Modern Trends in Infertility and Conception Control

VOLUME 4

Edited by:
Edward E. Wallach
Roger D. Kempers

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Edward E. Wallach, M.D.
Professor and Chairman
Department of Gynecology and Obstetrics
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Roger D. Kempers, M.D.
Professor of Obstetrics and Gynecology
Mayo Medical School
Consultant, Department of Obstetrics and Gynecology
Mayo Clinic
Rochester, Minnesota

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Sponsoring Editor: Nancy E. Chorpenning
Assistant Director, Manuscript Services: Frances M. Perveiler
Production Project Manager: Nancy C. Baker
Proofroom Supervisor: Shirley E. Taylor

Contributors

Nancy J. Alexander, Ph.D.
Professor, Obstetrics and Gynecology
Director, Applied Fundamental Research, CONRAD
Section of Reproductive Immunology
Department of Obstetrics and Gynecology
Eastern Virginia Medical School
Norfolk, Virginia

Nancy C. Allen, M.D.
Resident, Obstetrics and Gynecology
University of Tennessee
Memphis, Tennessee

Deborah J. Anderson, Ph.D.
Fearing Research Laboratory
Department of Obstetrics and Gynecology
Harvard Medical School
Boston, Massachusetts

Ricardo H. Asch, M.D.
Professor, Obstetrics and Gynecology
University of California, Irvine
Irvine, California

Bruce G. Bateman, M.D.
Associate Professor, Obstetrics and Gynecology
University of Virginia School of Medicine
Charlottesville, Virginia

Alan E. Beer, M.D.
Professor of Obstetrics and Gynecology and Microbiology and Immunology
University of Michigan Medical Center
Ann Arbor, Michigan

Richard E. Blackwell, Ph.D., M.D.
Professor, Obstetrics and Gynecology, Physiology and Biophysics
Director of the Division of Reproductive Biology and Endocrinology
Department of Obstetrics and Gynecology
University of Alabama at Birmingham Medical Center
Birmingham, Alabama

Beverly L. Brodie, M.D., F.R.C.S.C.
Fellow, Center for Fertility and Reproductive Research
Department of Obstetrics and Gynecology
Vanderbilt University Medical Center
Nashville, Tennessee

Robert G. Castadot, M.D., M.P.H.
Population and Public Health Specialist
World Bank
Washington, D.C.

Elizabeth B. Connell, M.D.
Professor, Department of Gynecology and Obstetrics
Department of Gynecology and Obstetrics
Emory University School of Medicine
Atlanta, Georgia

Marian D. Damewood, M.D.
Assistant Professor, Gynecology and Obstetrics
Director, IVF Program
Department of Gynecology and Obstetrics
The Johns Hopkins Hospital
Baltimore, Maryland

James F. Daniell, M.D.
Clinical Associate Professor, Obstetrics and Gynecology
Vanderbilt University
Private Practitioner
The Woman's Health Group
Nashville, Tennessee

Alan H. DeCherney, M.D.
John Slade Ely Professor of Obstetrics and Gynecology
Department of Obstetrics and Gynecology
Yale University School of Medicine
New Haven, Connecticut

Michael P. Diamond, M.D.
Assistant Professor, Obstetrics and Gynecology
Mellon Fellow, Reproductive Sciences
Department of Obstetrics and Gynecology
Yale University School of Medicine
New Haven, Connecticut

Paul R. Gindoff, M.D.
Assistant Professor, Department of Reproductive Endocrinology
Department of Obstetrics and Gynecology
Division of Reproductive Endocrinology
George Washington University
Washington, D.C.

Ruth M. Greenblatt, M.D.
Robert Wood Johnson Clinical Scholar
Assistant Clinical Professor, Medicine
Department of Medicine
Division of Infectious Diseases
University of California
San Francisco, California

Louise B. Grochow, M.D.
Assistant Professor, Oncology and Medicine
Department of Medicine
Division of Oncology
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Gilbert G. Haas, Jr., M.D.
Associate Professor and Chief
Section of Reproductive Endocrinology and Infertility
Department of Obstetrics and Gynecology
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma

Jouko Halme, M.D., Ph.D.
Associate Professor
Department of Obstetrics and Gynecology
UCLA School of Medicine
Los Angeles, California

H. Hunter Handsfield, M.D.
Associate Professor of Medicine
Department of Medicine
Division of Infectious Diseases
Harborview Medical Center
University of Washington
Seattle, Washington

Carl M. Herbert III, M.D.
Assistant Professor
Center for Fertility and Reproductive Research (C-FARR)
Division of Reproductive Endocrinology
Department of Obstetrics and Gynecology
Vanderbilt University School of Medicine
Nashville, Tennessee

King K. Holmes, M.D., Ph.D.
Professor and Vice-Chairman
Department of Medicine
University of Washington
Seattle-King County Department of Public Health
Seattle, Washington

George R. Huggins, M.D.
Associate Professor and Chairman, Department of Obstetrics and Gynecology
Francis Scott Key Medical Center
The Johns Hopkins School of Medicine
Baltimore, Maryland

Jaroslav Hulka, M.D.
Professor, Department of Obstetrics and Gynecology
The University of North Carolina
Chapel Hill, North Carolina

Raphael Jewelewicz, M.D.
Associate Professor and Director
Division of Reproductive Endocrinology
Department of Obstetrics and Gynecology
College of Physicians and Surgeons
Columbia University
New York, New York

Elton Kessel, M.D., M.P.H.
Consultant, International Federation for Family Health
Chapel Hill, North Carolina

James D. Kitchin III, M.D.
Professor, Obstetrics and Gynecology
University of Virginia School of Medicine
Charlottesville, Virginia

Gad Lavy, M.D.
Assistant Professor
Department of Obstetrics and Gynecology
Division of Reproductive Endocrinology
Yale University School of Medicine
New Haven, Connecticut

Patricia P. Mahlstedt, Ed.D.
Clinical Instructor
Department of Obstetrics and Gynecology
Baylor College of Medicine
Houston, Texas

Wayne S. Maxson, M.D.
Assistant Professor
Center for Fertility and Reproductive Research (C-FARR)
Division of Reproductive Endocrinology
Department of Obstetrics and Gynecology
Vanderbilt University
Nashville, Tennessee

Stephen D. Mumford, Dr.P.H., M.P.H.
President, Center for Research on Population and Security
Research Triangle Park, North Carolina

Ana Alvarez Murphy, M.D.
Assistant Professor
Department of Reproductive Medicine
University of California
San Diego UCSD Medical Center
San Diego, California

Wallace C. Nunley, Jr., M.D.
Department of Obstetrics and Gynecology
University of Virginia Hospital
Charlottesville, Virginia

David L. Olive, M.D.
Assistant Professor
Department of Obstetrics and Gynecology
The University of Texas Health Science Center at San Antonio
San Antonio, Texas

Alik Peretz, M.D.
Clinical Assistant Professor
Department of Obstetrics and Gynecology
Rambam Medical Center
Haifa, Bat-Galim, Israel

William G. M. Ritchie, M.D.
Clinical Associate Professor
Department of Radiology
University of Pennsylvania School of Medicine
Pennsylvania Hospital
Philadelphia, Pennsylvania

John A. Robertson
Baker and Botts Professor of Law
School of Law
The University of Texas at Austin
Austin, Texas

John A. Rock, M.D.
Director of Reproductive Endocrinology
Division of Reproductive Endocrinology and Infertility
The Johns Hopkins Hospital
Baltimore, Maryland

B. Jane Rogers, Ph.D.
Associate Professor
Center for Fertility and Reproductive Research (C-FARR)
Director, Semenology Laboratory
Division of Reproductive Endocrinology
Department of Obstetrics and Gynecology
Vanderbilt University School of Medicine
Nashville, Tennessee

Allen W. Root, M.D.
Professor of Pediatrics and Biochemistry
Department of Pediatrics
University of South Florida College of Medicine
Tampa, Florida
All Children's Hospital St. Petersburg
St. Petersburg, Florida

Michael J. Rosenberg, M.D., M.P.H.
Director, Reproductive Epidemiology Division
Reproductive Epidemiology
Family Health International
Research Triangle Park, North Carolina

Zev Rosenwaks, M.D.
Director, Jones Institute for Reproductive Medicine
Professor, Department of Obstetrics and Gynecology
Eastern Virginia Medical School
Norfolk, Virginia

Benjamin P. Sachs, M.D., D.P.H.
Director, Maternal and Fetal Medicine
Division of Maternal and Fetal Medicine
Department of Obstetrics and Gynecology
Harvard Medical School
Beth Israel Hospital
Boston, Massachusetts

Merlin H. Sayers, M.D., Ph.D.
Assistant Professor, Medicine
University of Washington
Puget Sound Blood Center
Seattle, Washington

William D. Schlaff, M.D.
Assistant Professor
Gynecology and Obstetrics
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Cecilia L. Schmidt, M.D.
Director, Reproductive Endocrinology/Infertility
Department of Obstetrics and Gynecology
University of Medicine and Dentistry of New Jersey
New Jersey Medical School
Newark, New Jersey

Anthony R. Scialli, M.D.
Director, Reproductive Toxicology Center
Assistant Professor
Department of Obstetrics and Gynecology
Georgetown University School of Medicine
Reproductive Toxicology Center
Columbia Hospital for Women Medical Center
Washington, D.C.

Sander S. Shapiro, M.D.
Associate Professor
Department of Obstetrics and Gynecology
Division of Reproductive Endocrinology
University of Wisconsin
University Hospital
Madison, Wisconsin

Dorothy I. Shulman, M.D.
Assistant Professor of Pediatrics
Department of Pediatrics
University of South Florida College of Medicine
Tampa, Florida
All Children's Hospital
St. Petersburg, Florida

Alvin M. Siegler, M.D., D.Sc.
Clinical Professor
State University of New York Health Sciences Center
Brooklyn, New York

Joe Leigh Simpson, M.D.
Professor and Chairman
Department of Obstetrics and Gynecology
University of Tennessee
Memphis, Tennessee

Carol Grace Smith, Ph.D.
Associate Professor
Department of Obstetrics and Gynecology
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Robert J. Stillman, M.D.
Associate Professor
Director of the Division of Reproductive Endocrinology and Fertility
Department of Obstetrics and Gynecology
George Washington University School of Medicine
Washington, D.C.

Marianne Styler, M.D.
Assistant Professor
Department of Obstetrics and Gynecology
Academic Health Science Center
New Brunswick, New Jersey

Craig H. Syrop, M.D.
Assistant Professor
Obstetrics and Gynecology
Division of Reproductive Endocrinology and Fertility
University of Iowa Hospitals and Clinics
Iowa City, Iowa

Howard J. Tatum, M.D., Ph.D.
Professor, Department of Gynecology and Obstetrics
Emory University School of Medicine
Atlanta, Georgia

Alan Trounson, Ph.D.
Centre for Early Human Development
Monash University
Queen Victoria Medical Center
Melbourne, Australia

Anne Colston Wentz, M.D.
Professor, Obstetrics and Gynecology
Director, Division of Reproductive Endocrinology
Center for Fertility and Reproductive Research (C-FARR)
Department of Obstetrics and Gynecology
Vanderbilt University School of Medicine
Nashville, Tennessee

Howard A. Zacur, M.D., Ph.D.
Associate Professor
Department of Gynecology and Obstetrics
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Luciano Zamboni, M.D.
Professor and Chairman, Department of Pathology
University of California
Los Angeles County Harbor-UCLA Medical Center
Torrance, California

Jaime Zipper, M.D.
Hospital Sotero del Rio
Puente Alto, Chile

Peter K. Zucker, M.D.
Assistant Professor
Obstetrics and Gynecology
Department of Gynecology and Obstetrics
The Johns Hopkins School of Medicine
Baltimore, Maryland

Preface

When the *Modern Trends* section of *Fertility & Sterility* was first established in December 1975, the purpose was to provide monthly reviews of contemporary subject matter provided by recognized authorities. The approach was immediately successful. The section was widely read from the outset and the material was often cited as reference sources. When the suggestion was initially made to amalgamate the first 36 contributions into a book, the idea was considered with skepticism. Yet, once the book was published, the response was once again strongly positive. The attraction of the book was that it served as a composite compendium containing up-to-date material of practical value arranged into sections and indexed. This arrangement of material appeals to the requirements of the practicing physician needing a ready reference to meet clinical situations with expert advice from the authoritative sources. This type of text appeals also to house officers and fellows during their ongoing process of acquainting themselves with the literature. At the same time, the comprehensive format has provided a solid resource for the academician in preparing teaching materials.

From the editor's standpoint the mission has been enjoyable. Over a 12-year period, we have reviewed a large number of manuscripts of the highest quality and have become acquainted with many outstanding leaders in the field of reproduction. That the original text was successful enough to re-enact the publication process three times in 12 years represents an achievement in itself, and provides a sense of permanence to the concept of the *Modern Trends* text.

This text is comprised of the 36 *Modern Trends* selections from *Fertility & Sterility* appearing between 1984 and 1987. The text can be viewed as representing 3 years of progress and achievement in diagnostic procedures and in therapeutic measures. The rapid growth of in vitro fertilization and related technology makes this volume contrast vividly with the first volume of *Modern Trends* published in 1979, in which in vitro fertilization had only just been clinically proved, sonography was in its infancy, and lasers had not yet been applied to infertility surgery. In addition, environmental aspects of reproduction are now highlighted as never before. We've come a long way since *Modern Trends* was established. Scanning the contents of each of the four volumes of *Modern Trends* serially creates a feeling of humility as one advance in our field eclipses the last. Volume 4 readily falls into seven sections: General Aspects of Reproduction; Reproductive Endocrinology; Developmental Abnormalities and Reproductive Potential; Female Reproductive Tract Surgery; In Vitro Fertilization; Male Infertility; and Contraception and Sterilization. Each section is preceded by an introduction that synthesizes the material encompassed by that section.

No textbook can be developed without significant input from various sources. All of the authors need to be acknowledged once again not only for

their contributions, but also for meeting deadlines and being flexible enough to make requested revisions. My co-editor, Roger Kempers, continues to reflect the finest qualities of journal editorship. Herbert Thomas, Executive Director of The American Fertility Society, needs to be acknowledged for having given the original impetus for a text. The understanding and support of Marcia Kempers and Joanne Wallach, as their husbands toiled away, contributed significantly to this project.

Carol Olson, Maria Esquela, and Lorraine Tamberino spurred on the editorial process with their secretarial and administrative talents. Nancy Chorpenning and the staff at Year Book Medical Publishers, Inc., were always there with their technical assistance. Finally, Volume 4 of *Modern Trends* is dedicated to our readers, who have encouraged us and provided the incentive for us to continue to prepare the monthly article for the *Fertility & Sterility* section and this book at 3-year intervals. The editors salute all of the above for their roles in making this text possible.

Edward E. Wallach, M.D.

Contents

SECTION I

General Aspects of Reproduction

In 1986 a record 125.8 million Americans, approximately 69% of the working age population, held full-time or part-time jobs. Of particular significance is the statistic that 57 million women were included in this work force. The trends indicate that this number will continue to rise. Many of yesterday's housewives are today's doctors, lawyers, teachers, secretaries, executives, computer programmers, reporters, and editors. Between 1960 and 1987, the percentage of women in the work place rose from 35.7% to 55.8%. In today's society with an increasing number of delayed marriages, employment-related stress, high divorce rate, and serious consideration of single parenthood, the implications for reproductive performance among American women are changing rapidly.

Oral contraceptives and intrauterine devices (IUD) were introduced in the United States during the early 1960s. Along with these new technologies developed specifically for prevention of fertility, we've experienced an increase in sexual freedom, deferment of both marriage and childbearing to an older age, and a prominent role for women in the work force. These sociologic changes in today's society, among others, have had a profound influence on the demographic pattern of reproduction. Entrance of the "baby boom" segment of our population (1942 to 1961) into the reproductive age together with their postponement of childbearing has changed the first-birth rate of women 30 to 35 years of age. In this group of women with at least 4 years of college education, the first-birth rate will have increased from 19.11/1000 in 1970 to 39.6/1000 by the end of this decade. In 1985 the number of births in the United States increased to almost 3.75 million with fewer deliveries of women in the 20 to 25 age range and more deliveries among women aged 30 to 35 years.[1] The implications of these figures are significant and they raise the issue of fecundity as an age-related phenomenon.

Changes in sexual mores affect patterns and incidence of sexually transmitted disease. The increase in number of women in careers has expanded and prolonged possibilities for their exposure to environmental hazards and to stress phenomena in the work place. Deferment of childbearing also prolongs the interval of risk for acquiring a variety of medical disorders prior to exercising their options for reproduction. Placing these considerations in practical terms, for a woman delaying pregnancy to beyond age 30 is associated with decreased fecundity. Among women seeking infertility evaluation, those older than 35 have cumulative pregnancy rates one half that of younger women.[1] The fact that this figure applies to women over 35 undergoing artificial insemination with husband's semen suggests factors attributable to age and not to decreased coital frequency. Exposure to multiple partners as well

as a prolonged time interval during which sexual exposure may occur increases the risk of acquiring pelvic inflammatory disease. The presence of endometriosis also correlates with voluntary delays in childbearing.

The genetics of maternal aging clearly indicate a strong correlation of fetal chromosomal abnormalities with advancing age. In patients 40 to 44 years of age, 6% of conceptuses demonstrate a chromosomal defect as compared to 1.6% between ages 35 and 39.[2] Although 95% to 99% of anomalous conceptuses are lost prior to viability, the risk of a trisomic birth continues to represent a significant problem for older women contemplating pregnancy. It is obvious that the pathogenesis of such genetic mishaps remains to be determined, but as Gindoff and Jewelewicz indicate in their chapter on age and reproduction, the "production line theory" may shed light on the problem. This theory suggests that oocytes ovulate in the order in which they were formed during fetal life, a proportion of the oocyte population suffering chromosomal damage during early prophase of the first meiotic division. Evidence suggests that endocrine abnormalities may alter the intrafollicular as well as the intrauterine environment, resulting in abnormal offspring or spontaneous abortion. An anti-estrogen preparation has been shown to reduce blastocyst formation when the oocyte has been exposed to this influence while still contained within the follicle prior to ovulation and fertilization.[3] Biologic aging may influence not only patterns of sexual behavior and the physiology of ovary and uterus, but also hypothalamic-pituitary function, resulting in defects in the corpus luteum, alterations in the duration of the follicular phase, and diminished ovarian estrogen synthesis.

When considering the influence of environment on reproductive performance, substance abuse must be among the prominent environmental hazards. An increasing percentage of women and teenagers now smoke. The high prevalence of smoking and its hazards to health, specifically the respiratory tract and cardiovascular system, are well known. Also appreciated during the past 25 years is the strong association between low birth weight infants and maternal smoking. We know less, however, about the influence of nicotine and other components of tobacco on early reproduction. That nicotine can act as an aromatase inhibitor raises speculation about its potential influence on the oocyte which may be dependent upon intrafollicular estrogen levels for normal function.[4] Stillman and his coauthors reveal the negative effect which smoking exerts on the many sites of action necessary for normal procreation. The chapter concludes with the hope that this knowledge may stimulate further investigation of the potential reproductive toxins associated with cigarette smoke and may help to persuade individuals to cease smoking. This is an optimistic, if not attainable, objective. Substance abuse and its effects on reproduction also form the theme for the Smith and Asch chapter. Unfortunately, the use of marijuana, cocaine, and other preparations has permeated our society such that an estimated 5% to 10% of women in the childbearing years use these illicit substances regularly.

Alcohol abuse is also prevalent among a significant number of women of reproductive age. The short-term effects of alcohol abuse during pregnancy on the fetus are well recognized as the "fetal alcohol syndrome." The normal function of the hypothalamic-pituitary gonadal system is extremely complex, involving not only hormonal interactions among several endocrine organs, but also metabolic pathways and cellular function. It is not surprising, therefore, that agents which have multiple sites of action, including central nervous system, liver, and cellular function in general, may exert diverse and profound effects on reproduction. Marijuana, one of the more widely used agents, for example, acts as an antigonadotropin and may inhibit ovulation in

the female; in the male testis marijuana inhibits protein and nucleic acid synthesis in the testis, impairing spermatogenesis. That a significant number of adolescents are being exposed to these agents also raises the concern over future impairment of their physiologic development and reproductive potential.

As an aftermath of the thalidomide tragedy in the early 1960s a conservative approach has been established with regard to drug use during pregnancy. The effects of any agent on the outcome of pregnancy and immediate condition of the fetus are frequently vividly apparent. However, the most subtle effects on reproductive performance and on the fetal germ cells are not so clear cut. Cigarette smoking is the most common addiction among women in the reproductive age group. Legal and moderately socially acceptable, cigarette smoking jeopardizes reproductive performance and the chances for a normal healthy life for the offspring if pregnancy is established. It is important to appreciate the likelihood of reproductive impairment by other agents even more dangerous, illicit, and socially unacceptable than tobacco.

Nicotine and anabasine, low molecular weight components of cigarette smoke, inhibit granulosa cell aromatase in a dose dependent manner.[5] Nicotine has also been shown to delay ovum cleavage in the rat.[5] Inhibition of aromatase activity and estradiol production by granulosa cells has important implications regarding drug-induced and environmental effects on estrogen dependent processes.[4] Cannabinoids may affect gonadal function, but their effects on fertilizability of ova and embryonic development have not been studied. The intrafollicular preovulatory environment is important for nuclear and cytoplasmic maturation of the oocyte and may affect its fertilizability and govern its potential for full and normal development. This concept has significant implications with respect to a relationship between environmental influences on the intrafollicular oocyte and subsequent fertility.

Responsiveness of many malignancies to chemotherapy and to radiation has led to sustained remissions or cure. Specifically success with treatment of Hodgkin's disease, leukemias, and certain cancers of childhood has yielded a sizeable number of adolescents and young adults who contemplate marriage and pregnancy. To this group of patients the potential injury to the reproductive system by the therapy which has spared their lives is a real concern. To those physicians who treat malignancies in the young, the realization that long-term cures are likely necessitates awareness of the effects of treatment on reproductive function. In contrast to pharmacologic agents used electively for benign conditions and to abused substances, the use of potent drugs and radiation therapy in cancer treatment is critical and not usually optional. The prospects for fertility after such treatment require the reproductive endocrinologist to possess a fine appreciation of the chances for conception, pregnancy outcome, and generational genetics of the offspring of those exposed to chemotherapy and radiation. The chapter prepared by Damewood and Grochow represents a cooperative effort of reproductive endocrinologist and oncologist to provide a resource for our counselling. They review the effects of chemotherapy and radiation on gonadal function in both men and women. Alkylating agents such as cyclophosphamide and chlorambucil produce azoospermia and premature ovarian failure in a dose-dependent manner. Isolated cases of reversible amenorrhea and restoration of spermatogenesis have been reported. Since the prepubertal gonad seems to have more resistance than that after puberty, the age at which therapy is provided may be an important variable. Interval since cessation of therapy also appears to be a factor in gonadal recovery. Sex differences in response

to radiation therapy have been described. As Damewood and Grochow point out, knowledge of the pharmacology of agents used, awareness of the reproductive aspirations of patients under therapy, and counselling about potential sexual and emotional problems following treatment are important issues for the physician. Cryopreservation of gametes offers prospects for fertility for patients who are at risk for gonadal failure following therapy for malignant disease. The contemporary procedure of ovum donation and in vitro fertilization provide new hope for such patients.

Agents used socially or for therapeutic purposes may have subtle and unanticipated influences on reproductive performance. Clearly, therefore, preparations used for their specific effects on the reproductive tract may exert "toxicity" which runs counter to the underlying purposes for employing them. Scialli, of the Reproductive Toxicology Center in Washington, directs his attention to three agents widely used for ovulation induction: clomiphene citrate, human menopausal gonadotropins, and bromocriptine. The discrepancy between ovulation rate and pregnancy rate with clomiphene therapy suggests that clomiphene may exert simultaneous proconceptional effects as well as antagonistic effects. Luteal phase defect may represent one possible explanation for the discrepancy, but Scialli provides reassuring data regarding pregnancy outcomes. Once pregnancy is achieved after clomiphene, the only complication reproducibly related to therapy is an increased incidence of multiple pregnancy. This complication is considerably more prevalent with gonadotropin therapy; the majority of adverse outcomes are associated with prematurity which usually accompanies multiple gestation. The question of whether to discontinue bromocriptine during pregnancy also receives a critical review. That the rates of congenital malformation associated with bromocriptine treatment do not differ from statistics for patients in general is also reassuring.

An understanding of the soundness of an experiment is a key in evaluation of its results and conclusions. Olive's chapter on the validity of studies regarding reproductive performance needs to be read and re-read by any physician, scientist, or counsellor bombarded with data, claims, and decision-making dilemmas. Indeed, it should be required reading before approaching the rest of this text. First, understand the study design. Is the study prospective or retrospective? Is there a source of comparison, i.e., control group? When no control group is used, we tend to attribute all pregnancies to success of the therapeutic intervention, a distinct pitfall. Do randomized controls always indicate equal allocation? Do we analyze data by pregnancy rates, or life table analysis? The intent of this chapter is to emphasize the possible shortcomings of study design, analysis, and conclusions. The tools for designing a sound study are clearly represented in Olive's chapter, helping us to understand biases, flaws, distortions, and limitations of clinical investigation. That the conduct of sound clinical investigation is more difficult than experiments performed in the more controllable confines of the laboratory is apparent.

Stress is an unavoidable component of an infertility problem. Environmental pressures can participate in reducing fertility. This phenomenon has been experimentally described in colonies of mice and rats in which population density and supply of food and water could be regulated. Despite ample food supply, increased crowding of cages has been shown to lead to combative behavior, infertility, smaller litter size, and increased infant mortality. Supplement the basic underlying cause of infertility in a given couple with the frustrations of being infertile, the stress of a demanding evaluation and treatment, and the depression, anger, and guilt associated with being unable

to conceive, and the original problem is markedly compounded. Awareness of these pressures is a vital part of the management. Mahlstedt views these phenomena through the eyes of a psychologist and underscores the importance of insight and communication in the successful physician-couple relationship.

Since the relationship between T-mycoplasma colonization of the reproductive tract and infertility was first postulated, the organism has been more commonly referred to as *Ureaplasma urealyticum* and *Mycoplasma hominis*. Now Styler and Shapiro refer to the taxonomic class in which these organisms are classified, Mollicutes. These are small self-replicating prokaryotes, possessing a trilaminar cell membrane but no cell wall. Virtually millions of dollars have been spent clinically, once an association had been suggested of these organisms to infertility, both for cultures and antibiotic therapy. But are all the facts regarding this association conclusive? Styler and Shapiro summarize for us, in their chapter, what is known to date about these organisms and their possible role in infertility, concluding that the role of genital Mollicutes organisms in induction of infertility can only be generalized. If such a relationship is ultimately established, *U. urealyticum* and *M. hominis* will probably be the organisms of note. The chapter leaves us hanging, not because of any lack of diligence on the part of the authors, but because of inadequacy of the existing evidence. On the contrary, they provide us with a thorough rendition of the current status of this organism. The reader should review the data carefully and make a choice as to whether or not to culture, if so when to culture, and if positive what antibiotic to use, whom to treat, and how to confirm a cure.

Edward E. Wallach, M.D.

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