs only a fraction of physicians, and for those physicians research is often not their primary activity. The expansion in

the number of full-time faculty in clinical departments that has occurred in the past three decades is mainly a response to increased clinical care activities and does not primarily reflect an increasing supply of investigators.[4]

Several factors that are examined in the next section, such as the impact of debt and the duration of training, can affect a physician's decisions at any of the mining points on the career pathway. These factors are often interdependent. For example, an individual's level of debt is likely to have a bearing upon his or her attitude to the difference in income between an academic career and a career in private practice. Indebtedness might also affect the decision to embark on a lengthy training period that postpones the date at which higher incomes can be secured.

DEBT

The extent to which an individual's level of indebtedness at various stages of education plays a role in decisions about the next stage of a career is not made completely clear by available studies. In particular, there is little information on the role of debt in the decision to enter a career in investigation.[*] One pertinent survey of third-year residents, mainly of the medical school class of 1987, showed that 59 percent of residents who had plans for postdoctoral research training indicated that their current levels of debt influenced those plans, "presumably negatively," according to the author.[5] In addition, the impact of debt repayment is felt more strongly later in a career, and additional debt is likely to be incurred.

OB/GYN residents appear to graduate from medical school with somewhat greater debt than other specialists. The average 1989 debt of prospective OB/GYNs ($45,757) was exceeded only by physicians entering emergency medicine ($48,709), physical medicine ($47,792), and surgical subspecialties ($46,162).[6] OB/GYN and emergency medicine had the highest proportion—16 percent—of medical school graduates with debt levels in excess of $75,000, compared with an average of 11 percent for all specialties.[7] In addition, between 1986 and 1989, the average level of debt for those intending to enter

[*] Available evidence deals with the relationship between debt levels and specialty choice, and indicates that only a weak relationship exists. However, much of this work was completed before high levels of debt became common for graduates of medical school; thus the full effect might not yet have been observed (U.S Department of Health and Human Services, *Report to Congress on an Analysis of Financial Disincentives to Career Choices in Health Professions*, Washington, D.C., Health Resources and Services Administration, Bureau of Health Professions, November 1986).

OB/GYN increased 31 percent, compared with an average of 26.5 percent for all medical students.

One indication of the possible impact of indebtedness is the income level needed to repay the debt. Taking into account the repayment schedules of the different types of loans a medical student is likely to use, as well as the definitions formulated by lending agencies of "comfortable" repayment-to-income ratios, a physician owing $50,000 must earn nearly $79,000 per year five years after graduation to comfortably repay the debt; it is "difficult" with an income of only $52,653.[8] For the 16 percent of OB/GYN residents who graduate from medical school with more than $75,000 in debt, clinical practice may look very attractive compared with academia. In 1988, OB/GYNs under the age of 36 had an average net income of $131,500, but nearly $146,000 would be needed to "comfortably" repay a debt of $75,000.[9] ,[10] By contrast, a full-time M.D. instructor earned, on average, $58,100 in 1988–1989 ($68,000 in 1990–1991), and an assistant professor averaged $104,300 ($121,500 in 1990–1991).[11] For the would-be investigator who takes a research fellowship after subspecialty training, income during those years is likely to be well below the $75,000 needed for comfortable repayment of a $50,000 debt. If additional debts are recurred during this subsequent training, they will cause greater repayment difficulties.[*]

Another economic consideration relating to debt is the security of an income stream. The physician entering academia is quite likely to be deterred by the combination of high debt, relatively low income, extended training, and the perception that grant funding and continuing support of untenured junior faculty are uncertain.

It is reasonable to conclude that individuals faced with repaying substantial debt will, in general, gravitate toward employment that provides enough of an income to make repayment less rather than more painful. OB/GYN department chairs and others in the specialty provided many anecdotes of individuals whose ability or willingness to continue on the path of investigation was destroyed by the burden of debt. Given the relatively small number of people with the perseverance, intellectual curiosity, and talent needed for investigation, the effect

[*] This point was emphatically made in a letter received by the committee: "Another issue which raises its head is the necessity for [research trainees] to take out loans during this period of training. One of our current fellows who has just completed training has loam outstanding of approximately $140,000. With the reality that sub-specialists are commanding salaries in execs of $150,000 per year in the private practice arena, and frequently realize multiples of that of two or three fold, it is difficult for one to accept further funding at $40,000 per year when they consider their outstanding loans and commitment to their families."

is significant when even a few of those with the necessary qualifies are deterred from research by the burden of debt. It is particularly disturbing if such debt results in the loss of one of the few OB/GYNs who have already accomplished research training.

Mechanisms that provide relief of debt—usually either forgiveness or repayment deferral—are well established as ways of diminishing economic barriers to entry into a field or of encouraging new entrants. The conviction that an economic incentive would help stimulate investigation in contraception and infertility lies behind a proposal in the current NIH reauthorization that would repay $20,000 of the educational loans of a professional for each year that he or she agrees to conduct research with respect to contraception or infertility. Forgiveness mechanisms can also be designed with payback requirements to prevent abuse and to increase retention in research. For example, the Public Health Service offers National Research Service Awards (NRSAs) that axe repaid by research or teaching for a time equal to the duration of NRSA support minus 12 months.[12]

FINDINGS: Debt, when viewed in the context of the accumulated weight of the many other deterrents to an investigative career, does result in the loss of talented individuals to the pool of OB/GYN investigators. The anecdotal evidence, their own experience, and data on specialty choice and debt repayment burdens, together with the very small number of OB/GYN physicians in the research training pipeline, convinced committee members that there is a need for a program that would decrease the deterrent effect of debt repayment. In the current funding climate, however, it is unrealistic to expect the public sector to be solely responsible for the costs of a program to provide debt relief for investigators in OB/GYN. The beneficiaries of strong research capability include not only the public but also the academic departments, the profession of OB/GYN, and the pharmaceutical industry. All of these entities should therefore participate in supporting a program to reduce the debt burden for young investigators. To ensure cost-effective use of resources, such a program should be restricted to young investigators of proven talent and should include mechanisms to ensure that recipients at least attempt to make a significant scientific contribution.

RECOMMENDATION: The committee recommends that a program to alleviate the burden of debt (e.g., loan forgiveness, deferral of repayment,

targeted fellowships or awards that eliminate the need to incur further debt, etc.) be established for physicians qualified in the specialty of OB/GYN who have demonstrated a serious intention to pursue a career in research. Since this program is targeted to only the few most promising individuals, its costs will not be great and should be borne by a consortium of OB/GYN professional associations, the pharmaceutical industry, academic departments of OB/GYN, and the Public Health Service. The program should be structured to identify the most promising individuals in need of assistance and should include mechanisms to encourage retention in research of individuals assisted by the program.

FOREGONE EARNINGS

For most physicians, the decision to pursue an academic or investigative career means that their income will be substantially below that earned in clinical practice. It is often claimed that it is particularly difficult to attract physicians into academic positions in OB/GYN because, as a relatively high-earning specialty, the difference between academic income and alternative earnings is greater than the difference that occurs for other specialties. Data do not support this contention, although they do confirm the existence of an income gap between academia and other forms of physician activity (Table 3-1).* Young physicians from OB/GYN, internal medicine, and surgery who enter academia earn only approximately 80 percent of the income earned by all physicians in those specialties. The size of the income gap is different at various ages, but for OB/GYN, internal medicine, surgery, and radiology, academic earnings are between 53 percent and 90 percent of the specialty earnings up to age 65. Of the six specialties for which data were available, psychiatry and pediatrics do not show a consistent earnings deficit for those physicians who enter academia. In sum, the income deficit for OB/GYNs is as great as but no greater than that experienced by other specialties, although the gap may nevertheless deter talented individuals from an academic research career.

* The income differential between practice and academia is likely to be larger for subspecialists than for generalist OB/GYNs.

TABLE 3-1: Percentage of Net Income of Academics in Relation to That of All Physicians in the Specialty

	Age				
	< 36	36–45	46–55	56–65	> 65
OB/GYN	80 %	53 %	70 %	87 %	N/A
Internal Medicine	80	63	71	85	132 %
Psychiatry	N/A	87	104	125	111
Surgery	80	57	73	89	145
Pediatrics	114	79	83	102	N/A
Radiology	90	66	69	77	N/A

SOURCES: Calculated from data in *Socioeconomic Characteristics of Medical Practice, 1989*, ed. Martin L. Gonzales and David W. Emmons, American Medical Association, Chicago, Ill.; William C. Smith, Jr., *Report on Medical School Faculty Salaries, 1988–89*, Association of American Medical Colleges, Washington, D.C.; and special tabulation of data from the Faculty Roster System of the Association of American Medical Colleges prepared by Paul J. Friedman, M.D., Professor of Radiology and De, an for Academic Affairs, University of California, San Diego.

Assuming some parallel between the choice of a specialty and the choice of a career in research, evidence on the role of expected income in a physician's choice of specialty may be viewed as surrogate data. Surveys of graduating medical school students and some econometric analyses generally indicate that future income is not an important factor in specialty choice.[13] ,[14] But one study found a correlation between the median net income of a specialty and the proportion of residency positions filled by U.S. medical school graduates.[15] Another, using a sophisticated econometric analysis, found that the effect of potential income differs for female and male physicians—in general, the higher the potential income, the higher the probability of selecting the specialty; but the choices of female physicians axe inversely related to potential income. This does not mean that women physicians are averse to money, but that there may be other factors associated with lower-paying specialties that axe of greater interest to women than foregone income.[16]

This latter finding implies that OB/GYN, in which more than 45 percent of residents in 1989 were women,[17] has a substantial pool of individuals for whom nonfinancial factors may be of prime importance. If the imagination of this group can be captured by the excitement of research, and if research offers

the job conditions they consider important (which might include such characteristics as flexible scheduling), the income differential between research and practice might be less problematical for OB/GYN than for specialties in which women play a lesser role.

Moving from quantifiable to anecdotal evidence, a much clearer picture emerges. Many academician believe that the extended training of the M.D. investigator, during which incomes are relatively meager,[*] together with the large incomes that can be earned in clinical practice in OB/GYN, make even the generous offerings of academia seem paltry. The *average* salary of a full-time assistant professor in a department of OB/GYN was $125,500 in 1990.[18] However, department chairs attempting to hire newly qualified subspecialists believe that an *initial* salary of at least $150,000 is needed to lure promising investigators to academia.[**] Although individuals with an academic or investigative bent find professional rewards in teaching, research, or academic administration that counterbalance financial sacrifice, it is clearly unrealistic to expect too large a sacrifice.

FINDINGS: OB/GYN, like other clinical departments, loses investigators because of the discrepancy between practice and academic income. There is little appreciable difference in foregone income between OB/GYN and the other specialties for which data were available. Since the specialty choices of female physicians are driven less by income considerations than by other factors, the high proportion of women in OB/GYN may work to the advantage of the field. But to realize this advantage, departments must,identify the characteristics of an academic and research life that are attractive to women and offer choices that fulfill the lifestyle needs of women.

[*] Recognizing the impact of meager stipends on the willingness of individuals to undertake research training, a 1989 task force that evaluated NIH biomedical research training programs proposed that trainee stipends be increased to levels comparable to those of house staff salaries ("Review of the National Institutes of Health Biomedical Research Training Programs, October 1989"; National Institutes of Health). NIH is expected to implement this recommendation in the near future.

[**] An additional problem noted by OB/GYN department chairs is that the salaries paid to faculty are so far in excess of the salary support of research grants that significant additional amounts must be found, which usually requires that the faculty member devote substantial time to clinical practice. This issue is discussed more fully later in this chapter. Committee members also noted that the higher salaries paid to M.D.s can alienate Ph.D.s, making it difficult to generate and maintain a creative training and working environment.

RECOMMENDATION: Leaders in departments of OB/GYN should accommodate the nonfinancial working needs of investigators to facilitate and ensure their continued involvement in research.

DURATION OF TRAINING

The effects of debt and foregone income are likely to interact with a third factor—length of training. Compensation for "trainees," whether as grants, fellowships, or salaries, is generally lower than for fully qualified individuals; therefore the amount of income foregone increases with the duration of training. If compensation is low enough, new debts may be incurred, particularly if family obligations grow as a physician/trainee marries and has children. Increases in the length of training thus have substantial financial implications that can influence career decisions.

The concept of a physician/scientist conducting research at the bedside to evaluate the effect of a new procedure or drug is still valid today. However, advances in molecular biology and the increasing convergence of basic and clinical research have changed the nature of much research conducted by physicians and expanded its range. James Wyngaarden, in aa article entitled "The Clinical Investigator as an Endangered Species," defined the physician/scientist in terms of both training and activity:

> An individual thoroughly trained in clinical medicine and also thoroughly trained in a scientific discipline, and who, in addition, participates in both clinical and experimental endeavors as a career role. Thus, I refer to the physician who is simultaneously a serious scientist, and far less to the clinician who may occasionally do some research.[19]

This description is sufficiently broad to encompass physicians engaged in a wide spectrum of investigational activities, and it certainly fits the physician/scientist who is the focus of this report.

Although the duration of training needed to fulfill various roles has not been specified, there is a strong relationship between the duration of postdoctoral training and later success in the competition for NIH support.[20] This may be due in part to self-selection (those with greater commitment to research are likely to invest in longer training) and in part to the expertise gained during the

extended training. Regardless of the reason, the finding speaks to a greater return on an investment in training if individuals commit to longer periods.

There is little agreement on the best way to tram physician/scientists. Some believe that M.D./Ph.D. programs are the optimal approach, while others debate the timing of science and clinical components. Several models exist, most of which include a concentrated involvement in research for at least two years, supervision by an experienced research mentor, presence in an active laboratory, and resources for each support.[21]

Physicians who have completed clinical training—whether they have earned the M.D. degree or completed specialty or subspecialty training—are not prepared to enter a career in which investigation will be a major activity. They are not equipped with the methodological tools to conceptualize and design sound research protocols. Nor do they have sufficient basic science knowledge and training at the bench to undertake investigation in, for example, the molecular aspects of biology—if that is where their interests lie. Residency and subspecialty programs often encourage or require courses in statistics and the conduct and publication of a research project. A physician who has maximized such opportunities may be sufficiently prepared to undertake some uncomplicated clinical research, but there is general agreement that substantial additional training is needed to embark on an investigative career.[*]

Specialty and Subspecialty Training in OB/GYN

The conventional training path for an individual who intends to enter academia in OB/GYN starts with residency, which requires four years in a graduate medical education program that has been accredited by the Accreditation Council for Graduate Medical Education. Only 36 months must be spent in clinical OB/GYN, but in practice, the complete period is spent in clinical education. Certain regulations controlling the residency experience make it difficult for a resident to participate in research training: no assignment to another discipline that removes the candidate from daily contact with OB/GYN

[*] This statement should not be taken to imply that physicians reach residency or subspecialty fellowships without any research experience. Opportunities to at least initiate research training occur at early stages. Funded research opportunities of three months or longer are often available for medical students, and one study found that research experience varied by school with between 28 percent and 85 percent of students reporting research experience at the schools studied (Scott Segal et al., "The Association Between Students' Research Involvement in Medical School and Their Postgraduate Medical Activities," *Academic Medicine* 1990; 65:530–533).

is allowed, and no more than six weeks' leave of absence may be taken in any one year.[22] These rules make it impossible for an individual to undertake extended research training. However, approximately two years ago an element of flexibility was introduced whereby the American Board of Obstetrics and Gynecology, Inc. (the organization that controls the specialty certification examination and eligibility processes), allows "modification of training to accommodate research for individuals preparing for academic careers."[23] This modification is granted on an individual basis and requires an application to the board from the individual and his or her program director before the residency starts.

Specialty certification is followed by at least two and sometimes three years of subspecialty fellowship,"[*] and at least one year of practice as a subspecialist. The board established three specialty divisions in 1972: gynecologic oncology, reproductive endocrinology, and maternal fetal medicine, each with formalized advanced training. The purposes were to "improve the health care of women with special problems by: (1) elevating standards of education, (2) enhancing the recruitment of qualified physicians, (3) improving the organization and distribution of patient care, and (4) increasing basic knowledge."[24] Although the extra years of subspecialty training may not be needed if an individual intends to pursue a career in research, the uncertainties of such a career cause many to believe that the physician must be fully qualified for a career in clinical practice. Academic departments and hospitals also often require subspecialty certification. In the past four years, the number of certified subspecialists who are full-time faculty has risen by 28 percent (160 individuals), and 109 schools have all three subspecialties represented on their faculties (only 5 schools have none).[25]

It is somewhat easier to fold research training into the subspecialty fellowship period than into residency—indeed, the fellowship requires that a thesis be accepted for publication in a peer reviewed journal. The third year of a three-year program concentrates on developing research skills. Only 10 of the 154 subspecialty programs are official (board-approved) three-year programs, but numerous additional programs require a three-year commitment.[26] Anecdotes suggest that some programs, particularly in reproductive

[*] The committee is aware of at least one four-year fellowship program. The Division of Gynecologic Oncology at the University of California, Irvine, offers two years of research training in a basic science laboratory, either inside or outside the department (previous experience with only one year of basic research having led to the conclusion that a minimum of two years is needed). This is followed by the two-year clinical fellowship.

endocrinology, have a heavy research orientation, offering about 18 months of laboratory experience. As with the residency program, subspecialty training can be modified to accommodate individuals who are preparing for an academic career, provided a request is made before starting the program. Since only one such application has been received by the board,[27] several conclusions are possible: that program directors have difficulty identifying prospective candidates before the start of the program, that there is no demand for the modification, or that the requirement for individual application is so cumbersome that it acts as a deterrent.

Despite the apparent emphasis on research during the fellowship years, the experience of committee members and others suggests that two to three years of additional intensive research training is usually needed, both as preparation for a research career and to become competitive with others seeking RO1 support.[*] An exception to the academic's need for extensive research training would occur for individuals whose principal occupations would be clinical practice and teaching, with only a minor involvement in the conduct of bedside clinical research.

In a presentation to the committee, the president of the American Board of OB/GYN emphasized that the encouragement of research is not included in the stated objectives and purposes of the board. Nevertheless, because program directors have urged flexibility that would allow research training to be interleaved with clinical training, the board allows exceptions to be made on an individual basis for those who want to incorporate research training into their education.[28]

Calls for greater flexibility have been heard for many years. In 1985 a symposium on the need for flexibility in academic OB/GYN residencies was held at the annual meeting of the American Gynecological and Obstetrical Society. Speakers reviewed past recommendations to allow several types of residency experiences to prepare OB/GYNs for several types of careers, including academia and research.[29] Other speakers reviewed the obstacles to the pursuit of research, including a lack of exposure to research during residency, the additional time required to satisfy subspecialty requirements and engage in research training, and the difficulty in keeping current in and excited

[*] The extensive clinical requirements of subspecialty fellowships are cited by Robert B. Jaffe in "The Need for Flexibility in Preparing Clinician/Scientists for Academic Careers," *American Journal of Obstetrics and Gynecology* [April 1986; 154(4):778–790], as making it difficult to free up time for research. He notes the need of reproductive endocrinologists to gain expertise in tubal microsurgery and in vitro fertilization as examples of such time-consuming activities.

about investigation during the long period of clinical education.[30] ,[31] The problem, according to the speakers, was that the burden of attaining high levels of expertise in both research and clinical care may be excessive; would it not be possible, they asked, to accept a narrower clinical competence for the limited number of people who will make research the primary focus of theft professional lives? The same problems are present today, and there is still no consensus on the "best" configuration of clinical and research training for an individual who is proceeding on the path to an academic research career. What is clear, however, is that the educational pathway defined by the board and the Residency Review Committee[*] discourages a smooth merging of residency and the subspecialty fellowship with the research training needed to achieve independent investigator status.

Fast-Track Training for Researchers in Other Specialties

It may be six to seven years after medical school before a would-be OB/GYN investigator starts intensive research training, and me to ten years before she or he is prepared to begin a career as an investigator. It is easy to believe that this lengthy process is a deterrent, both emotionally and financially. Many experts in other specialties believe that training should be shorter, and some specialty boards have instituted accelerated, or flexible, pathways for use by those entering research. For example, the American Board of Internal Medicine (ABIM) developed a Clinical Investigator Pathway as a response to national concern about a shortage of clinical investigators. The goal is to ease entry into research by permitting the trainee to return to the laboratory any time after finishing medical school, to become certified in internal medicine after only two years of residency training, and to be examined for board certification with his or her medical school graduation cohort. The trainee is then able to proceed into subspecialty training and research.[32] A subspecialty examination can be taken six or seven years after medical school graduation, by which time a

[*] The Residency Review Committee accredits residency programs for a specified number of residents for each postgraduate year. Thus a program must get permission for a resident who has left the program for research training to rejoin it at a later date, because a program that has filled its residency slots will then have an excess when the individual returns. Moreover, in general, residency programs are not allowed simultaneously to run programs of different lengths—for example, offer a four-year and a five-year program that allows a year of research. To do this, a program must receive permission from the Residency Review Committee.

candidate must have completed three years of full-time (at least 80 percent) research.[33] An early (second year of residency) commitment by the program director of a faculty position or salary for the trainee is intended to ensure that only motivated and potentially talented residents are offered the special pathway.

The history of attempts by ABIM to arrive at this pathway for clinical investigators indicates the difficulties in structuring an accelerated path that meets the goals of flexibility in the timing of clinical and research training, and reduction of the total training time. Earlier, ABIM instituted a "short track" that was intended to shorten the time to entry into subspecialty training. This track reduced residency time but lacked the current requirement that the saved time be spent in research. It was discontinued because it was used as a short-cut into subspecialty training by individuals who had no retention of entering into a career in clinical investigation.

Another example, both of an effort to encourage research through a reduction of training time and of problems encountered on the way to achieving a workable program, is found in pediatrics. The American Board of Pediatrics (ABP) in 1978 established a Special Alternative Pathway for candidates who were directing their career toward academic medicine. The pathway cut a year from the training period for initial certification. As in internal medicine, however, the accelerated route was used by too many candidates who did not enter academia, and ABP is therefore considering its discontinuation.[34] Because the ABP conceives of the generalist pediatrician as taking car of most clinical pediatric practice and of pediatric subspecialists as being academicians, it has extended subspecialty training from two to three years and added a research competency training requirement. There is today a "fast track" for candidates for subspecialty training who have demonstrated research competence, such as those with an M.D./Ph.D. This allows the candidate to eliminate up to one year of training and to waive the subspecialty research competency requirement.[35] While pediatrics and internal medicine differ from OB/GYN in important ways—for example, the need to develop and maintain surgical skills makes it more difficult for OB/GYN to mesh clinical and research training—there are lessons to be learned from the search for ways to diminish the deterrent of excessively extended training.

FINDINGS: The extended duration of training for a physician investigator in OB/GYN has a deterrent effect on some who would otherwise pursue a research career. The American Board of OB/GYN now allows individuals to apply for a waiver in the training; however, to date there have been few

applications for waivers. Some specialty boards have established special pathways for investigators—evidence that they believe that benefit is derived from abbreviating clinical training for physician investigators.

Committee members agreed that much of the education of a generalist OB/GYN is wasted when an individual selects a subspecialty; for instance, the OB/GYN oncologist neither delivers babies nor uses the reproductive endocrinology or genetics training that was required during residency. One alternative would be an academic track by which aa individual could select a subspecialty and research pathway after two years of residency, while others intending to enter general OB/GYN practice would continue through the third and fourth years of residency training. Numerous letters from chairs of departments of OB/GYN supported a reduction in training time through such means as creating a separate track for would-be investigators, reinforcing the perception that many in academia would support such reform.

RECOMMENDATION: The committee recommends that the American Board of Obstetrics and Gynecology immediately reexamine training requirements for generalists and subspecialists in OB/GYN to ascertain whet the training programs are unnecessarily long. A reduction in the time needed to obtain subspecialist status would allow those interested in pursuing a career in research and academic OB/GYN to achieve their goal more quickly than is possible today. The committee suggests consideration of a pathway that offers the option of moving to subspecialty fellowships after two years of residency. The committee also suggests that the American Board of OB/GYN carefully examine and evaluate the arrangements that other specialty boards have made to accelerate training for those with a clear intention of embarking on a career in research. These arrangements are examples of options that should be considered.

WOMEN AND RESEARCH

Women have a substantial representation in academic departments of OB/GYN—particularly at lower academic levels—but in general, they have a lesser propensity than men to enter research. This is likely to increase the shortage of research personnel unless special efforts are made to encourage research careers for women and to meet their particular needs.

Factors that encourage young physicians to pursue investigation as a career include early involvement in research, role models, an environment that contains other active investigators, and the support of mentors who facilitate socialization into research. These influences are needed regardless of gender, but some are difficult for women to attain, and there may be other aspects of the researcher's life that demand attention if more young women are to become engaged in a life of investigation.*

Studies of stress among residents do not speak directly to the question of whether lifestyle conflicts deter women from res h careers. These studies do, however, suggest that there are critical stages in the development of a research career at which the path of women could be eased. One study found a correlation between residents' level of dissatisfaction and the hours worked outside the home by the spouse. This problem is likely to be more severe for women since male spouses often put in more time outside the home than female spouses. Women residents also spent substantially more time than male residents on household chores. Furthermore, many institutions lack formal mechanisms for handling the pregnancies of residents (only 57 percent of teaching hospitals have maternity leave policies), and this, too, can lead to disruption and stress.[36] There is evidence that women in medicine feel that they must delay childbearing: 45 percent of respondents to a 1988 survey of women faculty in departments of medicine had theft first child after completing training. If childbearing is delayed, however, the demands of young children must be accommodated in the early phases of the academic career—years when tenure decisions axe made and when faculty members are under pressure to conduct productive research and publish their results.[37] Although several researchers have reported that family responsibilities do not consistently reduce the publication rates and salaries of women scientists and engineers, data also suggest that assistance with family responsibilities, such as providing child care, helps women sustain full-time employment.[38]

Some institutions have initiated policies that effectively stop the tenure clock for a limited period. Such policies can provide women, and others who need to spend time at home with children, relief from some of the pressures of trying to excel in the home and in professional settings. For example, Yale University School of Medicine allows faculty with "pressing personal or professional commitments" to take a part-time appointment. The faculty member who

* A similar quandary has been identified in pediatrics where women constitute 43 percent of instructor- and assistant professor-level faculty [H. T. Abelson and Anne Bowden Raleigh, "Women and the Future of Academic Pediatrics," *Journal of Pediatrics* 1990; 16(5):829–833].

chooses this route is allowed up to three additional years to achieve tenure, but is warned in the information guide of the school that laboratory experiments and patient care demands, as well as week-end and night call schedules, can cause conflicts with a "part-time" schedule.[39]

Studies of science and engineering students point to the isolation felt by women (and minorities)in science. Surveys reveal that women feel frustrated and discouraged, while men are more likely to report anger. Women report feelings of powerlessness, pressure, and isolation; their self-esteem is often lower than that of men of equal or lesser attainment. Women also report that they are not well integrated into student networks that disseminate important information.[40] This can be particularly harmful if women fail to get information about training and funding mechanisms, or about what is needed to progress in academia. [*] To offset this isolation, women faculty have organized networks that are believed to be effective. For example, at the University of Michigan, women faculty formed a supportive group and established a Women in Science Program whose activities include publishing a resource directory and running a speaker's bureau.[41]

Part of the sense of isolation may come from a lack of women role models and mentors. The data reviewed in Chapter 2 indicate that even in departments of OB/GYN, which have relatively large numbers of women, women are not well represented at higher faculty levels. Thus young women faculty in OB/GYN lack role models and mentors of their own gender. The importance of mentors has been documented for students at many levels of education; for successful careers in science; for sponsorship for faculty positions in academia; for promotion, tenure, fellowships, and grants; and for, successful careers in business. Whether women do better with mentors of the same gender is not established. However, according to one report, women students who chose women role models looked for "the exemplification of a career woman's total lifestyle"; men in the same situation looked for role models with outstanding reputations.[42] A survey of women with full-time appointments in academic departments of internal medicine revealed that 94 percent agreed that women medical students need role models of successful, tenured women faculty.43 The encouragement, support, and advocacy of a mentor will undoubtedly be

[*] Informal conversations with individuals interested in the progress of women in academia suggest that women are likely to be. come sidetracked by clinical care and teaching during the early faculty years, and are not well informed about the credentials needed to achieve tenure. This latter factor may contribute to the clustering of women in low academic positions; it also speaks to the need for mentoring.

enhanced if that individual has experienced and dealt with the family and time pressures and professional isolation of a woman in science. Young women also need role models who demonstrate that the demands of an investigative career are not incompatible with family life, that women can overcome the hurdles and establish successful investigative careers. It seems likely that a same-gender mentor could provide needed encouragement and sustained support that would help women overcome some of the inherent disadvantages they confront in pursuit of a career in science.

FINDINGS: It is vital for the health of the OB/GYN research enterprise that women not be lost to research because of obstacles that can be overcome by the profession. Women are entering OB/GYN in substantial numbers and now represent nearly half of all OB/GYN residents. Although women may be less deterred than men by the difference in income between academia and practice, women attempting a career in research are confronted with gender-related obstacles. These include the absence of same-gender mentors and role models. In addition, women appear to lack ace to the networks through which important information regarding academic advancement is transmitted. Some of these obstacles can be ameliorated by actions within the scope of departmental leaders.

RECOMMENDATIONS: The committee recommends that OB/GYN department leaders pursue ways to ameliorate the stresses that attend the life of women in science. In particular, the committee recommends that every effort be made to find women mentors and role models for women investigators, if not in the department of OB/GYN, then through networks of women physician investigators, across departmental lines, or at another medical school. Departmental leadership should emphasize the value it places on women accepting mentoring relationships with young women investigators. This should not, however, preclude mentoring relationships between men and women, which the committee also considers to be of major importance. **The committee also recommends that department chairs, in institutions in which no provisions exist for extending time to tenure for individuals with pressing personal commitments, engage the institution's decision-making groups in an effort to initiate such a policy.**

SUMMARY OF CAREER CHOICE FACTORS

Every individual who chooses to enter an academic investigative career engages in a number of trade-offs. On the positive side are the attractions of the intellectual stimulation of the academic environment, the excitement of research, and the status conferred by membership in the select club of higher education faculty. Additional benefits may include decreased clinical responsibilities and the rewards of teaching, as well as other factors. On the negative side are financial sacrifices that include lower earnings, greater difficulty in repaying debt, and greater insecurity owing to the uncertainty of grant funding and departmental support in the pretenure years. Another negative, which also involves financial loss, is the extended duration of training as an individual moves through residency, subspecialty training, and research training.

These factors apply to those in academic research careers, regardless of specialty. However, OB/GYN appears to be at a disadvantage in comparison with other specialties. Graduates of medical school who intend to enter OB/GYN have relatively high levels of debt (although they do not forgo any more income by entering academia than do internists, radiologists, or surgeons). However, OB/GYNs undergo an extended period of education and are generally unable to combine research training with clinical training, unlike some other specialties whose boards have developed "fast tracks" or flexible arrangements for investigators.

Finally, the high participation of women in OB/GYN can work both for and against the future supply of investigators. On the one hand, women physicians have been more willing than men to forgo income in order to gain some other desired end. On the other hand, women have entered science at lower rates than have men, and they have been less productive (in terms of publications) once the commitment was made. These differences may be due in part to the stresses of family life—in particular, responsibilities for childbearing and child care—that fall on their shoulders, and in part to a dearth of women role models and mentors, who could play an important role in the development and career trajectories of women physician investigators.

In sum, OB/GYN is not especially disadvantaged in the income differential between practice and further training, in the burden of debt repayment, or in the duration of training. Nor is the risk of failure for an OB/GYN investigator substantially greater than for other specialties. However, the weight of each of these factors together is likely to discourage some talented physicians from pursuing a research career unless they are cushioned from these obstacles by sustained support. **The committee believes that it is vitally important that**

individuals with the talent and inclination for research are identified early and that obstacles to their growth as investigators are diminished.

Recommendations throughout this report are intended to facilitate the recruitment and retention of investigators in OB/GYN.

REFERENCES

1. Arias, Irwin M. Training Basic Scientists to Bridge the Gap Between Basic Science and its Application to Human Disease. Sounding Board. New England Journal of Medicine 1989; 321(14):972–974 .
2. Segal, Scott, et al. The Association Between Students" Research Involvement in Medical School and Their Postgraduate Medical Activities. Academic Medicine 1990; 65(8):530–533 .
3. Association of American Medical Colleges. Clinical Research Manpower. The Report of the *Ad Hoc* Committee on Clinical Research Training. Washington, D.C.: Association of American Medical Colleges, February 1980.
4. National Research Council, in collaboration with the Institute of Medicine. Biomedical and Behavioral Research Scientists: Their Training and Supply. Vol. 1 : Findings. Committee on Biomedical and Behavioral Research Personnel. Washington, D.C.: National Academy Press , 1989.
5. Petersdorf, Robert G. Financing Medical Education. Special Article. Academic Medicine 1991; 666(2):61–65 .
6. Park, Randolph. AAMC Data Report. Graduating Medical Student's Debt and Specialty Choices. Academic Medicine 1990; 65 (7):485–486 .
7. Tabulation from the Association of American Medical College's 1989 Graduation Questionnaire.
8. Petersdorf, Robert G. Financing Medical Education. Special Article. Academic Medicine 1991; 66 (2):61–65 .
9. Ibid.
10. Smith, William C., Jr. Report on Medical School Faculty Salaries, 1988–89. Washington, D.C.: Association of American Medical Colleges, 1989.
11. Ibid.
12. National Institutes of Health. National Research Service Awards for Senior Fellows. Information Statement. Bethesda, Md., April 1989.
13. Association of American Medical Colleges. 1988 Graduation Questionnaire Results. Washington, D.C.
14. Yoder, Sunny G. The Influence of Economic Factors on Medical Students' Career Decisions. In: Medical Education and Societal Needs: A Planning Report for the Health Professions. Washington D.C.: Institute of Medicine; 1983.
15. Ebell, Mark H. Choice of Specialty: It's Money that Matters in the USA. Journal of The American Medical Association 1989; 262(12): 1630–1631 .
16. Marder, William D., et al. Physician Supply and Utilization by Specialty: Trends and Projections. AMA Center for Health Policy Research. Chicago, Ill. American Medical Association, 1988, pp. 84–86 .

17. Jolly, Paul, and Hudely, Dorothea M. AAMC Data Book. Statistical Information Related W Medical Education. Washington, D.C.: Association of American Medical Colleges, January 1991.
18. Association of American Medical Colleges. Report on Medical School Faculty Salaries 1990–1991. Section for Operational Studies. Washington, D.C.: Association of American Medical Colleges.
19. Wyngaarden, James B. The Clinical Investigator as an Endangered Species. Bulletin of the New York Academy of Medicine 1981; 57(6):415–426 .
20. Task Forces for Review of the NIH Biomedical Research Training Program. Review of the National Institutes of Health Biomedical Research Training Programs. Bethesda, Md.: National Institutes of Health, October 1989.
21. American Psychiatric Press. Training Psychiatrists for the 90s: Issues and Recommendations, ed. Carol C. Nadelson and Carolyn B. Robinawitz. Washington, D.C.: American Psychiatric Press, Inc. 1987.
22. American Board of Obstetrics and Gynecology. Bulletin for 1991. Seattle Washington: American Board of Obstetrics and Gynecology, Inc.
23. Ibid.
24. Merrill, James A. (Sub)Specialization in Obstetrics and Gynecology: Results of a Survey by the American Board of Obstetrics and Gynecology. American Journal of Obstetrics and Gynecology 1987; 156(3):550–557 .
25. Pearse, Warren H., and Graham, Kathleen K. Trends in Obstetrics-Gynecologic Academic Manpower and Research. Obstetrics and Gynecology 1991; 78(1):141–143 .
26. Telephone interview with staff American Board of Obstetrics and Gynecology, Subspecialty Division, July 1991.
27. Mishell, Daniel R., Jr., Chairman American Board of Obstetrics and Gynecology. Presentation to the IOM Committee on Research Capabilities of Academic Departments of Obstetrics and Gynecology. November 1990.
28. Mishell, Daniel R., Jr., President, American Board of Obstetrics and Gynecology. Presentation to the IOM Committee on Research Capabilities of Academic Departments of Obstetrics and Gynecology. November 1990.
29. Willson, Robert J. Flexibility in Obstetric-Gynecologic Residencies: Why Is It Necessary? American Journal of Obstetrics and Gynecology 1986; 154(4):777–778 .
30. Jaffe, Robert B. The Need for Flexibility in Preparing Clinician Scientists for Academic Careers. American Journal of Obstetrics and Gynecology 1986; 154(4):778–780 .
31. Hendrick, Charles H. Experience with Flexibility in an Academic Residency Program. American Journal of Obstetrics and Gynecology 1986; 154(4):780–785 .
32. John A. Benson Jr., President, American Board of Internal Medicine, personal communication, July 1990.
33. American Board of Internal Medicine. Clinical Investigator Pathway. Portland, OR: American Board of Internal Medicine, 1990.
34. Thomas K. Oliver, Senior Vice President, American Board of Pediatrics, personal communication, July 1990.
35. American Board of Pediatrics. Certification in Pediatric: Cardiology, Chapel Hill, N.C.: American Board of Pediatrics, November 1989.
36. Cited in Bickel, Janet. Women in Medical Education. A Status Report . New England Journal of Medicine 1988; 319:1579–1584 .
37. Levinson, Wendy, Tolle, Susan W., and Lewis, Charles. Women in Academic Medicine: Combining Career and Family. New England Journal of Medicine 1989; 321:1511–1517 .

38. Committee on Women in Science and Engineering. Women in Science and Engineering: Increasing Their Numbers in the 1990s. A Statement on Policy and Strategy. Office of Scientific and Engineering Personnel, National Research Council. Washington, D.C.: National Academy Press, 1991, p. 59 ,
39. Yale University School of Medicine. Information Guide for Junior Faculty. Published under the auspices of the Office of the Deputy Dean, New Haven, Conn. April 1990. pp. 13–14 .
40. Widnall, Sheila E. AAAS Presidential Lecture: Voices from the Pipeline. Science 1988; 241:1740–1745 .
41. Committee on Women in Science and Engineering. Women in Science and Engineering: Increasing Their Numbers in the 1990s. A Statement on Policy and Strategy. Office of Scientific and Engineering Personnel, National Research Council. Washington, D.C.: National Academy Press, 1991. p. 63 .
42. Erkut, Sumru, and Janice R. Mokros. Professors as Models and Mentors for College Students. American Educational Research Journal 1984; 21(2):399–417 .
43. Combining Career and Family. New England Journal of Medicine 1989; 321:1511–1517 .

4

NIH POLICIES AND STRUCTURE

Reproductive researchers and investigators in academic departments of obstetrics and gynecology (OB/GYN) have long felt themselves to be the neglected stepchildren of the National Institutes of Health (NIH). The complaints axe numerous: not only do they lack their own institute, but they axe poorly represented among NIH staff and are absent from the intramural program. Furthermore, several major areas of OB/GYN interest, including fetal research, cannot currently receive federal funding. In addition, it is said, OB/GYN as a clinical discipline suffers the same difficulties in garnering NIH funds that are experienced by all clinical investigators, including review by study sections on which basic scientists outnumber clinical scientists. However, there is also a belief that OB/GYN is particularly underrepresented.

This chapter addresses two questions: whether the complaints are valid, and if so, whether these factors have an impact on the support of research in departments of OB/GYN. There is no rigorous way to test the hypothesis that the factors believed to create difficulties for OB/GYN research in fact do so. Problems in attempting to study the impact of these factors include the large number of variables that would need to be controlled if one was to compare one field of science with another. TherefOre the discussion and findings of this chapter are based on the few available systematic reviews, on interviews with individuals at NIH and in departments of OB/GYN, and on the expertise and judgment of committee members.

ABSENCE OF OB/GYN IN THE NIH INTRAMURAL PROGRAM

The NIH intramural program, located mainly on the NIH campus in Bethesda, Maryland, absorbs roughly 11 percent of total NIH funds. However, the importance of the intramural program is not in its size. A 1988 study by the Institute of Medicine (IOM) described the intramural program as having multiple

roles in support of the NIH mission. While none of the roles or elements of the program is unique, the aggregate—comprising research laboratories, a clinical center, freedom from the competition for grants, a large group of scientists working together on a campus that provides opportunities for collaboration and interchange, a site for research training—creates a distinctive research environment.[1] Over the years, the intramural program has made large contributions to basic and clinical research, as well as providing training for some of the nation's most distinguished biomedical scientists. A 1969 review of its purposes and objectives noted its contribution to the overall NIH mission by providing "comprehensiveness of approach, scientific guidance, prestige and an unequalled opportunity for the development of future leaders."[2] But these purposes and accomplishments do not completely illustrate why it is important for a discipline to be represented in the intramural program. To answer that question, one must look at some of the tangible and intangible elements in the relationship between the intramural and extramural programs, and at some of the notions about the intramural program that prevail among NIH staff.

Despite the fact that the administration of extramural grants is kept at arm' s length from the rest of NIH, there is a widely held belief that the coexistence of the two programs, intramural and extramural, at the same location and under the same overall control is vitally important.[3] Some commentators cite the benefit that when intramural scientists are ready to leave the laboratory, a few transfer to the extramural program, bringing their knowledge and experience to grants and contracts administration; others note that some intramural scientists go on to become NIH leaders. According to one NIH extramural staff member, the virtually total absence of OB/GYN from the intramural program creates a sense of isolation and a vacuum where important communication should be occurring.[*]

Another intangible result of being excluded from the intramural program is the sense, reflected both within and outside of NIH, that the excluded discipline is held in low esteem. Some current and former NIH repre-sentatives, however, dispute the notion that this is the case for OB/GYN They point to an attempt in the early 1970s to establish OB/GYN in the intramural program as aa indication that NIH supports the idea of OB/GYN intramural research.[**]

[*] Some research in reproductive endocrinology is conducted in the NIH intramural program, and a little OB/GYN-related laboratory research is conducted by visiting fellows from overseas.

[**] Beds for OB/GYN to collect data on normal pregnancy and delivery, as well as a perinatal unit, were designed and constructed in the Clinical Center at NIH, but the beds were never opened Reasons for the failure to follow through on the plans included a lack of needed 24-hour blood bank and anesthesia services, expected problems in patient recruitment, and difficulty in recruiting OB/GYN clinicians because of the differential in pay between the NIH and private practice (based on personal communications from Duane F. Alexander, Director, National Institute of Child Health and Human Development, National Institutes of Health, and Ronald A. Chez, Professor and Director of Ambulatory Care, Department of Obstetrics and Gynecology, University of South Florida College of Medicine, 1990 and 1991).

The multidisciplinary scientific "culture" at NIH provides a distinctive training environment that is not fully duplicated in any other setting. More than 2,000 U.S. and foreign fellows (staff fellows, visiting fellows, Intramural Research Training Award fellows, etc.) are present on the NIH campus at any one time. Since the founding of the intramural program, approximately 25,000 M.D.s and Ph.D.s have received their training at NIH. Roughly one-third of the membership of the past 30 years of the American Society for Clinical Investigation received a portion of their training at NIH.[4]

OB/GYN may be the only major medical discipline that does not have a training program at NIH.[*] This exclusion is particularly disadvantageous to OB/GYN, since only a few of its academic departments have the critical mass of investigators needed to provide a stimulating, dynamic research training environment. Exclusion from the intramural program also has repercussions, as some legislators note, for the furtherance of the arch programs of existing investigators. The Senate Appropriations Committee, in its fiscal year (FY) 1992 report, cited a direct connection between the state of OB/GYN research and its representation in the intramural program:

> [The Committee] is concerned that while there are more than 2,000 researchers at the NIH there are only 3 in obstetrics and gynecology. The Committee urges the NICHD to increase the number of OB/GYN researchers at NIH and expand the OB/GYN research program. Research in this area has been severely hampered by the lack of highly qualified research scientists and doctors. In order to provide for both services and research needs in this area the Committee directs the National Institutes of Health to establish a clinical research program in gynecology and obstetrics within the National Institute of Child Health and Human Development.[5]

[*] The important role that NIH training can play in the development of research manpower is exemplified by dentistry. A dearth of scientists working in dentistry had plagued efforts to expand dental research since the inception of the National Institute of Dental Research. To rectify the situation, the institute (which, of course, includes an intramural research program) was used as a training ground for dental scientists through Public Health Service postdoctoral fellowships and guest worker positions (Ruth Roy Harris, *Dental Science in A New Age: A History of the National Institute of Dental Research*, Rockville, Md., Montrose Press, 1989, pp. 168–169).

The House Appropriations Committee agreed that "progress in gynecology and obstetrics research has been hampered by the absence of such a comprehensive program and a lack of emphasis on these fields of research."[6] The Senate report also made a specific connection between lack of research and high rates of infant mortality:

> The research of the NICHD in this critical area holds the promise of developing new knowledge to prevent or treat many of the conditions which result in infant death.... The Committee requests that NICHD develop a plan to initiate an intramural research effort to conduct research on pregnancy and perinatology....[7]

The National Institute of Child Health and Human Development (NICHD) is establishing a gynecologic intramural research program, based at the NIH clinical center, that will conduct both basic and clinical research on gynecologic disorders. In addition, a Perinatal Research Program is being put into place. This program will have three components:

1. a clinical research program, based at a D.C. hospital, focusing on preterm labor and intrauterine growth retardation;
2. a laboratory research component, based in a D.C. medical school; and
3. a program of clinical trials focusing on service delivery and support systems designed to reduce infant mortality.

The latter component will be established under a cooperative agreement with three medical schools and the D.C. Health Department. Eventually, 20 to 30 professionals at NIH will be involved in the program, as well as the staffs of the hospitals. However, although the House FY 1992 appropriations report earmarked $5 million for these activities, the Senate report did not mention an appropriation. NICHD leadership does not believe that there are funds in ongoing programs that could be used for this initiative. If the programs are to reach their intended potential, approximately $35 million will be needed within five years.[8],[9]

At the National Cancer Institute (NCI), initial explorations are under way to establish the feasibility of a gynecologic intramural program. The initiative for this effort came from leaders in the Society of Gynecologic Oncologists who

launched a series of conversations with NCI staff, during which they made the case for participation in the intramural program.*

As a result of the influence of two very different groups, two institutes can be expected in the near future to have formed the nucleus of an OB/GYN intramural program. (There is, however, some question as to whether NICHD's emphasis on work conducted off the NIH campus, and on service delivery, constitutes a true "intramural program" that will bring to OB/GYN the full array of benefits described above.) Whether these activities will grow beyond the symbolic to the meaningful—that is, to the point where the NIH intramural program becomes a significant force in OB/GYN training and research—cannot today be prophesied. But even if the intramural OB/GYN effort remains relatively small, some of the disadvantages of operating in the absence of an intramural program should be diminished: there will be at least a few intramural OB/GYN investigators with whom the extramural staff can confer; limited training opportunities will become available; and the status of OB/GYN investigation will be upgraded.

FINDINGS: The absence of an OB/GYN intramural program at the NIH places OB/GYN at a disadvantage in several ways. Some NIH extramural staff who work in OB/GYN feel that they lack a community of scientists on the NIH campus with whom they can communicate. Progress in OB/GYN research may be held back because the discipline is deprived of a unique environment for the conduct of research. Most important for OB/GYN, which has few outstanding sites for research training, is the loss of the exceptional training environment that has produced many of the nation's outstanding biomedical scientists. NIH has responded to initiatives from Congress and from OB/GYN leaders by setting in motion the beginnings of OB/GYN intramural activities, but these efforts are not likely to grow to a meaningful size unless they are appropriately supported.

RECOMMENDATIONS: Congress should ensure the success of recent initiatives to establish intramural programs in OB/GYN by appropriating the necessary funds. If efforts to obtain additional funds for intramural

* The society's leaders also argued for increased representation of gynecologic oncology on the extramural staff and on NCI advisory committees, and for modification of training grants to make them more accessible to gynecologic oncology fellows.

OB/GYN programs fail, however, NICHD and NCI should use existing money to establish intramural research and training programs in OB/GYN.

Leaders of the profession of OB/GYN have the responsibility to educate and inform those in decision-making positions about the importance and promise of an intramural program of OB/GYN research. Interest groups that have adopted women's health as an important issue have also been major players in the movement to establish OB/GYN intramural programs. OB/GYN leaders have participated in these groups and can continue to align themselves with these groups when their interests are parallel. (See Chapter 5 for further discussion of leadership issues.)

OB/GYN leaders should also work with NIH staff to identify key issues and otherwise encourage OB/GYN research. The success of a small group of OB/GYN leaders in persuading NCI leadership to launch intramural activities demonstrates the importance and effectiveness both of leadership initiative and of working closely with NIH staff. OB/GYN professionals and professional groups should work to identify issues that fall within the control of NIH staff, identify the pertinent staff members, and initiate exchanges with these individuals with a view to highlighting ways in which OB/GYN research can address important issues and is therefore worthy of encouragement and investment.

ABSENCE OF A FOCAL POINT FOR OB/GYN RESEARCH AT NIH

Pros and Cons of Creating New Institutes

Unlike diseases such as cancer and heart disease, and unlike medical practice areas such as dentistry and nursing, the reproductive sciences do not have an NIH institute or an independent NIH center whose sole or primary mission is the furtherance of knowledge in this area. Rather, OB/GYN and the reproductive sciences are part of the mission of NICHD, which is responsible for research on child and maternal health. NICHD is also the principal source of NIH support for OB/GYN departments. Other institutes come into play only to the extent that their interests overlap with OB/GYN—for example, reproductive cancers at NCI, infectious diseases of the reproductive system at the National Institute of Allergy and Infectious Diseases (NIAID), and so on.

Having an NIH institute or center devoted to a research area is not a prerequisite to the generation of major funding for that area. For example, neither AIDS nor Alzheimer's disease has an institute, but both are funded at

high levels. Nevertheless, many believe that a categorical institute provides a strong impetus to funding—which is why advocates for research in specific areas often lobby to establish institutes. This belief may not always be correct. In 1984, an IOM committee examining the organizational structure of NIH found it difficult to evaluate the impact of a new institute, concluding that it does not always result in a major acceleration of research.

This committee was better able to evaluate the impact on funding of establishing a new institute out of a previously existing one—the closest analogy to separating OB/GYN research from NICHD to form an institute. It found that when the National Eye Institute split off from the National Institute of Neurological Diseases and Blindness, its funding grew faster than the rest of NIH—but only for one year. The new institute did have a substantial impact in qualitative terms: by expanding the intramural program and developing workshops and programs emphasizing interdisciplinary research, the scope of vision research was considerably expanded. By contrast, when the National Institute on Aging split off from NICHD, funding for the new institute grew faster than the remainder of NIH for several years.[10] In short, splitting off a research field from an existing institute to form a new institute is no guarantee that additional funds will accrue to the field in the long run. On the other hand, activities such as those that expanded vision research at the new National Eye Institute can occur within an existing institute, if the leadership becomes engaged in promoting a research field. This occurred when the Heart Institute established the Lung Division, transforming lung research from an undeveloped area to a thriving research field. The 1984 IOM committee concluded that the scientific readiness of a field, together with dynamic leadership, can be more important than institute status as a catalyst for growth.[11]

Structure and Priorities of NICHD

NICHD, as the principal source of NIH support for OB/GYN departments, plays an important role in the welfare of OB/GYN research. NICHD was formed after a 1960 Presidential Task Force on Health and Social Security recommended the establishment of a child health institute to focus on the normal processes of maturation. Subsequent discussion broadened the scope of the proposed institute so that when NICHD was established in 1963 it was structured to support four areas of research: reproduction, growth and development, aging, and mental retardation. In 1968, the establishment of the Center for Population Research brought increased prominence to problems of fertility and infertility. In 1975, the Center for Research for Mothers and Children was put

in place to provide a focus for research and research training in the health problems of pregnancy, infancy, childhood, human learning, and behavior.[12]

Statements of the mission of NICHD unfailingly emphasize research on reproductive processes and the management of fertility, along with the physical and mental changes that are continuous throughout life. However, there are only three OB/GYNs on the staff of the NICHD extramural program, and all the directors of NICHD have been pediatricians. The same low priority for OB/GYN research is reflected in the composition of the councils and committees that advise the directors of NICHD and its centers on program planning directions:[*]

- The National Advisory Child Health and Human Development Council identifies promising areas of research and defines program priorities, primarily by awarding extramural grants and contracts in areas deemed to be of high priority.[13] The council also reviews the long-term plans of each of the NICHD centers. It is chaired by the director of NICHD (a pediatrician) and includes three other pediatricians and two OB/GYNs.
- The Maternal and Child Health Research Committee includes five pediatricians and two OB/GYNs.
- The Population R earth Committee, which emphasizes basic sciences and includes members with expertise in biochemistry, physiology, sociology, and demography, has one OB/GYN.[14]
- The Board of Scientific Counsellors, which advises on the intramural program, lacks any OB/GYN reputation. This should come as no surprise, since there is no OB/GYN intramural program.

In sum, the voice of OB/GYN is not loud in the councils of NICHD, particularly when compared with the voice of pediatrics; yet it is from these councils that the director and his staff receive advice for program plans.

Institute staff can also play an important role in promoting a research area. Staff are responsible for eking the input of the research community into the development of the research plans that determine funding priorities. They identify the topics that are the subject of conferences used to highlight research areas and to showcase multidisciplinary approaches to problems, thus allowing investigators to take advantage of relevant advances in other fields. Staff can

[*] The composition of NIH advisory committees is circumscribed by the charter of the committee Sometimes the charter specifies that holders of a certain position (e.g., NIH director) should be members; at other times it specifies particular expertise as a membership criterion.

also initiate requests for applications (RFAs) to prompt applications in priority areas and can use many other mechanisms to stimulate interest from the research community. There are few OB/GYN staffers at NICHD, however, and therefore few people whose primary interest is likely to be stimulating vigorous interest in OB/GYN research or supporting the OB/GYN research community in its endeavors to obtain funding.

FINDINGS: Being funded primarily by an institute whose chief focus is not OB/GYN puts OB/GYN research at a disadvantage. While the committee recognizes that the level of support received by departments of OB/GYN reflects in some measure the paucity and quality of applications, it also finds that NIH has a role in the process of developing research strength in OB/GYN departments. A scientific discipline can thrive in the absence of an NIH institute devoted to its field but only if the enthusiastic attention of NIH leaders is provided. Thus, the very small number of OB/GYNs on NICHD staff, the low representation of OB/GYN on NICHD councils and committees compared with pediatrics, and the pediatric leadership of NICHD are significant and suggest that OB/GYN research lacks visibility at that institute. Other institutes also have responsibility for areas of science that fall within OB/GYN research, such as the work of NCI on neoplasias of reproductive organs and that of the National Institute on Aging, which encompasses topics dealing with menopause. The committee urges all institutes to respond to the spirit of the recommendations below.

RECOMMENDATIONS: Institutes at NIH whose missions include areas of science to which OB/GYN contributes should affirm their commitment to reproductive health and ensure its appropriate priority in their programs. The committee believes that there is an urgent need for changes that emphasize the importance of OB/GYN research. Actions that would help overcome some of the problems OB/GYN research now confronts might include the National Institute of Child Health and Human Development changing its name to signal to the public and institute staff its commitment to and responsibility for reproductive health. NICHD could also recognize the importance of programs in reproductive health by establishing the position of deputy director for reproductive health or by appointing a board-certified OB/GYN to the position of deputy director. Further actions that might be considered by NICHD include increased representation of

OB/GYN on its staff, and the development of requests for applications (RFAs) on high-priority OB/GYN research topics identified in institute plans.

STUDY SECTIONS

Like many investigators who seek NIH funding, clinical investigators in departments of OB/GYN believe that the playing field is tilted against clinical research. They claim that the membership of the study sections that review their grants is overwhelmingly composed of basic scientists who not only fail to appreciate the scientific worth of clinical studies but also fail to understand that clinical investigation is necessarily less rigorous than bench science: the clinical investigator cannot control all the characteristics of the study population; ethical constraints, such as patients not receiving state-of-the-art treatment, make it difficult to select appropriate controls; confounding variables axe difficult to eliminate; and the costs of clinical investigation tend to be high in comparison with the costs of basic science.

The evidence is mixed on whether basic investigation does better than clinical investigation in NIH grants review. An unpublished study of 75,611 competing research applications found no statistically significant difference between the priority scores or funding of applications revolving human subjects compared with those that did not, and no statistically significant difference between applications from M.D.s and those from other applicants; however, the approval rate was 11 percent higher for applications that did not involve human subjects. This latter finding was confirmed by two other studies, and two out of three other studies also found differences in priority scores. In one, applications involving human subjects (evaluated by a review group on mammalian genetics) were 20 percent less likely to receive priority scores in the top quartile than were basic science applications—but the type of degree of the investigator was not related to the rating.[15] Using the degree of the investigator as an indicator of clinical versus basic research,[*] between 1975 and 1989, Ph.D.s had slightly better priority scores than M.D.s on RO1 applications, but in 1989, M.D.s had slightly higher success rates than Ph.D.s.[16]

[*] Since physicians may be principal investigators on basic science studies, and vise versa, this is by no means a perfect measure of clinical and basic science.

Given the unity about whether clinical investigation is disadvantaged in the review process,* one might ask whether the composition of the review groups makes a difference and whether the composition of the groups that review applications from departments of OB/GYN puts that discipline at a disadvantage. Assuming a relationship between the degree of the reviewers and the ability of the group to conduct fair reviews, there is some reason for increasing concern. Between 1979 and 1989, M.D.s fell from 42.2 percent to 28.4 percent of study section members (a drop of 13.8 percent), while applications from M.D.s fell from 30 percent to 25.6 percent of all applications (a drop of 4.4 percent).[17] If proportional representation is the issue, however, M.D. membership still slightly exceeded M.D. applications in 1989.

There is suggestive evidence that these data are irrelevant. An unpublished study of clinical research applications sent to six NIH review groups between 1977 and 1980 showed that approval rates and priority scores were not affected by the percentage of M.D.s among reviewers.[18] Nevertheless, many clinical investigators believe that NIH study sections as presently constituted are not appropriate for the evaluation of clinical investigation. Over the years they have called for separate review of basic and clinical investigations, by study sections composed of experts in such work.

The concern with the composition of study sections has to do with whether members have the expertise to evaluate the grant applications properly. It is often assumed that to fully understand the science and the context of the applications they review, study section members must be specialists in the relevant medical or scientific disciplines. In 1989, only 3 of the 1,434 study section members had OB/GYN as their primary area of expertise. The representation of OB/GYN was only a little better in other years (Table 4-1).

More interesting is the representation of OB/GYN on the four study sections to which most applications from departments of OB/GYN go for review: biochemical endocrinology, human embryology and development, reproductive biology, and reproductive endocrinology. Together these study sections review about 50 percent of all applications from departments of OB/GYN. Of the 60 members of these study sections, three listed OB/GYN as their primary area, and an additional four listed other clinical areas.[19]

* The question of whether applications for clinical research fare as well as applications for basic research is complicated by differing definitions of clinical investigation. Many people believe that only a subset of what is broadly defined as clinical investigation—that is, only clinical trials—have particular difficulty in getting funded.

TABLE 4-1: Primary Area of Expertise of NIH Initial Review Group Members—Selected Areas, 1977–1989

Specialty	1977	1981	1985	1989
Anesthesiology	2	2	4	5
Clinical Dentistry	5	6	9	14
Internal Medicine	111	105	135	117
Maternal/Child Health	0	0	0	1
Neurology	6	7	12	16
OB/GYN	**8**	**4**	**6**	**3**
Ophthalmology	10	10	8	7
Otorhinolaryngology	3	3	7	4
Pediatrics	12	23	26	19
Radiology	6	13	11	9
Surgery	20	15	26	21

SOURCES: DRG Peer Review Trends 1977–1986; DRG Peer Review Trends 1979–1989. Information Systems Branch, Division of Research Grants, National Institutes of Health.

What this means for OB/GYN is difficult to determine. The relatively low success rate of applications for grants from departments of OB/GYN (noted in Chapter 2) could be due to the poor quality of the work being proposed, a lack of understanding on behalf of the study section members, or some other reason. To try to get a bell (although limited and subjective) grasp on whether the composition of study sections is serving OB/GYN well, informal interviews were conducted with some past and present members of the reproductive biology study section. All of the members interviewed were OB/GYNs, on the assumption that they would be most sensitive to the evaluation of OB/GYN applications. The results of the interviews were inconclusive, revealing wide differences of opinion. On the one hand, some of those interviewed said that the Scientific Review Administrator (who is responsible for recruiting review group members and ad hoe members when needed) is sensitive to the need to bring in outside reviewers, especially for clinical proposals. In addition, according to this view, the basic scientists in the study section are responsive to explanations of the complexity of clinical investigation and will score applications appropriately when they understand that a proposed methodology is the best that can be formulated and that an important topic is being investigated. On the other hand, some interviewees said that OB/GYN is

particularly underrepresented and that clinical research does not get equal consideration because of the preponderance of Ph.D. members of the study section. On one point there was agreement among those interviewed: that the quality of applications from departments of OB/GYN is at least partly responsible for their low success rate, even taking into account the multiple problems that axe inherent in OB/GYN clinical investigation (e.g., the limit on invasive procedures that can be done on healthy, pregnant populations).

Some NIH staff emphasize that they can help investigators learn how to succeed in the grants process. While there is undoubtedly variation in the enthusiasm of NIH staff for such tasks as attending professional meetings to discuss grants procedures or convening groups of leaders and investigators at NIH to develop rapport with the research community, the committee is convinced that opportunities exist and that if they are used, they could make a difference in the success of applications from departments of OB/GYN.

FINDINGS: OB/GYN is sparsely represented in the membership of study sections, but it cannot be established that applications from OB/GYN receive unbalanced reviews. It is also clear that Scientific Review Administrators have a valuable fund of knowledge that, if tapped, might enable investigators to improve their grant-writing abilities and guide them to apply for different kinds of grants.

RECOMMENDATIONS: To ensure the dissemination of knowledge about grants processes, and to enable applicants to improve their applications and make full use of the many NIH funding mechanisms, members of academic departments of OB/GYN and members of professional societies concerned with OB/GYN research should explore all avenues of communication with NIH staff. Scientific Review Administrators, in particular, those of the four study sections in which the majority of applications from departments of OB/GYN axe reviewed, should continue to ensure that applications for grants in OB/GYN research are reviewed by individuals who are sensitive to the particular difficulties of working in OB/GYN clinical investigation and who have the in-depth knowledge of OB/GYN needed to ensure appropriate review. OB/GYN leaders can help by inviting Scientific Review Administrators to professional association meetings. NIH staff axe also urged to commit time and to use the mechanisms at their command to sustain such communication.

RESTRICTIONS ON NIH RESEARCH SUPPORT

Chapter 1 of this report noted that examination of the ethical implications of fetal research is beyond the scope of this study. The committee is concerned, however, with factors that have an impact on the vitality of the OB/GYN research enterprise and on the decisions of individuals to enter or remain in OB/GYN research. It therefore questioned whether a policy that in effect prohibits federal funding of arch in an area of growing clinical importance deters would-be investigators, and whether advances in the health of patients are adversely affected. In 1989, an Institute of Medicine committee developed a large clinical and basic research agenda that would further the practice of in vitro fertilization. Some of the scientific questions included in that agenda could only be answered through research using the human fetus.[20]

The committee found it difficult to find evidence that either contradicted or supported the notion that the lack of federal funds for fetal research deters people from OB/GYN research careers. Therefore it was forced to rely on the sense of its members—that numerous interesting research areas are not being funded and that thwarting the interest of young physicians in medically assisted conception and its supporting research deters individuals from a career in investigation.

The committee concluded that federal funding of fetal research offers the promise of significant advances in understanding implantation, developmental biology, and prenatal genetic diagnosis. The committee was also convinced that federal funding of such research would also significantly strengthen research initiatives in departments of OB/GYN by opening up new areas of investigation that would draw additional OB/GYN professionals into research.

REFERENCES

1. Institute of Medicine. A Healthy NIH Intramural Program: Structural Change or Administrative Remedies? 1988. Washington, D.C.: National Academy Press, 1988.
2. National Institutes of Health. NIH Intramural Research for Increasing knowledge. Program Report and Plan. Bethesda, Md.: Office of the Associate Director for Program Planning and Evaluation. Office of the Director, May 1, 1969, p. 12 .
3. Institute of Medicine. A Healthy NIH Intramural Program. Structural Change or Administrative Remedies? Washington, D.C.: National Academy Press, 1988.
4. Ibid.
5. U.S. Senate. Departments of Labor, Health and Human Services, and Education and Related Agencies Appropriation Bill, 1991. Report 101–516. 101st Cong. 2d sess. October 10, 1990, pp. 121–122 .

6. U.S. House of Representatives. Departments of Labor Health and Human Services, and Education and Related Agencies Appropriations Bill, 1992. Report 102–121. 102nd Cong. 1st seas. June 20. 1991, p. 86 .
7. U.S. Senate. Departments of Labor, Health and Human Services, and Education and Related Agencies Appropriation Bill, 1991. Report 101–516. 101st Cong. 2d seas. October 10, 1991, p. 121–122 .
8. Gaines, George W. Legislative Liaison Officer, National Institute of Child Health and Human Development, personal communication, July 1991.
9. Telephone interview with Alexander, Duane, Director, National Institute of Child Health and Human Development, September 27, 1991.
10. Institute of Medicine. Responding to Health Needs and Scientific Opportunity: The Organizational Structure of the National Institutes of Health. Washington, D.C.: National Academy Press, October 1984.
11. Ibid.
12. National Institutes of Health. Child Health and Human Development: An Overview and Strategy for a Five-Year Research Plan. Bethesda, Md. 1981.
13. Institute of Medicine. Funding Health Sciences Research. A Strategy to Restore Balance, ed. Floyd Bloom and Mark Randolph. Washington, D.C.: National Academy Press, 1990.
14. Mary Plummer, National Institute of Child Health and Human Development, personal communication, July 1991.
15. Cited in Cuca, Janet Melei. Scientific, Social and Other Factors in the Evaluation of Applications for NIH Research Grants. A dissertation submitted to the Graduate School of Arts and Sciences, Catholic University of America ; 1990.
16. National Institutes of Health. DRG Peer review Trends. Workload and Actions of DRG Study Section, 1979–1989. Bethesda, Md.: Statistics and Analysis Branch, Division of Research Grants, pp. 71 and 83 .
17. National Institutes of Health. DRG Peer Review Trends. Member Characteristics. 1979–1989. Information Systems Branch. Division of Research Grants. Bethesda, Md.: National Institutes of Health.
18. Cited in Cuca, Janet Melei. Scientific, Social and Other Factors in the Evaluation of Applications for NIH Research Grants. A dissertation submitted to the Graduate School of Arts and Sciences, Catholic University of America, 1990.
19. Walkington, Robert. National Institutes of Health Support of Research in Departments of Obstetrics and Gynecology. Appendix B, this volume .
20. Institute of Medicine, National Research Council. Medically Assisted Conception: An Agenda for Research. Washington, D.C.: National Academy Press, 1989.

5

DEPARTMENTAL AND LEADERSHIP ISSUES

DEPARTMENTAL ISSUES IN EXPANDING RESEARCH CAPABILITIES

Leaders able to convince others of the importance of obstetrics and gynecology (OB/GYN) research must emerge from the academic departments themselves and from among those individuals whose job it is to develop the research base of the discipline and nurture the next generation of clinicians and investigators. There is wide variation among departments of OB/GYN, both in their commitment to investigation and in their academic standing within their medical centers. Most knowledgeable people would agree that a small minority of OB/GYN departments are leaders in academic OB/GYN investigation and that these departments have a reputation for excellence in the medical center complex in which they operate. These departments, with a cadre of outstanding investigators, including basic scientists, are also the only ones that are considered able to provide an excellent environment for training the next generation of investigators.

Most academic departments of OB/GYN do not rank highly in the academic pantheon of their medical centers, but they nevertheless provide excellent clinical training and health care.[*] Indeed, such departments will, and should, remain at the heart of OB/GYN education. A number of departments fall between these two extremes: some attract consistent but relatively modest levels of research

[*] The lack of esteem in academia accorded to excellence in clinical care in the absence of investigation is emphasized by the following commentator: "even though the impact of health care is primary in establishing medical disciplines, each finds its status on the academic totem pole partly in terms of the substantiality of its intellectual base. A high-ranked specialty cannot be simply a service specialty devoid of an intellectually interesting area of knowledge that it cultivates and applies" (Clifford Grobstein, "Academic Departments of Obstetrics: A Perspective," in *The Current Status and Future of Academic Obstetrics*, ed. John Z. Bowers and Elizabeth F. Purcell, New York, N.Y., Josiah Macy, Jr. Foundation, 1980).

support; others are mounting an effort to move up the curve of investigative excellence. Given the limited number of young investigators and the limited financial support available for such progress, a careful strategy of strengthening the latter departments—those that are the most ready and interested in joining the ranks of the major players—is the approach most likely to be successful. Tills strengthening is an intrinsic piece of the process that must occur if OB/GYN research is to become a more vital part of the nation's research armaments. That is to say, funding from such agencies as NIH will not be forthcoming unless the human resources are available.

Because departments of OB/GYN are virtually unstudied, the committee was forced to rely on the opinions of eminent individuals in the field to gain a sense of both the barriers to progress and the possible solutions.

SOME PROBLEMS

The barrier cited most frequently and most forcefully by the chairs of academic OB/GYN departments was the need to generate income from clinical care, which represents a major problem when attempting to ensure that faculty have time for research.[*] Moreover, the dynamics of the situation, with reimbursement tightening and clinical care demanding ever more time, were perceived by many to be exacerbating an already dire situation. The following are some of the comments the committee received:

> The major problem facing departments attempting to establish or even maintain an existing research presence is the ever increasing demand to generate practice dollars to support these activities in a department. As costs increase while reimbursement for services and availability of grants dollars diminish, more and more faculty effort must be shifted to clinical care. Thus both the time necessary for productive investigation and the money necessary to support it is eroding at an accelerating pace. It becomes a Catch 22 situation.

[*] The pressure on faculty to generate clinical practice income is, to a great extent, the result of the high salaries required to attract physicians to academe. Comparing the salary of more than $125,003 earned by an assistant professor in OB/GYN with the $40,000–$50,000 earned by a Ph.D. in a basic science department highlights the problem.

* * * *

In most departments of OB/GYN, the clinical obligations of faculty axe extremely burdensome. This is a function of the large number of obstetric-gynecologic patients in the ambulatory areas as well as within the hospital setting as they relate to the number of faculty members in smaller OB/GYN departments. Many young OB/GYN investigators come out of scientific training programs with skills enabling them to compete but simply don't have the time to do so because of the clinical workload. Departments of OB/GYN do not have the luxury of providing 10–11 months of protected time for research and 1–2 months of attending, as is done in many departments of medicine and pediatrics. Department chairs are placed in a position of having to ensure high quality clinical care and teaching at the expense of faculty research time.

* * * *

Since coming to this university ... I have attempted unsuccessfully to generate a change in emphasis from clinical practice to a balanced approach of research and teaching along with clinical practice. It is my opinion that this department is not unique in [needing to emphasize] clinical practice ... in order to maintain the economic viability of the department. In a low population density state with limited tax base, public funding of higher education including medical schools is marginal at best. In such an environment the very existence of departments is threatened by the economic challenge of trying to retain excellent clinical faculty to carry out the teaching mission of the department, with research taking an ever-decreasing role.

* * * *

Because of [the low level of federal research support] departments must seek other sources for funding and generally end up with commercial funding through pharmaceutical companies, equipment manufacturers and the like, or from inside dollars if they have sufficient clinical income that they can develop research programs within the Department. In each of these cases the long-term support is not likely. The commercial companies tend to end support at the point that sale of product is possible. Inside funding depends so much on clinical care

> that it becomes a Catch 22. If sufficient time is devoted to clinical care to provide dollars, there is not time left for good research.

The sense of increasing dependence on clinical income is substantiated by data on medical school finances, which indicate that the problem is pervasive among clinical departments—in large part because of the salaries that must be supported. Revenues from medical services plans rose from 3 percent of total revenues in 1960–1961 to 27.4 percent in 1988–1989. Over the same period research revenues fell from 37.4 percent to 17.4 percent of total revenues.[1],[*] Yet although service income has replaced research income as the leading source of revenues, it does not follow that clinical income provides much discretionary money that department chairs can use to support investigation. A survey of medical faculty practice plans in 1980 found that 42 percent of revenues went to direct physician compensation, 11 percent to physician fringe benefits, and 33 percent to operating expenses. Only 12 percent of the revenues were transferred for medical school or departmental use.[2]

To estimate differences among departments in their sources of support, the committee analyzed data from a survey of 34 medical schools during 1983–1985. Practice funds contributed approximately 30 percent of total OB/GYN department funds—less than the percentage of such funds in five departments (psychology, orthopedics, anesthesiology, ophthalmology, and radiology), approximately equal to that in two others (pediatrics and medicine), but still higher than in four other departments.[3] Although OB/GYN departments are about average in the contribution of clinical income to departmental revenues, many OB/GYN chairs and other faculty members believe that OB/GYN has a particularly hard time generating this income. They note that although some services are lucrative, OB/GYN departments are relatively small, clinical earnings must support relatively high salaries and malpractice premiums, and OB/GYN coverage is particularly demanding of a practitioner's time. In addition, they say that the uncompensated care load for obstetrics is significant in many teaching hospitals.

Most of these complaints can be voiced by other specialties, but the convergence of these problems in OB/GYN is thought to create an especially

[*] The contribution of clinical income is probably underestimated, since some faculty members supplement their base salaries through practice income that is not on the medical school books but that would have to be made up by the school if faculty members did not receive this income. In addition, the data do not reflect hospital support of faculty salaries (communication to the IOM Committee to Plan a Study of the Research Capabilities of Academic Departments of OB/GYN, 1989).

that the most crucial impact is on the ability of departments to difficult environment for research. Letters to the committee suggest develop and nurture young physician investigators by protecting their time during the critical early years of theft development as researchers:

> Within an individual department, the biggest problem in developing new young faculty is in provision of the initial support. They must achieve major outside funding within two years or they must develop a clinical treatment program which supports their salary and overhead. Without such, most departments cannot continue support beyond two years and must ask the individual either to leave or change focus.
>
> * * * *
>
> Presently very few sources of salary support are available to new clinician investigators or basic researchers. Since the first two or three years after recruitment to a faculty position are the most crucial in determining the career path of most individuals, clinician-investigators might slide gradually into the clinical path if their time is not well protected and compensated for. Basic researchers might opt for industry where pay is more and the demands on their time are less.

Is the Past a Guide for the Future?

The history of the growth of today's leading OB/GYN res h departments exemplifies the importance of the role of the dean of the medical school. In many cases the dean was prepared to make an investment in developing a research-intensive OB/GYN department, sometimes because the school was attempting to become a major player in university research and was therefore investing in all clinical departments, at other times because OB/GYN lagged behind other departments and needed to be upgraded. In several cases the medical school investment was actually quite minor, either because a new chair brought major foundation funding with him or her or because foundation support was quickly obtained.

As noted in Chapter 2, the foundations that enabled these departments to grow to eminence in the past are not making similar contributions to reproductive science today. This does not mean that it is impossible to build a research department in today's environment. It does mean that department chairs must be very persuasive if they are to bring foundation funds into their

departments, whether for research training, space and equipment, faculty salaries, or research projects. It also means that department chairs must make the case for investment in OB/GYN research forcefully in the dean's office, where decisions are made that determine which departments will be the winners and which the losers in the allocation of resources.

Some Solutions

A department of OB/GYN that seeks to transform itself into a first-rank research center must develop the infrastructure on which a research enterprise can be built. Components of this infrastructure include faculty capable of bringing the next generation into the mainstream of investigation. One way of accelerating the process is through investment in established investigators; another is to initiate interdepartmental ties that facilitate multidisciplinary learning and research. The challenge is to accomplish this development in an environment in which it is difficult to create the financial cushion needed to sustain faculty development. Nevertheless, OB/GYN department chairs suggested a number of solutions.

Several chairs believe that it is possible (although difficult) to increase the amount of money that the faculty practice plan contributes for the support of investigation. For this approach to succeed, a department leader with a strong, eloquent commitment to research is needed. Clinical faculty are unlikely to be enthusiastic contributors to the support of a group whose work they may not value and whose members may be perceived as competing with clinical activities in terms of status as well as resources. Accomplishing this cross-subsidy without alienating clinical faculty requires that the chair convince them that enhanced investigative capabilities would benefit the department as well as the discipline as a whole.

A well-established strategy—and one strongly endorsed by chairs who wrote to the committee—for enhancing departmental research capabilities is the recruitment of basic scientists who bring essential knowledge and skills to the department and, ideally, work alongside OB/GYNs in collaborative efforts. Again, however, there are some problems: because the Ph.D. in a clinical department is sometimes viewed by his or her basic science peers as second class, it can be difficult to recruit first-rate Ph.D.s. It is often preferable for the departments of OB/GYN and the basic science department jointly to recruit the basic scientist and to secure a joint appointment. It may also be necessary to create equitable tenure evaluation criteria. These actions will help the basic scientist continue to develop by sustaining the connection with basic science

colleagues. In addition, for Ph.D.s in the department to augment the clinical research capabilities, rather than merely conducting basic research and increasing external research funding, a collaborative relationship must be established between the basic and clinical scientists. Success in such a plan requires a leader's commitment to collaboration and to development of creative ways of overcoming the natural segregation that would otherwise occur.

Another type of collaboration, one that received less emphasis in letters from department chairs but nevertheless represents a strategy for building research capacity, is interdepartmental collaboration. The many areas of mutual interest with other departments (including basic science departments), if fully exploited, can stimulate the research interests of young people in medical school and during their subspecialty fellowship years. Collaborative arrangements can also provide mentoring that is not available in the OB/GYN department, and potential young investigators can benefit from the laboratories of collaborating basic science departments. Collaborative activities can be building blocks for a department that does not yet have sufficient capacity to stand alone as a research entity: they can ensure a level of research activity while junior faculty move toward independence and the department establishes itself as a research center able to recruit investigators. Finally, interdepartmental collaboration can be used as the basis for creative and fundable protocols to address important clinical problems, and as the basis for training opportunities not available in an individual department. Obvious research areas with potential for interdepartmental collaboration include not only neonatology and endocrinology, but also epidemiology, statistics, and the behavioral sciences. The latter areas are particularly attractive, because important work remains to be done in them in relation to many OB/GYN issues and that work could be accomplished without major investment in laboratory space or equipment.

These strategies for building the research infrastructure—cross-subsidy, recruitment, and interdepartmental collaboration—require investments of time and departmental funds in varying combinations. To augment departmental funds, some chairs have established foundations that receive contributions from the public. These funds have helped in small but important ways, such as by carrying investigators for short periods of time between grants, by "buying" time for grant writing, and by protecting the time of young faculty.

FINDINGS: Academic departments of OB/GYN face particular difficulty in establishing and expanding their research capability. Other clinical departments are confronting the same problems as OB/GYN—the competing

claims of research and clinical services, growing constraints on reimbursement, large amounts of uncompensated care, and the struggle to protect the time of young investigators. The convergence of these circumstances in departments of OB/GYN creates a difficult environment for conducting research and developing new investigators. It is the responsibility of the chairs of OB/GYN depots to persuade the dean of the medical school, foundations, and others to invest resources in OB/GYN research; in this the chair is assisted to a sizable degree by the surge of interest in women's health issues. Strategies to establish an infrastructure for research include cross-subsidy (reserving a portion of clinical income to support investigation), recruitment (incorporating Ph.D. investigators into the departments), and collaboration (establishing interdepartmental mechanisms to facilitate interdisciplinary training and research).

RECOMMENDATIONS: Chairs of departments of OB/GYN should make a serious commitment to augment their research capabilities and to vigorously engage in informing medical school leaders and OB/GYN faculty of the potential of investment in research and research training. The committee recommends three specific strategies for increasing research activities:

- **increase the clinical income used to support research;**
- **conduct important epidemiological and behavioral research that is relevant to OB/GYN; and**
- **create interdepartmental research linkages.**

Chairs should also, when possible, establish a foundation that can receive contributions from patients and other supporters, to be used to support young investigators and for other purposes that encourage research.

LEADERSHIP

OB/GYN Leadership and Research

In any medical field there are individuals and organizations that most people will agree represent the leadership of some aspect of that field, such as teaching, advanced clinical care, or research. It is from these people and groups that the rank and file take their cues as to the important issues, and from whom the

outside world learns of the contributions of the field to the rest of society. In other words, leadership can have both an internal impact (helping to determine the positions and priorities of members of the profession) and an external impact (helping to determine how the field is viewed and whether it is worthy of public support).

It takes a serious commitment by a critical mass of this leadership to change the ethos of a profession. OB/GYN seems to have lacked that commitment. This lack may reflect the priorities of a field in which caring for women and securing their reproductive health have taken first place. In this, OB/GYN differs little from other fields of medicine—patient care is, after all, the purpose of medicine. Where OB/GYN does differ from many fields of medicine is in the low level of interest in research—an activity that provides the foundations for improvements in patient care—shown by both its academic leaders and its professional organizations.

Few research-oriented academics have risen to leadership positions in OB/GYN's professional organizations and used those positions to champion the cause of expanded research capabilities. This circumstance mirrors the dearth of academic departments in which research is a thriving activity and a major focus. And if a significant group of academic leaders are not actively making the case for expanded research, it is not surprising that professional organizations, whose membership is predominantly practitioners, display a low level of interest in advancing research.

The emergence of natural leaders from the academic ranks and their ascent to positions of influence should not be taken for granted. The need to smooth the path for potential leaders from academic medicine was understood by the executive director of the John and Mary R. Markle Foundation in the mid- to late 1940s.[4] The foundation therefore established scholarships for outstanding young academicians (including teachers, investigators, and administrators) that could be used for partial salary support and for laboratory, travel, and other expenses. Markle awardees were recognized by their peers as an elite group, and many of the scholars (17 out of 506 were OB/GYNs) became leaders in their fields. By one measure the program does not appear to have been effective (nominees who failed to get into the program advanced up the academic ladder as rapidly as the scholars, 80 percent of whom maintained that they would have remained in academic medicine without the scholarship), but it was viewed as such a success that it became the model for other awards. It is difficult to determine what made the program successful. Some suggest that the rigorous selection process, which included nomination and a commitment of support by the medical school, and a three-day selection meeting, was important. Others point to the annual two-day meetings at which scholars met with educators to

discuss issues in medical education, as well as the flexibility of the money and the honor of the award itself.

In sum, the leadership of academic OB/GYN can play a significant role m stimulating interest and investment in research. The assistance of a structured program to help those leaders emerge is invaluable.

Leadership and Its Impact Within the Discipline

Without strong leaders within the discipline of OB/GYN who accept responsibility for the furtherance of research capabilities, change is unlikely to occur. Lacking that leadership, OB/GYN will not overcome its reputation for lagging behind some other specialties in both financial and intellectual support of arch—and until that happens, OB/GYN will not attract the research-oriented young people needed to create and sustain a vital research capability.

The present situation has been described as a vacuum where research leadership ought to be, but there are encouraging, if small, signs that change is under way:

- Groups such as the American College of Obstetricians and Gynecologists (ACOG) strongly supported the Reproductive Scientist Development Program, which indicates their willingness to invest in the next generation of investigators. It also signals to the OB/GYN community the belief of those at the forefront of the field that research is an important priority.
- The Association of Professors of GyneCology and Obstetrics has reactivated its Council of University Chairs of Obstetrics and Gynecology (CUCOG), which is forming a committee to encourage research. This committee is expected to work with other organizations in developing and stimulating research in academia.
- Of the 126 chairs who responded to a questionnaire about topics they would like to have addressed in management seminars, 88 expressed an interest in seminars on developing research programs.[5]
- In another survey, department chairs identified research experience as among the qualities they lacked, reflecting an encouraging awareness of the need for research experience for those holding the position of department chair.[6]

Thus some OB/GYN groups are already moving in useful directions; yet even greater roles for them and others are feasible. For instance, they could (as some already do) hold meetings to showcase the latest research findings, and their annual meetings could increase the emphasis on research, on the work of

young investigators, and on exchanges between senior and junior investigators.

Facilitating the encouragement of leaders to further research is not easily accomplished, but there are lessons to be learned from activities undertaken by another specialty—psychiatry. This specialty had identified a situation very similar to the one that confronts OB/GYN: a dearth of investigators and a need to recruit young people into research, to enhance federal and other research support, and to get the weight of the discipline behind efforts to accomplish these goals. In 1985, the American Psychiatric Association established an Office of Research. This office is attempting to elevate the profile of research in the discipline in many ways: it publishes a quarterly report that highlights research policy shifts, legislative issues, and relevant published reports; it also acts as an information resource listing grant opportunities, training opportunities, and research meetings, as well as featuring discussions of training issues and exciting research developments. The office is developing data bases on research opportunities, training, and mentoring; in addition, it serves as a center for information on grant writing, peer review processes, animal research guidelines, and other topics of interest to those competing for funds.[7] The office sponsors research policy symposia and grant-writing workshops, and (in recognition of the role of legislative bodies in directing the allocation of science resources) it also helps government relations efforts by writing and distributing information for use as testimony on research issues.

FINDINGS: The discipline of OB/GYN has not developed a cadre of leaders for whom the stimulation of research is a primary mission. As a result, academic leaders struggling to develop research capabilities have an uphill battle. They must, for example, convince their own faculty that they, and the discipline as a whole, will benefit from efforts to support research—an important concept when financial sacrifices are demanded. The committee is heartened by recent initiatives that encourage research in OB/GYN and by academic leaders who express awareness of the need to encourage investigation. Much, however, remains to be done.

RECOMMENDATIONS: OB/GYN professional organizations should create opportunities for expanding research and for stimulating young members of the profession to view investigation as an exciting and valued activity. Useful mechanisms include special sessions at annual meetings and providing funds for interested residents to attend such meetings. In

addition, these organizations should combine resources to establish an office whose mission would be the encouragement of OB/GYN research. The Office of Research of the American Psychiatric Association is an interesting model.

The committee also recommends that a foundation set up a program to assist the advancement of potential research leaders. The Markle Scholars Program, the Macy program (described in Chapter 2), and other efforts to develop academic leaders should be examined to determine which of their characteristics should be replicated.

Leadership and Its Impact Outside the Discipline

A vital research enterprise is sustained both by the discipline itself and by the public and private groups that provide financial support. Leaders from the discipline must make the case for funding of research—in the words of an Institute of Medicine/National Academy of Sciences report,

> not as an entitlement but as an investment ... scientists [must] convey to the public and to Congress the powerful message of the value of support of biomedical research—its benefits for public health, its contribution to America's commercial viability, and its contribution to the richness of our culture.[8]

This message is pertinent to any sphere of science attempting to secure its share of research funds.

For better or for worse, congressional involvement in research decision making is growing. Not only does Congress appropriate the federal research money, but it increasingly ties that money to specific goals and activities.[9] If OB/GYN is to increase the contribution of federal funds to its research areas, it must participate in the education of those who influence appropriations. This requires that the leaders of the profession emphasize the role of OB/GYN research in the resolution of important problems.

The rise of federal funding of research in areas such as AIDS, cancer, and Alzheimer's disease illustrates the role of patient advocates, research leaders, and others. A case study of the rise of the Alzheimer's movement notes the necessity of raising both scientific and public awareness of the disease, and the significance of the associated social and health problems. One of the leading players in the movement to raise the level of support for Alzheimer's disease

research said that they had to make Alzheimer's disease a "household word"; another noted that, since Congress pays more attention to popular media than to scientific journals, it was important to use the media to disseminate research success stories. An equally important factor in the success of these efforts was the interaction of a wide range of groups including an advocacy organization, representatives of the National Institute on Aging, the media, representatives of Congress, and the neuroscientists who were interested in promoting the research.[10]

The 1990s offer an unprecedented opportunity for OB/GYN because of increasing public interest in women's health issues, an interest that OB/GYN leaders can tap into. Beginning with the June 1990 testimony of the General Accounting Office (GAO) before the Subcommittee on Health and the Environment of the House Committee on Energy and Commerce, in which the GAO commented on the National Institutes of Health's (NIH) implementation of a policy on including women in clinical trials, questions have been raised in the press, in Congress, and at lit about whether the nation's research enterprise is doing justice to women's health. The prominence being given to these issues strengthens the case for investing federal funds and medical school resources in departments of OB/GYN.

OB/GYN suffers from several disadvantages compared with some other areas of medicine that have achieved increases in federal funding for their research. One is that OB/GYN research does not seek the cure of a specific disease and therefore does not have a natural constituency with which to work. The second is that there is no specific institute at NIH whose leadership is interested in advancing OB/GYN research broadly. (To the extent that the National Institute of Child Health and Human Development [NICHD] is the discipline's advocate at NIH, help is limited to the areas that fall within the NICHD mission [see Chapter 4].) And, importantly, the leadership of OB/GYN has not traditionally played a strong role in government relations and is not well prepared to enter the fray today.

Despite these obstacles, there are several encouraging signs. ACOG has upgraded its efforts in the legislative arena and contributes to the work of groups active in drawing attention to women's health research issues. In addition, members of Congress have proposed actions in many areas of women's health. Provisions of the Women's Health Equity Act include ensuring the inclusion of women in the study population of clinical trials; establishing a permanent Office of Research on Women's Health at NIH; and increasing funding for research on breast and ovarian cancer, osteoporosis, infertility, and contraception. Other initiatives establish three specialized centers for contraceptive development and two for infertility research. It is encouraging to note that NIH has received

applications for these centers from OB/GYN departments and that OB/GYN is involved in applications from other departments.

The Office of Research on Women's Health at NIH is developing a research agenda, which has had input from the OB/GYN community. In addition, Congress has been sensitize to the growing cadre of women who are becoming active in demanding funds for research directed toward improving their health. NIH has a new director, Bernadine Healy, whose voice and authority are urging greater gender equity in research. Such activities offer opportunities that can be grasped by OB/GYN leaders to establish OB/GYN as the locus of care for women, and its research as a major contributor to the solution of specified problems that affect women.

FINDINGS: The 1990s offer an opportunity to increase public awareness and funding for OB/GYN research. Because of OB/GYN's largely clinical orientation, however, strong advocates for research have not emerged. There has been a recent surge of interest in research to improve the health of women. This is reflected in a major new research initiative proposed by Bernadine Healy, director of NIH, the establishment at NIH of the Office of Research on Women's Health, and an array of legislative proposals from Congress. The emerging realization of a need to foster research on issues related to women's health offers an unprecedented opportunity to confirm the role of OB/GYN research in this area.

RECOMMENDATIONS: The committee recommends that individuals with a strong interest in research be represented in decision making positions in leading OB/GYN professional organizations. These OB/GYN organizations, in turn, should expand their efforts to educate decision makers about the potential of OB/GYN research and the importance of accomplishing the research agenda laid out in the next chapter of this report.

REFERENCES

1. Association of American Medical Colleges. AAMC Data Book. Statistical Information Related to Medical Education. Washington, D.C.: Association of American Medical Colleges, January 1991.
2. Association of American Medical Colleges, staff communication, to the IOM Committee to Plan A Study of the Rose h Capabilities of OB/GYN. 1989.
3. Ibid.
4. The discussion of the Markle Scholars Program is based on a paper by Lawrence Longo, which appears as Appendix A in this volume.
5. George D. Wilbanks, President, Association of Professors of Gynecology and Obstetrics, personal communication, April 1991.
6. Bates, William G. Leadership Qualities of Obstetrical and Gynecological Department Chairmen of United States Medical Schools. Unpublished manuscript. Greenville Hospital System, Greenville, South Carolina.
7. Pincus, Harold Alan and Brenda Fasnacht. From the Office of Research. Psychiatric Research 1990; 5(1):2 .
8. National Academy of Sciences/Institute of Medicine. Forum on Supporting Biomedical Research: Near-term Problems and Options for Action. Summary. Washington, D.C., June 27, 1990.
9. U.S. Congress, Office of Technology Assessment. Federally Funded Research: Decisions for a Decade. Summary. OTA-SET-491. Washington, D.C.: Government Printing Office, April 1991, p. 2 .
10. Fox, Patrick. From Senility to Alzheimer's Disease: The Rise of the Alzheimer's Disease Movement. Milbank Quarterly 1989; 67:58–102 .

6

A RESEARCH AGENDA FOR DEPARTMENTS OF OBSTETRICS AND GYNECOLOGY

The previous chapters developed the themes that identifiable weaknesses exist in the OB/GYN research enterprise and that actions to strengthen and support investigation are needed. This chapter describes research topics, the accomplishment of which would significantly improve the health of women and the results of pregnancy. The breadth and depth of this research agenda underscore the importance of ensuring a thriving research enterprise in OB/GYN.

The criteria for inclusion of topics in the research agenda and the process used by the committee to develop the agenda axe described in Chapter 2. They are reiterated here because they emphasize the sense of the committee that OB/GYN has the potential to make important contributions to health. They also point to the committee's insistence that research topics included in the agenda should be directed toward the melioration of significant health problems and be particularly suited to the work of departments of OB/GYN. To ensure that the research agenda fulfills its purpose of highlighting the need for expanded research efforts in OB/GYN, the following criteria were applied:

- *The research should contribute to the resolution of an important health problem*. Importance can be defined in terms of high prevalence or incidence of a problem, or the serious effect of the problem on individuals who experience it. Importance can also be defined in terms of impact on the health care system where the costs of caring for the problem axe incurred.
- *The research approach should be promising*. That is to say, there should be reason to think that following the selected avenue of investigation will provide solutions or that answering the question posed by the research is an essential step in finding a solution.

- *The research should be done in a department of OB/GYN or in collaboration with members of such departments*. The mere fact that patients with the problem are first seen by an OB/GYN professional is not sufficient justification. Rather, OB/GYN must be the discipline with the knowledge or skill needed to accomplish the research. If the research is interdisciplinary, OB/GYN should be a necessary element. Lack of interest by other specialties would also be sufficient justification (i.e., the work would not be accomplished if OB/GYN did not do it).

During the period of this study, NIH initiated three activities that will result m research agendas that overlap many areas of the committee's work. The first of these is the Pregnancy, Birth, and Infant Research Plan of the National Institute of Child Health and Human Development. The second is a research agenda being developed by the Task Force on Opportunities for Research on Women's Health. This group, which was assembled by the Office of Research on Women's Health, has been asked to identify the research needed to improve the health of women at all stages of their lives. Its deliberations therefore include such areas as reproductive science and early developmental biology. Discussion at a workshop held by the task force emphasized the need to stress the epidemiological and behavioral aspects of research on women's health. Finally, NIH is engaged in an effort to develop a strategic plan and to that end has drawn on the expertise of several panels, including one on reproductive biology and development and one on infant health and mortality. In their initial work, both panels emphasized the personal and social consequences of unsolved problems in these areas. The panel on reproductive biology and development highlighted seven areas, each of which in whole or in part covers topics that the committee included in its research agenda: the control of reproductive function, infertility, contraception, the molecular basis of embryonic development in animal and plant models, environmental factors affecting reproductive biology and development, and postnatal growth.

In light of these large-scale efforts, the committee felt that it would be duplicative to produce a comprehensive and detailed research agenda. Instead, individual committee members were asked to highlight areas of investigation that meet the criteria listed above and that exemplify the range of questions that might fruitfully be investigated. Because there were no committee members with expertise in behavioral sciences, technology assessment, and outcomes analysis, the agenda outlined in the following sections does not sufficiently emphasize those areas. The committee therefore wishes to stress its opinion that **departments of OB/GYN, in conjunction with individuals with relevant**

expertise, are well suited to undertake investigation of many topics related to behavior that affects reproductive health, the technologies used by the field of OB/GYN, and the outcomes of care provided by OB/GYNs. The large number of patients who receive care in the OB/GYN clinics of academic centers represents an opportunity for clinically relevant epidemiological research—including research on the efficacy of treatment, on the natural history of disease, and on the prevention of disease. Faculty of departments of OB/GYN, in collaboration with epidemiologists, sociologists, statisticians, and health services researchers, have the patient base and the discipline-specific interests needed to investigate questions that other disciplines are not likely to undertake. The committee also believes that the advantages of the patient base and the knowledge that resides in departments of OB/GYN suggest that these departments should organize and conduct clinical/epidemiological trials that are often now initiated by other departments.

The following sections were written by committee members, as acknowledged, and are in large part based on background papers prepared for the committee, whose contributions are gratefully recognized (see Appendix C for a list of background papers).

OOCYTE AND FOLLICULAR DEVELOPMENT IN THE OVARY*

This section identifies areas of research within the broad field of ovarian function that are best and most appropriately pursued in departments of obstetrics and gynecology.

The ovary, an ever-changing tissue, is a multicompartmental tincture with different and variable biological properties. Responding to cyclic pituitary hormone secretion the various types of ovarian cells interact in a highly integrated manner to secrete sex steroids, elaborate a variety of regulatory proteins, and produce a fertilizable oocyte or egg. This section focuses on key unresolved areas in ovarian physiology. All axe viewed as important not only to the understanding of ovarian function but also to the promotion of fertility and fertility control.

* This section was written by Mary Lake Polan and based on papers by Eli Y. Adashi and Robert D. Koos.

Follicular Formation

The primordial germ cells that will become the ovarian eggs originate near the bottom of the embryo where they can be identified as early as the end of the third week of gestation. Migration of germ cells to their final location is accomplished prior to the fifth week of gestation. Whereas some chemotaxis is clearly operational, the precise cellular mechanism or mechanisms underlying the guidance of germ cells to the future ovary remain uncertain. Most importantly, germ cells appear unable to persist elsewhere, and thus the future ovary may be viewed as the only bodily region competent to sustain oocyte development. By the same token, these germ cells play an indispensable role in the induction of gonadal development. During the subsequent 2 weeks of intrauterine life (weeks 5–7 of gestation), often referred to as the "indifferent stage," the primordial ovarian structure constitutes no more than a bulge on the medial aspect of the urogenital ridge. By about 8 weeks of intrauterine life, the future eggs are subject to three simultaneous ongoing processes: mitosis, meiosis, and atresia. As a result of the combined impact of these processes, the number of germ cells peaks by 20 weeks of gestation only to be followed by relentless lifelong and irreversible attrition to a point when the oocytic complement is finally exhausted, thereby giving rise to the menopause.

The prophase of the first meiotic division occurs between week 8 and week 13 of fetal life. Once formed, these primary oocytes persist in prophase until ovulation decades later when meiosis is resumed and the first polar body is formed and extruded. Although the exact cellular mechanism or mechanisms responsible for this meiotic arrest remain uncertain, it is generally presumed that the granulosa cells surrounding the oocyte secrete a putative oocyte meiosis inhibitor (OMI) that arrests egg development. This hypothesis is predicated on the observation that denuded (granulosa cell-free) oocytes are capable of spontaneously completing meiotic maturation under in vitro circumstances. It is not until the first luteinizing hormone (LH) surge occurs, indicating ovulation at puberty, that the first meiotic division is in fact completed. Again, little consensus exists as to the cellular events at play. The first primordial ovarian follicle is noted by around 16 weeks of intrauterine life. It is generally accepted that primordial follicle formation ends no later than 6 months postpartum. There is little information regarding the morphogenic principles responsible for the follicular organization surrounding the oocytes, but it is certain that formation of primordial follicles, the first step in ovarian follicular development, is *independent* of pituitary hormonal secretion. This presumption is strongly supported by the recognition that gonadotropin resistance, such as that

encountered in the so-called "resistant ovary syndrome," does not preclude primordial follicle formation.

The mechanisms responsible for recruiting some, but not other, primordial follicles for further development are unknown. However, this phenomenon underlies the presumed waves of follicular growth responsible for follicular replenishment. Although other factors are undoubtedly at play, it is virtually certain that even the earliest phases of follicular development *beyond* the primordial follicle stage are dependent on the pituitary hormones, follicle-stimulating hormone (FSH) and LH. Support for this conclusion is again derived from studies of the so-called "resistant ovary syndrome," whereto the ovaries display no evidence of follicular maturation beyond the primordial follicle stage. As such, this experiment of nature demonstrates the virtually absolute gonadotropin dependence of early follicular growth beyond the primordial follicle stage.

Proposed Research

- *Elucidation of the events responsible for the transformation of endodermal cells into germ cell elements*. Have the cells in question been somehow imprinted so as to form a germ cell lineage? Or is the endodermal cell totipotential and thus in a position to form unique cellular elements such as a germ cell?
- *Understanding of the forces responsible for guiding the germ cell toward the proper location in the future ovary*. Clearly, chemotaxis appears to be at work. However, tissue remodeling appears equally inevitable, thus implicating extracellular matrix in the genesis of the required path.
- *Clarification of the cellular origins of the somatic follicular cells*—for example, the steroid hormone producing granulosa and theca-interstitial cells surrounding the egg. There is reason to believe that the germ cells may play a morphogenic role by inducing the appearance of their somatic counterparts. Similarly, new information is required as to why germ cells are unable to subsist in bodily regions other than the future ovary
- *Analysis of the cellular mechanism or mechanisms responsible for the initiation of meiosis and for its arrest at the prophase stage of the first division*. Clearer understanding of the ability of the mid-cycle surge to reinitiate meiotic division is required. The apparent biological differences between the cumulus

granulosa cells around the egg and those cells incorporated into the surrounding follicle must play a role.

- *Improved understanding of the role of putative intraovarian paracrine and autocrine regulators*. Understanding such cytokine-mediated mechanisms could eventually lead to improved therapeutic strategies.

Follicular Atresia

Literally translated, *atresia* (a Greek term) means the closure or obliteration ("a," not) of a normal body orifice or passage ("tresos," perforated). In the context of ovarian physiology, follicular atresia denotes the still enigmatic process whereby oocytes are lost from the ovary by means other than ovulation. In fact, atretic follicles are rendered incapable of ovulation. First noted in utero around month 6 of human gestation, atresia continues uninterrupted throughout life, thereby resulting in relentless and irreversible attrition of the ovarian germ cell endowment. It is noteworthy that the newborn human female enters life having lost as much as 80 percent of her egg cell endowment. By the onset of puberty, virtually 95 percent of all follicles have been lost. Of the residual follicular mass, only 400 to 500 follicles (i.e., less than 1 percent of the total) will ovulate in the course of a reproductive life span. Although clear-cut conclusions cannot be drawn at this time, it is generally presumed that postpubertal follicular atresia comprises an underlying tonic component reflecting a lifelong process on which losses of a cyclic, ovulatory nature are superimposed.

The forces guiding most but not all follicles toward certain demise remain unknown. Since all follicles appear to have comparable pituitary stimulation, one is forced to invoke the existence of as yet unrecognized intraovarian principles, the highly regionalized and exquisitely timed expression of which may well determine the direction of follicular development. This reasoning provides compelling arguments in favor of the concept of putative intraovarian regulators, presumably to exert in situ paracrine or autocrine modulatory effects at the follicular level.

The precise identity of the inciting atretic signal notwithstanding, recent advances suggest that follicular atresia represents an example of apoptosis, or programmed cell death, a relatively well-defined process first described by Kerr and colleagues in 1972. An active, energy-requiring process, apoptosis propels affected cells toward selective deletion. Viewed in this light, regulation of the

cellular complement revolves the concurrent and reciprocal processes of mitosis and apoptosis.

Much of the evidence identifying ovarian follicular atresia as an apoptotic process is morphologic in nature. Many of the morphologic features of atresia are reminiscent of the apoptotic process, suggesting that the two may be identical. However, these findings suggest that gonadotropin-primed follicles may respond to an as yet undescribed atretic signal with apoptosis.

Proposed Research

- *Understanding of the molecular events responsible for determining follicular fate*, which is a central goal of reproductive physiology. Clearly, if we could pharmacologically control and perhaps arrest the process of atresia, premature ovarian failure might be successfully treated and the age of the menopause substantially delayed. Likewise, fertility objectives could be served by an improved and augmented germ cell endowment.
- *Development of a reliable, reproducible experimental model for improved understanding of the atretic process*. None exist at this time.
- *Understanding of the apoptotic nature of the atretic process and, in particular, of the ionic events that appear to trigger the molecular enzymatic events.*
- *Focused investigation of potential putative intraovarian regulators concerned with the atretic process*. Although sex steroids have been extensively implicated in the genesis and prevention of atresia, the body of literature remains equivocal and insufficient.

Follicular Recruitment, Selection, and Dominance

The term *recruitment* is used to indicate that a follicle has entered the so-called growth trajectory, that is, the process whereto the follicle leaves the resting pool to begin a well-characterized pattern of growth and development leading to ovulation. Clearly, recruitment is a necessary but not sufficient condition for ovulation to occur.

Follicular selection implies the final winnowing of the maturing but not yet quite dominant follicular cohort to the size of the species-characteristic ovulatory quota, which for the human is a single follicle each month. In the human,

follicular selection is presumed to occur during the first 5 days of the cycle when the leading follicular diameter is 5–10 mm.

The term *dominance* refers to the status of the follicule destined to ovulate, given its presumed key role in regulating the size of the ovulatory quota. It is generally agreed that a selected follicle becomes dominant about a week before ovulation, that is, as early as days 5–7 of the cycle when the diameter is around 10 mm. The earliest hormonal index reflecting dominance, which is evident at times as early as days 3–5 of the cycle, is an increase in the circulating levels of estradiol in the vein draining the ovary later shown to bear the corpus luteum. According to one view, the follicle selected for ovulation is functionally (not merely morphologically) dominant in that it inhibits the development of other competing follicles on both ovaries. Presumably then, the dominant follicle takes on an active role in ensuring its preferred status. Inevitably, and for reasons not entirely clear, the dominant follicle continues to thrive under physiologic circumstances it has made inhospitable to others.

Proposed Research

- *Development of more specific markers capable of predicting the general well-being of the follicle in question and most importantly the quality of the resident oocyte*. Such parameters would be of clinical relevance to in vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT).
- *Improved understanding of existing known cytokine and growth factor regulators and the elucidation of the potential role of as yet unrecognized peptides*. Although the central role or roles of gonadal steroids m folliculogenesis are well accepted, the variable fate of follicles afforded comparable gonadotropic stimulation strongly suggests the existence of additional intraovarian modulatory systems. This kind of investigation should yield clues as to how a follicle is selected and spared from atresia.

Corpus Luteum Function

As interesting as cell growth during follicular development is the cessation of cell growth and/or cell death. Granulosa cells divide on average only once following the preovulatory LH surge and then differentiate into luteal cells.

Proposed Research

• *It would be interesting to determine if the block to cell proliferation involves known genes associated with suppression of cell growth (perhaps one or more of the recently discovered tumor-suppressor genes, such as the retinoblastoma, or RB) or new examples of similarly functional genes*. Action of the RB gene product involves TGF-B. Relatively little is known about TGF-B in the ovary except for cent reports by Schomberg and co-workers that at least forms of this factor axe synthesized there and that the expression of TGF-B2 is hormonally regulated.

It is now recognized that the extracellular matrix and cell surface molecules that specifically bind to matrix components play an important role in the regulation of cell growth and function. These include various glycosaminoglycans, like heparinsulfate, which are known to be synthesized by granulosa cells and axe present in the ovarian follicle. Almost nothing is known about the extracellular matrix or adhesion molecules in the ovary during the differentiation process from granulosa to luteal cell and during the lifetime of the corpus luteum.

Not surprisingly, numerous growth factors have been reported to be synthesized in the ovary. Despite the common belief that these factors play important roles in follicle rupture and corpus luteum formation and function, very little hard evidence about their specific actions and receptors is available. The only exception may be the insulin-like growth factors (IGFs), which have been the focus of several groups. Most of the studies on growth factors in the ovary have involved the addition of these factors to granulosa cells or other ovarian cell types in vitro and an examination of their effect on gonadotropin binding, steroid synthesis, and other markers of differentiated cell function. In the absence of adequate information about the spatial and temporal production of these factors and their receptors in the ovary, however, such studies are of limited value; the findings may or may not be of physiological importance.

The availability of sensitive molecular techniques such as in sire hybridization and reverse transcription-polymerase chain reaction now makes it possible to accurately determine where and when the genes for growth factors and their receptors are expressed in the ovary.

Leukocytes, Cytokines, and Ovarian Function

It has long been recognized that various leukocytes are present in the ovary and that their numbers increase dramatically in the corpus luteum. However, almost nothing is known about their possible role in ovarian function. There have been numerous recent reports of the presence of various cytokines in the ovary and of the effects of cytokines on the differentiated function of ovarian cells. These include various interleukins, tumor necrosis factor (TNF), transforming growth factors, platelet activating factor (PAF), and heparin. Heparin, a product of mast cells, appears to play an important role in the actions of various growth factors.

Proposed Research

- *Determine the physiological role of immune system—derived products on ovarian function.*

Follicular Fluid

We know surprisingly little about the specialized microenvironment of the follicle, and until we do, it will be impossible to understand completely how the follicle (1) synthesizes the hormones that integrate all reproductive function and (2) nurtures the gamete to maturity. This applies to the follicular fluid, which bathes the granulosa cells and developing oocyte. While follicular fluid has been readily available, we have only the most rudimentary knowledge of the biologically active materials that it contains. We know that human follicular fluid is a potent enhancer of serum-stimulated endothelial cell proliferation. Recent reports indicate that follicular fluid stimulates sperm motility and contains a chemoattractant for sperm. The level of chemoattractant activity correlates with fertilizability of the egg from the same follicle.

Proposed Research

• *The identification of this factor might lead to ways to identify healthy eggs and to promote the fertilization process with direct benefit for women using the new reproductive techniques of IVF and GIFT.*

Conclusion

Although traditional wisdom ascribes the role of "master gland" to the pituitary, the ovary may, in fact, play an active rather than a passive role in the initiation and maintenance of reproductive cyclicity and function. Thus, the ovary is central to a woman's reproductive capacity. Our limited under-standing of these reproductive events mandate continued and focused research in the areas of ovarian function described above. Not only is there an abundance of basic research topics that have important implications for solving problems of human fertility and infertility, but a better understanding of ovarian function would illustrate other normal and pathologic processes involving the regulation of cell growth and differentiation in many other organ systems.

The basic questions of physiology, cell growth, and differentiation are relevant to many human disease states that result in infertility and clinical aberrations of ovarian function. Such clinical problems as premature ovarian failure and anovulation, polycystic ovarian disease, and luteinized unruptured follicle syndrome are the province of gynecologists and obstetricians. It is, therefore, most appropriate that research on the intricacies of ovarian function be performed in departments of gynecology and obstetrics. These physician-scientists have the critical ability to investigate basic biological questions with the full knowledge and understanding of their relevance to human disease states. Not only does the gynecologist's interest, by definition, lie in the realm of ovarian function, but his or her understanding of the myriad facets of clinical aberration and disease allows for the critical link between basic scientific investigation and its applications to human disease with the potential for cure.

FERTILIZATION*

Reproductive cell biology can be considered the science basic to obstetrics and gynecology, but the literature, cell biology, physiology, and biochemical information dealing with the fertilization process is primarily comparative. Most of the information is derived from invertebrates, nonmammalian vertebrates, mammals such as rats and mice, and nonhuman primates. Little is derived from studies of humans.

* This section was written by Everett Anderson.

Ignorance about the basic science of the fertilization process in humans no doubt is revealed in the high failure rate of some human in vitro fertilization procedures. This failure rate underscores the point that conclusions drawn from mice, rats, rabbits, and hamsters may not wholly apply to humans. Animal models should not, however, be abandoned. Moreover, the high failure rate may be because certain aspects of the fertilization process are *unique* to humans. Therefore, there is some urgency about the acquisition of a fully detailed analysis of the cell biology, physiology, biochemistry, and molecular biology of the human fertilization process. Investigations of the basic science of the fertilization process in humans (and other animal models) by an obstetrician trained in cell biology, physiology, biochemistry, or molecular biology in a department of obstetrics and gynecology can and will make important contributions to our understanding of this important process.

What follows are general aspects of the fertilization process in mammals. For details, readers are directed to the references at the end of the chapter. This discussion also offers avenues of research that appear warranted to gain further insights into the fertilization process in humans.

Fertilization is a multistep phenomenon beginning with the interaction of the female and male gametes and the subsequent interaction of maternal and paternal chromosomes derived from the female and male pronuclei. During the process of fertilization each gamete becomes activated, which leads to biparental heredity and subsequent cleavage of the non-uninucleated zygote. Fertilization involves the following steps:

1. Sperm first become associated with the ovulated egg with its associated cumulus cells (granulosa cells). Sperm become associated with the cumulus cells, and some are attached to the extracellular coat or matrix known as the zona pellucida.
2. The associated sperm brads to the zona pellucide.
3. The bound sperm completes the important acrosomal reaction.
4. The acrosomal-reacted sperm then digests its way through the thick zona pellucida.
5. When the sperm reaches the perivitelline space (the space between the egg and the zona pellucida), it fuses with the plasma membrane of the egg.
6. The fusion of the sperm with the plasma membrane of the egg initiates the release of cortical granules, thereby musing the zona reaction and the release of the second polar body.
7. The decondensation of the sperm nucleus occurs.

8. The female and male pronucleus forms.
9. Cleavage of the zygote takes place.

As the sperm travels through the female reproductive system it becomes capacitated, that is, competent for fusing with the egg in the ampullary region of the oviduct. Over the head of the sperm is the acrosome, a lysosome-like organelle. In an effort to expose the inside hydrolytic enzymes to the zona pellucida, the acrosome undergoes the acrosomal reaction, which is Na^+ and Ca^{2+} dependent. This reaction consists of the fusion of the acrosomal membrane with the sperm membrane, thereby producing a series of hybrid vesicles. The hydrolytic enzyme acrosin (a trypsin-like proteinase) permits the sperm to penetrate or enzymatically digest its way through the zona pellucida.

The zona pellucida consists of three different glycoproteins of different molecular weights known as ZP (zona pellucida) 1, 2, and 3. Of interest is the fact that the mouse sperm receptor is the ZP3 glycoprotein, which consists of a 44,000-dalton polypeptide chain that has a number of asparagine-linked and serine-threonine-linked oligosaccharides covalently linked. It is believed that ZP3 is the acrosome reaction inducer alluded to above.

When the acrosome-reacted sperm makes its way by proteolysis through the thick zona pellucida, the postnuclear cap region of the sperm fuses with the plasma membrane of the egg. The fusion of the sperm with the egg's plasma membrane induces a *zona reaction*. The zona reaction is a biochemical change of the zona pellucida induced by the contents of the cortical granules. This biochemical change in the zona pellucida prevents other sperm from penetrating and sets up the *slow block* to polyspermy, the results of which induce pathological conditions. On the other hand, when the sperm fuses with the egg, depolarization of the egg's plasma membrane occurs within seconds. This transient alteration of the egg plasma membrane presumably results from an altered membrane permeability to certain ions. This depolarization of the egg plasma membrane after sperm fusion provides a *fast block* to polyspermy, a situation that is not well understood in mammals. However, a fast block to polyspermy in mammals should not be ruled out and requires further detailed investigations.

Cortical granules are glycoprotein-rich organelles that are produced by the corporation of the rough endoplasmic reticulum and the Golgi complex. These membrane-bound organelles migrate to the cortical cytoplasm where each becomes associated with the inner aspects of the egg plasma membrane. There is evidence that some of the cortical granules are released prior to ovulation. However, after sperm fusion, the remaining cortical granules fuse with the egg

plasma membrane, thereby intercalating their membrane into that of the egg. The conical granules, as reported by investigators, contain various hydrolytic enzymes such as proteinases and peroxidases, which are deposited within the perivitelline space and diffuse into the zona pellucida, thereby inducing the zona reaction mentioned above.

The fusion of the egg with the sperm initiates the activation process that alters the metabolic activity of the egg and sperm. As indicated earlier, the fusion of the egg produces *inter alia* the release of the second polar body, which means that the meiotic process is now complete—a process reinitiated by the sperm. This fusion also permits the continuation of a cascade of events that produces a maturation-promoting factor.

Following the release of the second polar body, the chromosomes form the female pronucleus, which contains a nucleolus and associated chromatin. Along with the formation of the female pronucleus is the formation of the male pronucleus. The condensed, incorporated *sperm nucleus* commences to lose its nuclear envelope, and the chromatin becomes dispersed and eventually acquires another nuclear envelope. The dramatic morphological changes, and no doubt biochemical changes, leading up to the formation of the male pronucleus prompted a classical embryologist to say that it is almost as if the sperm needed fertilizing.

The male and female pronuclei are large, round structures and it is difficult to tell which is female and which is male. The male and female pronuclei become closely opposed. Two asters that are established will become the poles of the mitotic spindle for first cleavage. The chromatin of each pronucleus condenses into individual chromosomes. The nuclear envelopes break down. Ultimately, the chromosomes move to the metaphase plate, and cleavage takes place, thereby forming two-unit nucleate blastomeres containing the chromosomal number of the investigated mammalian species.

Proposed Research

- *Continued investigation of the role of maturation-promoting factor(s) in the reinitiation of meiosis and the continuation of egg maturation.*
- *Continued investigation of the molecular biology of sperm chromatin processes.*
- *Continued investigation of the biochemical composition of cortical granules and the significance of cortical granule dehiscence prior to sperm-egg fusion, as well as their general role in the fertilization process.*

- *Determination of the physiology and biochemistry of germinal vesicle breakdown.*
- *Further investigation of the molecular events and physiology of the formation of maternal and paternal pronuclei.*
- *Determination of the physiology and biochemistry of male and female pronuclei (envelope) breakdown and the re-condensation of their chromosomes.*
- *Continued investigation of the molecular biology of the zona proteins and their significance to sperm binding. Particular questions include how are zona proteins related to the slow block to polyspermy, and how sperm receptors are inactivated?*
- *Continued investigation of the fast block to polyspermy following the sperm-egg fusion.*
- *Investigation of the biophysics of sperm-egg-cortical granule fusion.*
- *Continued investigation of the molecular biology of sperm capacitation.*
- *Continued investigation of the molecular biology of the acrosome reaction with an emphasis on understanding the significance of the hydrolytic enzymes and their role in the general process of fertilization.*
- *Definition of the molecular events of the first cleavage, focusing on the involvement of cyclins. Continued focus on each of the fertilization events, keeping in mind a possible means of interruption as a contraceptive tactic.*

FETAL GROWTH AND DEVELOPMENT*

Research in the area of embryonic and fetal development remains an important frontier of biomedical research. Because of their unique positions as the guardians of reproductive health, obstetricians and departments of obstetrics and gynecologists should have a central role in the development of research programs concerned with human developmental biology, including the study of early embryonic events and mechanisms underlying embryoinc and fetal growth. Such research draws on the techniques and methodologies of diverse disciplines including genetics, molecular and cell biology, and physiology. Leaders in departments of OB/GYN should take the initiative in promoting the study of fetal growth and differentiation using the array of methodologies made available through modern science. A broad approach to the study of fetal growth will not only provide an opportunity to examine the basis of growth and differentiation but will also stimulate investigation into fundamental aspects of placental

* This section was written by Joseph B. Warshaw.

function and fetal nutrition, including the study of mechanisms by which nutrients are transferred to the fetus from the maternal compartment. Departments of OB/GYN should also take the lead in examining environmental and genetic influences on fetal growth, and participate in the development of techniques and methodologies to diagnose and treat the fetus with structural or genetic defects or abnormalities resulting from maternal disease states. While there has been progress in our ability to diagnose fetal disease, the options for intervention remain quite limited. Research to develop such interventions should be vigorously pursued by departments of obstetrics and gynecology. Specific areas of research opportunity are outlined below.

Embryology and Congenital Malformations

Abnormal fetal development imposes a great societal economic burden, and its emotional costs to families and patients are incalculable. Three percent of infants will be born with a major malformation, and a much higher percentage of pregnancies terminate because of major chromosomal and/or structural defects. Congenital defects have their origin in early gestation, which is characterized by rapid cell division and organ development. The speed of these events is illustrated by closure of the neural tube between 19 and 29 days of gestation and by development of the heart from the time of the first heartbeat at 21 days to its differentiation as a four-chambered pumping organ by 56 days. Major malformations that can profoundly influence subsequent fetal growth and development are already established by the end of the third fetal month, and it is during this period of time that major genetic and structural defects commonly result in pregnancy loss. Obstetric investigators should participate in the challenge of understanding the basis of abnormal development.

Proposed Research

- *Investigation of the basis of genetic regulation of early embryogenic events, including the role of homeotic genes in both normal embryogenesis and in congenital malformations.*
- *Characterization and study of embryologic mechanisms, including cell-cell interactions, cell migration, cell matrix interactions, and programmed cell death, all of which are important in normal and abnormal development. Development and exploitation of tissue and embryo culture techniques to examine*

developmental mechanisms and teratogenic influences on development including a study of drug-induced malformations as well as those resulting from conditions such as maternal diabetes or abnormal immune states.

- *Investigation of endocrine and growth factor signaling that modulates fetal growth and organ maturation—for example, the basis of actions of muellerian inhibitory factor (MIF) and androgens in regulating sexdifferentiation.*

Fetal Growth and Placental Transport

The second trimester of pregnancy is largely a period of growth and functional refinement of organ systems that must be mature by the time of delivery. For example, the brain undergoes the waves of migration and differentiation that are the basis for neural integration and the behaviors necessary for postnatal survival. During this time there is rapid functional differentiation and growth of such systems as the lungs and gut.

During the third trimester, there is rapid fetal growth and deposition of storage fuels such as fat and glycogen, and the fetus quadruples in weight. Fetal growth throughout pregnancy can be influenced by genetic or environmental factors that are important subjects for obstetric investigation. Genetic disorders such as trisomy 18, Down's syndrome, or Turner's syndrome are obvious causes of fetal growth restriction, but the mechanisms by which aneuploid chromosomal defects result in abnormal fetal growth remain largely unexplored. Growth restriction resulting from decreased uteroplacental blood flow in such conditions as pregnancy-induced hypertension also continues to be an important cause of newborn morbidity and is representative of a group of problems that should be pursued vigorously by obstetric investigators.

Proposed Research

- *Placental transport during normal development and under conditions in which nutrient flow is compromised.*
- *The mechanisms by which specific disease states alter transport processes and the basic signaling mechanisms that regulate fetal growth and organ maturation. For example, infants of diabetic mothers with excessive substrate delivery and of large fetal size show a delay in organ maturation, whereas those with intrauterine growth restriction secondary to fetal malnutrition*

exhibit accelerated lung and brain maturation. The mechanisms underlying such changes are largely unknown.

- *Metabolic regulation during development.*

Congenital Infection and Substance. Abuse

Congenital infections can also have profound influences on fetal growth and should be part of the domain of obstetric research. This area includes viral infections such as cytomegalovirus disease, which is the most common congenital infection, and conditions such as congenital syphilis and toxoplasmosis. Congenital HIV infection is a national tragedy with thousands of infected infants, and there is a growing incidence of other sexually transmitted diseases that can have an impact on fetal and newborn health. The obstetric investigator must also be concerned about our modern epidemic of substance abuse, including heroin, alcohol, cocaine, and cigarettes. Cigarette smoking remains the most important cause of preventable mortality and morbidity, yet women continue to smoke during pregnancy. Research needed in these areas includes biological investigations as well as opportunities for epidemiologic and behavioral research.

Proposed Research

- *Studies of mechanisms of maternal to fetal transmission of viruses.*
- *Development of strategies to alter high-risk behaviors.*
- *Investigation of pathogenesis of defects resulting from congenital infection.*
- *Development of drug surveillance and treatment programs.*

Perinatal Research

There are opportunities for perinatal research in departments of obstetrics—as, for example, studies of mechanisms responsible for the transition from fetal to extrauterine life. Important developmental events include maturation of lung and the surfactant system, intestinal maturation, and the cardiopulmonary adaptations necessary for extrauterine survival. A major challenge will be to develop a more complete understanding of influences on

fetal growth and maturation so that new therapies and interventions can be developed that will ensure the most optimal fetal outcome. Since Liggins defined the role for glococorticoids in pulmonary lung maturation nearly 20 years ago, there have been a myriad of clinical studies and evaluations, but relatively few of these have been translated into clinical trials.

Proposed Research

- *Investigation of what controls the signaling that induces lung maturation in preparation for the extrauterine environment.*
- *Development of new therapies to induce maturation.*
- *Investigation of the influences of maternal disease states and environmental insults on maturational events.*
- *Refinement of techniques for fetal surveillance and the development of better indices for normal and abnormal function.*
- *Development of new systems to deliver drugs, replacement hormone therapy, or nutrients to the fetus.*

Epidemiological Research

There are clinical epidemiology research opportunities for departments of OB/GYN in defining and following at-risk populations and also in clinical trials involving obstetric patients. Programs in clinical epidemiology can be carried out in many institutions including those that would not have the resources for expensive and highly technical laboratory research programs. Almost every aspect of obstetric practice can generate important questions.

Proposed Research

- *How does prenatal care reduce perinatal morbidity?*
- *How can we measure the effectiveness of social and behavioral interventions in changing high-risk behaviors that impair and limit fetal development?*
- *How do specific obstetric interventions—for example, cesarian section and maternal nutritional supplementation—affect newborn outcomes?*

There are many additional research opportunities for departments of OB/GYN that are not developed here. These include technologies for fetal surveillance and diagnosis, which have opened a new window on early developmental events; embryology and fetal physiology have been a major focus of the new biology, and departments of obstetrics should be full participants in the research being conducted.

PRETERM LABOR*

Preterm birth is a major health hazard of humans worldwide, being the leading cause of newborn and infant mortality and the principal cause of significant, often severe, morbidity for infants who survive. And ironically, the successful salvage of very small neonates today is largely attributable to rapid advance in neonatal care, which makes it inevitable that even more premature infants are now destined to sustain life-long disabilities. The only apparent solution to this devastating health problem is the prevention of premature birth. There are a number of different causes of preterm birth, including maternal and fetal complications that mandate delivery independent of the onset of labor, and preterm rupture of the membranes. But regrettably, preterm labor remains a common problem not yet solved in spite of the widespread use of tocolytic agents to arrest myometrial contractions. Therefore, new approaches must be developed to enable us to arrest or prevent the parturitional process when preterm labor threatens a pregnancy.

Preterm, Premature Rupture of the Fetal Membrane

Preterm delivery is the natural outcome of preterm, premature rupture of the fetal membranes. After the integrity of the fetal membranes is compromised, by whatever cause, preterm labor commonly follows. If preterm labor does not begin soon after membrane rupture, infection by way of colonization by microorganisms arising in the vagina or endocervix will precipitate preterm labor or else threaten the fetus by way of fetal respiratory movemeats that carry the infected amniotic fluid into the fetal lungs. The incidence of preterm, premature rupture of the fetal membranes as the primary cause of preterm delivery varies somewhat among populations of pregnant

* This section was written by Paul C. MacDonald.

women, but generally accounts for 35 percent to 40 percent of preterm births. Despite the devastation wrought by this complication of pregnancy, our understanding of the regulation of synthesis and degradation of the extracellular matrix of the fetal membranes and contiguous decidua parietalis is primitive. The metalloproteinases have been isolated, the amino acid sequence is known, and the genes have been cloned. The same is true of the major metalloproteinase inhibitors. Much is known of the regulation of synthesis of these major determinants of extracellular matrix formation and degradation in other tissues, but little or no information is available concerning the fetal membranes.

Proposed Research

- *Research must be directed to understanding the regulation of synthesis and degradation of the extracellular matrix of the fetal membranes and contiguous decidua parietalis.*
- *It is suspected, but not established, that infection by way of the action of bacterial toxins (lipopolysaccharide, or LPS) may serve to initiate the formation of metalloproteinases that act upon the extracellular matrix of chorion laeve and amnion. We must ascertain if this is a mechanism by which fetal membrane rupture is commenced because if this is indeed the case, the condition is theoretically preventable.*

Complications of Pregnancy That Compromise Fetal or Maternal Well-Being Independent of the Onset of Labor

Depending on the population of pregnant women studied, 25 percent to 30 percent of preterm deliveries are mandated by complications of pregnancy that beset the mother or fetus, or both, that are independent of the onset of labor. Among the major categories of complications are pregnancy-associated hypertension that sometimes is also associated with abruptio placenta, diabetes mellitus, intrauterine growth retardation, and multiple pregnancies. Pregnancy-induced hypertension (PIH) or preeclampsia/eclampsia remains a common problem of pregnancy, especially in a first pregnancy. It is difficult to generalize about the incidence of hypertensive disorders in pregnancy because of the striking variations, depending on parity, socioeconomic status, and race

of the population examined. Nonetheless, in all populations of carefully monitored women, the incidence is greater than 2.6 percent. The subject is reviewed in Williams' *Obstetrics* (18th ed., pp. 656–657). Commonly, the incidence for hypertension among all pregnant women in the United States is believed to be 5 to 6 percent. With limited family size, however, a larger proportion of the obstetric population now is accounted for by women having their first child; and in nulliparous women, the incidence of PIH is much greater than in multiparous women. And with respect to the major problems of pregnancy, for instance, maternal death, fetal growth retardation, abruptio placenta, and so forth, all forms of hypertension in pregnancy must be considered high-risk factors. In approximately 50,000 pregnancies at Parkland Memorial Hospital, the incidence of pregnancy-reduced or pregnancy-aggravated hypertension was 13 percent. Indeed, 20 percent of nulliparous women developed hypertension. Although a largely indigent population was studied, it is a population in which the rate of delivery of prenatal care is high.

There is some optimism that modifications in the formation of prostaglandins at the level of platelets may reduce the incidence or severity of pregnancy-induced hypertension. Such modifications are accomplished by daily administration of low-dose aspirin. At best, however, this appears to be a temporizing approach, and little insight has been gained into the cause or methods of preventing this disorder that threatens fetal well-being and in some cases maternal health. Moreover, many pregnancies are threatened by failure of fetal growth, with or without coexisteat mammal hypertension. Yet we have no knowledge of the basic pathophysiology of the causes of severe fetal growth retardation.

Proposed Research

- *Research is needed on the pathogensis of pregnany-associated hypertension.*
- *Research must be directed toward defining the pathophysiology of the processes that mandate delivery prematurety even though independent of labor. Commonly, the obstetrician is faced with choosing between a deteriorating intrauterine environment for the fetus and the neonatal intensive care nursery for a sick newborn.*

Preterm Onset of Labor

Preterm labor in pregnancies with intact membranes accounts for 30–40 percent of preterm deliveries in most populations. The incidence of preterm birth in the past 10 years has not decreased despite the extensive use of B-mimetic tocolytic agents. Indeed, it is estimated that more than 100,000 pregnancies in the United States alone are treated each year with such agents; yet there is no evidence that such treatments have resulted in a significant reduction in preterm birth or perinatal mortality. The reasons for this are probably multiple, including severe side effects of such drugs in the mother, down regulation of beta-adrenergic receptors, and complicating factors of pregnancy that preclude the use of or the effectiveness of the tocolytic drugs.

For the past 25 years, investigators have sought to define the nature of a presumed uterotonin that is produced in incase amounts at or near term to cause the spontaneous onset of labor. The most thoroughly studied candidates have been oxytocin and prostaglandins. Yet it now seems likely that the generation of these uterine contractants, in increased amounts, occurs after the onset of parturition and not before. Perhaps such agents act in the normal parturitional process to facilitate and maintain labor once parturition is initiated by some other mechanism.

Possibly the most curious feature of normal human pregnancy is the remarkable tolerance of the uterus to its burden. The myometrial smooth muscle is, inherently, a contractile organ. Strips of human myometrium placed in an organ bath contract spontaneously. If a very small intrauterine device is placed into the uterine cavity of a nonpregnant woman, the uterine contractions commonly are so severe as to produce expulsion or to necessitate its removal because of the pain that occurs. But in normal pregnancy, the uterus remains quiescent, accepting intrauterine distention to accommodate an 8-pound baby, 1–2 pounds of placenta and fetal membranes, and 1 liter of amniotic fluid.

Proposed Research

- *Information must be assembled to understand the fundamentals of the maintenance of pregnancy and the spontaneous initiation of parturition at term.*
- *What are the physiological processes that effect such a stronghold on uterine contraction during human pregnancy?*
- *How are these processes translated at the biomolecular level?*

- *What is the role of the fetus in the maintenance of pregnancy and in the retreat from pregnancy maintenance at the end of normal gestation? It now seems very likely that retreat from pregnancy maintenance is the most likely choice of potential mechanisms for the initiation of spontaneous labor at term. Therefore, we must define in great detail the processes that bring this remarkable situation about.*
- *An understanding of the contractile properties of the uterus before and during pregnancy must be gained.*
- *The role of Ca* $^{2+}$ channels and Ca^{2+} sequestration must be understood as these apply to the uterus of pregnancy.
- *The contribution of the unusual hormonal milieu of human pregnancy to the maintenance of uterine quiescence must be investigated. Before we can realistically address the causes of preterm labor, an understanding of these processes operative in normal human parturition at term must be acquired.*

Preterm Labor and Infection

The only major clue to the cause of preterm labor is that "silent" infection in some pregnancies appears to lead to the premature onset of labor. It is envisioned that colonization of fetal tissues (fetal membranes [amnion and chorion laeve]) or maternal tissues (uterine decidua parietalis), or both, with microorganisms arising by ascending spread from the vagina or cervix, may cause preterm labor. Specifically, the elaboration of bacterial toxins may cause the generation of cytokines, namely, IL-1 and TNF-a, which act in many tissues to provoke prostaglandin formation. This may be true; but it has not been established definitively whether evidence of infection (inflammation) is the cause or the consequence of labor. That is, did inflammation cause the onset of parturition, or did labor beget the inflammatory processes? This is an extremely important issue because if infection is a common cause of preterm labor in pregnancies with intact fetal membranes, there is reason to believe that preterm labor in those instances could be prevented. On the other hand, if preterm labor leads to inflammatory processes, we would have no success in preventing preterm labor by use of antimicrobial agents. At present, millions of dollars are being expended each year to treat women with antibiotics to evaluate this issue. If inflammation follows the onset of labor, such ventures are doomed to failure.

There are other considerations of great importance in defining the cause of preterm labor. Clinical data make it clear that there must be a heterogeneous group of associated disorders. One of the common antecedents of preterm labor

is preterm cervical effacement and dilatation. A large number of pregnancies that terminate in preterm labor will be known to have preterm cervical dilatation without apparent increased myometrial activity for days to weeks before the onset of active labor. And in some such cases, the preterm labor is very prolonged; that is, slow cervical dilatation may continue with or without contractions noted by the pregnant woman for days. During this time of cervical patency without vigorous contractions, the forebag is exposed to microorganisms and bioactive agents in the vagina. Thus, the superimposition of an inflammatory response may both confuse and facilitate the progression of labor.

Proposed Research

- *Research must be conducted to establish the role, if any, of infection in the preterm onset of labor.*
- *An understanding of the cause or cause, of preterm cervical dilatation is urgently needed*. We must understand the role of this condition within the sequence of events that terminatej in the preterm onset of labor. In addition, it is commonly believed that extrauterine refections, such as pneumonia, appendicitis, and pyelonephritis are commonly associated with preterm labor.
- *The nature of the pathophysiology of the association with preterm labor and extrauterine infections also must be defined*. Other conditions, including fetal abnormalities with or without hydramnios, also seem to be associated with the preterm onset of labor. Thus, there may be multiple causes of preterm labor or else a common cause mediated by way of several contributing factors.

Role of the Obstetrician in Research to Define Physiological and Pathophysiological Mechanisms of Spontaneous Parturition at Term and the Preterm Onset of Labor

The obstetrician is ideally suited by training and experience to conduct fundamental studies related to the problem of preterm delivery and preterm birth, provided he or she has acquired skills in basic science research. The anatomical relationships of fetal and maternal tissues are understood best by the obstetrician. It is appreciably easier for the obstetrician to place in perspective the role of trauma sustained during labor and the physiological or

pathophysiological sequelae thereof in the category of consequence, not muse, of parturition. The obstetrician can appreciate the potential role of infection, whether it occurs before or during labor, in the parturitional process. The obstetrician also is best suited to distinguish between presumed preterm labor and labor that does in fact eventuate in preterm delivery. And the obstetrician is best suited to deal with the complications of pregnancy, revolving either the fetus or mother, or both, that may mandate delivery independent of the onset of labor. Thus, there is an urgent need for obstetricians trained in the basic sciences to conduct research to define the sequence of biomolecular events that lead to the initiation of parturition and to seek to identify the muses of preterm labor.

CONTRACEPTION*

There are numerous studies on the biological consequences of various contraceptives. Even though the focus of most research has been on the risks of contraceptives, the benefits continue to be elucidated. For example, it is now established that oral contraceptives (OCs) offer women protection against gonococcal pelvic inflammatory disease. (PID), anemia, ovarian cysts, and ovarian and endometrial cancer. There is also an array of evidence to suggest that women using OCs are also protected against osteoporosis and atherosclerotic cardiovascular disease. These are impressive beneficial effects for an agent that is taken primarily to prevent unwanted pregnancy. In spite of this, women are not happy with their contraceptive options. At best, 50 percent of current contraceptors are satisfied with their present method. Thus, there is an opportunity for research on contraceptive development with an emphasis on methods that will have beneficial effects for users.

Proposed Research

- *Develop contraceptives that protect women against breast and cervical cancer.*
- *Increase user satisfaction by offering contraceptors a wider array of choices.*

* This section was written by C. Wayne Bardin.

- *Provide contraception for some underserved groups including men, lactating mothers, teenagers, and permenopausal women.*
- *Develop contraceptives that protect women against sexually transmitted diseases (STDs).*

If contraceptive research is to be successful, it must be conducted with the cooperation of women who wish to have new and better methods of family planning. Departments of obstetrics and gynecology are in an almost unique position to develop new contraceptives since many young women seek advice from gynecologists for reproductive health care, including contraception. Thus, the gynecologist can study the desires of women and conduct appropriate clinical research into new contraceptive methods.

In the past, almost any kind of research in the field of reproduction has been considered contraceptive research with the view that any new finding could conceivably lead to a new method of fertility control. However, since new ideas can take up to 20 years to be developed into a method that can be used in clinical practice, one must reasonably conclude that a major portion of contraceptive research should focus on studies that will advance the introduction of new clinical entities in the foreseeable future, preferably within the lifetime of the investigator. As a consequence, the agenda that follows is focused on methods that could be completed in the present century, were funds available to conduct the research.

Contraceptive Implants

The recent introduction of Norplant has offered women a new option for long-term, low-dose, progestin-only contraception. In view of the acceptability of this method, it is clear that improved implants using levonorgestrel and other progestins such as 3-ketodesogestrel, ST 1435, and 19 nor-medroxyprogesterone acetate (19 nor-MPA) would be highly desirable. These highly potent progestins are good candidates for a single or double implant system that will provide contraception for 1 to 3 years. The ability to provide effective contraception with one or two implants would be a major improvement over Norplant, the six-capsule system, which is the only approved contraceptive implant. ST 1435 and 19 nor-MPA are structurally similar to progesterone, distinguishing them from most other currently marketed progestins, which are related to androgens and estrogens. Like progesterone, and unlike most other progestins, ST 1435 and 19 nor-MPA have no apparent effect on serum

lipoprotein patterns. In addition, the fact that some of these progestins, like progesterone, are rapidly metabolized by the liver after oral administration, suggests that they may be suitable contraceptives for lactating women, since any steroid transferred to the infant through the milk would be inactivated.

The contraceptive action of progestins used in implants must occur at dosages of 50 to 100 μg/day so that inhibition of ovulation and alteration of cervical mucus will occur at doses that can be delivered by this method. At these doses, many of these progestins have not shown unexpected effects m humans. For example, in clinical trials, ST 1435 had no apparent effect on carbohydrate metabolism, serum lipoprotein patterns, and hepatic proteins such as hormone-binding globulins. The most common complaint associated with implant use, and with all other forms of progestin-only contraception, is bleeding irregularities. Other side effects have been minor medical conditions, such as headache or acne.

Proposed Research

- *Develop new drug delivery systems for steroids that would improve the pharmacokinetic profile to eliminate long-term tail-off of drug release once implants were sufficiently depleted of steroid as to be ineffective.*
- *Assess the carcinogenic and other long-term effects of progestins on the breast, cardiovascular system, and other organs.*
- *Conduct and evaluate implants in clinical trials.*
- *Conduct long-term studies on NORPLANT to determine the health benefits and risks of long-term, low-dose, progestin-only contraception compared with combined oral contraceptives.*
- *Develop biodegradable implants that can be removed at any time and that do not have a long period of drug tail-off.*
- *Conduct studies in lactating women with ST 1435.*

Contraceptive Rings

Contraceptive rings (CRs) that deliver steroids by the vaginal route have several advantages over other methods of contraception. First, tings are convenient since, unlike oral contraception, they do not require daily administration or attention. Second, steady blood levels of steroid resulting from the ring's constant drug release allow for more efficient contraception, thus lowering

contraceptive dosage, which diminishes the likelihood of adverse effects. Third, if estrogen is included in the CR, the adverse reactions that may be associated with oral contraception are milder. Fourth, ring contraception is under user control, a feature desired by many women.

Contraceptive rings may be formulated in two ways. The first type consists of a progestin combined with an estrogen. Any progestin/estrogen combination used in contraceptive pills could, in theory, be used in CRs. A progestin/estrogen-containing ring is used for 3 weeks and is then removed for 1 week to allow menstrual bleeding. This 3 weeks-in/1 week-out schedule is continued for the lifetime of the ring. Such a formulation is designed to inhibit ovulation and to produce minimal menstrual disturbance. There are currently no combination rings on the market, but several are being developed.

The second type of ring is a progestin-only formulation. Once inserted, this CR remains in the vagina continuously, and its effectiveness depends on a combination of actions of the progestin, including inhibition of ovulation and thickening of cervical mucus. The only such CR available is one that delivers levonorgestrel (20 μg/day); it will soon be marketed in Europe. This CR has a failure rate of 3.0 percent but without a significant incidence of ectopic pregnancies. Since a large number of ectopic pregnancies were expected but not observed, it is possible that the vagina may be the optimal route for progestin-only contraception. The ring also offers a more convenient method of delivering continuous progesterone to women, and such rings have been shown to provide effective contraception in lactating women.

Proposed Research

- *Determine the optimal steroid for use in different CRs.*
- *Determine how much the hormone dose can be decreased without compromising effectiveness and safety.*
- *Perform specialized phase 2 studies on CRs to determine whether vaginally administered steroids are different from orally administered steroids with respect to ovarian function; lipoprotein levels; metabolism; effects on cervical, uterine, and vaginal pathology; and carbohydrate metabolism.*
- *Determine the long-term effects of CR use.*

Transdermal Delivery

Transdermal delivery of drugs has received increasing attention during the past decade because of the potential advantages of controlled continuous drug administration. Transdermal delivery of steroids is also an expanding field, especially in its application to hormonal replacement therapy. Transdermal application of estrogen has been used in the treatment of postmenopausal women. Percutaneous absorption of progesterone has been demonstrated in women as has treatment of male hypogonadism with transdermal testosterone. There are currently no transdermal contraceptives, but the popularity of this route of drug administration suggests that such methods would be highly acceptable. Both progestin-only and progestin/estrogen methods are possible. These drugs could be delivered by patches applied once each week or by a cream applied daily.

Proposed Research

- *Determine what type of transderrnal delivery will be most acceptable to women: high-tech patches vs. low-tech creams.*
- *Conduct optimization studies to select appropriate contraceptive steroids and their proper doses.*
- *Determine subject-to-subject variability in absorption using pharmacokinetic studies.*
- *Conduct local dermal irritation and toxicity studies. Conduct clinical studies for effectiveness.*

Intrauterine Devices (IUDs)

IUDs are the most widely used reversible methods of contraception in the world. Only sterilization is used by more couples as a method of birth control. The popularity of IUDs is due to their ease of use since they require no action by women once they are inserted. Furthermore, the improved designs of modern IUDs have increased their effectiveness and reduced side effects while providing contraception at a very low cost. In addition, IUDs can carry delivery systems that target drugs to a selected part of the reproductive tract. The prevalence of IUD use in Norway, Sweden, and Finland ranges between 20 and 30 percent of contraceptive users; in the United States, it is less than 14 percent.

These observations suggest that factors that are not operative in other developed countries influence IUD use in the United States.

Proposed Research

- *Conduct behavioral studies to determine why women do not wish to use IUDs and why many health care workers will not insert them.*
- *Develop effective methods to identify those women who are not good candidates for IUD use, that is, those who will have to discontinue IUD use because of bleeding and pain.*
- *Develop IUDs that act as barriers to infection of the upper reproductive tract.*
- *Develop hormone-releasing IUDs that will further reduce IUD side effects.*

Oral Contraception

There is such a bewildering array of combined oral contraceptives available to women throughout the world that it may be impossible to distinguish the relative risks and benefits of individual formulations. Since the doses of contraceptive steroids used in such pills have been progressively lowered, it is likely that the risks and benefits of currently used OCs are different from those used years ago. Thus, there is a continuous need to monitor the long-term effects of combination and progestin-only oral contraceptives, particularly in women who begin use of these agents at an early age. Although it is not reasonable to argue for the development of new Ocs based on progestins or estrogen/progestin combinations, new drug combinations would be welcome, such as the recently recommended method which uses progestin plus mellatonin for 3 weeks followed by mellatonin for 1 week when menstruation occurs. Since mellatonin is a hormone of seasonally breeding animals, its action in humans warrants study.

Proposed Research

- *Study the long-term consequences of Ocs, and determine the mechanism of action of mellatonin in women.*

Barrier Methods

There is a need for convenient formulations that when introduced before coitus will protect against the transmission of HIV and chlamydia, as well as other STDs, and will, in addition, provide protection against pregnancy. With heterosexual transmission of HIV being the principal route of infection worldwide and the percentage of AIDS caused by heterosexual transmission growing in the United States, there is a pressing need to offer protection against this mode of sexual transmission of the HIV virus. Although the widespread distribution of chlamydia refections and their consequences are not well known by the public, it is currently estimated that chlamydia infections are the most prevalent sexually transmitted disease. The classical disease mused by chlamydia is lymphogranuloma venereum (LGV). Although rare in the United States, LGV is common in developing countries, especially in central Africa. In this country, about 4 million chlamydia infections occur each year. It is a particular threat because infections frequently go undetected and thus cause tubal damage that results in infertility and ectopic pregnancies. When symptoms axe present, they can include cervicitis and salpingitis in women and urethritis and, occasionally, epididymitis in men. Although chlamydia can be successfully treated with antibiotics, damage is frequently severe before this condition is detected.

The goal of identifying novel spermicides has several motivations. Spermicidal agents approved for use in the United States are limited to surface-active agents (with the minor exception of phenylmercuric borate), with nonoxynol-9 (N-9) being by far the most widely used. Considerable evidence from both clinical trials and animal studies indicates that N-9 causes microulceration of the vagina. This is of concern since epidemiological evidence suggests that microulcerations increase susceptibility to HIV infection. At least as important as the need for alternative spermicides is the expectation that antifertility action would add to the incentive to use a product giving protection against one or more sexually transmitted diseases. Any new product that has both antifertility and anti-STD activity should perform as well as N-9, which will be the basis of selecting and testing new products. Unlike the forms of contraception mentioned above, development of barrier methods against HIV and other STDs will be long-term research projects, and is likely to be quite expensive.

Proposed Research

- *Select candidate compounds from results of previous screening tests on sperm and STDs.*
- *Test candidate compounds for evidence of antifertility effects and effectiveness against selected STDs in vitro. Prepare formulations (suitable for human use) of individual multiple compounds for animal tests. Test formulations in vitro.*
- *Test selected formulations for evidence of effectiveness in animal model systems.*
- *Prepare selected candidates for tests of effectiveness in humans.*
- *Conduct comparative trials in humans.*

Male Contraception*

There are no contraceptive methods for men other than condoms and sterilization, and while there are compelling reasons related to STD transmission to argue for increased utilization of those procedures, there is also a desire to provide new methods for this underserved population. The two approaches currently under investigation use drugs that either act directly on male germ cells or withdraw their hormonal support. To date, all drugs that act directly on germ cells have toxic effects and are relatively nonreversible, while hormonal suppression is readily reversible but is not as effective. The major approach to new contraceptives has been to improve hormone suppression using analogs of luteinizing hormone-releasing hormone (LHRH). controls the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary. However, large doses of LHRH analogs block the secretion of both of these hormones, which are necessary for the production of sperm. Administration of LHRH analogs in men has resulted in decreased serum testosterone, sperm counts, and sperm motility. If the LHRH analog treatment is supplemented with an androgen, there are no signs of androgen deficiency, but suppression of sperm production may be less effective depending on when the androgen is given in relation to the onset of analog treatment. Some studies suggest that an LHRH antagonist may be better than an agonist, but there are

* Although the work needed to improve male contraception does not always require the cooperation of OB/GYN investigators or their patients, it is included here to emphasize the committee's contention that this is an area that needs attention.

no studies in which the actions of agonists and antagonists have been compared when both are delivered from an optimally formulated release system.

Over the past several years, injectable and implantable peptide delivery systems have been formulated that could be effective for months to years when used as a component of a male contraceptive. This second component will be used as an androgen injection or implant.

Proposed Research

- *Determine whether LHRH agonists or antagonists are the optimal component of a male method.*
- *Develop long-term delivery systems for LHRH analogs.*
- *Select an appropriate androgen for long-term administration, and develop an appropriate delivery system.*
- *Conduct phase I and 2 clinical studies of the androgen and the LHRH analog.*
- *Investigate new approaches by developing methods that will interfere with the autocrine/paracrine control of germ cell maturation in the testis (a long-term objective).*

Antifertility Vaccines

The concept of antifertility vaccines was introduced with immunization against either human gonadotropin-beta (hCG-B) or fragments of this gonadotropin subunit. Currently, three clinical trials are under way to evaluate various forms of this contraceptive vaccine. In the future, a series of other antigens will be investigated.

Immunological approaches to contraception are likely to be very long-term approaches to contraception for a variety of reasons:

1. Antigens are not readily available and must be produced by direct synthesis or recombinant DNA technology.
2. It is unlikely that a single antigen will produce a uniform response in a heterogeneous population, such as humans.
3. There is a long delay from the onset of treatment while antibody titers rise.

4. For the vaccine to be used widely, the incidence of idiosyncratic reactions must be very low.

Sperm Antigens Since autoantibodies to sperm are associated with infertility, sperm antigens appear to be attractive candidates for antifertility vaccines. A major obstacle will be the lack of purified sperm protein in sufficient quantities owing to the scarcity of human sperm to perform the biological assay for antifertility activity. To avoid having to rely on human as a starting material for antigen isolation, it will be necessary to produce the sperm proteins by recombinant technology or to synthesize peptide segments of the sperm protein. Such an approach will require a team of scientists including molecular biologists (for cloning, DNA sequencing, and preparation of expression vectors), a protein chemist (for peptide synthesis), a reproductive biologist (for gamete and fertility testing), and an endocrinologist (for clinical trials). These researchers must accomplish the tasks below.

Proposed Research

- *Isolate a full-length cDNA that encodes promising sperm proteins, and determine their nucleotide sequences.*
- *Identify the nucleotide segment encoding the extracellular domain of membrane proteins and the entire sequence of secreted proteins; express such proteins in the baculovirus or similar expression system; and isolate expressed proteins for biological testing.*
- *Study the effect of immunization with the recombinant proteins and/or synthetic polypeptides.*
- *Produce a human dosage form, and test it in animals.*
- *Perform trials in humans.*

LHRH-Vaccine Used With or Without a Vaccine to the Luteinizing Hormone or FSH Receptor The rationale for tiffs approach is based on the principle of controlling LH and FSH actions by immunoneutralization. Although there are several immunological strategies to control LH and FSH activities, the one that has shown the most promise is LHRH coupled with a carrier protein. Animals given this antigen become infertile as titers rise. An attractive alternative approach is to interfere with hormone-receptor interaction on the surfaces of the selected target cells in the gonads (i.e., Leydig cells in the testis and luteal cells in the ovary for LH, and Sertoli cells and granulosa cells for FSH), by

immunoblocking the receptor. The achievement of cloning and sequencing of rat and porcine LH and rat FSH receptor cDNAs opened the path to produce the extracellular domain of the LH and FSH receptors by recombinant DNA technology, to synthesize specific peptide segments of the receptor, and to determine the receptor regions that participate in the binding of the hormone and in the stimulation of the signal-transducing pathway. Identification of these critical segments of the LH and FSH receptors offers an opportunity to interfere with hormone action by raising antibodies against these specific regions alone or in combination with the LHRH antigen. The objective is to demonstrate that immunization with specific LH and FSH receptor segments will result in alterations of reproductive functions and reduce a state of infertility in experimental animals. The same team approach will be used as for sperm antigens.

Proposed Research

- *Conduct trials of the LHRH vaccine in animals and humans.*
- *Prepare recombinant polypeptides of the LH and FSH receptors, and study their immunogenicity.*
- *Prepare synthetic peptide segments of LH and FSH receptors corresponding to the hormone-binding and adenylate cyclase-stimulating domains, and conjugate the peptides with a carrier protein.*
- *Establish immunogenicity of the LH and FSH receptor peptide segments by determining the interaction of antibodies developed against specific receptor peptide segments with the recombinant extracellular domain of the respective receptor, and with isolated ovarian and testicular membranes containing the LH and FSH receptors, respectively.*
- *Immunize male and female rats with various combinations of LHRH-antigen and specific LH/FSH receptor peptide segments, and determine their effects on sex steroid production, gonadotropin secretion, spermatogenesis, ovulation, and fertility.*

Medical Abortifacients

Since U.S. government funds, which support most biomedical research, may not be used for research on medical abortifacients, such research cannot be conducted without private support. Studies are vitally necessary to achieve

safer, more effective, and more acceptable methods for terminating pregnancy without surgery.

RU 486 is effective in terminating established pregnancies. When combined with a prostaglandin, RU 486 is 95 percent effective in inducing abortion in pregnancies of less than 7 weeks' duration; however, this combination reduces abdominal cramps and requires multiple trips to the clinic, which adversely affects acceptance and compliance. For medical abortion to be used widely in outpatient clinics, especially in inner-city clinics, effectiveness of the regimen ought to be increased to greater than 99 percent; it should be effective throughout the first trimester of pregnancy; and it should be administered in a way that will improve acceptance and compliance. There is also concern about the extremely limited availability of the RU 486 regimen. Since RU 486 is not and may not become widely available to women, and since, in any case, it should be seen as the beginning, not the end, of medical abortifacient development, work in this field should move forward vigorously. Thus, a better regimen beyond the one currently used (RU 486 plus prostaglandin) is still needed. Additionally, as noted, a separate and important issue is that RU 486 is not available to most women. Because RU 486's availability remains uncertain at best, the alternative drug regimen should not depend on RU 486. since it is probable that an antiprogestin will be a component of the new medical abortifacient, a substitute for RU 486 should be identified.

Proposed Research

- *Identify an antiprogestin that can be used as a substitute for RU 486 in a new medical abortifacient.*
- *Test combinations of an antiprogestin, anordrin analogs, progesterone synthesis inhibitors, and prostaglandins in pregnant animals to determine the lowest effective dosages in terminating pregnancy.*
- *Determine the window of effectiveness during the postcoital period when the combined drugs could be most effectively administered.*
- *Select the most promising combination of drugs for small-scale clinical trials, and perform the appropriate toxicology.*
- *Develop an appropriate delivery system so that the drug combination could be administered in only one clinical visit.*
- *Investigate the acceptability of new delivery systems to users and providers.*

INFERTILITY*

It has been said that infertility is reaching epidemic proportions in the United States. Certainly, the overall number of couples who are involuntarily infertile has increased, and today, as many as one in nine couples are unable to conceive a child. This increased incidence of infertility stems from a number of biological and sociological factors including an increased incidence of sexually transmitted diseases resulting in adhesions and tubal infertility, the increased number of women pursuing careers and delaying childbirth until their late 30s or 40s, and a wide variety of environmental toxins with putative effects on both male and female fertility Couples turn to the gynecologist, and to subspecialists in the gynecologic discipline of reproductive endocrinology, for clinical evaluation and therapy for infertility. This clinical need and the gynecologists' ongoing interest in the reproductive biological events of conception and implantation make it appropriate that the research issues of infertility be undertaken by departments of gynecology and obstetrics. These physicians care for infertile couples and are ultimately responsible for the therapeutic interventions resulting in successful pregnancy. Innovative and focused research in both the pathophysiology of infertility and its therapies will benefit the thousands of couples who are involuntarily infertile. Also, dissecting the basic processes that render both men and women incapable of conceiving children will certainly suggest new methodologies for fertility control and contraception.

In order to conceive a child, the following stringent requirements of both male and female physiology must be met. First, a sufficient number of motile sperm must be produced with the appropriate enzymatic apparatus to penetrate the zona pellucida of the oocyte. To achieve successful fertilization, the male gamete must be normal and functional, and the female oocyte must be properly matured by appropriate ovarian follicular development. Sperm motility is required to propel the sperm from the exocervix through the female reproductive tract to the ovarian follicle and the site of fertilization. An obligatory requirement for this transit is the presence of hospitable cervical mucus. At the time of ejaculation, sperm are deposited around the exocervix and require estrogenized, watery cervical mucus to maintain motility. We know almost nothing of the chemical changes of cervical mucus that allow sperm to pass into the uterine cavity or of the immunologic requirements and barriers that protect this open passageway into the female peritoneal cavity and prevent ascending

* This section was written by Mary Lake Polan.

infection. The female requirements are even more complex, mandating cyclic ovarian function, including the attendant hormonal fluxes that affect and prepare all the reproductive organs, the fallopian tube, uterine lining, and cervix for conception.

Once successful fertilization is acheived, the slowly developing human embryo must journey from the distal fimbria through the various portions of the tube and into the uterus in order to implant in the endometrium. The fallopian tube is far more than a simple conduit; patency is not sufficient. The complex but poorly understood interaction of ciliated tubal epithelium and muscle contraction, which actually transport the developing embryo, as well as the mechanisms for nourishing it during its week-long transit, must be perfectly timed for conception to occur. If aberrations occur, a very early and often undiagnosed pregnancy loss may result or, more seriously, the life-threatening situation of an ectopic pregnancy implanted along the course of the tube.

After the developing embryo reaches the uterus, midway through the luteal phase, the proper sequence of implantation events must occur to maintain the growing pregnancy. Although implantation of animal embryos has been well studied, we know that the reproductive events in humans are, in many ways, vastly different from those in lower mammals. Increased research on primate models of implantation, as well as information gleaned from the new reproductive technologies such as in vitro fertilization, are needed to enhance our knowledge of the events of human implantation.

In order to have a child, all of the above processes must work properly and in the appropriate chronological sequence. Infertility can result from abnormal physiologic response at any of the described points along the continuum of gamete function, fertilization, transport, and implantation. This section will define six major areas in which a focused effort of research would both increase our understanding of the basic reproductive physiologic processes and lead to new therapies that will allow infertile couples to conceive and bear children.

Proposed Research

- *A structured, comprehensive research program, including an epidemiologic description of the etiologies of infertility and basic research in cervical, tubal, and sperm development and function, would both expand our knowledge and the therapies available for infertile couples.*
- *Specific disease processes associated with infertility, such as endometriosis and tubal adhesions, need investigation.*

- *The new reproductive technologies of in vitro fertilization and gamete intrafallopian transfer (GIFT) offer a tremendous opportunity for understanding the specific cellular processes of human reproduction.*

Epidemiology

Many women's health issues are cloaked in emotional rhetoric without substantiating statistical support. An example is in vitro fertilization of which the public continues to be sometimes unaware, and at other times overly optimistic regarding the true success rates currently attainable. The entire area of infertility is dotted with suppositions and unsubstantiated estimates. It is "common knowledge" that infertility, is on the increase, perhaps in epidemic proportions, in this country. Yet recent epidemiological data have clarified that about 8.4 percent of reproductive-age women (15–44 years) had unresolved, impaired fecundity in 1982, and this percentage was virtually unchanged in 1988. However, there was a significant increase in the actual number of women reporting infertility, secondary to the trend of delayed childbearing and to the fact that more women were entering this age group (25–44 years), because of the "baby boom" generation. As an example, there was a 37 percent increase (from 454,000 to 620,000) in the number of women aged 35–44 who were without children from 1982 to 1988; however, expressed as a percentage for these years (21 percent), this figure was essentially unchanged.

Solid epidemiological data are lacking for relating many aspects of reproductive health and function to environmental toxins. Likewise, there is a dearth of solid data in the field of in vitro fertilization. Despite the attempts of a national registry in this area, the reporting is strictly voluntary, and there are no checks on the individual clinic's accuracy, and no punitive procedures for lack of reporting. Along these lines, even firm data on "normal" fecundity and fertility are difficult to obtain; monthly fertility (i.e., the chance of conceiving in any particular cycle) has been estimated from 9 percent to 25 percent, and estimations of chromosomal abnormalities in early pregnancy losses have ranged from 25 percent to 75 percent. If, indeed, nearly 50 percent of human oocytes and 10 percent of male sperm are karyotypically abnormal, substantial natural barriers to successful artificial reproduction are in place.

In the present climate of potentially unlimited achievement in reproduction, the concept that age is no barrier needs to be examined, both for practical as well as emotional reasons. Until very recently, it has generally been accepted that female fecundity is minimal after age 40 and virtually non-existent after age

45. Due to lavish publicity in recent in vitro fertilization cases, the public may now perceive age as no barrier to fertility. In fact, good studies clarifying the relationship of natural fertility and age currently do not exist. One simply cannot give a knowledgeable answer to the question from a 46-year-old woman (or even from a 40-year-old) regarding her chances of natural conception.

Sound epidemiological data on many aspects of women's health and reproductive function are lacking. The research areas discussed below are by no means an all-inclusive list but rather provide the starting point for a concerted effort to develop and maintain not only normative data on both male and female fecundity, but also the effect of both the environment and sociologic behaviors on fertility and childbirth.

Proposed Research

- *Research is needed on the effect of chemical contaminants on sperm and oocyte function. In addition, more research on the effect of such substances as alcohol, tobacco, and drugs on gametogenesis and fertilization is necessary.*
- *Firm, normative data on normal fecundity and fertility, and a multitude of other reproductive issues, are needed for comparative data as the newer reproductive technologies continue to expand.*
- *There is a need to ascertain the relationship between age and human (both male and female) fertility.*

Cervical Physiology and Function

The cervix is the gateway allowing sperm to enter the female genital tract. Concomitantly, it provides an entryway directly into the peritoneal cavity, potentially resulting in ascending refection. Thus, the cervix must not only allow entry of sperm but must protect against bacterial and vital infection. Remarkably little is known about the physiology of the secretions that facilitate sperm motility while providing an immunologic barrier.

The cervix is lined with a highly active secretory endothelium that produces mucus in a hormonally dependent fashion. Under the influence of circulating estrogen, the cervical mucus becomes thin, clear, and acellular allowing optimal sperm motility and passage into the female genital tract. After ovulation, when progesterone levels increase, the mucus changes to a thick viscous secretion that is virtually impenetrable to sperm. Not only is our knowledge of cervical

secretory physiology extremely limited, but there are no good diagnostic tests of mucus function that can be shown to correlate with conception or birth.

It is estimate that as many as 5 percent of infertility patients are unable to conceive because of a cervical factor: either inadequate or insufficient mucus or an antibody-mediated immunologic response to sperm.

It is hoped that the long-range outcome of studies described below will be improved therapeutic modalities to address questions of cervical infertility.

Proposed Research

- *Research is needed to understand the physical and chemical properties of cervical mucus that facilitate sperm motility and to develop solid criteria for diagnostic tests of mucus function.*
- *Study is needed of the relationship of cellular and antibody mediated immunologic function to normal sperm motility, as well as to the prevention of pelvic infection.*
- *More research is needed to define normal cervical function and immunology with the goal of improved therapies for cervical factor infertility.*

Fallopian Tube Function

The human fallopian tube is not simply a conduit for sperm and the newly fertilized embryo. It is a complicated structure of longitudinal and circular muscle surrounding a convoluted, ciliated epithelium, which is hormonally responsive to both steroids and proteinaceous growth factors. Little is known about tubal function and evaluation. Currently, the hysterosalpingogram provides radiologic information on tubal patency, but there are no tests to evaluate tubal function. Such research is of tremendous importance given the rapidly increasing incidence of ectopic pregnancy in the United States. In some populations, as many as 1 in 60 pregnancies occur in the tube, necessitating surgical intervention and often resulting in severe maternal morbidity and occasionally mortality.

Proposed Research

- *New techniques must be developed to evaluate tubal function and to describe the specific etiologies of abnormal tubal function.*
- *Studies are required to assess ciliary function and the role of muscular contractions in transporting the embryo into the uterus.*
- *The area of steroid and growth factor interactions with tubal epithelium requires a major research commitment.*
- *Normal implantation in the endometrium is modulated by a number of growth factors, and research into the role of growth factors in tubal function may provide important answers on the etiology and genesis of tubal ectopic pregnancies.*

Endometriosis

Despite more than 100 years of investigation and attempts at treatment, pelvic endometriosis remains a ubiquitous and enigmatic disease. Its incidence, etiology, and management consistently arouse controversy, and its relationship with infertility remains unclear. It has been estimated that 1–5 percent of reproductive-age women have endometriosis, whereas as many as 45–50 percent of women suffering infertility are so afflicted. In 1982, 2.4 million married couples in the United States were infertile; since that estimate was of married couples a decade ago, today's estimate yields a number in excess of 1.5 million women with endometriosis and infertility.

Although it is generally agreed that minimal, or stage 1, endometriosis is not a significant etiologic factor in infertility, the natural history of such early, untreated disease is completely unknown. Such mild disease may well be the cause of significant later morbidity.

The natural course of endometriosis and its etiology are also unclear. Sampson's theory of retrograde menstruation is widely accepted as the etiology. However, it does not explain why particular women are prone to develop the disease, whereas others are not. Recently it has been postulated that immunological factors are significantly involved in the causation of endometriosis; however, this concept, too, is under attack.

Thus, endometriosis is a major health problem in women, both because of its associated infertility and its resultant morbidity, and the reasons particular women develop the disease and others do not are obscure.

Proposed Research

- *Research is needed on the relationship of endometriosis to infertility.*
- *Basic and clinical research into questions of who needs treatment and what is the best modality could yield an excellent societal return on investment.*

Male Infertility

A male factor is listed as the Primary cause of infertility in 30 percent of couples, and is implicated as a contributory factor in an additional 20 percent of cases. Despite our awareness for decades of male factor infertility, there has been minimal progress in its diagnosis and treatment. Perhaps nothing more typifies the current state of affairs in this area than the two recent diametrically opposed statements regarding the postcoital (Simms-Huhner) test first described in 1888 and considered to be a mainstay of the initial infertility evaluation of a couple. On the one hand it is said that the postcoital test is an important and mandatory investigation in the workup of the infertile couple. On the other hand it is said that there is a problem of poor validity, and the test suffers from a lack of standard methodology, lack of a uniform definition of normal, and unknown reproducibility. Even worse, perhaps, is the recognition that the time-honored standard semen analysis may have minimal correlation with male infertility.

Controversies such as the above pervade the subject of male infertility and its management. Specific debates include the role of antibodies (male and female) and theft appropriate treatment, the value (if any) of hormonal treatment of various forms of male subfertility, the role of intrauterine and intracervical insemination in unexplained infertility, the necessity of, and the physiologic factors involved in, capacitation, and the acrosome reaction. The obvious corollary of a clear understanding of sperm function would be the ability to develop new methods of contraception based on interfering with the normal fertilization process.

Proposed Research

- *Research at the basic science level must be initiated before a true understanding of the causes and possible treatments of male infertility can be proposed.*

- *Research is needed into sperm-oocyte interaction, including details of fertilization and chromosome exchange, sperm acrosome reaction, sperm maturation, sperm metabolism, and detailed sperm morphology.*

In Vitro Fertilization and New Reproductive Technologies

A decade after the first in vitro fertilization (IVF) birth in 1978, the number of stimulation cycles initiated in women for the purpose of embryo transfer (ET) exceeded 25,000, despite its high cost (approximately $5,000 per cycle) and relatively poor success rate (14 percent for live-born infants), which has barely changed in the past 5 years. Were success rates of even 25 percent possible, it would be of major benefit to many more couples; because a success rate of 50 percent could eliminate most currently practiced infertility surgery, research in this area could be rewarding. Although many small clinical studies have been conducted in this area, no dramatic breakthroughs have resulted. However, recent reports involving co-culture of oocytes with maternal tubal or endometrial epithelial cells have suggested a new avenue of approach to this problem.

It has long been known that assisted reproduction is more successful in animals than in humans. Specifically, bovine ET, in which fertilization occurs in vivo (as opposed to in vitro) and the embryos are flushed from the uterus and then transferred (often after freezing) to a recipient uterus, routinely carries success rates of 60 percent. This and other observations, have led to the concept of very early embryo-maternal cell signaling, and an understanding that interaction is much more complex than previously envisioned. As a result a new " science" in this area is taking shape revolving chemical signaling (autocrine and paracrine), growth factors, follicular regulation of oocyte maturation, activation of the embryonic genome, and energy substrates and metabolism of the very early embryo.

Though distinct improvement in human IVF-ET success rates has not yet been forthcoming, a focused research effort might find specific etiologies for reproductive failures and specific corrections that might be offered. Perhaps even more exciting than the potential advances and success rates in IVF is the realization that research information gathered from in vitro studies may be directly applicable to natural human reproduction and population control. Such knowledge portends hope for controlling human reproduction, and on a worldwide scale.

Clearly, questions of human reproductive efficiency and infertility require a carefully formulated, rigorous research agenda. Such research would most

appropriately be conducted in departments of obstetrics and gynecology in which infertility patients are seen and cared for on a daily basis. Research on all areas of infertility is needed, not only to further the possibility of conception for infertile couples but to understand this basic reproductive function so that appropriate interventions can be made for population control. Research in reproductive biology and infertility has been hampered by lack of federal support, which is needed to advance knowledge of the basic processes of human fertilization and conception.

Proposed Research

- *Research using appropriate animal model systems in the primate and research utilizing human follicular fluid, corona, and cumulus cells should investigate the molecular biology of human fertilization and early cell division.*
- *Research should be conducted on the involvement of growth factors, activation of the embryonic genome, and metabolism in the very early embryo.*

PREMENSTRUAL SYNDROME*

The incidence of premenstrual syndrome (PMS) is difficult to evaluate precisely because of the great variability in symptoms and in the severity of these symptoms among women. Nonetheless, it is clear that a large number of ovulatory women are affected by significant aberrations in feelings of well-being and in some cases by severe distress during the luteal phase of the ovulatory cycle. Symptoms are sometimes so severe as to be disabling at some time after ovulation during each menstrual cycle. Therefore, this disorder constitutes a major health problem and may cause periodic loss of a large population from the work force. Yet despite the common occurrence of PMS among young women and despite our relatively advanced understanding of biomolecular events of the ovarian cycle, we have very little definitive knowledge of the cause of PMS.

In part this may be because of the reluctance of some segments of society. and science to accept PMS as a biological disorder that can be related to defined endocrinological events. But the lack of understanding is also attributable to an inability to identify meaningful differences in the hormonal changes of ovulatory women who do or do not suffer from PMS. In particular, there are no major

* This section was written by Paul C. MacDonald.

differences in the blood levels of estrogens or progesterone during the luteal phases of women with and without symptoms of PMS. No significant differences have been found in the rate of secretion of aldosterone among the two groups; and differences in blood levels of prolactin have not been detected. The same is true of plasma testosterone and androgen prohormones. Thus, it has not been possible to demonstrate a substantial difference in the hormonal milieu of women during the postovulatory phase of the ovarian cycle. There is a growing sense, however, that attempts to identify differences in the endocrinology of the luteal phase of the cycle may have been relatively superficial, considering the likelihood that steroid metabolites are bioactive and that the bioactions of these metabolites as well as the steroid hormone precursor may act by way of nongenomic processes.

For example, until recently, the metabolic fate of the majority (60–70 percent) of progesterone was not defined. In recent studies, it appears that this unaccounted-for metabolism of progesterone proceeds by way of initial 5a-reduction, which occurs in both hepatic and extrahepatic tissues. Extrahepatic metabolism may be especially important because this mechanism of progesterone clearance would avoid immediate conjugation of potentially bioactive metabolites, a process that occurs in the liver. It has also been demonstrated that metabolites of progesterone, especially those reduced in the 5a-position, are bioactive. In particular, such compounds act to cause anesthesia, analgesia, and anxiolysis in both humans and experimental animals. Therefore, it is highly possible that metabolites of progesterone affect biobehavioral events; moreover, differences in metabolism of progesterone among women may give rise to decided differences in the bioresponses of women when progesterone production rates are high. In addition, the withdrawal of progesterone metabolites, as occurs at the end of each nonfertile ovarian cycle and after pregnancy, may also contribute to modifications in well-being. Therefore, because of person-to-person variations in the metabolism of progesterone, the stereospecific nature of the bioactions of progesterone metabolites, and the potential for biobehavioral modifications with progesterone metabolite withdrawal, many aberrations in behavior and well-being could be the consequence of the recurrent production of progesterone in large amounts in otherwise normal young women.

It is also highly likely that bioactions of progesterone by way of classic progesterone receptor-mediated processes that may affect the well-being of women are yet to be defined. It was recently demonstrated, for example, that progesterone acts, at least in some tissues, to increase the activity of the enzyme enkephalinase, which degrades enkephalins and other highly active small peptides, such as atrial natriuretic factor, and substance P, as well as the endothelins -1, -2, and -3. If progesterone were to act to induce increased

enkephalinase activity in the brain, enkephalin withdrawal could obtain. If progesterone were to increase enkephalinase activity in the kidney, marked attenuation of the effect of atrial natriuretic peptide could occur, leading to sodium and water retention.

- ***Proposed Research*** *—The metabolism and bitactions of progesterone and its metabolites are fruitful areas for research to define the biological causes of symptoms referred to as the premenstrual syndrome.*

Studies of the role of endorphins in the precipitation of symptoms of premenstrual syndrome already are in progress in some laboratories, and the findings of these studies may be complementary to those suggested.

THE BRAIN AND REPRODUCTION*

Human reproduction, as in all mammals, is the consequence of a cascade of neuroendocrine events that originate in a central signal generator residing in the region of the arcuate nucleus of the mediobasal hypothalamus. The existence of this signal generator was first evidenced some 20 years ago by rhythmic, oscillatory time courses in the plasma concentrations of the pituitary luteinizing hormone (LH) in women[1] and rhesus monkeys,[2] leading to the conclusion that these hormonal patterns axe the consequence of the pulsatile release of the hypothalamic decapeptide, gonadotropin-releasing hormone (GnRH), into the pituitary portal circulation. This supposition has been amply verified by the direct measurement of this neuropeptide in pituitary portal blood of experimental animals lending the name "GnRH pulse generator" to the neural timing mechanism in the hypothalamus. Beyond the fact that in the unmodulated state, the pulse generator is activated approximately once per hour and that it is an intrinsic property of the mediobasal hypothalamus, little is known about the cellular basis of its operation. Evidence has been adduced in support of the view that the pulse generator may be resident within the GnRH-producing cells of the hypothalamus, but the integrating system that leads to the synchronous activation of a number of GnRH cells and to the rhythmic discharge of the neuropeptide remains to be elucidated. The hypothesis of a pacemaker outside

* This section was written by Ernst Knobil.

the GnRH system that signals the GnRH cells to secrete their product cannot be eliminated at present.[3]

During the follicular phase of the menstrual cycle, the period of the GnRH pulse generator, and that of the resultant gonadotropic hormone pulses, approximates one hour, but it is profoundly reduced during the luteal phase as a consequence of the action of progesterone on the hypothalamic system, an action mediated by endogenous opioid peptides.[4] While a minimal frequency of LH stimulation is required to maintain the functional integrity of the corpus luteum,[5] normal ovulatory menstrual cycles can be achieved in the absence of endogenous GnRH production by the administration of GnRH at an invariable frequency of one pulse per 680 or 90 minutes, leading to the conclusion that GnRH is a permissive component of the control system that governs the ovarian cycle in the higher primate, the regulation being achieved primarily by an interaction between the ovarian hormones and the gonadotrophs of the adenohypophysis.[4],[6] Thus, the preovulatory gonadotropin surge is initiated by a positive feedback action of estradiol acting on the pituitary that can proceed in the face of an unchanging ambient GnRH environment.

The pathophysiological consequences of alterations in the secretory patterns of GnRH have recently been extensively reviewed.[4],[7],[8] The total absence of GnRH production, as in Kallmann's syndrome, is characterized by an absence of gonadotropic hormone secretion and gonadal infantilism. This syndrome is associated with anosmia, a phenomenon that has received recent explication with the finding that, in mice, the GnRH cells have their origin in the olfactory placode of the embryonic brain. They migrate caudally to their ultimate location in the mediobasal hypothalamus.[9],[10] Apparently, in Kallmann's syndrome, this migration is interrupted by a midline defect. Less extreme disturbances in GnRH production can also lead to failures in follicular development, anovulation, and infertility. It has been estimated that some 15 percent of all infertility cases are attributable to anovulation,[11] but better data bases are needed before definitive quantitative judgments can be made in this regard. While isolated pituitary gonadotropin deficiency can be a cause of ovarian failure, a most infrequent phenomenon, anovulation is mainly attributable to hypothalamic dysfunction. This can be psychogenic or stress induced.[12] In the rhesus monkey, even seemingly mild perturbations in the environment can lead to arrest of the GnRH pulse generator.[13] A similar phenomenon can be reduce in such animals by the administration of the hypothalamic corticotropin-releasing factor, an action apparently mediated by endogenous opiates.[14] Morphine itself is a potent inhibitor of GnRH pulse generator activity.[15] The role of endogenous opiates in the mediation of the responses to actual stress, however, is still not entirely clear. Similarly, while hyperprolactemia can lead to derangements of

pulse generator activity and pituitary malfunction, the role of this peptide in the anovulatory states associated with lactation is quite uncertain.[16]

Severe exercise, as well as caloric deficits, leads to anovulation, undoubtedly occasioned by a reduction in GnRH pulse generator frequency or its complete arrest.[17] The link between caloric balance and the functioning of the GnRH pulse generator is unknown. While GnRH stimulates the secretion of both LH and FSH by the gonadotrophs (hence its name), the physiological control of the production of these two hormones is not the same. In addition to the stimulating role of GnRH, FSH secretion is preferentially inhibited by a family of peptides, the inhibins, produced largely by the gonads. While the physiological role of inhibin in the control of FSH secretion in the male is unambiguous,[18] its role in the control of the menstrual cycle remains to be fully elucidated. A related family of peptides, the activins, stimulate FSH secretion,[19] but their physiological roles are not clear at present. The roles of autotrine and paracrine factors in the control of gonadotropic hormone secretion and their interactions with GnRH are similarly conjectural.

The mechanisms underlying the ontogeny of the GnRH pulse generator remain a mystery. It is fully functional at birth and is inexplicably inhibited some weeks later to reawaken in anticipation of puberty.[20] In fact, puberty can be defined as the reactivation of the pulse generator following its quiescence during the long period of infancy. Elucidation of the nature of this normal inhibitory influence may provide clues to the muses of hypothalamic amenorrhea and the mechanisms of action of the negative energy balances that obtain in caloric deprivation and severe exercise, and vice versa.

The electrophysiological substrates of the GnRH pulse generator have now been identified and monitored in the rhesus monkey,[21] the rat,[22] and the goat.[23] In these models, each LH pulse is immediately preceded by a burst of multiunit electrical activity recorded from electrodes implanted in the mediobasal hypothalamus. During the rhesus monkey menstrual cycle, these volleys of multiunit activity last for about 2 minutes, whereas following ovariectomy their duration is some 15–20 minutes. This prolongation of electrical activity is abruptly reversed by estrogen administration.[24] While the marked increase in the duration of increased hypothalamic electrical activity observed in the absence of ovarian function is not accompanied by significant changes in the dynamics of the resultant LH pulses, it may well be related to the manifestation of other neural activities such as the autonomic discharges characteristic of "hot flashes" that have also been shown to be synchronous with LH pulses in postmenopausal women.[25]

Reproductive physiology can be considered the science basic to obstetrics and gynecology. The GnRH pulse generator and the remainder of the

hypothalamo-hypophysial unit are central to human reproduction as they are in all vertebrates studied to date. The malfunction of this apparatus probably accounts for a major portion of infertility, both persistent and transient. It may also play a role in one of the most vexing endocrine disorders of women, polycystic ovarian disease. It seems regrettable, therefore, that the neuroendocrinology of human reproduction has been a research area explored more by internists and pediatricians than by obstetricians and gynecologists. This exciting field should be attractive to physician-investigators bent on an academic career, especially those interested in the still neglected interface between the activity of higher brain centers and reproductive function.

Proposed Research

- *The nature, specific localization, and mode of operation of the GnRH pulse generator must remain a critically important subject for intensive investigation at the systems, cellular, and subcellular levels.*
- *While estradiol can initiate the preovulatory gonadotropin surge in the absence of changes in GnRH production, what actually happens during the normal menstrual cycle is not known and should be investigated.*
- *The quantitative role of neuroendocrine deficits in the causation of infertility in women must be defined.*
- *The mechanisms whereby "stress" inhibits the GnRH pulse generator and consequent ovarian function must be elucidated.*
- *The mechanisms whereby lactation, severe exercise, and caloric deficits lead to amenorrhea and infertility must be characterized.*
- *The mechanisms of action of a variety of modulators of GnRH pulse generator activity must be elucidated. The opiates, catechol amines, NPY, and other neurotransmitters are cases in point.*
- *It is now clear that the control of LH and FSH secretion by the pituitary gland is not the same. The role of activins and inhibins and other factors in the control of FSH secretion must be investigated in a physiological context.*
- *The mechanisms that cause the inhibition of the GnRH pulse generator shortly after birth and its reawakening at the time of puberty remain a complete mystery. The initiation of puberty continues to be a central, unsolved problem in human biology.*
- *The functional relationship between the hourly activation of the GnRH pulse generator and "hot flashes," synchronous events in postmenopausal women, should be a subject of concerted study with the aim of discovering the*

physiological basis of the phenomenon and its potential alleviation by alternatives to estrogen therapy.

MENOPAUSE*

It is estimated that there are more than 40 million women in the United States today who are postmenopausal; and it is likely that this number will continue to increase rapidly in the next few decades. At menopause, estrogen secretion by the ovaries ceases. As the adrenal cortex does not secrete estrogen, menopause is associated with severe estrogen withdrawal. Indeed, estrogen production in postmenopausal women is limited to the extraglandular formation of the biologically weak estrogen, estrone, principally in adipose tissue, from the aromatization of plasma androstenedione (derived primarily from adrenal secretion). Estrogen deprivation at menopause results in troublesome and distressing (sometimes disabling) symptoms such as vasomotor instability (hot flashes) and urogenital atrophy (vaginal dryness and shrinkage). In addition, estrogen deprivation facilitates the more rapid development of life-threatening disorders of aging, including osteoporosis and possibly atherosclerosis.

Estrogen treatment is very effective in preventing hot flashes and in promoting growth of the vaginal epithelium. It also is clearly established that estrogen treatment of postmenopausal women serves to retard the loss of bone density and reduce the risk of myocardial infarction. Severe osteoporosis in elderly women is life-threatening; the death rate from complications of bone fractures, especially those of the hip, in elderly persons is high. Yet relatively few postmenopausal women today are treated with estrogen for any extended time. This is a health issue of major concern today and one that must be addressed if we are to improve the quality of life for an enlarging population of elderly women in this country and around the world.

The risk of estrogen treatment of postmenopausal women, when estrogen is given in adequate but reasonable doses, is believed to be confined almost exclusively to the development of endometrial carcinoma. The risk of breast cancer in postmenopausal women treated with estrogen, if different from that m postmenopausal women not ingesting estrogen, is not clearly established; but the risk ratio must be small, if it is different from 1. Nonetheless, any potential risk of breast cancer, however small, cannot be dismissed because of the very

* This section was written by Paul C. MacDonald.

common occurrence of breast cancer in women. Namely, a very small increase in risk, if significant, would represent a large amber of affected women.

Presently, however, the major concern of estrogen treatment of most postmenopausal women is the risk of endometrial carcinoma. The risk ratio for the development of endometrial cancer in postmenopausal women ingesting estrogen is believed to be approximately 4 (for average duration of treatment and dose). This risk should be analyzed, however, in light of the belief that endometrial carcinoma that develops in estrogen-treated, postmenopausal women is ordinarily a highly differentiated neoplasm for which the cure rate is near 100 percent. In fact, the cure rate for endometrial carcinoma in general is very high, commonly stated as being greater than 85 percent when all cases axe included. But to avoid even this small risk, many physicians choose to add a progestin to estrogen treatment regimens. This choice is problematic.

There are a few studies dealing with the relatively short-term effects of such a regimen on the concentration of plasma lipoproteins; there are a few studies that address the effect of the addition of progestins on the maintenance of bone density; but there are no long-term studies to evaluate the potential for increased incidence of heart disease and stroke when progestins are added to estrogen treatment regimens. It has been argued that the progestin can be given in low doses and therefore should be safe. This is not necessarily correct if the effects of the progestin are intravascular at the level of platelets or vascular endothelial cells. Rather, this would constitute intravascular therapeutics of a nature similar to that upon which the use of low-dose aspirin is based. In addition, the problem of patient compliance with various estrogen treatment regimens when progestins are added also must be addressed.

Thus, there are many data supportive of the belief that estrogen treatment of postmenopausal women is salutary in the prevention of major disorders of the skeletal and cardiovascular system and in the relief of hot flashes and the cure of urogenital atrophy.

It is established that estrogen treatment alone is a risk factor only for the development of endometrial carcinoma, and that this risk is low and the disorder is highly curable. Therefore, is it necessary to add progestin to this low-risk, high-benefit therapeutic plan?

These are questions of vital importance to the health care of millions of postmenopausal women. The prospective, long-term studies that should be conducted are easily envisioned and clearly call for the participation of gynecologists who are expert in the management of problems of the postmenopause and who are expert in the follow-up examination and evaluation of the postmenopausal woman taking estrogen—including the sampling of the endometrium to identify the development of abnormal endometrial tissue. The

endocrinology of the postmenopause has been defined by gynecologists; and it is the gynecologist who is most familiar with the endocrinology of the postmenopausal woman. Thus, the gynecologist who is trained in the basic sciences can make important contributions to the study of the endocrinology and endocrine treatment of postmenopausal women. Indeed, it is difficult to envision the conduct of a study of postmenopausal women without the guidance of experienced gynecologists. Few other physicians are expert in the conduct of pelvic examinations w evaluate ovarian status or to monitor cervical, vaginal, or vulvar health or disease. Cancer screening for pelvic neoplasias is accomplished almost exclusively by gynecologists. Therefore, gynecologists should make a major effort to design and conduct research to define the optimum acceptable hormone treatment regimens for postmenopausal women.

Proposed Research

- *Long-term, prospective studies to evaluate the effects and side effects of combinations of estrogen and progestins in the treatment of postmenopausal women should be conducted.*
- *Studies are needed to explain why very few postmenopausal women are treated with estrogen.*
- *Studies are needed to discover and assess the risks of adding progestin to estrogen treatment.*

ONCOLOGY*

Gynecologic malignancies will account for approximately 71,700 cancer diagnoses in women during 1991 and 23,500 cancer-related deaths. The following section briefly describes the current state of knowledge regarding cancer of the reproductive system, emphasizing recent advances and promising avenues of future research.

* This section was written by Arthur L. Herbst.

Ovarian Cancer

Ovarian cancer is the most lethal gynecologic cancer. Of the 20,700 women diagnosed with this disease in 1991, 12,500 women will die. Most ovarian neoplasms are of epithelial origin, and these cancers occur mostly in women beyond the age of 45. Risk factors are not well understood, but it is believed that repetitive ovulation increases the risk. Thus, early menarche and late menopause are risk factors while oral contraceptive use appears to diminish the risk.

More than half of the cases of ovarian cancer are discovered in an advanced stage. Current techniques of potential diagnosis include pelvic examination by a health professional, vaginal ultrasound, and the measurement of an ovarian tumor marker, CA125. However, the latter is not specific, nor is it effective as a screening tool. Pelvic examination is unfortunately imprecise, and currently vaginal ultrasound is both expensive and not widely available nor proven as a cost-effective measure.

Proposed Research

- *What are the factors that predispose the development of ovarian cancer?*
- *What preventive measures can be identified that could be implemented on a wide scale?*
- *Is there a cost-effective method for early detection, such as the development and refinement of sensitive vaginal ultrasound, that would greatly improve survival?*

The genetic changes that accompany the neoplastic ovarian phenotype are being investigated. As mesothelial cells undergo transformation, synthesis of a unique 200-kilodalton protein has been detected. Although normal ovarian tissue and benign ovarian lesions do not express M-CSF and c-fms proto-oncogene expression is low, 78 percent of ovarian neoplasms express M-CSF and 89 percent express c-fms transcripts. TGF alpha is not expressed by normal ovarian tissue but is detectable in neoplastic ovarian tissue.

Neoplastic ovarian tissue also demonstrates a variety of genetic changes. Allelic loss of the retinoblastoma gene has been reported. Allelic deletion of the Ha-ras proto-oncogene is also common. The p53 tumor suppressor gene is frequently overexpressed and mutated in these neoplasms. Amplification of the c-myc proto-oncogene has also been reported.

Studies of this type on ovarian and other gynecologic tumors will provide information concerning tumors arising at nongynecologic anatomic sites and may provide answers to the issues of basic molecular and cell biology of neoplasia and the effect of growth factors on this process.

The treatment of ovarian cancer relies on aggressive operative debalking. The stage of the disease is the single most important prognostic factor. Currently, platinum based chemotherapeutic regimens are most effective and produce initial responses in 60 to 80 percent of patients with advanced-stage (stages 3 and 4) disease. Unfortunately, only about 15 to 20 percent of patients following these excellent responses become long-term survivors.

A dose-response relationship for ovarian cancer in chemotherapy treatment has been demonstrated and this provides a rationale for the intraperitoneal administration of therapeutic agents. It also offers a route for other cell-specific therapies. High-dose chemotherapy with autologous bone marrow transplantation has been investigated but has not proven thus far to be efficacious.

A promising new drag is Taxol, a plant-derived antineoplastic agent. The drug is currently under investigation through a National Cancer Institute (NCI)-directed trial. In spite of initial good responses, long-term survival in a large group has not been demonstrated.

While the intraperitoneal route is currently the topic of many trials and may prove to be effective, particularly in patients with minimal disease, experimental models need to be explored for tumor-specific, site-directed therapies. For example, tumor-specific antibodies, particularly those linked to cytotoxic radionuclides, offer a potentially efficacious method W improve current therapeutic results, particularly for chemotherapy-resistant tumors. In addition, site-directed chemotherapy may also provide improved therapeutic benefits. Currently, these strategies are limited by the lack of cell-specific agents. Although immunotherapy has not yet proved successful, this research is emerging as a potential and exciting new method of treatment. Advances in these areas offer the promise of markedly increasing survival in this usually lethal disease.

Proposed Research

- *Which genetic alterations, if any, play a causative role in neoplastic transformation merits further investigation.*

- *Are there methods, including human tumor clonogenic assay, which can provide useful information and important clues to guide therapists to the optimal form of chemotherapy for specific patients?*
- *What new agents or new approaches can be developed to kill the cancer cell—for example, novel delivery systems or specialized treatment approaches such as the improved use of intraperitoneal therapy as well as the immunologic development of new biological response modifiers?*

Uterine Neoplasms

Uterine neoplasms constitute the most common site of lower genital tract cancers in women, of the 33,000 new cases diagnosed in 1991, it is estimated that 5,500 women will die of this disease. There is evidence that the age-standardized incidence rates for endometrial cancer are rising.

Although unopposed estrogen appears to play a role in the etiology of most endometrial adenocarcinomas, this model is not universally applicable. Comparisons of neoplastic, hyperplastic, and normal endometrium have revealed differences at the molecular level that will provide mights into the changes accompanying the initiation and promotion of endometrial neoplasia. As aa example, normal endometrium is uniformly diploid and expresses PDGF beta, IGF-I, IGF-II, and the EGF receptor. Hyperplastic endometrium is characterized by an increased likelihood of a nondiploid DNA index and increased proliferative activity. Neoplastic endometrium exhibits frequent aneuploidy, loss of hormonal responsiveness, and a variety of proto-oncogene abnormalities.

The diagnosis of endometrial cancer is typically prompted by the onset of postmenopausal vaginal bleeding. Transvaginal ultrasonography shows promise as a means to detect the presence of uterine pathology utilizing color flow doppler. This offers a potential way to screen women for unsuspected uterine pathology. Transvaginal ultrasonography is also a useful way to determine the depth of myometrial invasion in cases of diagnosed carcinoma.

The prognosis for women with endometrial cancer is based on tumor grade and depth of invasion. The histopathological evaluation of endometrial carcinoma for prognosis may be further refined by the determination of DNA content, proliferative index, steroid receptor expression, and the presence of specific oncogene abnormalities. Hormone receptor status appears to be an important prognostic indicator. Preliminary studies indicate that receptor negative lesions with a high S-phase fraction behave more aggressively than

lesions without these characteristics. The presence of HER-2/neu amplification may also identify neoplasms that are more likely to recur and metastasize.

Surgery remains the mainstay of treatment for endometrial carcinoma since most patients present with clinical stage 1 disease. Adjunctive radiation therapy is reserved for patients with high risk factors that predict local/regional recurrence. Although radiation therapy is effective in decreasing pelvic recurrence, a beneficial effect on long-term survival has been difficult to demonstrate.

Progestins have been used in the treatment of recurrent endometrial cancer with a response rate of 30 percent for a median duration of 10 to 12 months. Responses are more likely when used to treat progesterone receptor-positive neoplasms, but not all patients who express hormone receptors respond to hormonal therapy.

Recent evidence suggests that the combination of chemotherapy and hormone therapy may offer enhanced responses and survival in uterine cancer.

Although uterine cancers are often hormone dependent, preliminary data have suggested that estrogen replacement therapy utilized in this group of women may enhance their survival and quality of life by diminishing the frequency of the deleterious effects of estrogen deprivation.

Proposed Research

- *Can transvaginal ultrasonography become a cost-effective tool for early uterine cancer detection, similar to the project described in the discussion on ovarian cancer?*
- *Specialized treatment trials are needed to determine optimal methods for combining chemotherapy and radiation therapy, as well as chemotherapy and hormone manipulation, to enhance responses in survival.*
- *What is the safety and risk of estrogen replacement therapy in those who have been successfully treated for uterine cancer?*

Cervical Cancers

Cervical cancers have fallen to third in frequency after endometrial and ovarian malignancies. In 1991, 13,000 cases will be diagnosed, and 4,500 cervical cancer-related deaths will occur. Five- and 10-year trends demonstrate a continuing decline in the number of cases of invasive disease with a

concomitant increase in the number of cases of dysplasia. These trends have been attributed to increasingly effective cytologic (pap smear) screening programs.

The etiology of cervical cancer, particularly squamous cell carcinoma, has historically been associated with multiple sexual partners, early age at the initiation of sexual activity, cigarette smoking, and a history of sexually transmitted diseases. The effect of certain dietary deficiencies as a risk factor for cervical dysplasia is debated. During the past decade, attention has been focused on the role of the human papillomavirus (HPV) in premalignant lesions of the cervix (dysplasia, carcinoma in situ, or CIN I, II, III). Although HPV has not been demonstrated as the causative agent of cervix dysplasia and neoplasia, its role as an important cofactor is generally accepted. More than 60 subtypes of HPV have been identified, but a much smaller number appear to be important in cervical pathology. HPV 6 and 11 are associated with benign condyloma or low-grade neoplasia and are retained in the episomal state, whereas HPV 16 and 18 are generally found in high-grade dysplasia and in invasive carcinoma and are usually integrated into the host genome.

Current evidence suggests that only 16 percent of cases of mild dysplasia will progress to higher grade premalignant lesions, while carcinoma in sire carries a major risk for progression to invasive cancers. Specific times for progression are unknown but in most cases are believed to take years. However, recently some patients have been diagnosed with cervical cancer in whom the rate of progression to malignancy appears to have been much more rapid.

The transforming activity of the HVP 18 LCR-E6-E7 region is approximately 10- to 50-fold more active in transforming activity than comparable regions of HVP 16. This may explain the biological aggressiveness of HVP 18 adenocarcinomas of the cervix diagnosed in young women.

Immunologic alterations also appear to play a role in susceptibility to HVP cervical infections and in aa increased susceptibility to cervical cancer. Chronically immunosuppressed women, such as renal transplant patients, are at increased risk of cervical cancer. Pregnant women, in a state of relative immunosuppression, demonstrate an increased rate of a variety of HPV subtypes compared with nonpregnant women.

A new reporting system for cytological abnormalities of the cervix, the Bethesda system, has been proposed to facilitate communication between the cytopathologist and the clinician as well as to replace the numerical Papanicolaou designation. This new classification proposes to combine the changes of CIN I and those resulting from an HPV infection into a single diagnostic group. To date, the Bethesda system has not been uniformly adopted by obstetrician-

gynecologists or by cytopathologists. There is concern among gynecologists that the adoption of the Bethesda system will exacerbate the already serious problem of overtreatment of HPV cervical lesions. Since premalignant cervical lesions are treated and followed predominantly by obstetrician-gynecologists, these problems offer an important are for research in departments of obstetrics and gynecology. Most current therapeutic approaches to premalignant conditions of the cervix are empirical, and analyses based on cost-effective approaches are needed. For example, in some European countries such as the Netherlands, patients with mild dysplasia are followed with Pap smears twice yearly while in the United States the condition is almost universally treated. As noted, the optimal approach to widely prevalent HPV cervical refections is not known.

The stage of invasive cervical cancer remains the single most important clinical prognostic indicator of 5-year survival. Approximately one-half of cervical cancer patients with stage 1 disease that recurs after a radical hysterectomy have negative surgical margins and retroperitoneal pelvic lymph nodes free of metastatic disease, indicating the need for better prognostic indicators. Amplification of the c-myc oncogene has been correlated in some, but not all, studies as a poor prognostic finding. Overexpression of the c-myc oncogene has also been associated with early recurrence and decreased 5-year survival. Cervical neoplasms that express the Ha-ras p21 protein are at increased risk for pelvic lymph node metastases.

Carcinomas confined to the cervix may be treated with radiation therapy or surgical therapy with comparable 5-year survival rates. Neoadjuvant chemotherapy with cisplatin shows promise as a means to reduce the size of the primary lesion and to decrease the incidence of metastatic nodal disease prior to surgery, particularly in advanced cases.

With the exception of women who develop central pelvic recurrence amenable to removal by exenterative surgery, recurrent cervical cancer following radiation therapy is fatal. Cisplatin is the most active agent for recurrent cervical cancer, but response rates are limited to 30 percent and cures are anecdotal.

Proposed Research

- *What is the influence of human immunodeficiency virus (HIV)-related immunosuppression upon the risk of cervical HPV infection, cervical dysplasia, and cervical neoplasia? This requires population studies.*

- *Do HPV infections require therapy and if so, which types are needed to reduce the frequency of cervical cancer?*
- *Can a methodology be developed to identify which "premalignant" cervical neoplastic conditions are at risk for progression?*
- *What are the optimal intervals for cervical cytologic screening?*
- *What are the optimal methods of treating various degrees of cervical intraepithelialneoplasia, and which are most cost-effective?*
- *What is the role of HPV virus in the genesis and progression of cervical neoplasia?*
- *What characteristics (oncogene amplification, for example) can be identified that will reliably predict aggressive tumor behavior and thus provide the basis for improved initial treatment strategies?*
- *How can the standard therapies of radiation or operation for cervical cancer be combined with newer modalities of chemotherapy or immunotherapy to improve survival?*
- *What new strategies can be developed to improve the therapy of recurrent cervical cancer, which currently is almost uniformly fatal?*

Vulvar Malignancies

Vulvar malignancies account for 3 to 4 percent of gynecologic neoplasms, and the majority of these are squamous cell carcinomas. The etiologic role of the human papillomavirus (HPV) in vulva dysplasia and neoplasia has not been fully determined. Microscopic evidence of benign HVP-associated lesions is found in conjunction with vulvar carcinomas. Using molecular biological techniques, HPV has been found in 30 to 80 percent of vulvar carcinomas. The difference in age-adjusted incidence rates for invasive cervical versus vulvar carcinoma, in addition to the observation that HVP is found more often in premalignant lesions versus malignant lesions of the cervix and vulva, suggests that the pathogenic role of HPV may be different in lesions of the cervix and of the vulva.

Vulvar and cervical neoplasms may share a common etiologic factor in HPV. However, the biological behavior of preinvasive vulvar disease appears to be different from that of cervical disease. There is little evidence to suggest that dysplastic lesions of the vulva have a significant probability of progression to invasive disease in the absence of appropriate treatment, as is the case for premalignant lesions of the cervix.

Not only is the biological behavior of preinvasive vulvar disease different from that of cervical disease—it is also less predictable. It appears that many of the vulvar premalignant lesions spontaneously regress, although there is currently no method to differentiate these cases from those that progress.

Surgery is the primary method of therapy of invasive vulvar carcinoma and consists primarily of radical vulvectomy or hemivulvecromy and inguinal-femoral node dissection. Radiation is used as an adjunct for advanced-stage tumors and to treat pelvic nodes in case in which the inguinal-femoral nodes are involved. Recently, less extensive surgical procedures for vulvar cancers, such as modified radical vulvectomy and unilateral lymph node dissection, have been advocated to achieve a more cosmetic result with presumed comparable therapeutic effectiveness. The potential for future use of chemotherapy as an independent and combined modality of treatment is similar to the situation described with cervical carcinomas.

Proposed Research

- *Clinical trials are needed to establish efficacy and safety of new treatments.*
- *What is the optimal method of therapy of premalignant lesions of the vulva, and can one identify which of these lesions actually require therapy? This should include investigation of rates of progression and regression, identification of lesions that require therapy, and determination of optimal screening intervals. Understanding the molecular biology of premalignant vulvar disease should help in this area of research.*

Breast Cancer

Breast cancer is the most common cancer in women. In 1991, 175,000 women will be diagnosed with this disease, and 44,500 will die. It has been estimated that 1 in 10 women in the United States will develop breast cancer during her lifetime, and some recent estimates indicate that the number may be close to 1 in 9.

Obstetrician-gynecologists, as care givers to women, are often primarily involved in the initial detection of breast cancer. Therapy is usually performed by surgeons, radiotherapists, and medical oncologists. Nonetheless obstetrician-gynecologists not only have a major role in the diagnosis of the disease but are also medically responsible for the major events in the life of a

woman that may bear on the causation or prevention of breast cancer such as pregnancy, lactation, oral contraceptive use, estrogen replacement, and the ordering of such screening tests as mammography. All of these provide areas of research that require the participation of departments of obstetrics and gynecology.

Most benign breast diseases are not considered premalignant, although the risk of cancer in women with benign breast disease may be increased. The use of oral contraceptives appears to decrease the incidence of benign breast disease, although their effect on the risk of breast cancer is unclear at present. Most studies have indicated no effect, although some have suggested an increased effect after long-term usage.

The NIH-sponsored cancer and steroid hormone (CASH) study suggests a decrease in the relative risk of breast cancer, diagnosed in the 40s for women who have used oral contraceptives. It appears that there is a strong interaction between parity and age, in which parity increases the risk of breast cancer in younger women and decreases the risk in older women. Some of the data suggest an acceleration phenomenon for cases that may have already been initiated, and such would be consistent with the effects of parity.

Future studies may be directed at classifying women into high- and low-risk groups. It is possible that measurement of proto-oncogenes may theoretically yield information concerning genetic risk. A 16-alphahydroxylation pathway for the degradation of estrogen has been observed in women with breast cancer. Suspected risk factors for breast cancer include obesity, a high-fat diet, hereditary (genetic) factors, and alcohol retake. These factors appear to be associated with an increase in the ratio of the urinary estrogen metabolite while those factors suspected to be associated with decreased risk (thinness, exercise, decrease in fish oil consumption, etc.) decrease the excretion.

Adjuvant therapy reduces relapse rates and prolongs survival among those treated for breast cancer. Endocrine therapy has emerged as a major treatment modality for early-stage disease. The anti-estrogen Tamoxifen improves survival in estrogen receptor-positive cases, particularly for women over the age of 50. Currently, a clinical trial is being conducted in Europe to ascertain the efficacy of long-term prophylactic Tamoxifen therapy on the prevention of breast cancer. However, long-term Tamoxifen therapy may increase the risk of liver cancer; it has also been suggested that it increases the risks of endometrial cancer and of cardiovascular disease.

The issue of hormone replacement therapy is assuming increased importance as larger numbers of younger women with early-stage breast cancer have been diagnosed. Currently, estrogen therapies are believed to be contraindicated m women who have been diagnosed with breast cancer. Yet there are no clear

data to substantiate the general belief that hormone replacement therapy increases the risk of recurrent breast cancer.

Proposed Research

- *What is the potential effect of oral contraceptives on pre- and postmenopausal breast cancer?*
- *Does prolonged oral contraceptive use or early initiation of use (prior to age 20) alter the risk of the development of breast cancer?*
- *Does prolonged estrogen replacement therapy alter the risk of breast cancer?*
- *Does the addition of a progestin (protective for endometrial carcinoma) alter breast cancer risks?*
- *Can estrogen replacement therapy be safely used in patients who have been successfully treated for breast cancer to avoid the morbidity of estrogen deprivation?*
- *Does tamoxifen therapy for breast cancer alter the risk of endometrial neoplasia?*
- *Can groups of high-risk and low-risk women be identified through metabolic hormonal investigation or through molecular studies such as those involving proto-oncogenes?*

Trophoblastic Disease

Trophoblastic disease is usually associated with pregnancy and occurs in the uterus, although similar tumors can arise at other sites such as the ovary. The most common variant of trophoblastic disease, hydatidiform mole, occurs in about 1,000–2,000 pregnancies. Most of these cases require no further treatment after surgical evacuation of molar tissue from the uterus, but some cases progress and require chemotherapy. The fact that these tumors all secrete hCG allows the measurement t of hormone as a specific marker for therapy. The development of a sensitive assay using the beta subunit of hCG has provided a unique tool to follow these patients.

Risk factors include young age at pregnancy (less than 15 years of age) or older age (more than 45 years of age), but the precise mechanism of development is not known. These diseases were the first to be cured by chemotherapy using initially methotrexate. Currently, actinomycin D is used for

low-risk cases. High-risk cases are treated with multiple agent chemotherapy with a more recent combination involving etopiside (VP16)- platinum (EP) or etoposide methotrexate, actinomycin-D, cyclophosphamide, and vincristine (oncovin) (EMA-CO). Brain metastases usually receive radiation. Although outstanding cure rates in this disease have been obtained with chemotherapy, fatalities still occur. The best results are for patients treated at large centers specializing in these diseases, and these centers are primarily located in departments of obstetrics and gynecology.

Proposed Research

- *What are the effects on future fertility of successful chemotherapy of trophoblastic diseases?*
- *What are the effects of chemotherapy in the mother on future genetic abnormalities in the offspring?*
- *What improved treatment strategies can be developed to help patients who currently succumb to the disease?*
- *What are the genetic or other causes that lead to the development of gestational trophoblastic diseases?*

SEXUALLY TRANSMITTED DISEASES*

The recent dramatic increase in sexually transmitted diseases (STDs) in the United States has had a major impact on the reproductive health of women.

Untreated or inadequately treated gonococcal and chlamydial infections result in approximately 1 million cases of pelvic inflammatory disease (PID) each year. The acute and chronic sequelae, which include infertility, tubal pregnancy, and chronic pelvic pain, are devastating to many women. The number of reported cases of syphilis among women has also increased and last year was the highest in 40 years. As a result, congenital syphilis has increased over 200 percent. More than 100,000 infants die or suffer birth defects because of STDs transmitted during pregnancy or at birth. Vital STDs including human immunodeficiency virus (HIV), genital herpes simplex (HSV), and human papillomavirus (HPV) also have become major problems. Genital herpes simplex vital refection is a painful, incurable disorder that affects many women.

* This section was written by Gloria E. Sarto.

An estimated 20 million women are infected with human papillomavirus and thus are at increased risk for carcinoma of the cervix. In 1990, the largest proportional increase in AIDS cases was among women. HIV infection in pregnancy can result in increased abortion, stillbirth prematurity, low-birthweight infants, and neonatal mortality. The health care costs to deal with sexually transmitted diseases and consequent sequelae are in the billions of dollars.

Major efforts will have to be directed toward early diagnosis and treatment to reduce the magnitude of the problems associated with STDs.

Proposed Research

- *Preventing sexually transmitted diseases by developing clinically effective and safe vaccines.*
- *Developing cost-effective tests for early diagnosis.*
- *Developing new therapies where needed and new cost-effective antibiotics that are easily administered and sufficiently acceptable to enhance compliance.*
- *Clarifying the natural history of genital infections.*
- *Defining behaviors associated with the acquisition and spread of sexually transmitted diseases.*
- *Characterizing the role of STDs in adverse pregnancy outcomes.*

Although an interdisciplinary approach involving microbiology, immunology, genetics, and molecular biology will be needed to meet some of these challenges, obstetrics and gynecology—because obstetricians and gynecologists are among the primary providers of health care for women—will have to play a major role in meeting these challenges, particularly in relation to epidemiologic studies and clinical trials.

Prevent Sexually Transmitted Diseases by Developing Clinically Effective and Safe Vaccines

The structural components of STD organisms have been intensively analyzed and dissected, providing information for a rational approach to vaccine development that can be utilized to prevent further infections. Vaccines have been developed and are in various stages of testing for gonorrhea, chlamydia, HSV, and HIV.

Proposed Research

- *Basic research on the microbiology, immunology and pathogenesis of STDs is essential to the eventual design and development of effective vaccines against them.*
- *Development of prototypes of vaccines for use in the prevention of N. gonorrhoeae, C. trachomatis, HIV, and HSV is under way and should be intensified with additional resources.*
- *The mucosal immune response to organisms that cause STDs is critical for the development of successful vaccines, which may stimulate both B- and T-cell limbs of the immune response. Consequently, detailed mapping and analysis of the epitomes of the proteins associated with STD organisms in eliciting immune response are necessary.*
- *The mucosal immune system of the human female genital tract and its role in the prevention of infection and/or susceptibility to infection should be studied more intensely.*
- *The function of the mucosal immune system, specifically, antigen-processing, humoral, and cellular immune responses and the effects of hormones on these responses, should be studied.*

Develop Cost-Effective Tests for Early Diagnosis of STDs

With the development of molecular probes and monoclonal antibodies, improved diagnostic methods have been developed for the early detection of STDs. With the recommendation that asymptomatic women undergo routine screening with these newer diagnostic tools, asymptomatic infections have been identified and treated, thus avoiding further development of complications and sequelae.

Proposed Research

- *Develop simple, inexpensive, rapid STD detection methods that are accurate in both symptomatic and asymptomatic women. Highest priority in this area is the development of a test for chlamydial infections. Development of a similar test for vital STDs, such as HSV, HPV, and HIV, is also critical.*

- *Investigate the safety, and efficacy of experimental antiviral drugs against HIV and treatment of opportunistic infections in both pregnant and nonpregnant women.*
- *Evaluate the efficacy, of treatment regimens for pelvic inflammatory disease in relation to preservation of normal reproductive function. This will require a long-term multicenter trial to adequately assess long-term outcomes.*
- *Develop improved methods to diagnose PID and to identify women at high risk for reproductive sequelae. Accurate, noninvasive approaches must be developed, particularly to address the challenges posed by atypical infections. Virulence factors and immunologic markers should be sought that are predictive of postinfectious infertility or ectopic pregnancy.*

Develop New Therapies Where Needed and New Cost-Effective Antibiotics That Are Easily Administered and Sufficiently Acceptable to Maximize Compliance

Antiviral drugs have been developed specifically for the treatment of HSV and HIV. These drugs have significantly decreased morbidity and, in the case of herpes, have decreased occurrence rates. Molecular studies have also delineated the mechanisms of antimicrobial resistance, an area of growing importance with the increasing spread of antibiotic-resistant *Neisseria gonorrhoeae,* acyclovir-resistant HSV, and AZT-resistant HIV.

Proposed Research

- *Develop curative antiviral agents for infections with HPV, HSV, and HIV. Studies are also needed to better define the effect of existing palliative therapies on transmission and progression of their infections.*
- *Evaluate PID treatment regimens for efficacy in preserving normal reproductive function, as well as for ability to achieve clinical and microbiological resolution of acute infection. This will require a multicenter clinical trial, with support for a minimum of 7 to 10 years, to permit adequate assessment of relevant long-term outcomes. The role of adjunctive PID therapy using anti-inflammatory or immunomodulating agents to reduce long-term sequelae should also be examined.*

- *Conduct further studies to document the safety and efficacy of STD/HIV regimens during pregnancy.*
- *Evaluate the safety and efficacy of experimental antiviral drugs against HIV and treatment of opportunistic infections in both pregnant and nonpregnant women.*
- *Expand community research programs for the treatment of HIV, and identify mechanisms to increase access to care, particularly among low-income women.*
- *Develop an understanding of the nature of pathogen-cell interactions, especially virus attachment and entry, in order to formulate effective strategies for interruption of transmission. Natural history studies of HPV infection and the influence of the immune system are critically important in attempts to prevent the development of cervical cancer.*
- *Encourage therapeutic studies of STDs that specifically address efficacy and safety as well as compliance and cost.*
- *Develop inexpensive, accessible therapeutics that can be used reliably by women who must frequently manage multiple responsibilities (e.g., family, job) despite declining health.*
- *Evaluate and develop clinical trial recruitment and retention procedures to facilitate enrollment and follow-up of women (e.g., access to primary medical care, child care, transportation to clinic sites, as well as other support services).*
- *Review clinical trial eligibility criteria in ongoing studies, specifically, inclusion/exclusion criteria that may be too restrictive and thus prohibit the participation of women (e.g., definitions of active drug use, pregnancy, anemia, elevated liver enzymes, etc.).*
- *Study and develop better barrier/contraceptive methods (e.g., condoms vs. female-controlled methods) and viricides that are effective, safe, and acceptable to women; especially needed are methods that can be controlled by women and that may be used without detection by their sexual partners.*

Clarify the Natural History of Genital Infections

Studies elucidating the pathogenesis of the microbial agents responsible for these refections have provided us with a better understanding of the factors responsible for the reduction of the disease process. In some cases, studies have identified the molecular basis of microbial attachments to mucosal surfaces and the subsequent immune response resulting in beth inflammatory changes and resistance to further infection.

Proposed Research

- *Describe the full spectrum of HIV-related illnesses and malignancies in women to fully evaluate current AIDS case definitions and standards of medical care for women.*
- *Establish prospective cohorts of women to determine the natural history and clinical presentation of HIV infection in women. Factors that affect the progression to AIDS among HIV-infected women should be identified, and the types of opportunistic infections that occur in women should be studied more intensively. Clinical, virologic, and immunologic markers of disease progression should be evaluated to the female-specific endpoints of disease progression.*
- *To better understand, prevent, and treat HIV infection in women, conduct studies to address the frequency and factors responsible for transmission of HIV to women with specific focus on STDs, stage of disease, hormonal influence, and age.*
- *Continue studies on the frequency and factors responsible for transmission of HIV from mother to child, and evaluate the use of therapy that prevents transmission.*
- *Initiate detailed studies on the impact of STD infections on HIV transmission and the impact of HIV on STD infections. For example, detailed studies on HPV infection in HIV-infected women should be conducted to determine the impact of HIV on HPV in the subsequent development of cervical cancer.*
- *Define the factors and mechanisms that alter risk of disease progression, such as HPV infection and its association with premalignant and malignant lesions of the genital tract. Epidemiologic studies are necessary to further define the factors required for initiation versus potentiation of typical cell growth.*
- *Conduct epidemiological and basic studies to better define the risk factors and biological mechanisms that influence progression of HPV infection to anogenital neoplasia. Urgently needed are HPV natural history studies that examine the roles of viral type and immune status.*
- *Examine the mucosal immune system of the human female genital tract, its relationship to other mucosal immune systems, and its role in the prevention of STDs and HIV infection. Specifically, antigen-processing, humoral, and cellular immune responses and the effects of hormones on the responses should be studied.*
- *Define the chronology and the host and pathogen factors involved in ascent of lower tract organisms into the endometrium and fallopian tubes, and*

subsequent tubal scarring. Development of improved animal models for PID would greatly facilitate this research.

- *Determine the clinical and microbiological spectrum, the frequency, and the natural history of atypical PID. Seroepidemiological studies of infertile women and women with tubal pregnancies strongly suggest that atypical or subclinical PID is responsible for a substantial proportion of these disorders.*

Define Behaviors Associated with the Acquisition and Spread of STDs

Major advances have been made in our knowledge of the epidemiology of STDs including HIV infections. Factors contributing to the recent epidemic of STDs among women are complex and appear to involve the interaction of a number of variables including socioeconomic status, exchange of sexual services for drugs, health care-seeking behavior, changes in population demographics, and residence in areas of high disease prevalence. The increasing STD rate has important implications:

1. rises in heterosexual adult STDs predict similar trends in congenital STDs;
2. community health education messages, generated by concerns about HIV, to reduce risky sexual behavior have not yet permeated minority heterosexual populations; and
3. because of the association of both genital ulcer disease and genital nonulcerative diseases with HIV transmission, control of STDs could further reduce HIV spread in this population.

Proposed Research

- *Investigate determinants of health care-seeking behavior in women, including the role of social networks and support systems in facilitating women's access to services.*
- *Develop a specific behavioral research agenda in STD prevention. Epidemiologic studies are needed to identify the type and prevalence of behaviors that put individuals at risk for transmission or progression of an STD.*
- *Identify behavioral risk factors; this work would be facilitated by a national survey of sexual behavior.*

- *Determine population rates for STDs, and conduct natural history studies for disease progression in specific, well-characterized populations.*
- *Study the psychosocial needs of HIV-positive women and their family systems (traditional and nontraditional, including lesbian women) as they cope with the chronic, crisis-oriented, and usually fatal nature of HlV disease. Give special attention to adolescent psychosocial needs with emphasis on suicide prevention and support strategies.*

Characterize the Role of STDs in Adverse Pregnancy Outcomes

Perinatal infections, specifically, Group B streptococcus, cytomegalovirus, and chlamydia, are being studied to determine their incidence and resulting mammal, fetal, and neonatal outcomes.

Proposed Research

- *Study factors such as the infecting pathogen, the stage of gestation during which infection occurs, chronicity of infection, and behavioral patterns such as drug abuse. Organisms should be specifically examined for virulence factors and for other markers associated with specific patterns of fetal or neonatal morbidity.*
- *Conduct further studies to demonstrate whether drugs such as acyclovir and zidovudine are safe and effective for use during pregnancy.*
- *Direct immunologic studies toward the protective immune responses during breastfeeding to identify the components in breast milk that are primarily responsible for inhibition of specific pathogens.*
- *Similarly, identify the role that breastfeeding plays in the transmission of certain infections such as HIV.*
- *Examine such factors as chronicity of infection and stage of gestation during which infection occurs to identify specific pathogens. Improved understanding of the immunobiology of pregnancy and the use of both natural and artificial animal models of STDs in pregnancy are likely to be important to productive research in this area. In addition, organisms should be examined for virulence factors or other markers associated with specific patterns of fetal or neonatal morbidity.*

REFERENCES

Oocyte and Follicular Development in the Ovary

Adashi EY 1990. The potential relevance of cytokines to ovarian physiology: The emerging role of resident ovarian cells of the white blood cells series. Endocrine Rev 11:454–464 .

Adashi E.Y., Resnick C.E., Croft C.S., May J.V., Gospodarowicz D. 1988. Basic fibroblast growth factor as a regulator of ovarian granulosa cell differentiation: a novel nonmitogenic role. Mol Cell Endocrinol 55:7–14 .

Baker T.G. A quantitative and cytological study of germ cells in human ovaries, Proc R Soc (Biol) 158:417 ,1963.

Bendell J.J., Dorrington J. 1991. Estradiol-17B stimulates DNA synthesis in rat granulosa cells: Action mediated by transforming growth factor-B. Endocrinology 128:2663–2665 .

Braw R.H., Tsafriri A. Follicles explanted from pentobarbitone-treated rats provide a model for atresia. J. Reprod Fertil 59:259 , 1980.

Buttyan R., Zakeri Z., Lockshin R., Wolgemuth D. Cascade induction of cy-myc and heat shock 70K transcripts during regression of the rat ventral prostate gland. Mol Endocrinol 2:650 , 1988.

Chao H.T., Ng H.T., Kao S.H., Wei Y.H., Hong C.Y. 1991 Human follicular fluid stimulates the motility of washed human sperm. Arch Androl 26:61–65 .

DiZerega G.S., Marut C.K., Turner and G.D. Hodgen. Asymmetrical ovarian function during recruitment and selection of the dominant follicle in the menstrual cycle of the rhesus monkey, J Clin Endocrinol Metab 51:698 , 1980.

Franchi L.L., A.M., Mandl, and S. Zuckerman. The development of the ovary and the process of oogenesis. In Zuckerman, S., A.M. Mandl, and P. Eckstein (eds.), The Ovary, Academic Press. London, pp.1–88 , 1962.

Goodman A.L. and Hodgen G.D. The ovarian triad of the primate menstrual cycle. Recent Prog Horm Res 89:1 , 1983.

Goodman A.I., and G.D. Hodgen. Between ovary interaction in the regulation of follicle growth, corpus luteun function, and gonadotropin in the primate ovarian cycle. II. Effects of lutaectomy and hemiovariectomy during the luteal phase in cynomolgue monkeys, Endocrinology 104:1310 , 1979.

Goodman A.L., and G.D. Hodgen. Between ovary interaction in the regulation of follicle growth, corpus luteum function, and gonadotropin secretion in the primate ovarian cycle. I. Effects of follicle cautery and hemiovariectony during the follicular phase in Cynomolgus monkeys, Endocrinology 104:1304 , 1979.

Hay M.F., Cran D.G., Moor T.M. Structural changes occuring during atresia in sheep ovarian follicles. Cell Tiss Res 169:515 , 1976.

Hirshfield A.N. 1991. Development of follicles in the mammalian ovary. Int Rev Cytol 124:43–101 .

Himelstein-Braw, R, A.G. Byskov, H. Peters, and M. Faber. Follicular atresia in the infant human ovary, J Reprod Fertil 46:55 , 1976.

Hodgen, G.D. The dominant ovarian follicle, Fertil Steril 38:281 , 1982.

Kerr J.F.R., Wyllie A.H., Currie A.R., Apopotosis: A basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 26:239 , 1972.

Koos R.D., Oison C.E. 1989. Expression of basic fibroblast growth factor in the rat ovary: Detection of mRNA using reverse transcription-polymerase chain reaction. Mol Endocrinol 3:2041–2048 .

Koos R.D., Olson C.E., Gustafson T.A. 1991. Expression of the epithelial cell mitogen keratinocyte growth factor (KGF) in the rat ovary-detection of mRNA in stroma and not in granulosa cells. Biol Reprod 44 (Suppl 1): No. 370 .

Moses H.L., Yang EY., Pietenpol. 1990. TGF-B stimulation and inhibition of cell proliferation: New mechanistic insights. Cell 63:245–247 .

Mulheron G.W., Schomberg D.W. 1990. Rant granulosa cell express transforming growth factor-B type 2 messenger ribonucleic acid which is regulatable by follicle-stimulating hormone in vitro. Endocrinology 126:1777–1779 .

Nilsson L., M. Wikland, and L. Hamberger. Recruitment of an ovulatory follicle in the human following follicle-ectomy and lutaectomy, Fertil Steril 37:30 , 1982.

Ohno S., H. Klinger, and N. Atkin. Human oogenesis, Cytogenetics 1:42 ,1962.

O'Shea J.D., Hay M.J., Cran D.G. Ultrastructural changes in the theoa interna during follicular atresia in sheep. J Reprod Fertil 54:183 , 1978.

Peluso J.J., England-Charlesworth C., Bolednder D.L., Steger R.W. Ultrastructural alterations associated with the initiation of follicular atresia. Cell Tiss Res 211:105 , 1989.

Peters H. Intrauterine Gonadal Development, Fertil Steril 27:493 , 1976.

Phillips H.S., Hains J., Leung D.W., Ferrara N. 1990. Vascular endothelial growth factor is expressed in rat corpus luteum. Endocrinology 127:965–967 .

Ralt D., Godendberg M., Fetterolf P., Thompson D., Dor J., Mashiach S., Garbers D.L., Eisenbach M. 1991. Sperm attraction to a follicular factor(s) correlates with human egg fertilizability. Proc Natl Acad Sci USA 88:2840–2844 .

Rose B.R., Koos R.D. 1988. The effect of human follicular fluid on endothelial cells: proliferation and DNA synthesis. Biol Reprod 39:88–95 .

Ross G.T. Gonadotropins and preantral follicular maturation in women. Fertil Steril 25:522 , 1974.

Seegar-Jones G., and M. de Moraes-Ruehsen. A new syndrome of amenorrhea in association with hypergonadotropism and apparently normal ovarian follicular aparatus. Am J Obstet Gynecol 104:597 , 1969.

Tsafriri A., Braw R.H. Experimental approaches to atresia in the mammals. Rev Reprod Biol (Oxford) 6:226 , 1984.

Uilenbroek J.T.J., Woutersen P.J.A., Van der Schoot P. Atresia in preovulatory follicles: gonadotropin binding in steriodogenic activity. Bio Reprod 23:219 , 1980.

Vlodavsky I., Bar-Shavit R., Ishai-Michaili R., Bashkin P., Fuks Z. 1991. Extracellular sequestration and release of fibroblast growth factor: A regulatory mechanism. TIBS 16:268–271 .

Witschi E., Migration of the germ cells of human embryos from the yolk sac to the primitive gonadal folds, Contrib Embryol 32:67 , 1948.

Zeleznik A.J., Ihrig L.L., Bassett S.G. Developmental expression of Ca++/Mg++-dependent endonuclease activity in rat granulosa and luteal cells. Endocrinology 125:2218 , 1989.

Fertilization

Chang, M.C. 1951. Fertilizing capacity of spermatozoa deposited into the fallopian tube. Nature 168:697–698 .

Ducibella, T., Rangarajan, S. and Anderson, E. 1988. The development of mouse oocyte cortical reaction competence is accompanied by major changes in cortical vesicles and not cortical granule depth. devel. Biol. 130:789–792 .

Ducibella, T., Anderson, e., Albertini, D., Aalberg, J. and Rangarajan, S. 1988. Quantitative studies of changes in cortical granule number and distribution in the mouse oocyte during meiotic maturation. Devel. Biol. 130:184–197 .

Dunbar, B.S. 1983. Morphological, biochemical and immunochemical characterization of the mammalian zona pellucida. In: *Mechanism and Control of Animal Fertilization* , ed. J.F. Hartman, pp. 140–175 , New York.

Hafez, E.S.E. and Semm, K.(eds.) 1986. *In Vitro Fertilization and Embryo Transfer* . New York: Alan R. Liss.

Hedrick, J.L.(ed.) 1986. *The Molecular and Cellular Biology of Fertilization: Gamete Interactions* . New York: *Plenum* .

Igusa, Y., Miyazaki, S. and Yamashita, N. 1983. Periodic hyperpolarizing responses in hamster and mouse eggs fertilized with mouse sperm. J.Physiol. (London) 340:633–647 .

Jaffee, L.A., Sharp, A.P. and Wolf, D.P. 1983. Absence of an electrical polyspermy in the mouse. Devel. Biol. 96:317–323 .

Jagiello, G. and Vogel, H.J. (eds.) 1981. *Bioregulators of Reproduction* . New York: Academic Press.

Kinlock, R.A., Mortillo, S., Stewart, C.L. and Wasserman, PM. 1991. Embryonal carcinoma cells transfected with ZP3 genes differentially glycosylate similar polypeptides and secrete active mouse sperm receptor. J. Cell Biol. 115:655–664 .

Longo, F.J. 1987. *Fertilization* . New York: Chapman and Hall.

Saling, P.M. 1989. Mammalian sperm interaction with the extracellular matrices of the egg. Oxford Review of Reproductive Biology 11:339–388 .

Selman, K. and Anderson, E. 1975. The formation and cytochemical characterization of cortical granules in ovarian oocytes of the golden hamster, *Mesocricetus auratus*. J. Morphol. 147:251–271 .

Wassarman, P.M. 1987. The biology and chemistry of fertilization. Science 235:553–560 .

Wassarman, P.M. 1987. Early events in mammalian fertilization. Ann. rev. Cell Biol. 3:109–142 .

Wassarman, P.M. 1988. Zona pellucida glycoproteins. Ann.Rev.Biochem. 57:415–442 .

Yanagimachi, R. and Noda, Y.D. 1970. Physiological changes in the post-nuclear cap region of mammalian spermatozoa: A necessary preliminary to the membrane fusion between sperm and egg cells. J. Ultrastruct. Res. 31:486–493 .

Fetal Growth and Development Embryology and Congenital Malformations

Bernfield, M: Developmental biology: preventive medicine for neonatology. Pediatr Res, 27:21–27 ,1990.

Buchanan, T., Freinkel,N., Lewis, N.J., Metzger, B.E. and Akazawa,S.: Fuel mediated teratogenesis: The use of D-mannose to modify organogenesis in rat embryos *in vivo* . J. Cane Invest. 75:1927–34 ,1985.

Goulding, M.D., Gruss, P.: The homeobox in vertebrate development. Curr Opin Cell Biol. 1:1088–93 ,1989.

Heyner, S., Farber, M., Rosenblum, I.Y.: The insulin family of peptides in early mannalian development. Curr Top Dev Viol. 24:137–59 , 1990.

Hollenberg, M.D.: Growth factors, their receptors and development. Am J Med Genet. 34:35–42 , 1989.

Kessel, M. and Gruss, P.: Murine Development Control Genes. Science. 249:374–379 , 1990.

Mummery, L.L. and van de Eijnden-van Raatj, A.J.M.: Growth factors and their receptors in differentiation and early murine development. Cell Differentiation and Development. 30:1–18 , 1990.

New, D.A.: Whole embryo culture, teratogenesis and the estimation of teratologic risk. Teratology. 42:635–42 , 1990.

Stiles, A.D. and D'Ercole, A.J.: The insulin-like growth factors and the lung. Department of Pediatrics. J Respir Cell Mol Biol. 3:93–100 , 1990.

Tabin, C.J.: Retinoids, homeoboxes and growth factors: Toward molecular models for limb development. Cell. 66:199–217 , 1991.

Fetal Growth and Placental Transport

Battaglia, F.C. and Meschia, G.: Introduction to Fetal Physiology. Academic Press, New York. pp. 257 , 1986.

Battaglia, F.L. and Meschia, G.: Fetal nutrition. Ann Rev Nutr. 8:43–61 , 1988.

Browne, C.A. and Thorburn, G.D.: Endocrine control of fetal growth. Biol Neonate. 55:331–46 , 1989.

Chad, T.: Hormonal control of growth in the human etus. J Endocrinol. 123:3–9 , 1989.

Davenport, M.L., D'Ercole, A.J. and Underwood, L.E.: Effect of maternal fasting on fetal growth, serum, insulin-like growth factors (IGF's), and tissue IGF messenger ribonucleic acids. Endocrinology. 126:2062–7 , 1990.

de Pablo, F., Scott, L.A. and Roth, J.: Insulin and insulin-like growth factor I in early development: Peptides, receptors and biological events. Endocr Rev. 11:558–77 , 1990.

de Pablo, F. and Roth, J.: Endocrinization of the early embryo: An emerging role for hormones and hormone-like factors. Trends Biochem Sci. 15:339–42 , 1990.

Hill, D.J. and Han V.K.: Paracrinology of growth regulation. J Dev Physiol. 15:91–104 , 1991.

Congenital Infection and Substance Abuse

Andiman, W.A.: The infant of the human immunodeficiency virus-Infected mother. Seminars in Perinatology. 13:1–65 , 1989.

Bandstra, E.J.: Substance abuse in the perinatal period. Seminars in Perinatology. 15:263–32 , 1991.

Evans, At.T. and Gillogley, K: Drug use in pregnancy: Obstetric perspectives. Clin Perinatol. 18:23–32 , 1991.

Stagno, S.: Significance of cytomegaloviral infections in pregnancy and early childhood. Pediatr Infect Dis J. 9:763–4 , 1990.

Perinatal Research

Gross, I.: Regulation of fetal lung maturation. Am J Physiol. 259:337–44 , 1990.

Gluckman, P.D., Breier, B.H., Oliver, M., Harding, J., and Bassett, N.: Fetal growth in later gestation —A constrained pattern of growth. Acta Paediatr Scand Suppl 367:105–10 , 1990.

Low, J.A.: The current status of maternal and fetal blood flow velocimetry. Am J Obstet Gynecol. 164:1049–64 , 1991.

Phillips, A.F., Porte, P.J., Stabinsky, S., Rosenkranz, T. S. and Raye, J.R.: Effects of chronic fetal hyperglycemia upon oxygen consumption in the ovine uterus and conceptus. J. Clin Invest. 74:279–286 , 1984.

Uzan, S., Beaufils, M., Breant, G., Bazin, B., et al.: Prevention of fetal growth retardation with low-dose aspirin: Findings of the EPREDA trial. Lancet. 337:1427–31 , 1991.

Warshaw, J.B.: Intrauterine growth retardation. Pediatr Review 8:107–114 , 1986.

Epidemiological Research

Chalmers, I.: Inquiry into stillbirths and infant deaths. BMJ. 299:339–40 , 1989.

MacDonald, M.G., Ginzburg, H.M. and Bolan, J.C.: HIV infection in pregnancy: Epidemiology and clinical management. J Acquir Immune Defic Syndr. 4:100–8 , 1991.

Mugford, M., Piercy, J. and Chalmers, I.: Cost implications of different approaches to the prevention of respiratory distress syndrome. Arch Dis Child 66:756–64 , 1991.

Sowers, J.G.: Preventive strategies in education: History, current practices and future trends regarding substance abuse and pregnancy prevention. Bull NY Acad Med. 67:256–69 , 1991.

Preterm Labor

Cunningham F. G., MacDonald P.C., Gant N.F., Williams Obstetrics 18th Ed. Appleton and Lange, East Norwalk CT, 1989, pp. 656–657 .

Hack, M., Horbar J.D., Malloy M.H., Tyson J.E., Wright E., Wright L. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Newwork, Pediatrics 1991; 87:587–97 .

Leake R. D., Oxytocin. In: Initiation of Partuirition: Prevention of Prematurity. MacDonald P.C., Porter J.C., eds. Ross Laboratories, Columbus, Ohio: 1983; 43–8 .

Leveno K. J., Little B.B., Cunningham F.G., The national impact of ritodrine hydrochloride for inhibitin of preterm labor. Obstet. Gynecol. 1990; 76:12–5

MacDonald P.C., Koga S., Casey M.L., Decidual activation in parturition: examination of amniotic fluid for mediators of the inflammatory response. Ann NY Acade Sci 1991; 622:315–30 .

The Onset of Labor: Cellular and Integrative Mechanisms. McNellis D., Challis J.R.G., MacDonald P.C., Nathanielz P.W., Robets J.M., eds, Preinatal Press, Ithaca NY, 1988.

Stahlman M. T., Newborn Intensive Care: Success or Failure? J. Pediatr 1984; 105:162–7 .

Contraception

Bardin, C.W.: NORPLANT contraceptive implants. Obstetrics and Gynecology Report 2:96–102 , 1990.

Bardin, C.W.: Long-acting steroidal contraception: An update. International Journal of Fertility 34:88–95 , 1989.

Bardin, C.W., Sivin, I., Nash, H., Robertson, D. et al.: Norplant R. contraceptive implants. Fertility Regulation Today and Tomorrow. (E. Diczfalusy and M. Bygdeman, eds.), Raven Press, New York, pp. 143–152 , 1987.

Djerassi, C.: The bitter pill. Science 245:356–361 , 1989.

Lincoln, R., Kaeser, L.: Whatever happened to the contraceptive revolution? *Family Planning Perspectives* 20:20–24 , 1988.

Mishell, D.R., Jr.: Medical Progress-Contraception. *New England Journal of Medicine* 320:777–787 , 1989.

Sivin, I., El Mahgoub, S., McCarthy, T., Mishell, D.R., Jr. et al.: Longterm contraception with the levonorgestrel 20 mcg/day (LNg 20) and the copper T 38OAg intrauterine devices: A five-year randomized study. *Contraception* 42:361–378 , 1990.

Sivin, I., Mishell, D.R., Jr., Victor, A., Diaz, S. et al.: A multicenter study of levonorgestrel-estradiol contraceptive vaginal rings. II-Subjective and objective measures of effects. An internal comparative trial. *Contraception* 24:359–376 , 1981.

World Health Organization Task Force on the Safety and Efficacy of Fertility Regulating Methods. The TCu380A, TCu220C, Multiload 250 and Nova T IUDS at 3,5 and 7 years of use-Results from three randomized multicentre trials. *Contraception* 42:141–158 , 1990.

Infertility

Bongso A., N.G., S-C, Fong, C-Y, Ratman S., Cocultures: a new lead in embryo quality improvement for assisted reproduction, Fertil. Steril. 1991: 56,179 .

Calvo L., Vantman D., Banks S.M., et al., Follicular fluid-induced acrosome reaction distinguishes a subgroup of men with unexplained infertility not explained by semen analysis, Fertil. Steril. 1989: 52,1048 .

Cohen B.L., The postcoital test, Infert. Reprod. Med. Clinics 1991: 2,317 .

Edwards R. G., Causes of early embryonic loss in human pregnancy. Human Reprod. 1986: 1,185 .

Gleicher N., El-Roeiy A., Confino E., Friberg J., Is endometriosis an autoimmune disease?, Obstet. Gynecol. 1987: 70,115 .

Griffith C.S. and Grimes D.A., The validity of the postcoital test, J. Obstet. Gynecol. 1991: 162,615 .

Guzick D.S., Clinical Epidemiology of endometriosis and infertility, Obstet.Gynecol.Clin.NorthAmer. 1989: 16,43 .

Iritani A., Current status of biotechnological studies in mammalian reproduction, Fertil, Steril. 1988: 50,543 .

Kennedy S.H., Autoantibodies in endometriosis-epiphenomenon?, Letter to the editor, Fertil. Steril. 1990: 54,544 .

Mosher W.D. and Pratt W. F., Fecundity and infertility in the United States: incidence and trends, Fertil. Steril. 1991: 56,192 .

Mosher W.D. and Pratt W. F., Fecundity and infertility in the United States, 1965–1988. Advance data from vital and health statistics, No. 192, Dec. 4, 1990. Hyattsville, MD: National Center for Health Statistics.

Mosher W.D., New from NCHS: Fecundity and infertility in the United States, Am.J.Public Health, 1988: 78,181 .

Roberts C. J. and Lowe C. R., Where have all the conceptions gone?, Lancet, 1975: 1,498 .

Sauer M. V., Paulson R. J., and Lobo R. A., A preliminary report on oocyte donation extending reproductive potential to women over age 40, N.Engl.J.Med. 1990: 323,1157 .

Society for Assisted Reproductive Technology, In vitro fertilization-embryo transfer (IVF-ET) in the United States: 1989 results from the IVF-ET registry , Fertil.Steril. 1991: 55,14 .

Strathy J. H., Molgaard C. A., Coulam C. B., et al., Endometriosis among fertile and infertile women, Fertil.Steril. 1982. 38,667 .

Vlanderen W. and Treffers P., Prognosis of subsequent pregnancies after recurrent spontaneous abortion in first trimester. Brit.Med.J 1987: 295,92 .

West C. P., Age and infertility, Brit.Med.J. 1987: 294,853 .

Wrambsy H. Fradga K., and Liedholm P., Chromosome analysis of human oocytes recovered from preovulatory follicles in stimulated cycles, *New England Journal of Medicine* . 1987: 361,121 .

Premenstrual Syndrome

MacDonald P.C., Dombroski R, Casey ML: The recurrent secretin of progesterone in large amounts: An endocrine/metabolic disorder unique to young women? Endocrine Rev., November 1991.

The Brain and Reproduction

1. Dolais, J., A-J. Valleron, A-M. Grapin and G. Rosselin. Etude de l'hormone luteinisante humaine (HLH) au cours du nycthemere. C.R. Acad. Sci. (Paris) 270:3123 , 1970.
2. Dierschke, D.J., A.N. Bhattacharya, L.E. Atkinson and E. Knobil. Circhoral oscillations of plasma LH levels in the ovariectomized rhesus monkey. Endocrinology 87: 850 , 1970.
3. Knobil, E. The GnRH Pulse Generator. Control of puberty in the rhesus monkey. In: *Control of the Onset of Puberty. III* , H.A. Delemarre van-de Waal, T.M. Plant, G.P. Van Rees, J. Schoemaker (eds.), Exerpta Medica, Amsterdam, 1989, p. 11 .
4. Leyendecker, G., S. Waibel-Treber and L. Wildt. The central control of maturation and ovulation in the human. In: *Oxford Review of Reproductive Biology* , Vol. 12 , S.R. Milligam (ed.), Oxford University Press, Oxford, 1990, p. 93 .
5. Hutchison, J.S. and A.J. Zeleznik. The rhesus monkey corpus luteum is dependent upon pitutiary gonadotropin secretion throughout the luteal phase of the menstrual cycle. Endocrinology. 115:1780 , 1984.
6. Knobil, E. The neuroendocrine control of the menstrual cycle. Rec. Prog.Hormone Res. 36:53 , 1980.
7. Crowley, W.F., Jr., M. Filicori, D. Spratt and N. Santoro. The physiology of gonadotropin-releasing hormone (GnRH) secretion in men and women. Rec. Progr. Hormone Research 41:473 , 1985.

8. Reame, N., S.E. Sander, G.D. Case, R.P. Kelch and J. C. Marshall. Pulsatile gonadotropin secretion in women with hypothalamic amenorrhea: evidence that reduced frequency of gonadotropin-releasing hormone secretion in the mechanism of persistent anovulation. J. Clin. Endocrinol. Metab. 61:851 , 1985.
9. Wray, S. Evidence that cells of the gonadotropin releasing hormone system are derived from progenitor cells in the olfactory placode. In: *Control of the Onset of Puberty. III* , H.A Delemarre-van de Waal, T.M. Plant, G.P. Van Rees, J. Schoemaker (eds.), Exerpta Medica, Amsterdam, 1989, p. 23 .
10. Schwanzel-lukuda, M., D. Dick and D.W. Pfaff. Luteinizing hormone-releasing hormone (LHRH)-expressing cells do not migrate normally in an inherited hypogonadal Kallmann syndrome. Brain Research 6:311 , 1989.
11. Precis IV: Update in Obstetrics and Gynecology, H.C. Visscher (ed.), American College of Obstetrics and Gynecology, 1990, p. 315 .
12. Liu, J.H. Hypothalamic amenorrhea: clinical perspectives, pathophysiology and management. Amer. J. Obstet. Gynecol. 163:1732 , 1990.
13. O'Byrne, K.T., J-C. Thalabard, P.M. Grosser, R.C. Wilson, C.L. Williams, M-D. Chen, D. Ladendorf, J. Hotchkiss, and E. Knobil. Radiotelemetric monitoring of hypothalamic gonadotropin-releasing hormone pulse generator activity throughout the menstrual cycle of the rhesus monkey. Endocrinology 129:1207–1214 , 1991.
14. Gindoff, P.R., and M. Ferin. Endogenous opioid peptides modulate the effects of corticotropin releasing factor on gonadotropin release in the primate. Endocrinology 121:837 , 1987.
15. Kesner, J.S., J.M. Kaufman, R.C. Wilson, G. Kuroda, and E. Knobil. The effect of morphine on the electrophysiological activity of the hypothalamic luteinizing hormone releasing hormone pulse generator in the rhesus monkey. Neuroendocrinology 43: 686 , 1986.
16. McNeilly, A.S. Suckling and the control of gonadotropin secretion. In: *The Physiology of Reproduction* . Vol. 2 , E. Knobil and J.D. Neill (eds.), Raven. Press, New York, 1988, p. 2323 .
17. *The Menstrual Cycle and its Disorders: Influences of Nutrition, Exercise and Neurotransmitters* , K.M. Pirke, W. Wuttke, U. Schweiger (eds.), Springer-Verlag, Berlin, 1989.
18. Medamurthy, R., S.A Abeyawardene, M.D. Culler, A. Negro-Vilar and T. M. Plant. Immunoneutralization of circulating inhibin in the hypophysiotropically clamped male rhesus monkey *(Macaca mulatta)* results in a selective hypersecretion of follicle-stimulating hormone. Endocrinology 126:2116 , 1990.
19. McLachlan, R.I., K.D. Dahl, W.J. Bremner, R. Schwall, C.H. Schmelzer, A.J. Mason and R.A. Steiner. Recombinant human activin-A stimulates basal FSH and GnRH-stimulated FSH and LH release in the adult male macaquize *Macaca fasciculans* , Endocrinology 125:2787 , 1989.
20. Plant, T.M., M.D. Fraser, R. Medamurthy and V.L. Gay. Somatogenic control of GnRH neuronal synchronization during development in primate: a speculation. In: *Control of The Onset of Puberty III* , H.A. Delamarre-van de Waal, T.M. Plant, G.P. Van Rees, J. Schoemaker (eds.), Exerpta Medica, Amsterdam, 1989, p. 111 .
21. Wilson, R.C., J.S. Kesner, J-M. Kaufman, T. Uemura, T. Akema and E. Knobil. Central electrophysiologic correlates of pulsatile luteinizing hormone secretion in the rhesus monkey. Neuroendocrinology, 39:256 , 1984.

22. Kimura, F., M. Nishihara, H. Hiruma, and T. Funabashi. Naloxone increases the frequency of the electrical activity of luteinizing hormone releasing hormone pulse generator in long-term ovariectomized rats. Neuroendocrinology 53:97 , 1991.
23. Chronic recording of electrophysiological manifestation of the hypothalamic gonadotropin-releasing hormone pulse generator activity in the goat. Neuroendocrinology 53–393 , 1991.
24. Kesner, J.S., R.C. Wilson, J-M. Kaufman, J. Hotchkiss, Y. Chen, H. Yamamoto, R.R. Pardo and E. Knobil. Unexpected responses of the hypothalamic gonadotropin-releasing hormone "pulse generator" to physiolcgical estradiol inputs in the absence of the ovary. Proc. Natl. Acad. Sci., 84:8745 , 1987.
25. Williams, C.L, J-C. Thalabnard, K.T. O'Byrne, P.M. Grosser, M. Nishihara, J. Hotchkiss and E. Knobil. Duration of the hypothalamic gonadotropin-releasing hormone (GnRH) pulse generator phasic electrical activity and the dynzmics of luteinizing hormone (LH) pulses in the rhesus monkey. Proc. Natl. Acad. of Sci. 87:8580 , 1990.

Menopause

Bergkvist L., Adami H-O, Persson I., Hoover R. Schairer C.: The risk of breast cancer after estrogen and estrogen-progestin replacement. N Engl J Med 321:293–297 , 1989.
Matthews K.A., Meilahn E., Kuller L.H., Kelsey S.F., Caggiula A.W., Wing R.R.: Menopause and risk factors for coronary heart disease. N Engl J Med 321:641–646 , 1989.
Nordin B.E.C., Need A.G., Chatterton B.E., Horowitz M., Morris H.A.: The relative contributions of age and years since menopause to postmenopausal bone loss. J Clin Endocrinol Metab 70:83–88 , 1990.
Rubin G.L., Peterson H.B., Lee N.C., Maes E.F., Wingo P.A. Becker S.: Estrogen repalcement therapy and the risk of endometrial cancer: Remaining controversies. Am J Obstet Gynecol 162:148–154 , 1990.
Williams S.R., Frenchek B., Speroff T., Speroff L: A study of combined continuous ethinyl estradiol and norethindrone acetate for postmenopausal hormone replacement. Am J Obstet Gynecol 162:438–446 , 1990.

Oncology Ovarian Neoplasms

Cancer Facts & Figures-1991. American Cancer Society, 1991.
Andolf E, Jorgensen C, astedt B. Ultrasound examination for detection of ovarian carcinoma in risk groups. Obstet Gynecol 75:106–9 , 1990.
Baiocchi G, Davanagh JJ, Talpaz M et al. Expression of the macrophage colony-stimulating factor and its receptor in gynecologic malignancies. Canc 67:990–6 , 1991.
Baker VV, Borst MP, Dixon D et al. C-MYC amplification in ovarian carcinoma. Gynecol 38:340–3 ,1990.
Bauknecht T, Birmelin G, Kommoss F. Clinical significance of oncogenes and growth factors in ovarian cancer. Steroid Biochem Mol Biol 37:855–62 , 1990.
Herbst AL. Neoplastic diseases of the ovary, in Herbst AL, Mishell DR, Stenchever M, Droegemueller W. Comphrehensive Gynecology, 2nd edition, Mosby-Year Book, Inc., St. Louis, 1992.

Howell SB, Kirmani S, McClay EF et al. Intraperitoneal cisplatin-based chemotherapy for ovarian carcinoma. Semin Oncol 18:5–16 , 1991.

Isola J, Kallioniemi OP, Korte JM et al. Steroid receptors and Ki67 reactivity in ovarian cancer and in normal ovary: correlation with DNA flow cytometry, biochemical receptor assay, and patient survival . J Pathol 162:295–301 , 1990.

Jacobs I, Oram D, Fairbanks J et al. A risk of malignancy index incorporating CA125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynecol 97:922–929 , 1990.

Khoo SK, Hurst T, Kearsley J et al. Prognostic significance of tumor ploidy in patients with advanced ovarian carcinoma. Gynecol Oncol 39:284–8 , 1990.

Li SB, Schwartz PE, Lee WH, Yang-Geng TL. Allele loss at the retinoblastoma locus in human ovarian cancer. J National Canc Inst 83:637–40 , 1991.

Schilthuis MS, Aalders JG, Bouma J et al. Serum CA125 levels in epithelial ovarian cancer:relation with findings at second look operations and their role in the detection of tumor recurrence. Br J Obstet Gynecol 94:202–7 , 1987.

Slotman BJ, Baak JP, Rao BR. Correlation between nuclear DNA content and steroid receptor status in ovarian cancer. Eur J Obstet Gynecol Reprod Biol 38:221–7 , 1991.

Van Niekerk CC, Boerman OC, Ramaekers FC, Poels LG. Marker profile of different phases in the transition of normal human ovarian epithelium to ovarian epithelium to ovarian carcinomas. Am J Path 138:455–63 ,1991.

Viel A, De Pascale L, Toffoli G et al. Frequent occurrence of Ha-ras allelic deletion in human ovarian adenocarcinomas. Tumori 77:16–20 , 1991.

Uterine Neoplasms

Ayhan A, Yarall H, Ayhan A. Endometrial carcinoma: a pathologic evaluation of 142 cases with and without associated endometrial hyperplasia. J Surg Oncol 46: 182–4 ,1991.

Ayoub J, Audet-Lapointe P, Methot Y et al. Efficacy of sequential cyclical hormone therapy in endometrial cancer and its correlation with steroid hormone receptor status. Gynecol Oncol 31:327 ,1988.

Berchuck A, Rodriguez G, Kinney RB et al. Overexpression of HER-2/neu in endometrial cancer is associated with advanced stage disease. Amer J Obstet Gynecol 164:15–21 ,1991.

Borazjani G, Twiggs LB, Leung BS et al. Prognostic significance of steroid receptors measured in primary metastatic and recurrent endometrial carcinoma. Amer J Obstet Gynecol 161:1253–57 , 1989.

Borst MP, Baker VV, Dixon D et al. Oncogene alterations in endometrial carcinoma. Gynecol Oncol 38:364–6 ,1990.

Bourne TH, Campbell S, Steer CV et al. Detection of endometrial cancer by transvaginal ultrasonography with color flow imaging and blood flow analysis: a preliminary report. Gynecol Oncol 40:253–9 , 1991.

Brumm C, Riviere A, Wickens C, Loning T. Immunohistochemical investigation and northern blot analysis of c-erbB-2 expression in normal, premalignant, and malignant tissues of the corpus and cervix uteri. Virchows Arch A 417:477–84 , 1990.

Creasman WT, Henderson D, Hinsshaw W, Clarke-Pearson DL. Estrogen replacement therapy in the patient treated for endometrial cancer. Obstet Gynecol 67:326–30 , 1986.

Granberg S, Wikland M, Karlsson B et al. Endometrial thickness as measured by endovaginal ultrasonography for identifying endometrial abnormality. Amer J Obstet Gynecol 164:47–52 ,1991.

Herbst A L. Neoplastic diseases of the uterus, in Comprehensive Gynecology, 2nd edition, Herbst AL, Mishell DR, Stenchever MA and Droegemueller W (editors). Mosby-Year Book, Inc. St. Louis, 1992.

Kacinski BM, Chambers SK, Stanley ER et al. The cytokine CSF-1 (M-CSF) expressed by endometrial carcinoma in vivo and in vitro, may also be a circulating tumor marker of neoplastic disease activity in endometrial carcinoma patients. Int J Radiat Oncol Biol Phys 19:619–26 ,1990.

Lindahl B and Gullberg B. Flow cytometrical DNA and clinical parameters in the prediction of prognosis in stage I–II endometrial carcinoma. Anticanc Res 11:397 ,1991.

Morrow CP, Bundy BN, Kurman RJ et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group Study. Gynecol Oncol 40:55–65 ,1991.

Reynolds RK, Talavera F, Roberts JA et al. Regulation of epidermal growth factor and insulin-like growth factor I receptors by estradiol and progesterone in normal and neoplastic endometrial cell cultures. Gynecol Oncol 38:396–406 , 1990.

Rosenberg P et al. Flow cytometric erbB of DNA index and S-phase on paraffin-embedded early stage endometrial cancer: an important prognostic indicator. Gynecol Oncol 35:50–4 ,1989.

Satyaswaroop PG and Mortel R. Hormonal treatment of endometrial carcinoma: an overview and new development in biology. J Steroid Biochem Mol Biol 37:997–1001 ,1990.

Cervix Neoplasms

Herbst AL. Malignant disease of the cervix, in Comprehensive Gynecology, 2nd edition, Herbst AL, Mishell DR, Stenchever MA, and Droegemueller W (editors), Mosby-Year Book, Inc., 1992.

Alberts DS, Garcia D, Mason-Liddil N. Cisplatin in advanced cancer of the cervix: an update. Semin Oncol 18:11–24 ,1991.

Alloub MI, Barn BB, McLaren KM et al. Human papillomavirus infection and cervical intraepithelial neoplasia in women with renal allografts. Br Med J 298:153–156 ,1989.

Baker VV, Hatch KD, Shingleton HM. Amplification of the c-MYC proto-oncogene in cervical carcinoma. J Surg Oncol 39:225–8 ,1989.

Crook T, Wrede D and Vousden KH. p53 point mutation in HPV negative human cervical carcinoma cell lines. Oncogene 6:873–5 ,1991.

Cullen AP, Reid R, Campion M, Lorincz AT. Analysis of the physical state of different human papillomavirus DNAs in intraepithelial and invasive cervical neoplasm. J Virol 65:606–12 ,1991.

de Vet HC et al. The effect of beta-carotene on the regression and progression of cervical dysplasias: a clinical experiment. J Clin Epidemiol 44:273 ,1991.

Dottino PR, Plaxe SC, Beddoe AM et al. Induction chemotherapy followed by radical surgery in cervical cancer. Gynecol Oncol 40:7–11 ,1991.

Herbst AL. Intraepithelial neoplasia of the cervix, in Comprehensive Gynecology, 2nd edition. Herbst AL, Mishell DR, Stenchever MA, and Droegemueller W (editors), Mosby-Year Book, Inc., St. Louis, 1992.

Herbst AL. The Bethesda System for cervical/vaginal cytologic diagnoses: a note of caution. Obstet Gynecol 76:449– ,1990.

Hayashi Y, Hachisuga T, Iwasaka T et al. Expression of ras oncogene product and EGF receptor in cervical squamous cell carcinomas and its relationship to lymph node involvement. Gynecol Oncol 40:147–51 ,1991.

Khoury GG, Bulman AS, Joslin CA, Rothwell AI. Concomitant pelvic irradiation, 5-fluorouracil and mitomycin C in the treatment of advanced cervical carcinoma. Br J Radiol 64:252–60 ,1991.

Kurman RJ, Malkasian GD, Sedlis A, Soloman D. From Papanicolaou to Bethesda: the rationale for a new cervical cytologic classification. Obstet Gynecol 77:779–82 ,1991.

Matorras R, Ariceta JM, Rememteria A et al. Human immunodeficiency virus-induced immunosuppression: a risk factor for human papillomavirus infection. Amer J Obstet Gynecol 164:42–4 ,1991.

Naisell K, Roger V, Naisell M. Behavior of mild cervical dysplasia during long-term follow-up. Obstet Gynecol 67:665 , 1986.

Palefsky J. Human papillomavirus infection among HIV-infected individuals. Implications for development of malignant tumors. Hematol Oncol Clin N Am 5:357–70 ,1991.

Pinion SB et al. Oncogene expression in cervical intraepithelial neoplasia and invasive cancer of the cervix. Lancet 337 (8745):819 ,1991.

Piver MS. Invasive cervical cancer in the 1990s. Semin Surg Oncol 6:359–63 ,1990.

Riou G, Le MG, le Doussal V et al. C-myc Proto-oncogene expression and prognosis in early carcinoma of the uterine cervix. Lancet 1:761–3 ,1987.

Riou G, Bourhis J, Le MG. The c-myc proto-oncogene in invasive carcinomas of the uterine cervix: clinical relevance of overexpression in early states of the cancer. Anticanc Res 10:1225–32 ,1990.

Sagae S et al. RAS oncogene expression and progression in intraepithelial neoplasia of the uterine cervix. Canc 66:295 , 1990.

Schafer A, Friedman W, Mielke M et al. The increased frequency of cervical dysplasias-neoplasia in women infected with the human immunodeficiency virus if related to the degree of immunosuppression. Amer J Obstet Gynecol 164:593–9 ,1991.

Scheffner M, Munger K, Byrne JC, Howley PM. The state of the p53 and retinoblastoma genes in human cervical carcinoma cell lines. Proc Nation Acad Sci 88:5523–27 ,1991.

Smiley LM, Burke TW, Silva EG et al. Prognostic factors in stage lb squamous cervical cancer patients with low risk for recurrence. Obstet Gynecol 77:271–5 ,1991.

Villa LL and Schlegel R. Differences in transformation activity between HPV-16 map to the viral LCR-E6-E7 region. Virology 181:373–7 ,1991.

Wang CC. Altered fractionation radiation therapy for gynecologic cancers. Cancer 60:2064–2067 ,1987.

Vulvar Neoplasms

Burke TW, Stringer CA, Gershenson DM et al. Radical wide excision and selective inguinal node dissection for squamous cell carcinoma of the vulva. Gynecol Oncol 38:328–32 ,1990.

Daling JR, Chu J, Weiss NS et al. The association of condyloma accuminata and squamous carcinoma of the vulva. Br J Canc 50:533–35 ,1984.

De Villers EM, Schneider A, Gross g, Zur Hausen H. Analysis of benign and malignant urogenital tumors for human papillomavirus infection by labelling cellular DNA. Med Microbiol Immunol 174:281–6 , 1986.

Heaps JM, Fu WS, Montz FJ et al. Surgical-pathologic variables predictive of local recurrence in squamous cell carcinoma of the vulva. Gynecol Oncol 38:309–14 , 1990.

Herbst AL. Premalignant and malignant diseases of the vulva, in Comprehensive Gynecology. Herbst AL, Mishell DR, Stenchever MA, and Droegemueller W (editors), 2nd edition, Mosby-Year Book, Inc., St. Louis, 1992.

Homesley HD, Bundy BN, Sedlis A et al. Assessment of current international Federation of Gynecology and Obstetrics staging of vulvar carcinoma relative to prognostic factors of survival (a Gynecologic Oncology Group Study). Amer J Obstet Gynecol 164:997–1003 ,1991.

Mabuchi K, Bross DS, Kessler I. Epidemiology of cancer of the vulva. A case-control study. Cancer 55:1843–48 , 1985.

MacNab JCM, Wilkinshaw SA, Cordiner JW, Clements JB. Human Papillomavirus in clinically and histologically normal tissues of the patients with genital cancer. N Eng J Med 315:1052–1058 ,1986

Newcombe PA, Weiss NS, Daling JR. Incidence of vulvar carcinoma in relation to menstrual, reproductive and medical factors. JNCI 73:391–396 ,1984.

Park JS, Jones RN, McLean MR et al. Possible etiologic heterogeneity of vulvar intraepithelial neoplasia. A correlation of pathologic characteristics with human papillomavirus detection by in situ hybridization and polymerase chain reaction. Cancer 67:1599–607 ,1991.

Pilotti S, Rotola A, D'Amato L et al. Vulvar carcinomas: search for sequences homologous to human papillomavirus and herpes simplex virus DNA. Mod Pathol 3:422–8 ,1990.

Podczaski E, Sexton M, Kaminski P et al. Recurrent carcinoma of the vulva after conservative treatment for "microinvasive" disease. Gynecol Oncol 39:65–8 ,1990.

Rusk D, Sutton GP, Look KY, Roman A. Analysis of invasive squamous cell carcinoma of the vulva and vulvar intraepithelial neoplasia for the present of human papillomavirus DNA. Obtset Gynecol 77:918–22 ,1991.

Breast Neoplasms

Cancer Facts & Figures-1991. American Cancer Society, 1991.

Clark GM and McGuire WL. Follow-up study of HER-2/neu amplification in primary breast cancer. Canc Research 51:944–8 ,1991.

Cross SS and Ismail SM. Endometrial hyperplasia in an oophorectomized woman receiving Tamoxifen therapy-case report. Br J Obstet Gynecol 97:190 ,1990.

Dickson RB. Stimulatory and inhibitory growth factors and breast cancer. J Steroid Biochem Mol Biol 37:795–803 ,1990.

Fornander T, Rutqvist LE, Cedermark B et al. Adjuvant Tamoxifen in early breast cancer: occurrence of new primary cancers. Lancet 1:117–120 ,1989.

Gusberg SB. Tamoxifen for breast cancer: associated endometrial cancer. Canc 65:1463 ,1990.

Howe G, Rohan T, Decarli A et al. The association between alcohol and breast cancer risk: evidence from the combined analysis of six dietary case control studies. Int J Canc 47:707–10 ,1991.

Kelsey JL, Gammon MD. The epidemiology of breast cancer. CA 41:146 ,1991.

Love RR. Prospects for antiestrogen chemoprevention of breast cancer. JCNI 82:18–21 ,1990.

Malfetano JH. Tamoxifen-associated endometrial carcinoma in postmenopausal breast cancer patients. Gynecol Oncol 39:82–84 ,1990.

Miller AB. Risk/benefit considerations of antiestrogen/estrogen therapy in healthy postmenopausal women. Prev Med 20:79–85 ,1991.

Paffenbarger RS, Fasal E, Simmons ME et al. Cancer risk as related to the use of oral contraceptives during fertile years. Cancer 39:1887,1977 .

Prentice RL. Tamoxifen as a potential preventive agent in healthy postmenopausal women. JNCI 82:1310–1311 , 1990.

Ravnihar B, Seigel DG, Linder J. An epidemiologic study of breast cancer and benign breast neoplasias in relation to oral contraceptives and estrogen use. Eur J Canc 15:395 , 1979.

Romieu I, Berlin JA, Colditz G. Oral contraceptives and breast cancer. Review and meta analysis. Cancer 66:2253–63 , 1991.

Chachter LP, Rosencweig M, Canetta R, et al. Overview of hormonal therapy in advanced breast cancer. Semin Oncol 17 (suppl 6):38–46 , 1990.

Spicer D, Pike MC, Henderson BE. The question of estrogen replacement therapy in patients with a prior diagnosis of breast cancer. Oncology-Williston-Park 4:49–54 , 1990

Vessey MP, Doll R, Sutton PM. Oral Contraceptives and breast neoplasia: A retrospective study. Br Med J 3:719 , 1972.

Trophoblastic Disease

Herbst AL. Gestational trophoblastic disease, in Comprehensive Gynecology, 2nd edition. Herbst AL, Mishell DR, Stenchever MA, and Droegemueller W (editors). Mosby-Year Book, Inc., St. Louis, 1992.

Bagshawe KD. Risk and prognostic factors in trophoblastic neoplasia. Cancer 38:1373 , 1976.

Curry SL, Blessing J, DiSaia P et al. A prospective randomized comparison of methotrexate, actinomycin D, and chlorambucil (MAC) versus modified Bagshawe regimen in "poor prognosis" gestational trophoblastic disease. Gynecol Oncol 26:407 , 1987.

Jacobs PA, Szulman AE, Funkhouser J et al. Human triploidy: relationship between parental origin of the additional haploid complement and development of partial hydatidiform mole. Ann Hum Genet 46:223 , 1982.

Li MC, Hertz R, Spencer DB. Effect of methotrexate therapy upon choriocarcinoma and chorioadenoma. Proc Soc Exp Biol Med 93:361 , 1956.

Lurain JR, Brewer JI. Treatment of high-risk gestational trophoblastic disease with methotrexate, actinomycin D, and cyclophosphamide chemotherapy. Obstet Gynecol 65:830 , 1985.

Lurain JR, Brewer JI, Torok EE et al. Natural history of hydatidiform mole after primary evacuation. Amer J Obstet Gynecol 145:591 , 1983.

Morrow P, Nakamura R, Schlaerth J et al. The influence of oral contraceptives on the postmolar human chorionic gonadotropin regression curve. Amer J Obstet Gynecol 151:906 , 1981.

Vaitukaitis JL, Braunstein GD, Ross GT. Radioimmunoassay which specifically measures human chorionic gonadotropin in the presence of human luteinizing hormone. Amer J Obstet Gynecol 113:751 , 1972.

Wong LC, Choo YC, Ma HK. Modified Bagshawe's regimen in high-risk gestational trophoblastic disease. Gynecol Oncol 23:87 , 1986.

Yordan EL Jr, Schlaerth J, Gaddis O et al. Radiation therapy in the management of gestational choriocarcinoma metastatic to the central nervous system. Obstet Gynecol 69:627 , 1987.

Sexually Transmitted Diseases

National Institute of Allergy and Infectious Diseases: Sexually Transmitted Diseases Research Program, National Institutes of Health, Rockville, Md. 1990.

APPENDIX A

PREPARING FOR THE TWENTY-FIRST CENTURY IN THE REPRODUCTIVE SCIENCES:

THE HISTORY AND PRESENT STATUS OF RESEARCH TRAINING IN OBSTETRICS AND GYNECOLOGY

LAWRENCE D. LONGO [*]
Division of Perinatal Biology
Departments of Obstetrics, Gynecology, and Physiology
Loma Linda University School of Medicine

> ". . . the development of our departments [of obstetrics and gynecology] has demonstrated beyond question the critical importance of research efforts and the presence of investigators, for the intellectual health and successful function of our teaching programs"
> (Douglas, 1976).

Above the mantel at his home at 13 Norham Gardens, Oxford, Sir William Osler, Regius Professor of Medicine at Oxford University, had a tryptych with paintings of three great physicians: Thomas Linacre, Thomas Sydenham, and William Harvey. Linacre stood for learning in the classics, Sydenham for practice, and Harvey for science (Cushing, 1925). The physician-scientist embodies these three facets of the scientifically educated clinician, who in addition to his role as a healer, advances the scientific frontiers of medicine.

Today, biomedical research is in the midst of an era of discoveries focused on the cellular and molecular basis of living systems and disease states. Advances at the molecular level in genetics, regulation of cell function,

[*] Prepared for the Institute of Medicine Committee on Research Capabilities of Academic Departments of Obstetrics and Gynecology.

immunology, and developmental biology have created opportunities in the reproductive sciences. In addition, novel approaches to the prevention, diagnosis, and treatment of reproductive diseases are appearing.

Despite conceptual and technological developments, however, there exists a crisis in academic obstetrics and gynecology in both research and in research training. In part, this is due to forces external to the specialty–economic, ethical, political, and social. But there is also a dearth of physician-scientists and clinical investigators who can contribute to advances in the reproductive sciences and serve as role models for students, house staff, and others. In sum, too few obstetricians and gynecologist are being adequately trained to pursue research opportunities.

Thus, for academic obstetrics and gynecology, current circumstances present a paradox. Never before have the opportunities been so great–and the resources so limited (Martin, 1991). Departments of obstetrics and gynecology are increasingly confronted by the need to provide highly technical clinical care, to perform manifold social functions, and to maintain large, private practices to generate income. Biomedical scientists in these departments are coming under growing pressure to justify their research. As obstetrics and gynecology approach the twenty-first century, the clinical investigator, particularly the physician-scientist, is seriously threatened by an increasingly sophisticated research enterprise, decreased time for careful thought and work, and diminishing federal and private resources for support.

In the coming years, the future of obstetrics and gynecology as a whole will depend, in great part, on the health and well-being of its academic departments. In turn, the state of these departments depends, in considerable measure, on their role in research in the reproductive sciences. As Jack Masur, former director of the Clinical Center at the National Institutes of Health, (NIH) observed, "Hospitals with long traditions of excellence have demonstrated abundantly that Research enhances the vitality of teaching. Teaching lifts the standards of service, and Service opens new avenues of investigation." (This statement appears at the entrance to the main auditorium in the NIH Clinical Center.)

This paper explores the roles of the private sector and more briefly those of the National Institutes of Health in helping to produce research leaders in obstetrics and gynecology.

TRAINING PATHS

Innovative developments and advances in obstetrics and gynecology have resulted from research in the basic sciences. During the 1950s and 1960s, following their residency training, many individuals who sought academic careers spent several years in a basic science department or a research-oriented clinical department. A few of these individuals were supported by the Markle Scholar Program or the Macy Foundation; many were funded by the National Institutes of Health (see the later discussion below). In the 1970s, with the advent of subspecialty programs (gynecologic oncology—1972; maternal and fetal medicine—1973; reproductive endocrinology—1973; [Randall, 1989]), many individuals completed 2 or 3-year programs in these fields before joining academic departments. In a few cases, they also spent a year or two in research. Thus, a generation of well-trained clinical subspecialists joined academic departments with little or no experience in either laboratory or clinical research.

For physicians-scientists, it has become increasingly important to spend 2 or 3 years in basic research training (IOM, 1985). Some individuals participate in basic research as part of their M.D./Ph.D. physician-scientist training program. Recent reports have described some aspects and relatively long-term results of the Duke (Bradford et al., 1986), Washington University (Frieden and Fox, 1991), and other (Martin, 1991) M.D./Ph.D. programs.

PRIVATE FOUNDATION FUNDING FOR RESEARCH TRAINING: 1950 TO 1985

The Markle Scholar Program: A Case Study

Between 1948 and 1974, the John and Mary R. Markle Foundation supported the Program of Scholars in Medical Science.*

The foundation itself was begun in 1927 by John and Mary R. Markle "to promote the advancemeat and diffusion of knowledge … and promote the general good." From 1936 to 1947, the foundation's chief activity was to provide small grants-in-aid for medical research. With the end of World War II, expenditures for medical research by the federal government increased dramatically, dominating national research funding. Thus, in 1946, the newly

* The discussion of the Markle Scholars Program is based on Strickland and Strickland (1976).

appointed executive director, John McFarlane Russell, after spending a year visiting 30 medical schools in the United States and Canada and consulting with other educators and scientists, concluded that the foundation could provide a unique service and contribute to medical science by supporting people who wanted to remain in academic medicine. The scholarship would permit a young medical researcher to "earn a bit more, have tenure long enough to prove his worth, ... have a respectable academic appointment and a nationally recognized title, [and] adequate laboratory facilities and equipment for his research" (Russell, 1947). The concept of the program was support of outstanding young academicians who showed great promise, rather than the funding of research projects. Initially, the foundation provided $5,000 per annum for up to 5 years to supplement support by the scholar's institution.

The purpose of the program was "to improve medical education and research by giving both recognition and financial support to bright young teachers, investigators, and administrators, and helping them to prepare for positions of leadership in academic medicine." By providing funds so that the medical school, in a variety of ways, could enrich the opportunities and resource of those selected, the foundation hoped to contribute toward the improvement of medical school faculties. Of the 506 individuals selected, only 17 were obstetrician/gynecologists (Table A-1). This figure contrasts with 162 in internal medicine and subspecialties, 110 in surgery, and 61 in pediatrics.

The selection process had three steps: (1) initial nomination by the medical school; (2) selection of finalists by regional committees of distinguished laymen, who evaluated individuals on the basis of values and motivation; and (3) final appointment of the scholars by the foundation's board of directors. The medical schools nominated one person per year, choosing an individual who was considered truly committed to research and/or teaching in clinical or basic science. Schools nominated their brightest and best young "stars." The sponsoring institution was also required to make a significant and continuing commitment to the scholar.

The selection committee was chosen for its perceived abilities in picking individuals who would be leaders and in "judging them as human beings." At the annual 3-day selection meeting, candidates were evaluated on "breadth of character, personality, and potential leadership." This selection process, which was thought by some to be a great strength of the program, would today probably be seen as placing an excessive emphasis on personal qualities.

TABLE A-1: Markle Scholars in Obstetrics and Gynecology: 1951–1974

Name	Institution	Year Commenced
Gordon W. Douglas, M.D.	New York University	1952
Leo J. Dunn, M.D.	Medical College of Virginia	1964
John R.G. Gosling, M.D.	University of Michigan	1960
Perry A. Henderson, M.D.	University of New Mexico	1969
Edward H. Hon, M.D.	University of Southern CA	1955
John B. Josimovich, M.D.	University of Pittsburgh	1964
Theodore M. King, M.D., Ph.D.	Johns Hopkins University	1967
Kermit E. Krantz, M.D., Litt D.	University of Kansas	1957
William A. Little, M.D.	University of Miami	1962
James A. Merrill, M.D.	University of Oklahoma	1957
Robert W. Noyes, M.D.	Stanford University	1953
Robert I. Merritt, M.D.	Saint Catharines Hospital	1956
Landrum B. Sherries, M.D., Ph.D.	Columbia University	1951
Donald P. Swartz, M.D.	Albany Medical College	1958
John D. Thompson, M.D.	Emory University	1957
James C. Warren, M.D., Ph.D.	Washington University	1961
Richard Wilson, M.D.	University of Toronto	1962

SOURCE: Strickland and Strickland (1976).

Although initially intended for only 10 scholars per year, the program proved so popular that within a few years, 20 to 25 individuals were being appointed annually. In 1950, the annual stipend was raised to $6,000, and in 1958 it was raised to $7,500. Grant money was often used for partial salary support, laboratory and library expenses, and travel. In general, the foundation required only brief annual financial statements from the institution and reports by the scholar at the end of the second and fifth years. At the end of an individual's 5-year scholarship, the executive director of the program or his associate, visited the young academician and prepared a report on his or her progress and contributions. Because the overall purpose of the Markle Awards was to improve the standards of academic medicine, considerable attention was given to medical education. Thus, although many scholars spent much of their time in research, the majority devoted 25 to 50 percent of their time to teaching.

A feature of the Markle program was a series of annual 2-day meetings in which the scholars and other educators discussed key issues related to medical education. These meetings, organized and run by the scholars themselves,

considered such topics as "The Teacher in Medical Education," "Science and the Humanities," "Academic Medicine and Public Policy," "Medicine in a Changing Society," and "Scholarship Versus Society's Needs: A Conflict in Academic Medicine." Because these presentations and discussions were not published, it is difficult to ascertain their impact on medical education or academic medicine.

Although originally intended as a postfellowship program in medical research, by the 1960s, the program's emphasis had evolved to one of nurturing individuals for leadership in medical education. In 1961, NIH initiated its program of Research Career Development Awards (RCDA) and Research Career Awards. Some have suggested that the 5-year RCDA program was modeled after the Markle scholarships.

In the years that followed the establishment of the NIH awards, it became increasingly clear that the Markle program no longer played the key role it once had in keeping first-class minds in research. This change was reflected in the modification of the title of the program in 1962: from "Scholars in Medical Science" to "Scholars in Academic Medicine." One impetus for this shift was a perception that, with the development of federal programs to support young investigators, there was perhaps an overabundance of researchers. Thus, before his retirement from the foundation, Russell elected to terminate the program. The last group of scholars was chosen in 1969 (their awards continued until 1974).

In assessing the strengths of the program, in addition to the financial support, important elements that have been identified by some observers include the program's flexibility and the unresricted nature of the money. Overall, the awards provided a stimulus to excellence and achievement. For the scholar and the institution he or she represents, the Markle Award was a major recognition and a key to growth and stability in academic medicine.

Russell himself did not believe that the true impact of the awards could ever be assessed. Near the program's end, it was determined that 96 percent of the scholars had remained in academic medicine. Merlin K. Duval, a Markle scholar (1956–1961) who served as assistant secretary for health and scientific affairs in the Department of Health, Education, and Welfare, was quoted as saying, "The greatest strength of the Markle Program was that it served as an example of a premise that has subsequently been adopted by both private foundations and the Federal Government: to wit, one gets a great deal more out of investing in a man than in a subject".

The Markle program is said to be a model for the Milbank Memorial Foundation Awards (given from 1964 to 1969), and the Robert Wood Johnson Foundation Clinical Scholars and Health Policy Fellowship programs, as well as the programs of the Commonwealth Fund and Carnegie Corporation.

A measure of the program's import is the variety of leadership positions that the scholars assumed. For instance, as of 1975, the Markle ranks included a Nobel laureate, 3 university presidents, 7 vice presidents, 2 vice-chancellors, 1 provost, 11 medical school deans, 14 associate deans, 134 departmental chairpersons, and numerous other top administrators. However, the nominees who were not selected for the program but who remained in academic medicine advanced up the academic ladder as rapidly as the Markle scholars in rank and salary. Almost 80 percent of the scholars interviewed maintained that they would have remained in academic medicine even without the Markle Award. It might be questioned, therefore, to what extent the program had a major impact on the entry of young scientists into academic medicine, or their retention or advancement.

For more than a quarter of a century, Markle scholars have symbolized leadership in American medical education. Many believe that the program has also made an impact on medical research, although quantifying that contribution is impossible. In sum, it is believed that the program benefited academic medicine and medicine in general "far in excess of the small amount of money the Foundation [contributed] to this large field".

Josiah Macy, Jr. Foundation

In 1955, the Josiah Macy, Jr., Foundation. recognizing the need for a scientific approach to obstetrics and gynecology and the requirement of laboratory training for full-time academicians elected to devote "at least the next ten years" to the area of reproduction. The goal was to develop reproductive biology as the basic science of academic obstetrics. A key figure in this decision was Howard Canning Taylor, Jr., chairman of Columbia University's College of Physicians and Surgeons and a figure of wide influence both within and outside the specialty (Bowers and Purcell, 1980). This program initially sponsored training at three centers: Columbia, Harvard, and Washington universities. Later, the departments of obstetrics and gynecology at Boston University, Cornell, Johns Hopkins, Michigan, Northwestern, Oregon, Pennsylvania, Yale, and the University of Uruguay (Montevideo) were included in the program. To accomplish its goals for reproductive science, the foundation established a program of faculty development, conferences and seminars, and medical student research.

The three original departments of obstetrics and gynecology chosen for the program were encouraged to expand r search in the reproductive sciences. To achieve this, the Macy foundation provided the following to selected individuals

in a residency program: (1) salaries and research expenses for 2 years of research training in the basic sciences; (2) supplemental salary support on completion of that 2 year period and during completion of the residency; (3) and on completion of the residency, salary and funds for research while launching an investigative career. In addition, the foundation provided support for basic scientists to participate with obstetricians and gynecologists in multidisciplinary research. Ten individuals were chosen as Macy Faculty Fellows m Reproductive Biology (Table A-2), and about 30 Macy Postdoctoral Fellows in Obstetrics and Gynecology were partially supported at various schools (Table A-3). Fellowship awards were $15,000 per year for 3 years. In 1963, the Macy Foundation endowed professorships in obstetrics at both Columbia's College of Physicians and Surgeons and the Harvard Medical School (Macy Foundation, 1965 Annual Report). By 1966, when the Macy program ended, about 50 individuals had received some training support for an academic career in obstetrics and gynecology. By 1979 15 of them has become departmental chairmen (Bowers and Purcell, 1980).

TABLE A-2: Macy Faculty Fellows in Obstetrics and Gynecology

Fellow	Institution
John W. Choate	University of Rochester
Carlyle Crenshaw, Jr.	Duke University
John P. GustIon, Jr.	Western Reserve Univ.
Richard J. Hildebrandt	University of Florida
Cecil Jacobson	George Washington University
Robert B. Jaffe	University of Michigan
Theodore M. King	University of Missouri
Emmet J. Lamb	Stanford University
Jacques F. Roux	Albert Einstein
William Spellacy	University of Miannesota

SOURCE: Josiah Macy, Jr., Foundation (1966).

TABLE A-3: Macy Postdoctoral Fellows in Obstetrics

Name	Institution
Karlis Adamsons, Jr.	Columbia University
Joseph J. Barlow	Harvard Medical School
Theodore C. Barton	Harvard Medical School
Jack N. Blechner	University of Florida
Arthur C. Christakos	Duke University
Charles Donald Christian	University of Arizona
Philip A. Coffman	Center for Population Research/NICHD
Robert Duemler	Washington University
Theodore Fainstat	Northwestern University
Ira C. Gall	Washington University
Donald Peter Goldstein	Harvard Medical School
Donald A. Goss	Vanderbilt University
John W. Grover	Harvard Medical School
Samir Hajj	American University of Beirut
Dennis Hawkins	University of London
Andre Hellegers	Georgetown University
Arthur Herbst	Harvard Medical School
Jaroslav F. Hulka	University of North Carolina
Howard N. Jacobson	Harvard Medical School
John B. Josimovich	University of Pittsburgh
Theodore M. King	Albany Medical College
Michael M. Levi	Columbia University
John L. Lewis, Jr.	Cornell Medical College
A. Brian Little	Case Western Reserve Univ.
William A. Little	University of Miami
Paul C. MacDonald	University of Texas/Southwestern Med School
Girgis Mikhail	Jefferson Medical College
Horst Naujoks	Genetic Research Laboratory/University of Frankfurt

Name	Institution
Harry Prystowsky	University of Florida
Ralph M. Richart	Columbia University
John G. Robertson	University of Edinburgh
Seymour L. Romney	Albert Einstein School of Meal.
Kenneth J. Ryan	Case Western Reserve Univ.
Hilton A. Salhanick	Harvard Medical School
Eugene C. Sandberg	Stanford University
John Joseph Sciarra	University of Minnesota
Wolfgang Tretter	Columbia University
John Urquhart	University of Pittsburgh
Raymond L. Vande Wiele	Columbia University
A. Stark Wolkoff	University of Kansas
David WuTakau	Medical College, Taiwan
Richard Wurtman	Massachusetts institute of Technology
Clement Yahia	Harvard Medical School

SOURCE: Josiah Macy, Jr., Foundation (1966).

An additional Macy contribution was a Summer Scholarship Program for medical student research in reproduction. Sixteen of these awards were made available annually to each of the 15 medical schools (Macy Foundation, 1956–60; 1980 Annual Reports).

The Macy Foundation also sponsored an interdisciplinary conference program to facilitate communication among various fields and specialties. Over the course of two decades, the foundation organized more than 20 conference groups, each group holding five annual meetings (Fremont-Smith, 1957). Conference participants were limited to 25 individuals: 15 to 20 regular members attended the five annual conferences, and the balance were guests. In addition to conferences held on gestation during the 1950s, the Macy Foundation supported conferences on "Teaching the Biological and Medical Aspects of Reproduction to Medical Students" (Macy Foundation, 1966) and "Teaching Family Planning to Medical Students" (Macy Foundation, 1968).

A conference hosted jointly by the Macy Foundation and the National Institute on Child Health and Human Development (NICHD), "The Current Status and Future of Academic Obstetrics," was of interest from the standpoint of research training in obstetrics and gynecology (Bowers and Purcess, 1980). In report after report, leaders in academic medicine in general and in obstetrics and gynecology in particular stressed (1) the extent of research opportunities in the reproductive sciences, (2) the paucity of well-trained physician-scientists in the specialty, and (3) the need to correct this imbalance. Norman Kretchmer, then director of NICHD, sum the situation: "Reproductive research and departments of obstetrics and gynecology would benefit mutually from more emphasis on training young investigators and on fostering cooperation and collaboration among diverse research areas" (Bowers and Purcell, 1980, pp. 55–57; see also pp. 33–39 and 164–167).

Overall, between 1955 to 1965, the Macy Foundation allocated $5.37 million to develop talent in academic obstetrics and gynecology. From 1965 to 1970, it awarded an additional $1 million to help develop the field of reproductive biology and improve instruction in obstetrics and gynecology.

Ford Foundation

Increased interest in and enthusiasm for the reproductive sciences were spurred in the late 1950s and early 1960s by awareness of the problem of world population growth and by optimism about the potential contribution of the biological sciences to its solution. This optimism was base in large part on the successful development of oral contraceptives and the intrauterine device. During this period, the World Health Organization began its population program, the Population Council was founded, and NIH developed specific programs to support research in reproductive biology and fertility.

Beginning in 1952, the Ford Foundation began to support research in the reproductive sciences, particularly in contraceptive development and safety; it also supported research and training in the social sciences relating to population issues and family planning programs in developing countries. At the end of that decade, it appointed a committee to determine the steps it should take to develop the scientific basis for a program in population control. The work of the committee led to the establishment of centers for studies in reproductive endocrinology and neuroendocrinology at several major universities. The foundation also provided considerable monies to the Population Council to support contraceptive development and demographic studies.

In addition to research, the Ford Foundation sponsored several hundred preand postdoctoral research fellowships in the United States and Europe (Bowers and Purcell, 1980). For 3 years, from 1980 to 1983, the foundation also joined with the Rockefeller and Andrew W. Mellon foundations to fund reproductive research in fertility regulation, providing about $1 million per year to this effort (Ford Foundation, 1982). In 1990, however the foundation's population program was reorganized to place increased emphasis on the social science aspects of reproductive health (Ford Foundation, 1990).

Rockefeller Foundation

In its early years, the Rockefeller Foundation programs concentrated on public health and helped to support full-time faculty at several medical schools, in particular, Johns Hopkins, Rochester, and Iowa (Comer, 1964). It funded research in the reproductive sciences through the National Academy of Sciences/National Research Council Committee on Research in Problems of Sex, as well as through grants to selected research groups. In 1965, the foundation instituted a program to study problems associated with population growth.

In addition to grants to major research centers, the Rockefeller Foundation supported a program of 1 to 3 year fellowships for research training. Of eight such awards per year, "two or three went to physicians in academic obstetrics" (Bowers and Purcell, p. 61). In 1977, the foundation established a division of population sciences, led by Sheldon Jerome Segal.

Andrew W. Mellon Foundation

Beginning in 1977, the Andrew W. Mellon Foundation joined in the support of research and research training in the reproductive sciences. To carry out its objectives, the foundation mounted a multifaceted program that included support for fundamental research and research training, in addition to support for research and training in demography, policy analysis with respect to family planning, and technical assistance to developing countries.

The Mellon "young investigators" program in reproductive biology has provided support to promising young scientists both U.S. and foreign citizens, during their postdoctoral research training. It has also provided some start-up funds to help support junior faculty.

The overall program goal has been "to foster the development of excellent young investigators..." (Mellon Foundation, 1985). Initial awards from the

program went to Columbia and Harvard universities and to the Population Council. The following year (1978), awards were made to Baylor College of Medicine, Johns Hopkins, Mayo Clinic, University of California, San Francisco, and the University of Pennsylvania. Subsequently, several other institutions were added. To date, 17 centers have been supported in part by this program; the 4 centers receiving the largest amounts for reproductive biology have been the Population Council, University of California at San Francisco, University of Pennsylvania, and Baylor College of Medicine.

In 1980, Mellon joined with the Ford and Rockefeller foundations in joint support of focused research projects in reproduction. After 3 years, however, the Ford Foundation withdrew from this effort following a shift in program emphasis (Mellon Foundation, 1985). By the end of 1989, when the program was discontinued, the Mellon Foundation had contributed $9.3 million to the research effort. From 1977 to 1988, Mellon Foundation appropriations for population totaled $73.8 million. Of this, about half ($27.5 million, or about $2.4 million per year) was used to support promising young investigators in reproductive biology (Mellon Foundation, 1990). As of 1991, the Mellon Foundation has continued to fund some research and research training in the reproductive sciences. Much of this support is directed toward demographic and applied contraceptive research (Mellon Foundation, 1990).

A 1986 study of the impact of Mellon Foundation funds in research training found that although it was premature to evaluate the program's full impact, productivity measured in terms of publication records was "outstanding." Mellon-supported investigators were also successful in securing subsequent NIH funding; their rate of funding was comparable to that of NIH-supported trainees (Haseltine and Campbell, 1986).

FEDERAL SUPPORT FOR RESEARCH TRAINING

The National Institutes of Health and the National Institute of Child Health and Human Development

In 1945, at the end of World War II, Vannevar Bush, President Roosevelt's science advisor, outlined his visionary policies for federal support of peacetime health research in *Science—The Endless Frontier* (Bush, 1945). Bush foresaw both the need for fundamental biomedical research and the key role that

universities and colleges could play in advancing knowledge in the health sciences.

The forerunner of the National Institutes of Health, the Laboratory of Hygiene, opened in 1887 as a one-room attic laboratory at the Marine Health Service Hospital on Staten Island in New York. This was reorganized into the National Institute of Health in 1930 (National Institutes of Health, 1930), and in 1938 moved to its current location in Bethesda, Maryland. By 1961, a Center for Research in Child Health had been established in the Division of General Medical Sciences. In addition, a task force reported that year to President John F. Kennedy that research into the physical, intellectual, and emotional growth of children was severely handicapped by not having a centralized organizational structure. This group called for a new institute to launch a concentrated attack against disorders of development.

NIH Research Training Programs

Over the past several decades, NIH has developed a number of mechanisms for the support of research training (Table A-4). In the 1950s, the training grant mechanism emerged as a vehicle for the development of academic physicians. Originally, its purpose was not only to develop research but to train clinical specialists and subspecialists in underrepresented fields such as cardiology. Individual fellowship awards originated at about the same time. These awards (the F series) and institutional training grants (the T series) provide support for 2 to 3 years through National Research Service Award (NRSA) funds. Career development awards (the K series), such as those for clinical investigators (K08) and physician-scientists (K11, K12), are made for 3 to 5 years in support of clinical or basic science research training (Table A-4). In addition, individuals with more advanced research experience may compete for independent research funding through a First Independent Research Support and Transition (FIRST) Award (R29) or a research project grant award (RO1). Another funding mechanism is the Research Career Development Award (IO4), a 5-year award with partial salary support.

In 1958, NIH expanded research training programs in embryology and developmental physiology (Taylor, 1961). During the 1960s, routine clinical training was excluded from NIH-funded training mechanisms. In 1973, under the Nixon administration, all training grants and fellowships were discontinued, but because Congress was persuaded of the vital role of federal support in producing researchers to meet national goals in health research, it passed the National Research Service Award Act (P.L. 93–348) in 1974 which reinstated

training grants and fellowships. However, in an attempt to ensure that trainees who accepted federal support rotended to enter a career in research, it included a payback requirement of service.

While NIH support for research training has benefited medicine in general, and obstetrics and gynecology in particular, it has also undoubtedly played a role in the shift of such support by private foundations to other endeavors, in which their directors perceived that their presence would have a greater impact.

TABLE A-4: NIH Research Training and Research Mechanisms

Mechanism	Requirement	Duration Years	Purpose
F3, Postdoctoral fellowship (individual	Doctoral degree	2	Allow development of basic science expertise
T32, Postdoctoral Training grant (institutional)	Doctoral degree	2	Allow development of basic science expertise
K08, Clinical Investigator Award (CIA)	M.D.	5	Prepare clinicians for career as independent investigators
K11, Physician Scientist Award (PSA; (individual)	M.D.	5	Allow individuals with clinical training to develop independent basic research skills
K12, Physician Scientist Award (institutional)	M.D.	5	—
RO1, Research project Grant	Doctoral degree	5	Support further development of junior faculty to maximize research efforts
R29, First Independent Research Support and Transition (FIRST) Award	Doctoral degree	5	Support newly independent investigators with no more than 5 years research experience since completing postdoctoral training or equivalent

Mechanism	Requirement	Duration Years	Purpose
K04, Research Career Development Award (RCDA)	Doctoral degree, independent research support	5	Support development of independent program research program
F33, Senior fellowship	Doctoral degree		—

OBSTETRICS AND GYNECOLOGY RESEARCH TRAINING: 1985 TO THE PRESENT

American Gynecological Society

At its 1953 annual meeting, the American Gynecological Society (AGS) appointed a committee to determine whether the field of obstetrics and gynecology was attracting its share of first-rate students. The following year the committee reported its findings. As a result, the society passed a resolution which stated in part:

> Whereas the committee report indicates that there is in fact a disproportionately small number of "talented" men (i.e., men talented with respect to research and scientific investigation) entering Obstetrics and Gynecology and
>
> Whereas the American Gynecological Society is composed of men largely responsible for academic and scientific standards m this profession, therefore
>
> Be it resolved that the study be continued with committees or subcommittees of the following general character:

1. A Committee on the Undergraduate Curriculum.
2. A Committee on the Residency Program.
3. Committee on the Development of Research. (Taylor, 1961, p. 9)

These subcommittees were appointed, and circulated a questionnaire to obstetrics and gynecology departmental chairmen. In addition, because it recognized the limitations of this approach, the society obtained financial assistance from the Josiah Macy, Jr., Foundation to support a more complete survey by a professional educator.

Earle T. Engle, professor of anatomy at Columbia's College of Physicians and Surgeons and an outstanding reproductive physiologist, was selected for this task. From October 1956 to December 1957, he visited departments of obstetrics and gynecology in 44 medical schools, spending 1 to 3 days at each, interviewing faculty, house staff, students, and others. Just after completing his survey, Engle died. Over the next several years, drafts of his report, his notebooks, and his daily log were reviewed and organized into a document entitled "Recruitment of Talent for a Medical Specialty" (Taylor, 1961); the material was mainly devoted to problems in undergraduate medical education in obstetrics and gynecology and in the residency training programs. Because of a perception of the inadequacy of research in obstetrics and gynecology, as compared with other clinical departments, and the realization that the specialty could not truly progress without strengthening its knowledge base, the report also considered problems related to research and research training.

The AGS questionnaire to departmental chairmen included questions on whether departments of obstetrics and gynecology received their share of research monies, space, and facilities. Although about half of the respondents believed there was no limitation on their facilities, there were also no criteria to judge what was adequate. In addition to these questions, the committee asked whether talented students were deterred from entering the field because of a perceived lack of research opportunities. Only 3 percent of the 559 medical students and 14 residents interviewed stated that they had based their selection of specialty on the challenging nature of research problems in the field. Thus, a perceived lack of research opportunities in obstetrics and gynecology apparently played little role in the choice of that specialty.

Engle noted that despite good retentions, what was too often lacking were two essential ingredients: "adequate facilities … and investigators skilled in the application of experimental methods" (Taylor, 1961, p. 111). Of the 44 departments he visited, 29 had no or inadequate laboratory space. Of the 15 departments whose facilities were judged to be adequate, all but one had a

full-time staff including basic scientists. Some of these departments included clinicians with research training. Although Engle found that "few mean with these backgrounds are yet ready ... theirs is the promise for the future" (Taylor, 1961, p. 116).

In an attempt to determine what changes had occurred since its original survey 5 years previously, in 1959, the AGS committee sent a second questionnaire to 106 departmental chairmen. Eighty-five percent of respondents replied that their department was actively engaged in developing future workers and/or investigators in obstetrics and gynecology (Taylor, 1961) but the number of investigators was not given. Half of the chairmen agreed about the need for basic science fellowships, and two-thirds believed that there should be more space and money for research. Overall, the consensus was that they needed "more and better basic research" and "more facilities" (Taylor, 1961).

A handicap that had been noted in the development of first-rate research programs in departments of obstetrics and gynecology was the scholastic standing of students choosing the specialty. The report included an independent study of students' specialty selection. Students entering obstetrics and gynecology tended to be "intellectually less able than those attracted to the other major [specialties]" (Taylor, 1961, p. 39). In addition, a questionnaire sent to 515 students at 11 medical schools who were to graduate in 1959 revealed that half of the students entering obstetrics and gynecology were from the lower third of their class, with few candidates (15 percent) from the upper third and only the rare individual from the top 10 percent (Taylor, 1961). Moreover, 40 percent of departmental chairmen said that lack of ideas, energy, and motivation were the chief factors limiting the research efforts of their departments (Taylor, 1961).

The AGS committee consequently recommended the following: (1) more emphasis on research, improved facilities, and increased funding; (2) creation of research professorships in obstetrics and gynecology; and (3) "the development of large numbers of individuals skilled in clinical obstetrics and gynecology and in the technique of laboratory research" (Taylor, 1961. p 243). Committee members noted that their emphasis on research was not originally intended but that they had found that research was the area in which the range of excellence was "perhaps the greatest, and it is in respect to research that comparisons can be most easily made." In addition, they stated that "it is upon the success or failure in this field that the prestige of academic obstetrics and gynecology most depends" (Taylor, 1961, p. 144).

The long-term impact of this report is not easy to assess. On the one hand, the departments at Columbia University and the University of California at Los Angeles (where two of the three subcommittee chairs were chairmen) continued

to grow and prosper. In addition, obstetrics and gynecology departments m other research-intensive institutions, such as Johns Hopkins, the University of California at San Francisco, the University of Texas Southwestern, Yale, and several others, flourished. The report also played a vital role in the establishment, two decades later, of the Kennedy-Dannreuther fellowship program. On the other hand, it would appear that in most departments of obstetrics and gynecology, the conclusions of the report fell on deaf ears.

American Association of Obstetricians and Gynecologists Foundation Scholarship Program

Since 1984, the American Association of Obstetricians and Gynecologists Foundation (AAOGF), the philanthropic arm of the American Gynecological and Obstetrical Society (AGOS), has supported outstanding young obstetrician-gynecologists for 2 years of postresidency (and/or postfellowship) research training. The Foundation of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons (as the organization was originally called) was established in 1929 with funds raised by members. Subsequent bequests to the foundation by James Kennedy of Philadelphia and Walter T. Dannreuther of New York increased the endowment substantially. In 1981, the American Association of Obstetricians and Gynecologists merged with the American Gynecological Society to form AGOS, with the AAOG Foundation continuing as an independent entity. Donations by AGOS members, as well as a substantial bequest from the estate of J. Bay Jacobs, have further increased the foundation's endowment.

In the 1970s, the foundation worked to improve undergraduate and resident education in obstetrics and gynecology, and in 1983, it began to support research training in the specialty. The purpose was to help individuals who would conduct research, serve as role models to other potential investigators, attract more search funds, and improve the status of academic obstetrics and gynecology (Mitchell, 1990). Initially (in 1984), the foundation supported one Kennedy-Dannreuther fellow for two years. From 1985 to 1987, it annually supported two trainees, and since 1988 it has supported three trainees per year. In 1987, the Burroughs Wellcome Fund joined the AAOG Foundation in helping to support one fellow for 2 years. In 1989, the appellation AAOG Foundation Scholar was given to individuals in the program.

Initially, fellows received a stipend of $35,000 per year. In 1990, this was raised to $40,000 per annum, with the stipulation that the institution add at least

$15,000 per year. Applicants for this 2 year award must have completed at least 1 year of their residency, be allowed to devote 90 percent of their time to laboratory or clinical investigation, and have demonstrated a long-term commitment to research and academic obstetrics and gynecology. In addition, beginning in 1988, the AAOG Foundation joined in helping to support the Reproductive Scientist Development Program (see below).

Establishment of the AAOGF Scholarship Program occurred in part because of the perceived need for research-trained obstetricians and gynecologists. Several surveys that had been conducted earlier indicated that 200 to 300 individuals per year were required to flu positions in academic obstetrics and gynecology (Messer et al., 1979; Pearse et al., 1981). In addition, some leaders recognized that increased emphasis on clinical subspecialty training was, in effect, decreasing the laboratory research expertise of young academicians. These factors, coupled with a sense that obstetrician-gynecologist investigators were becoming less competitive in obtaining research funding, helped to persuade the Kennedy-Dannreuther Committee of the need for increased emphasis on basic research in departments of obstetrics and gynecology.

OTHER FOUNDATIONS AND PHARMACEUTICAL COMPANIES

American College of Obstetricians and Gynecologists

The primary professional organization for obstetricians and gynecologists, the American College of Obstetricians and Gynecologists (ACOG) supports and administers several programs and fellowships for basic and clinical research training. For example, ACOG helps to support one of the Reproductive Scientist Development Program awardees (see below) and administers several fellowships sponsored by pharmaceutical companies. These include the Ciba-Geigy "Fellowship for Research in Endocrinology of the Postreproductive Woman," and two Ortho Pharmaceutical Company "Academic Training Fellowships" (see Table A-5).

Society for Gynecologic Investigation

Organized in 1953 by a small group of investigators in departments of obstetrics and gynecology, the Society for Gynecologic Investigation (SGI) has developed into probably the premier research organization in the reproductive sciences (see Longo, 1983). Throughout its history, the SGI has fostered and

promoted a spirit of inquiry in departments of obstetrics and gynecology; it has also served as a forum in which young investigators in both and clinical reproductive sciences could present their work. It has not supported research projects or research training. In 1989, the SGI council voted to help support the Reproductive Scientist Development Program, and currently is working to supply matching funds (see below).

TABLE A-5: Private and Combined Private/Federal Fellowships and Awards in the Reproductive Sciences

Institution/ Foundation	Purpose	Amount (Dollars)	Duration (Years)	Number Year
American Association of Onstetricians and Gynecologists Foundation/ American Gynecological Society	Basic research in reproductive sciences	40,000	2	2–3
American College of Obstetricians & Gynecologists CIBA	Study the endocrinology of the post-reproductive woman	25,000	2	1
Ethicon	Study innovations in gynecologic surgery	20,000	1	1
Ortho Academic Training Fellowship	Improve skills in basic research/ training/health/ care delivery	30,000	1	6

Institution/ Foundation	Purpose	Amount (Dollars)	Duration (Years)	Number Year
Berlex Foundation Scholar Award	Reproductive medicine	50,000 +10,000[a]	1	1-2
International Research Fellowship	Human repro-reproductive research	75,000[b] +15,000[a]	2-3 +3	3-4
Burroughs Wellcome	Support for one AAOG fellowship	35,000	2	1
Reproductive Scientist Training Program NIH/ NICHD, AAOGF/ AGOS, ACOG, APGO,AFS, GynoPharma	Cell and molecular biology in the reproductive sciences	50,000 +10,000[a]	2-3 +3	3-4

NOTE: NIH/NICHD = National Institutes of Health/National Instituite of Child Health and Development.

[a] For research supplies.

[b] Includes travel funds.

Berlex Foundation

Beginning in 1988, the Berlex Foundation has made one or two awards per year to Berlex "scholars." The award ($60,000 per year—$50,000 in stipend monies and $10,000 in laboratory support) is made to a clinician-investigator for work on a clinically related research project in reproduction (see Table A-5). In addition, the foundation supports an annual International Research Fellowship in human reproduction for a senior investigator.

Reproductive Scientist Development Program

The idea of the Reproductive Scientist Development Program arose in the mid-1980s from concerns about the quantity and quality of basic research conducted in departments of obstetrics and gynecology by clinicians. In September 1986, at the time of the annual meeting of the American Gynecological and Obstetrical Society, an ad hoc group met to discuss development of a research training program for gynecologists. This group included representatives from the American College of Obstetricians and Gynecologists (ACOG), the American Gynecological and Obstetrical Society (AGOS), the Association of Professors of Obstetrics and Gynecology (APGO), and the Society for Gynecologic Investigation (SGI). The group outlined several goals and objectives for the program: the securing of both input and financial assistance from the leading organizations in obstetrics and gynecology; training for clinicians in excellent basic science laboratories; at least 5 to 6 years of research training (2 or 3 years in the laboratory and 3 years in a department of obstetrics and gynecology to become established as an investigator); and selection of outstanding candidates who had completed a residency in obstetrics and gynecology and had a long-term commitment to research.

In May 1987, the ad hoc committee submitted an application to the National Institutes of Health (NIH) for a multidisciplinary, multi-institutional program to tram obstetrician-gynecologists as physician-scientists. The program emphasized cell and molecular biology and related fundamental sciences; its overall goal was to identify the brightest and best individuals in departments of obstetrics and gynecology and to provide them with basic science,knowledge and skills. Specific objectives of the training program were as follows: (1) to increase the awareness and the attractiveness of a career in investigative academic obstetrics and gynecology among potential academicians; (2) to facilitate research training of obstetrician-gynecologists in the basic biomedical sciences; and (3) to stimulate the retention and maximal productivity of trainees by guaranteeing their placement as faculty members in a medical school department.

Beginning in 1988, 3 to 4 individuals per year have embarked on this 5 to 6 year rigorous training program in cellular and molecular aspects of reproductive science. As of July 1991, 12 individuals were in the program (Table A-6), which is jointly funded by NIH and several private groups. These latter include the American Fertility Society, the APGO Council on Resident Education in Obstetrics and Gynecology, Ethicon, Inc., and GynoPharma, Inc. Each of these groups provide "matching" funds for one trainee.

TABLE A-6: RSDP Trainees and Their Support for Full Time Laboratory Investigation: 1988 to the Present

Trainee	Year(s)	Sponsoring Inst.	Source of Support[a]
Setsuko K. Chambers	1988–1990	Yale University	ACOG
Karen P. Beckerman	1988–1991	Washington Univ.	AGOS/AAOG Fdn. (1988–1990)
Thomas J. Musci	1988–1991	University of CA/SF	Gynopharma, Inc.
Deborah A. Driscoll	1989–1991	University of PA	National Institutes of Health
James H. Segars, Jr.	1989–1991	Natl. Inst. of Health	Am. Fertility Soc.
John Yeh	1989–1991	Harvard University	APGO/CREOG
Robert A. Kaufmann	1990–1992	Wayne State Univ.	ACOG
Karen K. Smith-McCune	1990–1992	University of CA/SF	AGOS/AAOGF
Susan A. Arnold-Aldea	1991–1993	Harvard University	Johnson & Johnson Medical
Kimberly K. Leslie	1991–1993	Univ. of Colorado	APGO/CREOG
John L. Mershon	1991–1993	Univ. of Cincinnati	AFS
Michael C. Snabes	1991–1993	Baylor Col. of Med.	Gynopharma, Inc.

NOTE: RSDP = Reproductive Scientist Development Program.
[a] The source of support for all individuals includes NIH.

PROBLEMS OF RESEARCH TRAINING

General Problems

As noted earlier, the training required to be a first-rate specialist/subspecialist in obstetrics and gynecology and to gain scientific expertise is lengthy and arduous. Some general questions include the following: To what extent does one lose research potential by the end of a residency and/or fellowship? How can one create interest among the "brightest and best" students, residents, or fellows in many departments that lack role models? In addition, it is unclear to what extent potential applicants are aware of the opportunities in academic research and the training programs that are available.

Problems in Establishing a Research Program

To obtain adequate funding for research programs, departments and individuals must compete nationally. In many instances, uncertainties of funding cloud the attractiveness of an academic career.

As pointed out by Movsesian (1990), because the average duration of an NIH grant is about 4 years, new physician-scientists face the challenge of three consecutive cycles—an initial review and two competitive renewals to obtain continuous funding over a 10 year period. At NICHD, 1989–1990 success rates were 16 percent for new RO1 applications and 22 percent for competitive renewals. Of course, an investigator can increase his or her chances of success by submitting more than one application for each award. Movsesian has calculated that a minimum of 18 applications would be required to ensure a 50 percent chance of funding through three cycles. If each cycle resulted in a grant that lasted 4 years, this translates into an application submitted every 8 months (Movsesian, 1990).

With the increasing professionalization of research, one must be a full-time investigator to remain competitive. The physician-scientist will find it increasingly difficult to stay at the forefront of the field and still care for patients any more than a minimal amount of time. Thus, a critical need is a supportive environment—the departmental chair, colleagues, and the dean of the physician-scientist's institution or school must protect the beginning investigator and provide financial and moral support. The pressure to generate income too often means that the young physician-scientist or clinical investigator is required to perform services, at the expense of research. And yet, for the young investigator financial support is critical. Although the active research program is the *sine qua non* of an academic department, few departments can afford such a program without outside support.

MANPOWER IN ACADEMIC OBSTETRICS AND GYNECOLOGY CURRENT STATUS AND FUTURE NEEDS

Recent History

Because consideration of research training in the reproductive sciences must be viewed in the context of academic obstetrics and gynecology in general, it is appropriate to consider the recent history of departmental human resources and projections for the future. Several studies provide data on the number of

specialists and subspecialists in American medical schools during the past two decades. Of about 30,000 obstetricians and gynecologists in the United States in 1990, about 8 percent, or 2,500, were in academic medicine (Table A-7). For academic obstetrics and gynecology this represents an increase of about 45 percent since 1980 (Pearse et al., 1981; Pearse and Graham, 1991).

On the basis of these studies, several trends are apparent (Table A-7). The number of faculty per school shows strong, study growth from 1965 to 1975, accelerated growth from then until 1980, a relatively constant level from 1980 to 1983, and renewed growth from 1983 to 1990. Despite the 1980–1983 plateau, the overall growth rate for the last seven years has been essentially constant at 4.1 percent per annum. This correlates well with the growth from 1965 to 1980 and thus with the general increase over these years. Between 1977 and 1990, the number of academic subspecialists has grown steadily, but during the past 7 years this growth has occurred at a slower rate than that of the general faculty (Table A-7).

The data on researchers per school are not as complete or well defined. As of 1990, of the total M.D. members of departments of obstetrics and gynecology, about one-third (789 of 2,287) were engaged in research, chiefly clinical (Table A-7). Of these, perhaps 5 to 10 percent conducted basic research. The data included all those who committed 20 percent or more of their time to research and comprised both physician investigators and Ph.D.s.

The Future

The outlook for academic obstetrics and gynecology during the decade of the 1990s is mixed, and several scenarios are possible.

To what extent research in departments of obstetrics and gynecology will expand during the years ahead depends to a great degree on the funds available for clinical and basic investigation and on the manpower available to compete successfully for funds. As noted in the 1991 manpower study by Pearse and Graham, most department chairmen voice a "need" for more researchers (a total of 436 during the next 5 years), although no distinction was made in the need for physician-scientists versus the need for clinical investigators.

The situation for physician-scientists is even less clear. On the one hand, it would appear that many more physician-scientists and clinical investigators are essential, beth now and in the future. On the other hand, slower faculty growth or limited funding may decrease the opportunities for new physician-scientists.

Assuming that, at the outside, one-third (about 40) of obstetrics and gynecology departments are research intensive; assuming each can support 5 to

8 physician-scientists (to have a critical mass of such investigators), a total of 300 physician-scientists (i.e., 7.5 for each department) would be deployed in such department. In addition, if each of the 40 departments in the middle tier of research had 2 to 3 physician-scientists, that would equal another 100 such researchers (i.e., 2.5 each). This scenario projects a need for about 400 physician-scientists in departments of obstetrics and gynecology. Available data (RO1 recipients, SGI membership, etc. suggest that there are only about 70 reproductive physician-scientists in departments around the country, many of them are department chairs or division chiefs and/or soon to retire. A gap thus exists between the current supply of physician-scientists and an "ideal" number for the specialty.

The development of about 12 first-rate physician-scientists per year (the current level) would yield 120 in 10 years. Although that number would have quite an impact on departments of obstetrics and gynecology, it falls far short of the need. Moreover, not every trained individual will proceed to an investigative career. As Smith (1989) has emphasized, the creative scientist is not necessarily the one with the most intelligence or the one who works the hardest. Some very bright individuals are ineffective scientifically, while others less intellectually gifted are highly productive. This disparity may present problems in identifying and selecting for training the most promising individuals. Smith has also counseled that in view of the long training period and other variables, it is "more prudent to overshoot … than undershoot" the needed numbers (Smith, 1989, p. 111).

LESSONS LEARNED

During the past several decades, key discoveries in fundamental and clinical research have led to a revolution in the reproductive sciences. Work on on understanding biological functions now occurs on the cellular and molecular levels, and with the technological tools now available, opportunities for further advances have never been more promising. The potential to expand knowledge and understanding of reproduction and improve health care for women and infants is enormous.

TABLE A-7: Manpower in Academic Obstetrics and Gynecology: 1965–1990

Item	1965[a]	1970[a]	1975[a]	1977[b]	1980[c]	1983[d]	1986[e]	1990[f]
Number of schools	61	78	104	119	123	129	132	136
Total faculty				1,556	2,032	2,088	2,421	2,952
Ph.D.s				232 (14.9%)	270 (13.3%)	304 (14.6%)	381 (15.7%)	441 (14.9%)
Total faculty/school	6.4	8.8	11.3	13.2	16.4	16.2	18.3	21.6
Subspecialists				214	368	448	581	741
(% of M.D. faculty)				(17%)	(23%)	(28%)	(31%)	(32%)
Subspecialists/schools[g]								
Maternal/fetal				1.3	1.8	2.0	2.5	3.1
Oncology				1.3	1.4	1.6	1.7	1.8
Reprod. endocrinology				1.2	1.4	1.6	1.7	1.8
Vacancies/school				2.0	1.6	1.5	2.6	2.3
Additional faculty				708	701	762	771	1,039
next 5 years[h] (% increase)				(46%)	(34%)	(36%)	(32%)	(35%)

Item	1965[a]	1970[a]	1975[a]	1977[b]	1980[c]	1983[d]	1986[e]	1990[f]
Faculty involved in research[i]								
Total						998 (46%)	1,558 (64%)	1,195 (34%)
M.D.							—	789
Ph.D.							(100%)	(92%)
Faculty involved in research/school						7.7	11.7	10.3
Additional research faculty						525	485	436
next 5 years[h] (%increase)						(53 %)	(31%)	(36%)

[a] Spellacy et al., 1977.
[b] Messer et al., 1979.
[c] Pearse et al., 1981.
[d] Pearse et al., 1985.
[e] Pearse et al., 1987.
[f] Pearse and Graham, 1991.
[g] Figures indicate number of subspecialists per school reporting subspecialists.
[h] Projected increase.
[i] In the 1983 and 1986 studies, the amount of time was not stated. In the 1990 study, this was 20% or greater.

Nonetheless, many would argue that the past and present contributions of obstetricians and gynecologists to these advances are not what they should be. In fact, many leaders in reproductive research maintain that the quantity and quality of research in departments of obstetrics and gynecology are totally inadequate, and prospects for future improvement are dim. Thus, a challenge for obstetrics and gynecology is to increase and improve research and research training in the reproductive sciences. The following is intended to outline some fairly obvious yet important points that derive from the above analysis. Although most of what follows applies to physician-scientists, much of it also applies to clinician investigators.

Importance of Research Training in the Reproductive Sciences

Research training programs contribute to the nation's scientific capital of new insights, innovations, and paradigm shifts by promoting the flow of well-trained young scientists into research careers. Such training provides unique preparation for identifying research opportunities related to human diseases. Many of the challenges of clinically related research cannot be met by M.D.s employing Ph.D.s to do their laboratory work. Neither will many of the conundrums of the field be solved by scientists who lack a clinical background. This effort will require well-trained, first-rate physician-scientists and clinical investigators who bring both their clinical perspective and insights and their scientific skills to the new challenges of reproductive science. Thus, academic obstetrics and gynecology must propagate the physician-scientist and provide an environment of nurture and support.

Because improved research training leads to increased scientific competence, over the long term it will lead to improved quality of research. Such career development, however, should not be left to happenstance. The number of obstetrician-gynecologists who apply for and receive NIH research grants is unacceptably low. A vital mission for the specialty is to educate additional reproductive physician-scientists.

Because of the long training period required for a physician-investigator. current and future needs must be carefully considered. Unfortunately, there are no firm data on which to make such projections.

Centers of Excellence

By definition, a research-intensive department contributes important basic and clinical discoveries to the reproductive sciences. It also serves as an "ecological habitat" for physician-scientists and clinical investigators. Finally, it is an environment in which medical students and house staff are stimulated to seek an academic career.

Because the university is the locus of most reproductive research training, the effectiveness of that experience depends on the availability of qualified faculty research mentors. Thus, the loop of mentors working with trainees who in turn become mentors must be preserved and enlarged. It is evident that, however desirable it might be, each of the 120-odd departments of obstetrics and gynecology in the country neither can nor will make a major commitment to research. Nonetheless, in addition to the current dozen or so research-intensive departments, more centers of excellence must be developed. Forty such departments would only represent one-third of the total, yet could have an enormous impact on research and research training. For such centers to develop will require the leadership of visionary, hardworking chairmen/chairwomen and division heads with research experience and a commitment to such an agenda.

Discovery of Potential Physician-Scientists

Physician-scientists and clinical investigators for the reproductive sciences are often attracted to research as medical students or residents. Indeed, many students choose their residency on the basis of possibilities in this regard. In the past, the majority of such individuals have come from a handful of research-intensive departments (see later Addemdum). Mechanisms are needed to identify potential physician-scientists and to make more college students, medical students, and residents aware of opportunities and career paths in the reproductive sciences.

Residency-Fellowship Training

The clinical training of an obstetrician gynecologist subspecialist requires 6 or 7 years after award of the M.D. degree. Postdoctoral training in basic research requires an additional 3 or more years in the laboratory. Clinical investigator training demands at least 1 or 2 years in addition to the subspecialty

fellowship. Combining these learning experiences to educate a physician-scientist or clinical investigator is thus a lengthy, demanding process.

Research Training

Development of a physician-scientist requires a committed individual, an outstanding mentor, an appropriate training duration, a learning environment with increasing responsibilities, and an in-depth rigorous research experience. An effective training program requires a minimum of 2, and preferably 3, years in the laboratory with 90 percent or more time devoted to research (IOM, 1985; Lenfant, 1989). Such programs should be structured with increasing responsibility. In addition, the trainee should maintain a close relationship with his or her mentor to inculcate the value system appropriate to the conduct of scientific research. Its developers hope that the Reproductive Scientist Development Program can serve as a model in this regard.

Post-Research Training

Perhaps the most critical period for the developing physician-scientist (and clinical investigator) is that of emergence from the status of a graduate student to that of an independent investigator. Such individuals must be provided with the right conditions for growth and development. These may include relief from debt and a reasonable income, guaranteed research support for 3 to 5 years, restricted clinical responsibilities, and freedom to concentrate on one's field of interest.

Clinical Investigators

The clinical investigator plays a key role in designing, conducting, and interpreting clinical trials, metabolic studies, drug evaluations, epidemiologic studies, and related research. There is consequently a need for more and better trained clinical investigators in obstetrics and gynecology. Leaders of subspecialty training programs and those responsible for their certification should work to improve meaningful research opportunities for subspecialty fellows. This will require looking beyond the ever-expanding technological arena to

increase training in epidemiology of reproductive problems, biostatistics, clinical research study design, clinical trials and protocols, and other such topics.

The Role of Private Foundations

The Markle Scholarship Program had an impact on the quality of academic medicine far out of proportion to the money it provided. Although this effect was particularly apparent in departments of internal medicine, pathology, pediatrics, and general surgery, it could also be seen in departments of obstetrics and gynecology. In addition, the Josiah Macy, Jr., Foundation and the programs of the Ford, Mellon, and Rockefeller foundations helped to strengthen some of the more research-intensive departments of obstetrics and gynecology. These programs demonstrated that a relatively small amount of money can have a significant impact in a field. As Smith (1989) has noted, the cost of training is extremely low in comparison with the ultimate investment in the scientific research of those who are supported.

Private foundations and health-related corporations must collaborate in this enterprise. Industry and pharmaceutical companies profit from the discoveries of graduates of research training programs and should help to support such research training.

Follow-Up

An essential element of training the physician-scientist is long-term evaluation. Despite the enormous effort that has been put into research training, relatively little thought has been devoted to the outcome of training, or how the process could be optimized.

Tracking mechanisms should follow the progress of trainees. In addition, a system should be established to review and assess periodically whether goals of the programs are being met. Such evaluations will build a body of knowledge in an area that, as yet, is still poorly understood.

CONCLUSION

As noted on a previous occasion, "the challenge that lies before us is to not rest on past achievements, but to look to the future. The problems we face are

to use the future wisely, to use our talents wisely, and to use our funds wisely" (Longo, 1988). Training young obstetrician-gynecologists to pursue scientific problems at both the fundamental and clinical levels promises to continue to enlarge our understanding of all aspects of reproduction, including improved care for women and children.

ADDENDUM:

Only a few obstetrician/gynecologists have been Markle Scholars, Macy Fellows or have received Research Career Development Awards (see Table A-4 and A-5). In general, these individuals have achieved, or are continuing to achieve distinction in the profession. To obtain additional insights into the factors that influence physician-scientists in obstetrics and gynecology to choose a career in research and to identify the ingredients of a successful research program, the author sent a short questionnaire to each living obstetrician/gynecologist who was a former Markle Scholar (MS) or Macy Fellow (MF), or who had received a Research Career Development Award (RCDA) since 1975. Survey questions are given below. About half of the total group of these individuals replied (8 of 15 MSs, 8 of 10 MFs, and 7 of 8 RCDAs) for a total of 22 (one individual was both an MS and MF). Because the responses from individuals in three groups were so similar, they will be treated together. What follows is a tram of their responses with selected excerpts.

GENERAL BACKGROUND

1. *During what years did you hold your scholarship or fellowship?* For Markle Scholars, this was from 1951 to 1974; for Macy Fellows, from 1956 to 1966; and for Research Career Development Award recipients, from 1975 to 1989.
2. *What was the subject of your research or scholarship during that period?* Respondents were fairly evenly divided between reproductive endocrinology and maternal-fetal medicine (about 40 percent each) with a few

individuals in oncology and other areas such as anatomy or immunology of reproduction.

3. *What individual or individuals was most important in affecting your decision to enter academic medicine?* In what capacity did you know him or her? Almost without exception, the respondents gave the names of one or two key figures in obstetrics and gynecology who inspired them to excel. These included Allen C. Barnes, Nicholson J. Eastman, Charles H. Hendricks (mentioned by 3 persons), Arthur Hertig, William C. Keetel, Harry McGaughey, Joseph L. Seitchik, and Howard C. Taylor. In the reproductive basic sciences these included Leslie B. Arey, Donald H. Barron, and Ernst Knobil. Most of the respondents were either medical students or residents in about a dozen of the most research-intensive departments of obstetrics and gynecology when they came under the influence of these individuals.
4. *At what phase of your career did you make this decision?* Again, about half of the respondents made their career decision while a medical student, and the other half while a resident. None were fellows. This result agrees with an Institute of Medicine report (1983) that decisions for a arch career are often made in medical school (see also Burns, 1984, and Cadman, 1990).
5. *What factors were most important in making that decision?* The most common responses were the challenge of problems solving and intellectual stimulation and the desire to use newer approaches to solve biological questions m reproduction. One person recalled the stimulation received from Alpha Omega Alpha (national medical honor society) monthly meetings.

SCHOLARLY PRODUCTIVITY

1. Please provide names and academic appointments of research fellows (both M.D.s and Ph.D.s) whom you have trained.
2. List your major research grants, NIH, and other.
3. Please list your other awards, honors, and distinctions. (for the above three questions you may wish to sent me a copy of your C.V.)
4. What do you regard as your greatest contribution to academic Obstetrics and Gynecology? Replies to this last question centered on the theme of interesting students, residents, and fellows in research in obstetrics and gynecology. One person expressed it as "fostering curiosity in young people," while another phrased it as "not killing the dreams of the young!"

RESEARCH TRAINING IN OBSTETRICS AND GYNECOLOGY

1. Many individuals distinguish between physician-scientists doing basic research in a clinical department and clinical investigators who perform more patient-oriented research. Do you believe that distinction should be made? Among respondents to this query, 15 states yes, 5 no, and 3 were of no opinion. there were no discernible differences in response by individuals in the three groups.
2. If so, what is your perception of the current status and future needs of physician-scientists in academic Obstetrics and Gynecology? Despite the lack of unanimity of opinion to the previous question, the overwhelming response to this query was that there is a need for more clinical and basic science researchers, and a great need for 2 to 3 year "junior scientist" post-subspeciality fellowships in both basic science and clinical research. One individual stated the need as 400 to 600 such investigators for the 130 or so medical schools.
3. What do you believe to be the key elements in training physician-scientists? The points mentioned by respondents included good role models, a mentor who stimulates one to excel, broad-based laboratory experience, and protected time for research. Without exception, the respondents mentioned the need for stable financial support.

   One respondent also suggested that medical schools should reserve some admission positions for applicants who already have a doctoral or at least advanced research training. He also suggested that more medical students should be exposed to physician-scientists in departments of obstetrics and gynecology, so that potential recruits will be imbued with the excitement of research, problem solving, and research opportunities in reproduction.
4. What do you believe to be the major problems in training new reproductive physician-scientists? Again, without exception, all respondents stressed the importance of money, both increased grant monies and stable funding for the long-term in research. Other issues mentioned included: the problem of relatively few academic departments being truly committed to research, the financial disparity between research and clinical practice, inherent conflict between clinical activity and fundamental research, "time consuming academic bureaucracies," and the "Lorelei-like attraction of private practice."
5. What lessons would you care to share vis-a-vis research training in our specialty? What suggestions would you make as to how the needs for physician-scientists in obstetrics and gynecology can be met? Overall, there was a consensus on the seriousness of the problem, in that the specialty needs many more physician-scientists and clinical investigators. A key issue here was the

need for increased funding for both research and research training. Several individuals suggested reviving something similar to the Markle/Macy scholarship programs to provide adequate support for the fellowships and training. One person emphasized that one must "do research you enjoy in an area that will be viable and that will sustain you for forty years, and stay current."

Others stressed the need for more centers of excellence and more department chairs who are committed to academic research. A typical reply was the following:

> "Presently, most departments of obstetrics and gynecology do not have adequate research teams for training physician-scientists. The first priority should be directed toward creating such teams through developmental grants. Emphasis should be placed on encouraging young investigators to delve into new areas of research. A mix of M.D.s and Ph.D.s with dual appointments should also be encouraged. Developmental grants could be limited to 5 years or so, after which the group should apply to the regular funding agencies."
>
> Two other issues are of significance: Deans of medical schools, chairpersons, or directors of obstetrics and gynecology departments should be sensitized to the issue of the critical shortage of physician-scientists within the specialty. They should be encouraged to support more basic research within the clinical departments.

Several respondents stressed the need to either create a separate residency-fellowship track to tram physician-scientists, with perhaps a Ph.D. option, or to modify subspecialty training by including more research. One person stated that "presently, subspecialty training emphasizes clinical competence and does not prepare the individual for competitive basic research funding. Most residents elect to pursue the recognized subspecialty, because this is the only option opened to them."

Finally, a particularly thoughtful respondent mentioned that we "need a value system that rewards *academic* productivity."

REFERENCES

Beeson, P.B. How to foster the gain of knowledge about disease. Perspect. Biol. Med. 23:S9–S24 , 1980.

Bowers, J.Z., and E.F. Purcell (eds.). The Current Status and Future of Academic Obstetrics. Report of a Conference Supported Jointly by the National Institute of Child Health and Human Development and the Josiah Macy, Jr., Foundation. New York, Josiah Macy, Jr., Foundation, 1980.

Bradford, W.D., S. Pizzo, and A.C. Christakos. Careers and professional activities of graduates of a medical scientist training program. J. Med. Educ. 61:915–918 , 1986.

Bush, V. Science—the endless frontier: A report to the president. Washington, DC: United States Government Printing Office, 1945.

Corner, G.W. A History of the Rockefeller Institute. 1901–1953, Origins and Growth. New York: Rockefeller Institute, 1964.

Cushing, H. The Life of Sir William Osier. 2 vols. Oxford: Clarendon Press, 1925.

Douglas, G.W. Centennial insights. Am. J. Obstet. Gynecol. 126:739–743 , 1976.

Ford Foundation. Annual Report, October 1, 1981, to September 30, 1982. New York: Ford Foundation, 1982.

Ford Foundation. Annual Report, October 1, 1989 to September 30, 1990. New York: Ford Foundation, 1990.

Fremont-Smith, F. The Josiah Macy, Jr., Foundation Conference Program. In: Gestation: Transactions of the Third Conference, Villee, C.A. (ed). New York: Josiah Macy, Jr., Foundation, 1957.

Frieden, C., and B.J. Fox. Career choices of graduates from Washington University's Medical Scientist Training Program. Acad. Med. 66:162–164 , 1991.

Haseltine, F.P. and A.A. Campbell. The Impact of Fellowships Supported by the Andrew W. Mellon Foundation. Center for Population Research. Washington, D.C.: National Institute of Child Health and Human Development, 1986.

IOM (Institute of Medicine). Personnel Needs and Training for Biomedical and Behavioral Research. Report of the Committee on National Needs for Biomedical and Behavioral Research Personnel. Washington, D.C.: National Academy Press, 1985.

Lenfant, C. (Chairman, Steering Committee). Review of the National Institutes of Health Biomedical Research Training Programs. Bethesda, MD: National Institutes of Health, 1989.

Longo, L.D. Fundamental and clinical research and patient care: A triad for progress in reproductive medicine. Am. J. Obstet. Gynecol. 159:6–12 , 1988.

Longo, L.D. A Short History of the Society for Gynecologic Investigation, 1953–1983. Los Angeles: The Society, 1983.

Macy Foundation. Annual Reports. New York: Josiah Macy, Jr., Foundation, 1956–1960, 1965, and 1980.

Macy Foundation. Report of a Macy Conference. Teaching the Biological and Medical Aspects of Reproduction to Medical Students. New York, Hoeber Medical Division, Harper & Row, 1966.

Macy Foundation. Teaching Family Planning to Medical Students. New York: Josiah Macy, Jr., Foundation, 1968.

Martin, J.B. Training physician-scientists for the 1990s. Acad. Med. 66:123–129 , 1991.

Mellon Foundation. Report of the Andrew W. Mellon Foundation, from January 1, 1985, through December 31, 1985. New York: Andrew W. Mellon Foundation, 1985.

Mellon Foundation. Report of the Andrew W. Mellon Foundation, from January 1, 1990, through December 31, 1990. New York: Andrew W. Mellon Foundation, 1990.

Messer, R.H., Pearse, W.H., and J.G. Fielden. Academic Manpower for Obstetrics and Gynecology in the United States. Obstet. Gynecol. 53:649 , 1979.

Mitchell, G.W. Professor of OB/GYN, University of Texas Health Science Center. Lever to Lawrence D. Longo, 2 November 1990.

Movsesian, M.A. Effect on physician-scientists of the low funding rate of NIH grant applications. N. Engl. J. Med. 322:1602–1604 , 1990.

National Institutes of Health. Successor to the Hygienic Laboratory. Public Health Report 45:1409–1412 , 1930.

Pearse, W.H., E.C. Davidson, Jr., and J.G. Fielden. Trends in obstetric-gynecologic academic manpower—1980 . Obstet. Gynecol. 58:233–236 , 1981

Pearse, W. H., Davidson, E.C., and J.G. Fielden. Trends in Obstetric-Gynecologic Academic Manpower-1983. Obstet. Gynecol. 65:147–150 , 1985.

Pearse, W.H., Fielden, J.G., and Donald M. Sherline Obstetric-Gynecologic Academic Manpower-1986. Obstet. Gynecol. 70:403–405 , 1987.

Pearse, W.H., and K.K. Graham. Trends in obstetric-gynecologic academic manpower and research. Obstet. Gynecol. 78:141–143 , 1991.

Randall, C.L. Developments in the Certification of Obstetricians and Gynecologists in the United States 1930–1980: The American Board of Obstetrics and Gynecology. Seattle, WA, American Board of Obstetrics and Gynecology, 1989.

Russell, J. Informal Survey of Medical Education and Research, Madre Foundation, New York, New York, May 1947, pp. 12–14 .

Smith, L.H. Training of Physician/Scientists. Pp. 107–120 in Institute of Medicine: The 1989 Report of the Committee on National Needs for Biomedical and Behavioral Research Personnel, Vol. 3 , Commissioned Papers. Washington, D.C: National Academy Press, 1989.

Spellacy, W.N., S.A. Birk, and W.C. Buhi. A National Survey of Medical School Obstetrics and Gynecology Departments, 1965 to 1975. J. Med. Educ. 52:901–905 , 1977.

Strickland, T.G., and S.P. Strickland. The Madre Scholars: A Brief History. New York: The John & Mary R. Markle Foundation, 1976.

Taylor, H.C., Jr. (ed.). The Recruitment of Talent for a Medical Specialty. A Report to the American Gynecological Society on the Problem of Procurement of Academic and Scientific Personnel for Obstetrics and Gynecology. St Louis: C.V. Mosby Co., 1961.

Wyngaarden, J.B. The clinical investigator as an endangered species. N. Engl. J. Med. 301:1254–1259 , 1979.

APPENDIX B

NATIONAL INSTITUTES OF HEALTH SUPPORT OF RESEARCH IN DEPARTMENTS OF OBSTETRICS AND GYNECOLOGY*

ROBERT A. WALKINGTON

The National Institutes of Health (NIH) is the major supporter of biomedical research conducted in the nation's universities and medical schools. In 1989, 60 percent of funds for biomedical research in academic institutions came from NIH, compared with 8 percent from private, non-profit sources and 6 percent from industry.[1] In medical schools, over 75 percent of funds for sponsored research comes from the federal government, the majority from NIH.[2] NIH support in FY 1989 included over $500 million for clinical trials, $245 million to support research training, $90 million for career development awards and $120 million to support beginning researchers.[3] Since it is peer reviewed in national competition, NIH support is considered a standard of excellence. For this reason it can be used to leverage other support: from the community, from private sources and from industry.

For more than a decade there has been concern that clinical research is not adequately supported. This is thought in part to be because physician-scientists are relatively unsuccessful in winning NIH peer awards. The following comments are indicative of interwoven concerns.

* This paper was prepared for the Institute of Medicine, Committee on Research Capabilities of Academic Departments of Obstetrics and Gynecology.

"Whether for lack of time, expectation of greater funding, more ability to control variables or other reasons, the physician-investigator has turned away from involvement in human research. Obtaining funding for human studies is considered so difficult that many investigators are discouraged and in some instances, bitter."[4]

"Concerns of insufficient access to research support have been voiced by a variety of individual surgical investigators. Frustrated by a perceived inability to successfully compete for NCI grant support, some surgical oncologists have criticized aspects of the current NCI peer-review mechanisms for awarding grants."[5]

"It is essential to understand that in 1988 it is effectively impossible for an individual investigator to obtain NIH funding for human investigation."[6]

"If I leave here (Intramural Program) I will leave research" [because its impossible to get a grant for clinical research].[7]

"Friedman told the board that clinical investigators do complain that is very difficult to get RO1 grants: 'The perception is that they receive poorer priority scores and inferior funding', he remarked. 'If one looks at...comparisons by program...it's evident, that year by year, there are inferior funding rates for the clinical proposals compared to the preclinical proposals' Friedman stated. 'This does not indicate whether the proposals are good or not'; 'I would argue that some of them are [good]. What we need is [the submission of] more good clinical proposals.'"[8]

The evidence to support these concerns is mixed. Different studies, using different data bases and or time periods, have produced different results. A study conducted at NIH in the early 1980s showed that between 1976–1981 only 63 percent of clinical applications were approved compared with 74 percent of basic science applications. The study also found that approved clinical applications received poorer priority scores than did those dealing with basic research.[9] M.D. applicants in 1985 had a higher disapproval rate (9.1 percent) than Ph.D. applicants (6.8 percent). During the decade 1975–1985, Ph.D.s had consistently slightly better priority scores than M.D.s on competing RO1 applications. [10] Recent NIH data, however, indicate that between 1987 and

1989 M.D.s had slightly higher success rates than Ph.D.s in competing for research-project grants, of which the majority are RO1s.[11]

A 1986 study indicated that between 1975 and 1985 the number of ROI applications from M.D.s and M.D./Ph.D.s increased by 30 percent, compared with an increase of 83 percent in applications by Ph.D.s. The proportion of new applications submitted by M.D.s dropped from 31 percent of total R01 applications in 1975 to 25 percent in 1986.

There is also concern that the number of physicians in clinical research is declining, though conclusive data are lacking.[12] ,[13] ,[14] ,[15] , [16] ,[17] Particular concern is expressed over the shortage of physicians involved in patient oriented clinical research. Reasons suggested for the decline include:

- increasing indebtedness of medical school graduates;
- increasing difficulty of maintaining competency in both science and medicine;
- perceived insecurities associated with extramural research funding for clinical investigation;
- problems associated with financial soundness of academic departments combined with increasing demands for faculty to engage in clinical practice;
- expectations with less willingness to undergo relative deprivation;
- the paucity of role models and inadequate mentoring; and
- curriculum deficiencies in medical schools.[18]

In addition to the general problems related to NIH support of clinical research and the physician-scientist, specific concerns have been expressed about the paucity of research conducted in departments of OB/GYN. The IOM Planning Committee for the current study concluded that departments of OB/GYN lagged in receiving support from NIH for research and speculated that:

> "possible causes related to the politicalization of problems relating to the status of the fetus, lack of organizational focus for reproductive research at NIH, the lack of a national consensus concerning the ethical issues raised by some reproductive research ... there is also the possibility that the absence of OB/GYN presence in the NIH intramural program results in a relative disregard of OB/GYN research."[19]

NIH support appears to be hindered by three interrelated problems: 1) the quality of the research being proposed 2) the nature of the research, and 3) the

organizational structure and management of NIH in general and with regard to the review of grant proposals. There are a few studies that illuminate the quality of OB/GYN research, or research proposals: In 1986, research grant applications (competing RO1s) from OB/GYN departments had the poorest average priority scores of nine clinical departments studied—a decline from FY 1979 when OB/GYN ranked in the middle (5th of 9) of the clinical departments studied.[20] A study focusing on clinical oncology support from the National Cancer Institute showed that between FYs 1980 and 1985 OB/GYN departments had success rates substantially lower than departments of medicine, pediatrics and radiology. While the success rated varied greatly from year to year, for 3 of the 6 years the rate for OB/GYN was substantially lower than that of the other departments. The decline in success rates between 1980 and 1985 was greater for OB/GYN than the three other departments studied.[21]

A measure of the research intensity of a department is the degree to which faculty are involved in research. A 1989 Association of American Medical Colleges (AAMC) study, analyzed the distribution of full-time faculty of U.S. medical schools who are principal investigators on NIH or Alcohol, Drug Abuse and Mental Health Administration (ADAMHA) research awards by department and degree. The study linked the AAMC Faculty Roster (1988)—with records of NIH and ADAMHA research awards (FY 1987). This linkage allowed awards made to affiliated hospitals to be credited to the appropriate department. OB/GYN departments ranked 11th of 17 clinical departments with 9.8 percent of their faculty being principal investigators, compared with an average of 14 percent for all clinical departments. Examination of the data by the degree of the principal investigator reveals that the discrepancy between OB/GYN and more research intensive departments can be attributed to the M.D. and M.D./Ph.D. faculty. Ph.D.s in OB/GYN departments are principal investigators at a rate above the average for all clinical departments (Ph.D.s in OB/GYN departments ranked 6th of 17 clinical departments; M.D and M.D/Ph.D.s ranked 12th). (Table B-1).[22]

According to a 1986 survey of academic manpower in OB/GYN departments, almost all the Ph.D. faculty and 61 percent of the M.D. faculty reported involvement in research.[23] A survey in 1990 asked faculty to indicate if they spent at least 20 percent of their time in research. Although 92 percent of the Ph.D. faculty indicated that they were so involved, only 38 percent

TABLE B-1: Percentage of Full Time Faculty, in Clinical Departments Who are PIs on NIH/ADMHA Awards (1988)

	Total Full Time Faculty		Total M.D.s	
Department	No.	%PIs	No.	%PIs
Opthalmology	1,014	36.5	650	25.7
Neurology	1,637	23.9	1,101	18.4
Dermatology	365	22.5	291	20.0
Int. Medicine	13,448	19.9	10,894	17.7
Pathology	1,152	17.0	656	13.9
Public Health	1,127	15.7	445	10.6
Other Clinical	69	14.5	21	19.0
Otolaryngology	543	14.2	296	6.4
Pediatrics	5,724	13.4	4,503	11.9
Psychiatry	5,244	12.1	2,858	8.1
OB/GYN	2,265	9.8	1,687	5.9
Surgery	5,031	9.5	4,038	7.0
Radiology	3,884	8.3	2,786	3.2
Orthope. Surgery	730	7.8	569	4.4
Anesthesiology	2,649	3.5	2,186	1.6
Phy. Med/Rehab.	548	1.2	341	0.9
Family Medicine	1,539	1.2	1,127	0.7
Total/Average	45,969	14.0	34,449	11.1

of the M.D. faculty were.[24] Because of differences in the wording of questions the two surveys are not comparable. Roughly comparable data exist for departments of internal medicine. A study in the early 1980s indicated a more intense involvement in research of physician faculty in departments of internal medicine than in departments of OB/GYN in 1990, with 50 percent of internal medicine faculty with an M.D. degree spending at least 20 percent of their time

	Total M.D./ Ph.D.s		Total Ph.D.s	
Department	No.	%PIs	No.	%PIs
Opthalmology	61	39.3	245	69.4
Neurology	148	37.8	315	35.6
Dermatology	22	40.9	43	34.9
Internal Medicine	875	31.1	1,261	33.9
Pathology	122	25.4	280	22.1
Public Health	48	14.3	472	25.0
Other Clinical	2	0.0	41	12.2
Otolaryngology	28	25.0	171	27.5
Pediatrics	275	28.4	614	21.8
Psychiatry	197	18.8	1,728	20.2
OB/GYN	126	13.5	320	32.2
Surgery	268	17.9	540	25.9
Radiology	169	13.6	696	29.0
Orthope. Surgery	23	13.0	81	34.6
Anesthesiology	181	8.8	157	22.3
Phy. Med/Rehab.	18	5.6	97	6.2
Family Medicine	25	0.0	265	6.8
Total/Average	2,589	24.3	7,327	26.9

SOURCE: AAMC Medical School Faculty Roster (1988) linked with IMPAC record of research grants (NIH and ADAMHA) and Contracts (NIH) that received funds during FY 1987.

engaged in research. Seventy seven percent of the faculty with Ph.D. degree spent at least 10 percent of their time in research.[25]

Although data are not available on the level of NIH support for research in reproductive issues, or for women's health in general, there are strongly held views about the interest of NIH in those topics. It should be remembered that human embryo research cannot be supported by federal funds. The following comments from letters from chairman of departments of OB/GYN to the IOM committee indicate some concerns:

> "Funding has been confused by the political turmoil surrounding sex education, abortion and contraception. Because of this departments must seek funding outside the federal government; pharmaceutical and equipment companies etc. or find clinical income to support research".
>
> "Funding has moved from NIH and NSF to pharmaceutical companies with interests in product development. Some types of clinical research (sohographic studies of the fetus in utero) are impossible to fund through NIH, despite their importance. These studies are conducted with support from clinical income, but not at the standard of peer reviewed funding".

In addition to the political, and ethical ramifications of some areas of OB/GYN research, many OB/GYNs in medical schools believe that NIH lacks interest in reproductive issues and women's health in general. Again, comments from some department chairmen indicate these concerns:

> "Lack of NIH commitment to women's health research is evidenced by composition of study sections, no separate institute and few NIH OB/GYNs".
>
> "The governance of NIH is neither responsive nor interested in women's issues. They will only act if they think they can direct funds to other specialties. An example is the lack of representation by chairman of OB/GYN departments in the governing councils of the NIH. The NIH Advisory Committees are comprised of approximately 3,056 individuals; of those only 26 are OB/GYNs yet the most common cause for admission to most acute hospitals are in OB/GYN. I would agree with the GAO that arrogance and indifference summarize the attitude of the NIH towards women's issues and departments of OB/GYN. The NIH is not "national" in that is not representative of

the nation or its health issues, as more than half of the nation are women".

The data and beliefs cited indicate a need to examine more closely what has been happening to OB/GYN departments in the competition for funds, and a need to indicate where one might seek change to improve the outcome.

NIH SUPPORT FOR OB/GYN RESEARCH

Overview

"Federal funding of research in academic departments of OB/GYN in the United States has never been substantial and the situation is no different today."[26]

In FY 1978, the majority of federal support for OB/GYN departments came from the Department of Health, Education and Welfare (DHEW), now the Department of Health and Human Services, with a small amount coming from the Agency for International Development. Of the money from DHEW, over 90 percent came from NIH with small amounts from ADAMHA and the Bureau of Maternal and Child Health. The picture in FY 1989 was similar, with HHS providing the large majority of federal support, and most of that coming from NIH.

Figure B-1 shows total NIH support for OB/GYN departments in both current and constant (1968) dollars. Growth in constant dollars has been modest, from $7 million in 1968 to $12 million in 1989 (71 percent). Between 1968 and 1989 OB/GYN departments slightly increased their share of NIH funds—current dollar support to OB/GYN departments grew by 570 percent while overall NIH research support grew by only approximately 550 percent. Between 1978 and 1989, support to OB/GYN departments increased by approximately 190 percent while overall NIH support grew by approximately 150 percent. The increased support of departments of OB/GYN in the 1980s is actually more impressive than the percentages indicate since the two institutes providing the majority of the support the National Institute of Child Health and Human Development (NICHD) and the National Cancer Institute (NCI) both had budget increases below the NIH average for the decade.

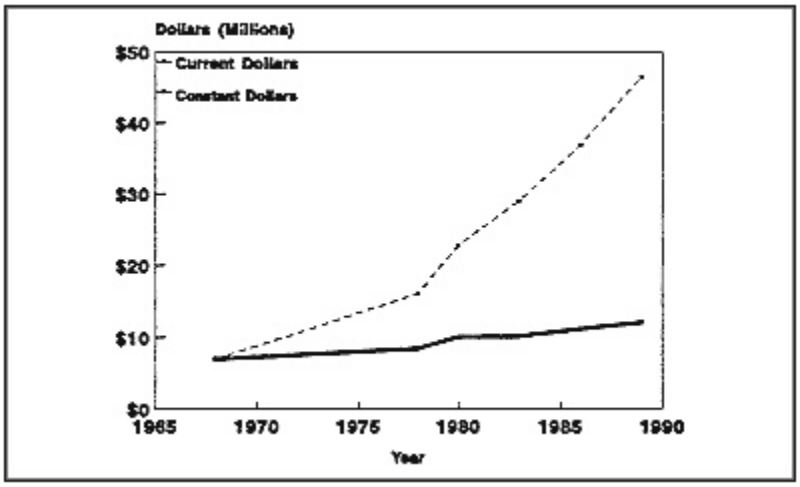

Figure B-1: NIH support of departments of OB/GYN, current and constant (1968) dollars.
SOURCE: Special tabulation by NIH.

OB/GYN departments received a fairly constant share of NIH funds going to medical schools—1.5 percent in 1968, 1.4 percent in 1978 and 1.5 percent in 1989. OB/GYN faculty received approximately 2.7 percent of the NIH/ADAMHA awards to clinical departments.* However, the departments received slightly less than would be expected on the basis of size of faculty, since OB/GYN departments had approximately 3.7 percent of the total full time medical schools faculty and 4.8 percent of the flail time faculty in clinical departments in 1988.

* It should be noted that these figures understate the actual funds going to OB/GYN departments. This is caused by the fact that the NIH data system does not allocate funds awarded to separate administrative units to the department even though the research may be directly related. Thus if a medical school has a center for reproductive research or population studies which is not administratively part of the OB/GYN department, research conducted in the center will not appear in the departmental total. However, there is no reason to believe this under reporting has increased over time or is more common for OB/GYN departments than for other clinical departments and thus should not effect longitudinal or cross department comparisons.

NICHD has been the major NIH supporter of OB/GYN departments, providing 69 percent of support in 1968, falling to 56 pete t in 1978, returning to 69 percent in 1989. Support from the NCI fell from 31 percent in 1978 to 9 percent in 1989, although in 1989 it was still the second largest NIH funder of OB/GYN departments. The National Institute of Allergy & Infectious Diseases (NIAD) increased its support of OB/GYN departments, mostly because of a $1.7 million contract to study prenatal transmission of HIV. The Heart, Lung and Blood Institute (NHLBI) and the Division of Research Resources (DRR) also showed major increases, the latter due largely to a grant and a cooperative agreement with Emory University for "support of animal resources available to all qualified investigators without regard to scientific disciplines or disease orientation." (Table B-2).

TABLE B-2: NIH Support of Departments of OB/GYN By Institute, FYs 1968, 1978, 1989

Institute	1968	1978	1989
NICHD	$4,793,336	$8,977,923	$32,023,354
NCI	823,276	4,997,132	4,362,099
NHLBI	213,314	451,276	1,859,406
NIA	—	448,292	774,409
NIADDK	898,441	930,580	1,656,883
NIDR	16,000	187,040	—
FIC	10,661	77,541	55,496
NIGMS	73,265	59,114	389,055
NIDCDS	—	15,200	1,013,612
NIAID	—	—	2,494,911
DRR	120,031	—	946,000
NIEHS	—	—	796,639
NEI	—	—	161,632
Total NIH Support	6,948,324	16,144,098	46,533,496
Percent of NIH Support to Medical Schools	1.5 %	1.4%	1.5%

Table B-3 shows competitive and noncompetitive NIH awards to OB/GYN departments, 1980–1989, by number and type of award (later tables reflect only competitive awards—new or competing continuations). OB/GYN department support more than doubled ($22.8 million to $46.5 million), however, since the size of awards increased, the number of awards increased more modestly. The number of research grants increased, but the number of contracts declined from 11 to 7, although contract dollar support more than doubled. Awards for training grants and fellowships combined fell in both number and dollars. These trends generally reflect the overall NIH experience during the decade.

TABLE B-3: Total NIH Awards to OB/GYN Departments (By Major Type)
Thousands of Dollars 1980–1989

	Total Awards		Research Grants		Contracts	
Year	No.	$	No.	$	No.	$
1980	246	22,764	202	20,676	11	1,373
1881	236	26,084	212	24,444	8	1,256
1982	232	26,009	203	23,871	9	1,601
1983	233	28,978	200	25,792	13	2,713
1984	251	33,479	222	29,869	11	3,112
1985	246	36,415	222	33,383	9	2,525
1986	256	36,947	222	34,563	10	1,694
1987	275	41,902	250	39,493	9	1,943
1988	272	45,454	247	44,602	9	3,184
1989	258	46,533	235	42,678	7	3,229

	Training Grants		Fellowships	
Year	No.	$	No.	$
1980	7	338	26	377
1881	6	236	10	148
1982	5	246	15	291
1983	4	200	16	268
1984	4	21	14	278
1985	4	270	11	237
1986	4	247	20	443
1987	3	185	13	280
1988	7	445	9	222
1989	7	371	9	255

The number of OB/GYN departments receiving awards fluctuated slightly, and in 1989 was three fewer than in 1980. There was little change in the distribution of awards (number and dollars) among OB/GYN departments between 1980 and 1989 (Table B-4), with ten departments receiving approximately 50 percent of the funds and 40 percent of awards. In 1989 only 4 departments had more than 10 awards while 15 had only one award, 17 had two awards and 9 had three awards. This distribution is similar to, but somewhat more concentrate than, the distribution of total NIH funds: 20 medical schools received 50 percent of NIH extramural funds going to medical schools in FY 1989. This concentration of research in a relatively small number of institutions highlights the difficulty of developing new and successful research efforts in part because of the limited number of locations that are suitable for expanded research training.

While the number of applications from departments of OB/GYN fluctuated from year to year, applications from M.D.s decreased. The number of applications from Ph.D.s increased. Ph.D.s also achieved a higher success rate than M.D.s (Table B-5).

TABLE B-4: Total NIH Awards to OB/GYN Departments and Awards to Top Ten Departments, Thousands of Dollars, 1980–1989

Year	No. of Depts. w/ Awards	Total Awards		Awards to Top Ten			
		No.	$	No.	%	$	%
1980	70	246	22,764	102	41	11,400	50
1981	69	236	26,084	88	37	12,865	49
1982	69	232	26,009	81	35	12,511	48
1983	71	233	28,978	82	35	13,439	46
1984	72	251	33,479	95	38	15,550	46
1985	69	246	36,415	100	41	17,661	48
1986	69	256	36,974	97	38	17,985	49
1987	70	275	41,902	99	36	20,153	48
1988	69	272	45,454	110	40	21,341	47
1989	67	258	46,533	102	40	24,856	53

The past decade has seen little change in which departments of OB/GYNs received the majority of NIH awards. Of the departments ranked in the top 10 in 1980, 8 were in the top ten in 1989 (and one was 11th). Only one of departments in the top 10 in 1980 dropped significantly in the ranking—that department was in the top 10 for the first 5 years of the decade but subsequently fell to 24th place. A total of only 15 departments were ranked in the top 10 during the decade.[*]

[*] The previous discussion referred to all awards, competing (new and competing continuations) and noncompeting. The following sections discuss competing applications only.

TABLE B-5: Success Rates of Competing Applications from OB/GYN Departments by Degree of Principal Investigator, 1980–1989

Number of Year	Applications	Awards	Success Rate
All Applications			
1980	216	82	38.0%
1981	247	54	21.9
1982	242	68	28.1
1983	227	63	27.7
1984	308	88	28,6
1985	322	66	20.5
1986	331	83	25.1
1987	259	76	29.3
1988	268	74	27.6
1989	249	52	21.0
Total	2,669	706	26.5
M.D. Applications			
1980	87	33	37.9%
1981	115	17	17.7
1982	96	27	28.1
1983	79	11	13.9
1984	122	42	34.4
1985	124	19	15.3
1986	123	24	19.5
1987	102	27	26.5
1988	101	33	32.7
1989	64	12	18.7
Total	1,013	245	24.2

Number of Year	Applications	Awards	Success Rate
Ph.D. Applications			
1980	110	42	38.2%
1981	115	33	28.7
1982	130	38	29.2
1983	133	46	34.6
1984	166	42	25.3
1985	177	43	24.3
1986	178	50	28.1
1987	145	48	33.1
1988	152	38	25.0
1989	167	36	21.5
Total	1,473	416	28.2

Support by Institute

As noted earlier, support for departments of OB/GYN comes mainly from a few NIH institutes, with NICHD providing the majority of such support. Slightly more than a quarter of all competing applications from departments of OB/GYN were awarded support. Applications to NIDDK had the highest ess rate with 28.9 percent of approved applications funded. Applications to NICHD and NCI (nearly 85 percent of total OB/GYN applications) had success rates of 26.7 and 24.9 respectively. Applications from departments of OB/GYN to NHLBI and NIAID were less successful in winning awards (Table B-6). No trend in success rates by institute over the decade was discernible.

TABLE B-6: NIH Competing Applications from OB/GYN Departments by Funding Institute, 1980–1989

Number of Institute	Number of Applications	Number Awarded	Percent Awarded
NICHD	1,759	469	26.7
NCI	457	114	24.9
NHLBI	110	18	16.4
NIAID	49	6	12.2
All Other	211	75	35.6
Decade Total	2,669	706	26.5

Support by Review Group

Each application submitted to NIH is assigned to an Initial Review Group (IRG) to be assessed for scientific merit and assigned a priority score if recommended for approval. Applications recommended for approval by the IRGs axe then reviewed by an institute's National Advisory Council and considered for funding. Funding is based primarily on the score assigned by the IRG but consideration is also given to the amount of money available for extramural research and the contributions the proposed activity would make to advancing the mission and programs of the institute.

Although there are a large number of IRGs, a small number of them review the majority of applications submitted by OB/GYN departments. In 1989, for example, 54 IRGs reviewed applications submitted by OB/GYN departments, 27 received only one application and another 11 received only two or three applications. On the other hand, four IRGs, Biochemical Endocrinology, Human Embryology and Development, Reproductive Biology and Reproductive Endocrinology (created in 1985) together received 50 percent of all competing applications from OB/GYN departments during the past decade. In 1989 these four IRGs reviewed 125 out of the 247 applications submitted, with Reproductive Biology reviewing the largest number.

Table B-7 shows the success rates (number of awards divided by number of applications) for applications from OB/GYN departments sent to the four IRGs which review the greatest number of applications from OB/GYN departments. Applications from OB/GYN departments reviewed by the

Biochemical Endocrinology and Reproductive Biology study sections had the highest success rates of the four. Although success rates varied from year to year, in general OB/GYN departments experienced a slight decline in sucks rates in the second half of the decade. The three IRGs that were active for the entire decade (Reproductive Endocrinology was created in 1985) all saw their workload from departments OB/GYN increase in the middle of the decade and then decrease to the previous level or slightly lower in the last several years.

OB/GYN Departments Compared with Other Clinical Departments

Another way to assess the success of OB/GYN departments in the competition for NIH funds is to compare them with other clinical departments. Medicine, the largest clinical department, was chosen for comparison with OB/GYN because it is a recognized leader in clinical research; pediatrics, because it "shares" an institute with OB/GYN and because of its numerous interrelationships with OB/GYN; surgery was chosen because of its emphasis on technique; and radiology because it is closer to OB/GYN in faculty size than the other clinical departments, and because it is similar to OB/GYN in terms of percent of faculty who were principal investigators on NIH/ADAMHA grants. Data on grant applications from urology departments are not available. Data on two surgical subspecialties which would have provided interesting comparisons, orthopedics and otolaryngology, were available but the number of full time faculty and grants submitted were too small for analysis.

TABLE B-7: NIH Competing Applications from OB/GYN Departments, Success Rates by Selected IRGS, 1980–1989

Year	Submitted	Awarded	Success Rate	Success Rate of OB/GYN in All IRGs
Reproductive Biology				
1980	40	14	34.1%	37.8%
1981	49	17	34.0	21.8
1982	50	15	30.0	27.8
1983	52	17	32.7	27.6
1984	61	15	24.6	28.1
1985	59	15	25.4	20.2
1986	43	12	27.9	25.2
1987	41	14	32.6	28.7
1988	44	12	27.3	27.6
1989	40	6	15.0	20.9
Total	479	137	28.6	
Reproductive Endocrinology				
1985	12	0	0.0%	20.2%
1986	21	9	42.9	25.2
1987	26	5	19.2	28.7
1988	24	5	20.8	27.6
1989	26	4	15.4	20.9
Total	109	23	21.0	26.2

Year	Submitted	Awarded	Success Rate	Success of OB/GYN ins Rate All IRGs
Biochemical Endocrinology				
1980	31	13	41.9%	37.8%
1981	36	11	36.1	21.8
1982	54	18	33.3	27.8
1983	35	13	37.1	27.6
1984	51	10	19.6	28.1
1985	44	13	28.3	20.2
1986	35	10	28.6	25.2
1987	34	10	29.4	28.7
1988	25	5	20.0	27.6
1989	25	6	24.0	20.9
Total	370	111	30.0	26.2
Human Embryology and Development				
1980	34	11	32.4%	37.8%
1981	28	3	10.7	21.8
1982	29	1	3.4	27.8
1983	34	2	5.9	27.6
1984	33	17	47.2	28.1
1985	48	6	12.5	20.2
1986	27	5	18.5	25.2
1987	26	9	33.3	28.7
1988	29	8	27.6	27.6
1989	29	6	20.7	20.9
Total	317	68	21.5	26.2

In reviewing the comparisons among departments it is important to remember the relative sizes of the departments (Table B-8). Internal medicine had nearly six times as many full time faculty in 1988 as OB/GYN, while pediatrics and surgery had more than twice as many as OB/GYN. Radiology departments had almost twice as many full-time faculty as departments of OB/GYN.

TABLE B-8: Full Time Faculty and Competing Applications, Selected Clinical Departments, 1980–1989

	Full Time Faculty 1988		Competing Applications 1980–1989	
Department	Number	Percent	Number	Percent
OB/GYN	2,265	7	2,667	6
Pediatrics	5,724	19	6,801	15
Radiology	3,884	13	3,325	7
Surgery	5,031	17	6,117	13
Medicine	13,448	44	27,238	59
Total	30,352	100	46,148	100

Departments of internal medicine submitted a disproportionately large number of applications (59 percent of the total with 44 percent of faculty). Applications from OB/GYN, pediatrics and surgery are roughly proportionate to their faculty size, and radiology is underrepresented relative to faculty size.*

OB/GYN departments had significantly lower success rate for the decade than internal medicine, pediatrics or radiology. While the success rate for surgery was also higher than OB/GYN the difference was not statistically significant (Table B-9). Data suggest that weakness in the success rates of OB/GYN departments became more acute in the second half of the decade.

* These comparisons are not exact since the number of faculty in 1988 is compared with applications to NIH for a decade.

TABLE B-9: Success Rates of Competing Applications from Selected Clinical Departments Overall and by Degree of Principal Investigator, 1980–1989

Department	Number of Applications	No. of Awards	Success Rate
All Applications			
OB/GYN	2,669	706	26.5%
Medicine	27,240	10,242	37.6*
Pediatrics	6,801	2,105	31.0*
Radiology	3,335	1,111	33.4*
Surgery	6,117	1,742	28.5
Total	46,148	15,866	34.4
M.D.			
OB/GYN	1,013	245	24.2%
Medicine	17,684	6,962	39.4*
Pediatrics	4,327	1,134	37.7*
Radiology	920	278	30.2*
Surgery	3,522	1,059	30.1*
Total	27,466	9,956	36.3
Ph.D.			
OB/GYN	1,473	416	28.2%
Medicine	7,126	2,428	34.1*
Pediatrics	1,794	478	26.7
Radiology	2,127	745	35.0*
Surgery	2,038	547	26.9
Total	14,558	4,614	31.7

* Significant at 95% confidence level when compared with OB/GYN

Degree of Principal Investigator

The pattern changes if we look at performance by degree of the principal investigator. Table B-10 displays the percentage of full time faculty that are M.D.s and the percentage of grant applications from their departments that they submitted. Most full time faculty have the M.D. degree (ranging from 72 percent in radiology to 81 percent in medicine). M.D.s in departments of internal medicine, pediatrics and surgery, submitted between 58 percent and 65 percent of applications from their departments, while only 28 percent of the applications from radiology and 38 percent of the applications from OB/GYN came from M.D.s. Internal medicine was the only department, at to show an increase in the percentage of applications by M.D.s between 1980 and 1989 decade. During that period M.D.s in OB/GYN had the lowest success rates and the fewest awards among the five departments. Internal medicine did significantly better that the other departments in every year while there was some annual variation among the other departments. OB/GYN was at or near the bottom in most years of the decade.

TABLE B-10: Percent of Total Faculty that are M.D.s Compared with Percentage of Grant Applications to NIH Submitted by M.D. s, Selected Clinical Departments, 1980–1989

Department	M.D.s as Percent of Full Time Faculty	M.D. Grant Applications as Percent of Department's Applications
OB/GYN	74	38
Pediatrics	79	64
Radiology	72	28
Surgery	80	58
Internal Med.	81	65

The picture with regard to applications submitted by Ph.D.s is different (Table B-9). Ph.D.s, in OB/GYN departments were more competitive than their M.D. colleagues in the department and their approval rate trailed only Ph.Ds in

medicine and radiology. Between 1980 and 1989, the number of applications from Ph.D.s and their approval rates increased in all five departments.

Investigator Initiated Research (RO1s)

The NIH supports a wide variety of research and research training activities. However, the core of NIH research support is the investigator initiated research grant, the RO1. The RO1 is intended "...to support a discrete, specific project in an area representing the insterests and competencies of the principal investigator." The majority of NIH awards are for RO1s—in 1989 they constituted 62 percent of all research grants. Of the five depots analyzed, departments of medicine submitted the largest number of RO1 applications, had the most approved and funded and had the highest success rates in the period 1980 to 1989 (Table B-11). The differences in success rates for the decade between OB/GYN and medicine and radiology were statistically significant. Again, applications for RO1s from OB/GYN departments declined in competitiveness during the later years of the decade.

TABLE B-11: Success Rates of RO1 Applications, Selected Clinical Departments, 1980–1989

Department	Number of Applications	No. of Awards	Success Rate
All Applications			
OB/GYN	1,954	458	23.4 %
Internal Medicine	16,336	5,145	31.5*
Pediatrics	4,369	1,106	25.3
Radiology	2,538	771	30.4*
Surgery	4,258	1,044	24.5
Total	29,455	8,524	28.9

Department	Number of Applications	No. of Awards	Success Rate
M.D.			
OB/GYN	628	112	17.8%
Internal Medicine	10,146	3,313	32.7*
Pediatrics	2,676	694	26.0*
Radiology	625	155	24.8*
Surgery	2,216	550	24.8*
Total	16,291	4,824	29.6
Ph.D.			
OB/GYN	1,190	314	26.4%
Internal Medicine	4,620	1,367	29.6*
Pediatrics	1,247	291	23.3
Radiology	1,682	556	33.1*
Surgery	1,645	416	25.3
Total	10,384	2,944	28.4

* Significant at 95% confidence level when compared with OB/GYN.

Most RO1s from departments of internal medicine and pediatrics were submitted by M.D.s, while in radiology and OB/GYN most RO1s were submitted by Ph.D.s. The situation in surgery was different. Between 1980 and 1989, 58 percent of RO1s were submitted by M.D.s. However, towards the end of the 1980s the percentage of applications from M.D.s fell, and, there was a modest increase in the percentage of applications submitted by Ph.D.s.

Between 1980 and 1989, OB/GYN departments experienced a comparatively low success rate (Table B-11)—the differences between OB/GYN and the other four departments were statistically significant. However, Ph.D.s from

departments of OB/GYN experienced a success rate in the middle of the five departments, significantly below internal medicine and radiology, and above pediatrics and surgery (not statistically significant). Data suggest a modest deterioration in the competitiveness of OB/GYN departments in the second half of the decade.

NIH SUPPORT FOR OB/GYN RESEARCH TRAINING

Fellowships and Institutional Training Awards

NIH has supported research training for many years and while the magnitude of such support has declined since the 1960s it is still a major focus of NIH effort. In FY 1989, funds for research training totaled $262 million, or 4.3 percent of the total extramural program. This compares with FY 1980 when funding totaled $182.8 million, or 6.6 percent of the extramural budget. Training support is in the form of fellowships which NIH awards directly to individuals, and training grants which NIH awards to institutions which in turn select individuals as trainees. In FY 1989, NIH directly and through training grants supported approximately 11,500 individuals in research training, slightly less than half at the post-doctoral level. Post-doctoral awards were divided between M.D.s, 2,582 (48 percent) and Ph.D.s 2,787 (52 percent). Over the decade (1980 to 1989) the number of M.D.s supported increased from 2,100 to nearly 2,600 per year while the number of Ph.D.s declined from 3,600 annually to 2,800.

Table B-12 provides information on training grant and fellowship applications from five clinical departments. The departments differed markedly in the degrees of their trainees and fellows. While between 1980 and 1989 three quarters of the applications from surgery and two thirds of those from medicine and pediatrics were submitted by M.D.s, in radiology only 35 percent and in OB/GYN only 28 percent were from M.D.s. There was little difference among the five departments in success rates for training (T and F) grants between 1980 and 1989, but because of the small numbers of applications and grants it is hard to draw conclusions.

TABLE B-12: Success Rates of Traineeships, Fellowships and Career Development Award Applications, Selected Clinical Departments, 1980-1989

	Trainees/Fellowships (T/F)			Career Development (K)		
Department	No. Applications	No. of Awards	Success Rate	No. Applications	No. of Awards	Success Rate
All Applications						
OB/GYN	194	84	43.3%	69	21	30.4%
Medicine	3,613	1,777	49.2	1,738	729	42.0
Pediatrics	671	265	39.5	445	177	39.8
Radiology	192	86	44.8	66	20	30.3
Surgery	564	207	36.7	200	66	33.0
Total	5,234	2,419	46.2	2,518	1,013	40.2
M.D.s						
OB/GYN	56	24	42.9%	52	18	34.6%
Medicine	2,316	1,001	43.2	1,412	620	43.9
Pediatrics	425	172	40.5	343	137	39.9
Radiology	68	28	41.2	43	12	27.9
Surgery	406	151	32.5	151	53	35.1
Total	3,271	1,376	40.4	2,001	840	42.0

In addition to research training, NIH supports the renewal of the biomedical research community through a number of career development programs. Total funding for these programs was $90 million in 1989, nearly double the 1980 level of $47.5 million. However, as a portion of the extramural budget, career development support fell from 1.7 percent in 1980 to 1.5 percent in 1989. In 1980 all career development awards were made to individuals; however, since 1984 a few institutional awards, each of which generally supports several individuals, have been made. Individual awards continue to predominate

absorbing over 90 percent of the funding to career development with roughly 1,200 awards per year. There were three institutional program awards in 1984. These increased to 21 during the last three years of the decade.

While the total number of researchers receiving career development awards has been relatively constant between 1980 and 1989, there has been a change in the mix of researchers. In 1980, 495 M.D.s and 736 Ph.D.s received individual career development awards. By 1989 the number of individual awards to M.D.s had risen to 873 and the number of awards to Ph.D.s had declined to 350. In addition in 1985 there were 9 institutional program grants which made multiple awards to physicians (there was no equivalent program for Ph.D.s). In 1989 12 institutional awards were made to support M.D.s.

Changes in the career development programs have occurred. The program of modified research career development awards (K04s), which supported the majority of Ph.D.s, was reduced. A major expansion of the program for clinical investigators designed to develop skills in clinical research (K08s) took place. Two new programs for physician scientists, K11 and K12 (one individual and one institutional) were created. These physician scientist awards, unlike the clinical investigator awards, are designed to support newly trained clinicians in the "development of independent research skills and experience in a fundamental science". For the institutional (program) awards this experience is to be developed "within the frame work of an interdisciplinary research and development program."

Applications from OB/GYN departments for career development awards experienced success rates comparable to the other four departments, but departments of OB/GYN submitted few applications (Table B-12). Between 1980 and 1989, OB/GYN departments moved from the lowest success rate of the five departments to the highest success rate, both overall and for M.D.s. Unlike training grants and fellowships, most career development award applications from all five departments were submitted by M.D.s—ranging from 65 percent in radiology to 81 percent in medicine, with OB/GYN, surgery and pediatrics having approximately three quarters of their applications from M.D.s.

Departments of OB/GYN averaged only two competitive career development awards per year between 1980 and 1989. Awards to M.D.s increased during the 1980s, while support of Ph.D.s decreased. The number of individuals supported in the last three years is larger than the number of awards because the NIH data system counts the K-12 award for the Reproductive Scientist Development Program (which supports three scientists) as a single recipient. The number of Modified Research Career Develop net Awards (K04s) declined during the decade while the number of Clinical Investigator Awards (K08s) and Physician Scientist Awards (K11) in departments of OB/GYN increased. Over

the past six years more than two thirds of the awards have been either K08s or K11 (in approximately equal numbers).

Number of Individuals in Departments of OB/GYN with NIH Training Support

It is difficult to determine the number of people in departments of OB/GYN whose research training has been helped by NIH support. While NIH codes data on the recipients of traineeships and fellowships on its records, and also has data on career development awards, those at NIH most familiar with these data files do not consider them to be reliable. However, by using several different files and source some approximate numbers can be generated: Physicians m OB/GYN departments received 18 competing career development awards between 1980 and 1989 (individuals normally receive support for two to four years). In addition to individual awards there was one institutional K award during the decade, thus roughly 20 OB/GYN M.D.s were supported by NIH career development awards. In addition, nine individual physicians in OB/GYN departments received National Research Service Fellowships directly from NIH and eight OB/GYN departments received training grants from NIH. While it is not possible to determine how many individual M.D.s received support under the institutional awards, it is generally believed that most of the programs were small. This, coupled with the fact that four of the eight institutional grants were made in FY 1988 for awards to begin in FY 1989, make it unlikely that more than 20 to 25 individuals received support under the training program during the decade of the 1980s. Adding together the career development "K" awards (seventeen individuals, one institutional award) and the research training awards (nine individual fellowships and eight training grants under the National Research Service Awards Program) it is likely that approximately fifty OB/GYNs received research training from NIH during the decade of the 1980s.

Beginning Research Awards

To help new biomedical researchers develop from working under a mentor to independence, NIH uses the R-29 grant, the First Independent Research Support and Transition (FIRST). These grants are designed "... to underwrite the first independent investigative efforts of an individual; to provide a reasonable opportunity to demonstrate creativity, productivity, and further promise and to help in the transition to traditional types of NIH research project

grants".[27] The grants are for 5 years, are not renewable, are limited to $350,000 in total and $100,000 in a single year.

The R-29 (FIRST grants) replaced similar R-23 grants in the mid 1980s, therefore departmental comparisons below include both types of awards. In 1989, 1,711 R-29 awards were made in the amount of approximately $152 million. This represents an increase from 0.8 percent of the NIH extramural research budget in 1980 ($20 million) to 2.7 percent in 1989.

Like several other grant mechanisms, OB/GYN and radiology made little use of R-23 and R-29 grants between 1980 and 1989. OB/GYN submitted few applications and had low success rates, which declined during the second five years of the decade. OB/GYN had the lowest success rate of the five departments for both the periods, 1980–1984 and 1985–1989 (Table B-13). The number of applications from M.D.s, presents a similar picture to that for traineeships and fellowships, although it is not as extreme. Over half of the R23/R29 grants from departments of pediatrics, medicine and surgery came from M.D.s, while only 31 percent of those from OB/GYN departments and 13 percent of those from radiology were from M.D.s. M.D.s from OB/GYN had success rates significantly lower than any of the comparison departments.

Institutional Grants

In addition to individual awards, NIH supports larger multi-project research efforts. The two most important are program projects (P01s) and research centers, a generic term which includes a number of different types of centers-specialized, core, comprehensive, animal, and general clinical research centers.

Program project grants (PO1s) are broad-based, long term multidisciplinary research activities organized around a basic theme. The individual sub-parts or components '...must have scientific merit and essential elements of unity and interdependence that constitute a system of research activities and projects directed toward the overall goal of the program". These grants involve large numbers of researchers and in addition to supporting the interrelated research projects can also support both basic resources and clinical components used by the overall group. The number of program project grants awarded and funding rose in the past decade. The number of awards increased from 535 to 793 and funding increased from $297.5 million to $683 million. While few in number, compared for example to RO1s, they are the second largest grant in terms of funding.

TABLE B-13: Success Rates of R23 and R29 Applications, Selected Clinical Departments, 1980–1989

Department	Number of Applications	No. of Awards	Success Rate
All Applications			
OB/GYN	165	29	17.6%
Medicine	1,909	652	34.2*
Pediatrics	607	189	31.1*
Radiology	181	68	37.6*
Surgery	411	122	29.7*
Total	3,273	1,060	32.4
M.D.s			
OB/GYN	51	4	7.8%
Medicine	1,024	345	33.7*
Pediatrics	344	114	33.1*
Radiology	23	7	30.4*
Surgery	213	60	28.2*
Total	1,655	530	32.0

* Significant at 95 % confidence level when compared with OB/GYN.

Between 1980 and 1989 OB/GYN departments were relatively successful in the competition for program project grants (P01), with success rates failing approximately in the middle of the five comparison departments (Table B-14). The number of applications from each department is small and none of the differences between OB/GYN and the other four departments is statistically significant. With the exception of an increase in the number of applications from departments of medicine there are no discernable trends over the decade. In fact the most significant fact about OB/GYN performance with regard to P01s is the small number of applications—on average less than 3 per year and a total for the decade of only 28. This is only a quarter of the number submitted by

radiology, the department with the next fewest applications. Since program project grants are only awarded to institutions with developed research programs, the small amber of applications may indicate that few OB/GYN departments believe they have the research programs that would allow them to compete successfully.

Research center grants together are the third largest grant activity in terms of dollars awarded. While there are 10 different types of center grants, the two largest are the specialized (P50) and the core (P30) which between them accounted for approximately 60 percent of the number and 57 percent of the dollars for center grants in 1989. The core grants (P30s) are designed to provide "... shared resources and facilities for categorical research by a number of investigators from different disciplines who provide a multidisciplinary approach to a joint research effort or from the same discipline who focus on a common research problem".[28] Specialized centers (P50s), on the other hand, not only provide supportive ancillary activities but also provide support for an overall set of research activities to mount "... a multidisciplinary attack on a specific disease entity or biomedical problem area.[29] These latter grants are similar to program project grants except that awards are usually based on specific announcements from an NIH institute or division and are more closely monitored by NIH. The number of new center grants NIH can award is limited by Congress which also earmarks some specific center programs to receive awards. In some years in the 1980s, congressional floors on the number of RO1s reduced the number of center grants made by NIH.

OB/GYN departments were competitive for P30 and P50 grants, having had the highest success rate of any of the five departments between 1980 and 1989. However OB/GYN departments submitted on average only three applications per year (Table B-14). Of the five departments only departments of medicine made major use of center grants, submitting 71 percent of applications during the decade. Like program project grants (P01s) center grants are difficult to obtain. In general such grants go only to institutions with a successful research track record.

TABLE B-14: Success Rates of Program Project and Center Grant Applications, Selected Clinical Departments, 1980–1989

Department	Number of Applications	No. of Awards	Success Rate
PO1s			
OB/GYN	28	13	46.4%
Medicine	646	336	52.0
Pediatrics	121	57	47.1
Radiology	100	47	47.0
Surgery	140	65	46.4
Total	1,035	518	50.0
P30s – P50s			
OB/GYN	33	24	72.7%
Medicine	601	334	55.6
Pediatrics	111	54	48.6
Radiology	9	5	55.5
Surgery	90	47	52.2
Total	844	464	55.0

SUMMARY OF NIH SUPPORT OF DEPARTMENTS OF OB/GYN

The previous sections presented information on NIH support of OB/GYN department research and research training activities. In this section the main points are summarized.

On the positive side, between 1980 and 1989 the increase in funding of OB/GYN departments exceeded the NIH increase in funding of all clinical departments. The percentage of NIH support to medical schools received by OB/GYN departments remained relatively constant since the late 1960s, at about 1.5 percent of the total. However, by one measure OB/GYN wins less

than its share of funding—with about 4.8 percent of full-time faculty in clinical departments of medical schools OB/GYN receives only about 2.7 percent of the funds awarded by NIH/ADAMHA to clinical departments.

While there is no evidence that the ability of OB/GYN departments to compete for NIH support seriously deteriorated between 1980 and 1989, there is a reason to be concerned about several aspects including the low level of NIH funding compared to some other departments, and the competitive state of physician investigators in OB/GYN department.

NICHD has been, and continues to be, the major supporter of OB/GYN departments, providing nearly 70 percent of NIH funds to the departments in 1989. NCI is the second largest supporter, however, its contribution declined from approximately 30 percent in 1978 to less than 10 percent in 1989. No other institute provides as much as 5 percent of the total funding for OB/GYN departments.

The total number of NIH awards to departments of OB/GYN varied from year to year between 1980 and 1989, but was slightly higher in 1989 than in 1980. The increase was in research grants (primarily RO1s), and a slight decline occurred in the number of traineeships, fellowships and research contracts awarded. The number of OB/GYN departments receiving NIH awards in any one year ranged from a high of 72 (in 1984) to a low of 67 (in 1989).

It is important to remember that while the mix of M.D.s to Ph.D.s was similar in the five departments we analyzed, the mix of grant applications was not. M.D.s in the departments of internal medicine, pediatrics and surgery submitted between 58 percent and 65 percent of the departments' grant applications, and the proportion increased through the 1980s. M.D.s in departments of radiology submitted 28 percent, and those in departments of OB/GYN submitted 38 percent. M.D.s from departments OB/GYN and radiology had the fewest applications of the five departments, and for the decade OB/GYN departments had the lowest success rate. Ph.D.s from OB/GYN departments fared better, with a success rate that put them in the middle of the five departments analyzed.

The picture with regard to RO1s is similar. Between 1980 and 1989, applications from OB/GYN departments had the lowest success rates (the differences in success rates between departments of OB/GYN and internal medicine and radiology were statistically significant). The success rate of RO1 applications submitted by M.D.s from OB/GYN departments were significantly lower than submissions by M.D.s in the four other departments. Ph.D.s in OB/GYN departments had a success rate below that of internal medicine and radiology and above that of pediatrics and surgery. The differences between Ph.D.s from departments of OB/GYN and Ph.D.s from departments of internal

medicine and radiology were statistically significant. The competitive position of the Ph.Ds from OB/GYN declined during the later years of the decade.

OB/GYN departments were more successful in obtaining training grants and fellowships. While none of the differences are statistically significant, OB/GYN was the most successful of the five departments with regard to awards for training grants to M.D.s during the period 1980–1984. The success rate declined during the second 5 years of the decade both absolutely and relative to the other departments. A smaller percentage of the trainees in OB/GYN and radiology are M.D.s, compared with internal medicine, surgery, or pediatrics.

The success rate of OB/GYN departments in winning career development awards improved during the second half of the decade rising from the lowest to the highest success rate among the five departments analyzed. This pattern holds both for all career development awards and for those going to M.D.s. However OB/GYN department M.D.s only submitted a total of 52 applications for career development awards in the 1980s.

Both M.D.s and Ph.D.s from OB/GYN departments have been relatively unsuccessful in obtaining R-29 (FIRST) awards. Moreover, M.D.s submitted few applications (51 from departments of OB/GYN compared with 1,024 from departments of internal medicine).

By contrast OB/GYN departments have been relatively successful in obtaining both program-project grants and center grants but submitted few such applications—on average three program-projects and three center grant applications a year between 1980 and 1989. This dearth of applications may reflect both the amount of effort required to develop these applications and the fact that NIH staff will, on occasion, discourage applications from clearly noncompetitive institutions.

NIH ADMINISTRATION AND STRUCTURE

Two kinds of problems effect NIH support of research in departments of OB/GYN. One pertains to research grants submitted by M.D.s, particularly RO1s and R29s, which have a relatively low success rate. The second relates to program-project grants, center grants, career development grants, and to some degree fellowships, for which the problem is not success in obtaining funding but rather the fact that M.D.s from OB/GYN departments submit very few applications.

This review is not able to determine the reasons for the low success rates and, in some programs, low application rates. The causes could be quality of

the research being proposed, the substance of the research (reproductive research and research into issues concerning women's health) or the nature of the review and the composition of the review committees. Most RO1s are reviewed in the individual study sections of the Division of Research Grants. A few RO1s, usually in response to specific announcements, may be reviewed by groups set up by the supporting institute. Of more than 50 members of the four initial review groups which together review approximately 50 percent of the applications submitted by OB/GYN departments only three list OB/GYN as a primary area of expertise and only four others listed another clinical area.

This review of data pertaining to applications for funding from departments of OB/GYN does not shed light on the concern that there are characteristics of NIH that create barriers to adequate funding of OB/GYN research and women's health issues in general. These characteristics include:

- A paucity of women at high levels in NIH.
- The lack of a women's (or OB/GYN focused) institute.
- Lack of an OB/GYN intramural program.
- The pediatric orientation of NICHD's leadership.

Moreover, the budgets of the two institutes that are the major funders of OB/GYN research have not grown as fast as the total NIH budget. For 8 of the 10 years between 1980–1989, NICHD had award rates for research grants below the NIH average. In 1989, 12 of the 14 institutes and other awarding units had award rates higher than NICHD. While the impact of these factors on the funding of OB/GYN is impossible to quantify, conversations with NIH staff and others indicate that some could be important.

The question of why there is no OB/GYN intramural program at NIH has been asked for some years—the answers most often heard are that obstetric patient accrual would be difficult, the range of ancillary services needed would be hard to support and OB/GYNs will not work for low federal pay. While its not clear if, or how, the lack of intramural OB/GYN affects extramural OB/GYN research, some people claim that it leads to a lack of internal advocates for OB/GYN and that NIH staff dealing with OB/GYN grants feel isolated. Moreover, since the OB/GYN research community is the NIH "client" contact between NIH staff and the investigators cannot achieve the informal collegial relationship needed to generate creative thinking and ongoing excitement about the discipline. However, as a result of Congressional pressure, NICHD is planning to establish an intramural gynecological research section on campus. They are recruiting for an individual certified in gynecology to head the research program, direct its clinical consultative service and its

endocrinology fellowship program. NCI has also indicated a willingness to meet with leaders in academic gynecology to discuss the possibility of establishing a gynecology branch as well as increasing support for research in gynecological oncology.

Whether it would be helpful for OB/GYN or women's health to have an institute devoted to the discipline is debatable. It is argued that relying on an institute whose primary mission is children and development relegates OB/GYN to a secondary position. This is reinforce by the tradition of having a pediatrician direct the institute. Moreover, there is a lack of visibility and organizational identification that might attract the attention of Congress to issues in OB/GYN, and allow an NIH intramural constituency to systematically develop programs. On the other hand, it is argued that a women's or OB/GYN institute would relieve the existing funders (NICHD, NCI, NIA, etc.) of the obligation to pursue OB/GYN questions, and would create a "ghetto" for OB/GYN and women's issues. In the light of ongoing developments concerning issues in women's health, such as the establishment of the Office of Research on Women's Health, and with NIH in the process of generating a research agenda for women's health, there may exist now an impetus at NIH that will allow OB/GYN and other women's health research to flourish.

Actions and Further Analysis Needed to Improve NIH Support of OB/GYN Research

1. Study is needed to examine charges that clinical research does not receive a fair scientific review at NIH.
2. The charters of the study sections that review the majority of OB/GYN applications, their composition and the applications reviewed should be analyzed to determine whether there are problems with the composition of membership.
3. OB/GYN academic leaders should review the career development award (Ks) and the FIRST grants (R29) to determine if there axe features of the programs that are discouraging OB/GYN participation. If such features axe found, they should meet with appropriate NIH leaders to encourage necessary changes. NIH institutes have a great range of options in how programs are structured and which mechanisms are used.
4. It is appropriate that representatives of gynecological oncology continue to meet with NCI leadership given the institutes's decreasing support for OB/GYN research over the past decade. Given the range of women's health issues that axe the responsibility of NIA and its relatively low level of support

for OB/GYN research, it might also be appropriate for OB/GYN leaders to meet with representatives of that institute.

The creation of the Office of Research on Women's Health is a positive step, and the office can play an important role as a coordinator, advocate and honest broker. It will also play a role in creating a research agenda and in monitoring the responsiveness of NIH to women's health needs. However, the major strength of NIH is in its individual institutes and increased support for OB/GYN can only come from increased awareness and support from the individual institutes.

REFERENCES

1. National Institutes of Health. *NIH Data Book, 1990* . NIH Publication No. 90–1261. September. Bethesda, Maryland.
2. Association of American Medical Colleges. 1988–1989. U.S. Medical School Finance Section for Operation Studies, July 1990. Washington, D.C.: Association of American Medical Colleges.
3. National Institutes of Health. NIH. Data Book 1990.
4. Sherman, Barry, and Myron Genel. 1983. Human Investigation in the 1980s: Themes from the Scottsdale Conference, *Clinical Research* 31:570–571 .
5. Avis, Frederick P., Ellenberg, S. and Friedman, M. 1988. Surgical Oncology Research. *Annals of Surgery* . 207(3) 262–268 .
6. Sherman, Barry. 1988. Position Paper Prepared for Institute of Medicine Committee. Resources for Clinical Investigation.
7. Personal Interview, 1990.
8. Health Policy and Biomedical Research News of the Week. 1990. "Blue Sheet", Vol. 33 , No.50. December 17.
9. Cuca, J. A. 1990. Scientific, Social and Other Factors in the Evaluation of Applications for NIH Research Grants. Ph.D. Dissertation. The Catholic University of America, Washington, D.C.
10. National Institutes of Health. 1986. Peer Review Trends 1976–1985. Division of Research Grants. Bethesda, Maryland.
11. National Institutes of Health. 1990. Extramural Trends. FY 1980–1989. Division of Research Grants. Bethesda, Maryland.
12. Arias, I.M. 1989. Training Basic Scientists to Bridge the Gap Between Basic Science and Its Application to Human Disease. *New England Journal of Medicine* , 321:972–974 .
13. Healy, B. H. 1988. Innovators for the 21st Century: Will we Face a Crisis in Biomedical Research Brainpower. NEJM. 319:1058–1064 .
14. Healy, B. H. 1989. The Human Factor at the Endless Frontier. Circulation. 79:959–965 .
15. Kelley, W. N. 1985. Personnel Needs for Clinical Research: Role of the Clinical Investigator. Clinical Research 33:100–104 .
16. Kelley, W. N. 1988. Are We About to Enter the Golden Era of Clinical Investigation? Journal of Laboratory and Clinical Medicine 111(4):365–370 .

17. Wyngaarden, J. 1981. The Clinical Investigator as an Endangered Species. Bull New York Academic Medicine. 57(6):415–426 .
18. Smith, Lloyd H. Jr. 1989. Training of Physician Scientists. Background Paper for National Research Council, Committee on Biomedical and Behavioral Personnel. Washington, D.C. National Academy Press.
19. Institute of Medicine. 1989. Research Capabilities of Academic Departments of Obstetrics and Gynecology: Report of a planning Committee. Washington, D.C.
20. National Institutes of Health. 1988. Peer Review Trends. 1976–1985. Division of Research Grants. Bethesda, Maryland.
21. Avis, Fredrick P., Ellenberg, S. and Friedman, M. 1988. Surgical Oncology Research. *Annals of Surgery* . 207(3) 262–268 .
22. Association of American Medical Colleges. 1989. Distribution of Full Time Faculty at U.S. Medical Schools who are Principal Investigators by Department. A series of tables prepared for the National Institutes of Health. Washington, D.C.
23. Pearse, Warren H., et al. 1986. Obstetric and Gynecological Manpower. *Obstetrics and Gynecology* . Vol. 70 , No.3. Part 1. September, 1987.
24. Pearse, Warren H., et.al. Trends in Obstetric and Gynecological Academic Manpower and Research 1977–1990. (In press 1991)
25. Gentile, Nancy O., et.al. 1987. Research Activity of Full Tune Faculty in Departments of Medicine. Washington, D.C. Association of Professors of Medicine and Association of American Medical Colleges.
26. Kretchmer, Norman. 1980. The Support of Academic Obstetrics: The Public Sector in the Current Status and Future of Academic Obstetrics. Edited by John Bowers and Elizabeth Purcell. 1980. New York, NY: Josiah Macy, Jr. Foundation.
27. Association of American Medical Colleges. U.S. Medical School Finance 1988–1989. Section for Operational Studies, July 1990. Washington, D.C.: Association of American Medical Colleges.
28. National Institutes of Health. 1989. Orientation Handbook for Members of Scientific Review Group. Division of Research Grants. Bethesda, Maryland.
29. National Institutes of Health. 1989. Activity Codes, Organizational Codes, and Definitions Used in Extramural Programs. Division of Research Grants. Bethesda, Maryland.

APPENDIX C

BACKGROUND PAPERS FOR THE RESEARCH AGENDA

Ovarian Control and Follicular Development
Eli Y. Adashi, M.D.
Department of Obstetrics and Gynecology
Division of Reproductive Endocrinology
School of Medicine
University of Maryland at Baltimore
Baltimore, Maryland
The Corpus Luteum
Frederick J. Auletta, Ph.D.
Departments of Obstetrics & Gynecology and Biochemistry
The University of Vermont College of Medicine
Burlington, Vermont
Gynecologic Oncology
Vicki V. Baker, M.D.
Department of Obstetrics & Gynecology
College of Medicine
University of Cincinnati Medical Center
Cincinnati, Ohio

Micromanipulation: Clinical and Basic Research
Jon W. Gordon, M.D., Ph.D.
Department of Obstetrics & Gynecology and Reproductive Science
Mt. Sinai Medical Center
New York, New York

Ovarian Function
Robert D. Koos, Ph.D.
Department of Physiology
School of Medicine
University of Maryland at Baltimore
Baltimore, Maryland

Aging and Menopause
Veronica A. Ravnikar, M.D.
Department of Gynecology
Massachusetts General Hospital
Boston, Massachusetts

Implantation, Placentation, and Placental Function
Jerome F. Strauss, III, M.D., Ph.D.
Department of Obstetrics and Gynecology
Division of Reproductive Biology
University of Pennsylvania Medical Center
Philadelphia, Pennsylvania

In Vitro Fertilization, Male Infertility, Endometriosis, and Epidemiology

Gordon C. Wolf., Ph.D., M.D.
Department of Obstetrics and Gynecology
Division of Reproductive Endocrinology
The University of New Mexico School of Medicine
Albuquerque, New Mexico

Sexually Transmitted Diseases

Richard L. Sweet, M.D.
Department of Obstetrics and Gynecology and Reproductive Sciences
University of Pittsburgh
Pittsburgh, Pennsylvania
Judith N. Wasserheit, M.D.
Sexually Transmitted Disease Branch
National Institutes of Allergy and Infectious Diseases
Bethesda, Maryland