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Contraception:
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A SYMPOSIUM

Division of Medical Sciences
Assembly of Life Sciences
National Research Council

NATIONAL ACADEMY OF SCIENCES
Washington, D.C. 1979

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COMMITTEE ON CONTRACEPTIVE TECHNOLOGY

ELWOOD V. JENSEN, Charles B. Huggins Professor of Biological Sciences and Director, Ben May Laboratory for Cancer Research, University of Chicago, Chicago, Ill., *Chairman*

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LUIGI MASTROIANNI, JR., William Goodell Professor and Chairman, Department of Obstetrics and Gynecology, University of Pennsylvania School of Medicine, Philadelphia, Pa.

JANE A. MENKEN, Senior Research Demographer, Office of Population Research, Princeton University, Princeton, N.J.

WARREN B. MILLER, Principal Research Scientist, American Institutes for Research in the Behavioral Sciences, Palo Alto, Calif.

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Enriqueta C. Bond
Henry S. Parker
Frances M. Peter
Daniel L. Weiss

Foreword

The National Research Council fulfills its charge in a number of ways, but this symposium represents one of the most productive modes, that is, to enlist the services of top-flight scientists to design a definitive, relevant program for the exchange of information, to secure the contributions of eminent speakers, and to attract an audience that is best able to disseminate the fruits of the conference. It would not have been possible without the efforts of Dr. Philip Handler, President of the National Academy of Sciences, who instigated and nurtured the development of this conference.

The field of human reproduction is not new to the National Research Council. The Division of Medical Sciences, before it merged into the Assembly of Life Sciences, maintained a Committee on Human Reproduction from 1947 to 1951 and a Committee for Research on Problems of Sex from 1921 to 1962. The work of the latter committee was funded by both the Ford Foundation and the Rockefeller Foundation, two of the sponsors of this symposium. As many of you know, that committee supported Dr. Kinsey through difficult times.

The Academy has also made contributions in the field of population beyond studies on the physiological and technical aspects. Shortly after President Kennedy addressed the Annual Meeting of the Academy in 1961, the Committee on Science and Public Policy (COSPUP) was established. Its membership was drawn from members of the Academy.

The very first report of COSPUP, which was published in 1963, concerned the growth of world population. That report was credited

with heightening local, national, and international interest in birth control and provoking the U.S. Government to make a major change in policy with respect to responding to requests from other nations for assistance in birth control.

Two years later COSPUP published a second report—one on the growth of the U.S. population. It is interesting to note, and is perhaps relevant to our present undertaking, that this report occasioned allegations that the United States was attempting to influence population reduction in the Third World nations while permitting its own to grow.

We are all aware of the changing policy since that time, of the great interest throughout our country and throughout the world, in the study of population. Indeed, with respect to a different situation, a member of the Governing Board of the National Research Council recently remarked, "The most important problem in the world today is population."

That is the problem addressed in this volume.

A wide variety of expertise in contraceptive technology is represented by the distinguished speakers at the symposium. The first papers concern the state of contraception today throughout the world; each presentation is followed by a formal discussion. The second portion of the symposium is devoted to descriptions of new methods and research horizons. In the last group, one paper and a formal discussion address the psychosocial aspects of contraception. The final topic is concerned with the status of funding and the costs of reproductive science research and contraceptive development. A summary of the entire proceedings concludes the volume.

This symposium establishes yet another important basis for continuing efforts in the field of population problems in which the Academy will actively participate.

We are grateful for the dedicated efforts of the symposium's Organizing Committee, which was cochaired by Dr. Elwood V. Jensen and Dr. Sheldon J. Segal, and for the contributions of individuals who made their time and expertise available.

Many thanks are also extended to those agencies and foundations that provided funds to support the symposium—the National Institute of Child Health and Development, the Ford Foundation, the Population Council, and the Rockefeller Foundation.

Frank W. Putnam, *Chairman*
Assembly of Life Sciences

Preface

This symposium, which was held on May 16–17, 1978, at the National Academy of Sciences (NAS), Washington, D.C., reflects a growing concern of the Academy with the problem of population growth and the social and economic challenge it presents to the people of essentially all nations. In the opinion of many, an exponential increase in human demand for a finite quantity of material resources represents the most serious of threats to the future of the human race. Accordingly, the Assembly of Life Sciences of the National Research Council was approached by NAS President Philip Handler in 1977 with a request that it examine the current state of knowledge in reproductive biology and its application to fertility control to determine what role the Academy might play in furthering progress in a field so important to the welfare of the world.

Responding to President Handler's mandate, the Assembly established, within the Division of Medical Sciences, a Committee on Contraceptive Technology, with the responsibility of organizing a symposium in which experts from various areas of population research and fertility control might come together to exchange views as to where we stand, where we would like to go, what we need, and what the Academy might do to help. In setting up the program, the committee decided to begin with a critical look at the accomplishments and deficiencies in the experience to date, to be followed by a survey of new approaches under development and a glimpse of some of the basic research frontiers in reproductive biology that, hopefully, may lead to

improved methods of fertility regulation. Since any technique, no matter how effective biologically, has value only if it is accepted and used, consideration was given to the psychosocial aspects of contraception and, finally, the current needs and prospects for funding of population research.

The committee is grateful to the staff of the National Research Council, in particular to Dr. Daniel L. Weiss for the organization of the symposium; to Dr. Henry S. Parker, staff officer for the symposium, and to his successor, Dr. Enriqueta C. Bond; and to Ms. Frances M. Peter, staff editor of the proceedings.

It is our hope that the information and ideas expressed at the symposium and recorded in this volume will serve both to increase awareness of the reality of the population problem and to provide stimulus for more effective application of present contraceptive technology and more intensive search for new knowledge. If so, the committee is successful in its mission.

Elwood V. Jensen, *Chairman*
Committee on Contraceptive
Technology

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CONTRACEPTION TODAY

ELWOOD V. JENSEN
Session Chairman

The Need for New Contraceptives

GEORGE ZEIDENSTEIN

My basic premise is that desirable individual, family, and social objectives can and need to be served by advances in knowledge about the human reproductive systems leading to better contraceptives. The main purposes of this paper are to offer some reasons in support of this premise, to encourage acceleration of contraceptive development, to indicate some directions in which I believe we should move in effecting this acceleration, and to urge that laboratory research and field testing in this area be undertaken only with the broad participation of those who will ultimately use the final contraceptive methods produced.

REASONS FOR AND BENEFITS FROM EXPANDED CONTRACEPTIVE RESEARCH

Sexually active couples can control their fertility in only four ways: periodic abstinence, contraception, sterilization, or abortion. People in all parts of the world who decide to restrict their fertility by one or more of these methods do so primarily in pursuit of individual and family aspirations—to provide a good home, to enhance affection and opportunities for their children, and to increase their chances for personal and familial fulfillment.

These aspirations can be frustrated or even crushed by unwanted pregnancy, and, as the figures on unplanned and undesired fertility attest, people are often unsuccessful in their attempts to prevent births. In the United States, where contraceptive knowledge and methods are

relatively widespread, an estimated 15% of all births are unwanted and an additional 29% of them are unplanned (Commission on Population Growth and the American Future, 1972). The signs are strong that high rates of unwanted fertility and the desire to limit fertility exist side by side throughout the world.

Given the four alternatives by which people can limit their fertility—abstinence, contraception, sterilization, or abortion—it seems clear that public policy should favor the availability and use of contraceptives. However, the most effective modern contraceptives, the pill and the IUD, are associated with troublesome side effects that frequently lead to discontinued use. Methods that appear less troublesome, such as condoms, diaphragms, vaginal spermicides, and periodic abstinence, also tend to be less reliable in preventing pregnancy and, for many users, detract from sexual enjoyment to an unacceptable degree. Therefore, our conclusion must be that the desires of women and men to limit fertility, without experiencing distressing side effects or diminishing sexual enjoyment, are frequently not achievable with current contraceptive methods.

Not only are individual and familial happiness and well-being being frustrated by the nonavailability of safer, easier to use, and more effective contraceptives, but important social goals are frustrated as well. Individual fertility can translate into success or failure for public policies designed to slow population growth as part of developmental strategies, to limit the need for abortion, or to reduce the number of pregnancies among unmarried adolescents.

Thus, in seeking to expand our knowledge about the reproductive process and to develop better contraceptives, there are other considerations at least equally as important as the specific ones. These considerations, which should concern scientific researchers and agency administrators, public and private donors, university and pharmaceutical company officials, and others involved in the development of contraceptives, include:

- contraceptive safety and consumers' rights,
- reducing the need for abortion,
- adolescent pregnancy,
- fertility reduction,
- fertility regulation and family health, and
- basic human rights.

Contraceptive Safety and Consumers' Rights

Most Americans expect to have only the children they want. Yet one-third of the married couples using contraceptives are likely to fail in the prevention of an unwanted conception within 5 years (Ryder, 1973). A major reason for this is that available contraceptives, while they are improvements over methods widely used prior to 1960, have limited efficacy, safety, acceptability, and continued use.

Use of the most effective contraceptives that are easily reversible—the pill and the IUD—is associated with troublesome side effects and safety risks that fall especially on women. For example, long-term users of the pill have an increased chance of stroke, gallbladder disease, myocardial infarction, hypertension, and other circulatory diseases. The risks of death due to heart disease are increased among women who smoke or who have other risk factors.

Some women who use the newer, more easily retained IUD's experience problems of discomfort, aggravated menstrual periods, and increased incidence of pelvic inflammatory disease. Retention rates, and hence effectiveness, are lower among women who have not had children. There also is uncertainty about long-term problems that may be associated with use of various IUD's.

Increased concern about such problems among the approximately 20 million American couples who rely on the most effective contraceptives is accompanying a perceptibly rising tide of dissatisfaction with current technology (Forrest *et al.*, 1978). The signs of concern and disenchantment are to be found in the growing interest in contraceptive regulation and research among consumers' and women's organizations and in indications that a shift away from pill use may be under way in the United States. Early 1978 pill prescription figures suggest a possible downturn for the first time since the pill was introduced. Recent reports from publicly supported family planning programs, college health services, and manufacturers of diaphragms and contraceptive foams indicate that at least some women in the United States are moving away from the pill and back to the same barrier methods that were being abandoned a decade ago in favor of the pill. In addition, surgical sterilization is on the rise for both women and men.

The sexually active person is now faced with an uncomfortable choice between use of highly effective methods, with varying degrees of uncomfortable side effects and safety risks, and methods that may be safer but are more likely to detract from sexual enjoyment and are less effective in preventing pregnancy. It would be surprising if most people were satisfied with these options.

Beyond the fact of their very wide use, contraceptives have two characteristics that separate them from most other drugs and devices. First, the majority of users are healthy, not sick, so the benefit/risk assessment of contraceptives must differ from that applied to strictly therapeutic drugs. Second, risks associated with contraceptives can extend beyond the individual user to the next generation; for example, they can result in an unwanted child or a damaged fetus.

Consumers are entitled to expect that marketed products have been and will continue to be subjected to rigorous testing designed to identify potential threats to health. Consumers are entitled to the facts. Only when they get them can informed judgments be reached.

Expanded contraceptive research must document the adverse as well as the beneficial effects of contraceptives. It must also contribute toward discovering the most effective means of communicating adequate and appropriate information to consumers. The use of contraceptives, like most other drugs, involves balancing benefits, for example, the prevention of pregnancy and the avoidance of risks associated with childbirth, against the potential risks of their use. Because there is no contraceptive that is absolutely safe, effective, and acceptable to all people, research that facilitates informed decisionmaking is especially important.

Reducing the Need for Abortion

Unwanted pregnancy poses a fundamentally disquieting dilemma. Couples and, too often, women alone can be faced with the decision of whether to bear a child in what may be undesirable circumstances or to seek an abortion. For those who believe that abortion is morally wrong, or who are too poor to pay for competent services, the situation can be particularly traumatic.

During 1976 an estimated 1.2 million abortions were performed in the United States, and one-third of them were obtained by teenagers (Alan Guttmacher Institute, 1976). Tens of millions of abortions are performed each year outside the United States, often under conditions and with techniques that pose serious risks to the woman's life or health. In these circumstances, it should be a central and top priority of health policy to ensure that women can readily and safely terminate unwanted pregnancies.

Many abortions each year are associated with inadequate contraception. Therefore, at the same time that high priority must be assigned to developing safe, effective, and inexpensive procedures to detect and terminate impregnation soon after conception, it appears obvious that

research leading to new and improved contraceptives will foster a downturn in the incidence of abortion. On that basis alone, there should be a wide consensus that such research is a high social priority.

Adolescent Pregnancy

Beginning a family is a demanding process at any age. But for young women and girls, and for their children, early childbearing may foreshadow a terribly limited future. It is estimated that 40% of the approximately 10 million girls aged 15 through 19 in the United States have had premarital sexual experience. Of these 4 million sexually active adolescent girls, about 28% have become pregnant one or more times. Only one in five girls who had not intended a pregnancy reported regular use of contraceptives (Zelnik and Kantner, 1978).

There are serious health consequences associated with early childbearing for both mother and child. Moreover, there are such social realities as lack of day-care facilities, problems of financial support, and absence of educational facilities that are geared to the needs of pregnant teenagers. Consequently, young women electing to bear and raise children face severe hardships.

This problem will not be solved solely by advances in contraceptive methods or by early abortion. There is an obligation to see that young people better understand the consequences of early pregnancy, the responsibilities of childbearing and childrearing, and the use of contraception. It is also critical that the acute hardships endured by young mothers be alleviated by provision of medical care, day care, and educational services that are responsive to their special problems.

But we must not lose sight of the fact that the development of safe and easy-to-use contraceptives, attractive to those new to the experience of sexual relations, would also help greatly. It is unfortunate, at the very least, that doctors have so few options available that they are presently prescribing the pill to teenagers, whose menstrual and ovulatory cycles are only becoming established and who take the pill without sufficient medical evidence on early and prolonged use. Furthermore, if both young women and men are to develop responsible attitudes toward sex and its potential consequences, advances in male methods that are appropriate to this age-group could make a significant contribution.

Society cannot afford to lose the potential of young women and men who are handicapped by beginning a family before they want to or are able to do so adequately. It is not socially desirable that children be born before their parents have an opportunity to live a healthy and full life. No family or community should have to accept the added burdens that these

unplanned and, in some cases, unwanted lives can place on their resources. Dollars spent on prevention would more than justify the cost.

Fertility Reduction

If current trends persist, it appears that the world will have approximately 6 billion inhabitants by the year 2000 and that the global population will stabilize at approximately 8 billion about the year 2100 (Frejka, 1978). Although these projections are far lower than earlier ones of 8 to 10 billion by the year 2000, there is no reason for complacency, especially since continued rapid population growth rates in the poorer countries still frustrate the enhancement of human welfare sought by their people and their governments. The demand for birth control services in many countries remains unmet, and it is only beginning to be addressed in countries where birth planning is a high social priority or where the means for birth planning are provided within national health care systems. Furthermore, in the poorest of nations, where the pace of change is slow, traditional reasons for having large families sometimes remain valid within the local context. In those situations, substantially lower rates of population growth will be achieved only as other development efforts affect underlying social and economic conditions, thereby reducing the need and desire for many children and increasing the demand for effective contraceptive methods.

All nations and families could reduce fertility more rapidly if a more varied range of contraceptives, which are sensitive to differences in customs, health, diet, and other culturally relevant factors, were available to meet their needs. And human welfare everywhere is likely to benefit if fertility rates continue to decline and population growth rates slow even further over the coming years.

Fertility Regulation and Family Health

It is widely accepted that the bearing of many children can be detrimental to the good health of the children as well as of the mother. However, in many parts of the world, social and economic pressure to bear many children has been strong. Until recently, the woman who was disposed to resist these pressures had one major recourse—abortion, in many cases illegal—unless she and her spouse were willing to use condoms, to practice withdrawal, or to abstain.

Changes in social attitudes and in governmental policies over the past two decades have produced circumstances in many societies that are more supportive of contraceptive use. But even where family planning is

encouraged, other governmental policies, or their absence, may discourage the pursuit of nonmothering roles. In these circumstances, women may see little reason or opportunity to resist traditional pressures to have very large families.

But we can be heartened that the concern of governments for the health of their citizens is broadening. Birth planning measures are being added to the established emphasis on disease and mortality. Moreover, there appears to be a growing recognition that health is more than the absence of tangibly evident disease—that it is a positive state of physical, mental, and social well-being. However, efforts are only beginning to give meaning to and measure this broadened health concept, and little is known about the effect of fertility on many aspects of physical and mental health.

Several generalizations can be based on the best available empirical studies. First, age is an important factor affecting the outcome of pregnancy. Various risks to women of childbearing age (for example, fetal mortality, maternal mortality and morbidity, and stillbirths) tend to be high at very young ages, then decline to a minimum among mothers in their twenties, after which they increase continuously to the end of childbearing years. Second, closely spaced births add to the rate of risks at all ages. Third, cultural and environmental factors exert a strong influence on the absolute rates of different risks. To the extent that poor health (nutritional inadequacy, infectious and other diseases), low income, and inadequate medical care coexist with reproduction at very young and older childbearing ages, risks associated with age and birth order are sharpened.

Combined, these factors suggest that individual couples can improve the likelihood of normal childbearing by conscious spacing and limiting of children despite the fact that they may have little direct control over the level of health risk that is prevalent in their societies. Fertility regulation provides one real means by which couples can minimize rates of infant mortality, congenital defects, and other health risks regardless of the quality of living conditions or available medical care. To the extent that new contraceptives meet the needs of potential consumers and are more widely accepted and used in both developed and developing countries, they will assist in improving family health.

Basic Human Rights

Human rights, as they pertain to the practice of contraception, are significant in at least three respects. First, a child should have the right to be wanted and loved and to be given the maximum opportunity to live a

full life. Second, a couple should have the right to have only those children it wants. For a poor couple struggling to take steps toward a better life, the inability to control their fertility may only add to their belief that all efforts to control their future are futile. Third, a woman should have the right to bear only as many children as she believes are consistent with good health, to plan childbearing in a manner least restrictive of other opportunities for her personal growth and contribution to society, and to avoid excessive safety risks in using contraception.

Effective contraceptive methods provide a means other than abortion by which a woman can control fertility if she wants to limit or space the children she bears. By minimizing disruptions caused by unwanted pregnancy, women can both maximize their productivity and pursue alternatives previously foreclosed by almost constant childbearing and childrearing. The ability to have only wanted children will not produce instant equality of the sexes, but removal of the restrictions imposed by unwanted high fertility can free women to participate in and contribute to society in ways that are critically important to the development of nations, families, and individuals.

There is increasing evidence, at least in the United States, that many couples would like to share the responsibility for contraception. In one study, 84% of the adult males questioned believed contraceptive responsibility falls on both partners; 70% said they would use a new contraceptive for males if one were available (Anonymous, 1973).

Certainly there is interest in and concern about childbearing among men in all parts of the world. Advances in male contraceptive methods should result in a more even sharing of contraceptive responsibility and risk, but development of methods for men has lagged far behind development of methods for women. In part, advancement has been impaired by lack of funds. Additional research could reduce the burden carried by women alone.

SCIENTIFIC NEEDS, CAPABILITIES, AND FUTURE DIRECTIONS

If the case for further contraceptive research seems compelling, the natural questions then become,

- What should be done next?
- Do we have the capacity to do it?

I need not dwell here on how contraceptive research is conducted in the fields of biology, chemistry, and medicine. There is a continuous

process in biomedical research from fundamental studies to applied research to product development, with all of the experimental steps, frustrations, and breakthroughs along the way. At present, between 2,500 and 3,500 scientists, mostly in the United States, are directly engaged in fundamental reproduction research, and many others are doing related basic biological research (Segal, 1978). Between 1970 and 1975, 45,000 papers were published on reproduction and contraceptive development (Greep *et al.*, 1976). More than two-thirds of the basic research in this country is funded by the Federal Government, primarily by the National Institute for Child Health and Human Development (NICHD). In 1977, NICHD's Center for Population Research gave grants totaling $22 million for this purpose (Segal, 1978). This will increase to $28 million in 1978. Nevertheless, many U.S. scientists are not able to pursue research in this area because of a shortage of funds. In 1979, close to 70% of the projects expected to be approved by scientific review committees will not be funded (Segal, 1978).

This funding problem is not confined to fundamental biomedical research in reproductive biology and contraceptive development. Both money and mechanisms are also needed in order to apply fundamental knowledge in goal-oriented work leading to contraceptive testing and the development of the most promising leads. Private industry is expected to be most active in the later stages of development of those contraceptive methods for which the possibility of profits appears highest. Where methods appear promising but not very profitable, the public sector may take the lead. For example, the National Institutes of Health, the U.S. Agency for International Development, the World Health Organization, and the International Committee for Contraception Research fund public efforts with money from both the public sector and private foundations. In sum, public dollars support several hundred able scientists working on all stages of research in a wide variety of settings, and private sector support is increasing in areas that promise high return on its investment.

Status of Present Research

The intermediate goal in all reproduction research is the identification of those points in the reproductive chain in both sexes at which interference can occur in a safe, effective, and acceptable manner. Against the backdrop of the less than ideal contraceptive methods that are currently available, there is a continuing search for improved methods. Some research is concentrated on refinements of present methods. Medicated intrauterine devices, postcoital estrogens, and prostaglandin abortifacients are among the methods based on new applications of fundamental

research. Two IUD's, the Copper T and the Copper 7, have been tested and approved for use in a number of countries and represent significant improvements over earlier devices in terms of lowered incidence of pain, bleeding, and expulsion, even among never-pregnant women, but the full story of their safety and lifespan is not yet known.

Because of the long time needed for animal testing and product refinement between the stages of fundamental research and final clinical trials, it is possible to survey the scientific landscape now and to determine those methods of fertility control that we are likely to see in the next decade. Among these possible new methods are:

- vaccination against human chorionic gonadotropin;
- pharmacologic suppression of the corpus luteum;
- long-acting forms of contraceptive steroids, including injections, subdermal implants, and vaginal rings;
- barrier methods using new materials, designs, and modes of use and administration;
- male contraceptives; and
- improved methods of abstinence based on periods of fertility and infertility.

Part of the reason that the development of contraceptives for men has lagged far behind that for women is biological. Men have fewer points in the reproductive chain of events that are realistically vulnerable to interference. Another part of the reason is the lack of funding for pursuing leads for male contraceptives. About 85% of the NICHD money for reproductive research is provided for research on methods for females. There is a grave shortage of competent investigators to compete for the limited available funds, a fact underscoring the need for further training in reproductive biology with emphasis on the male.

As noted above, many men are now willing to share in the responsibility for fertility regulation, and recent developments in the area of reproductive physiological research in males indicate that several diverse forms of contraception may be feasible. Procedures interrupting the secretion or action of any of the brain, pituitary, or testicular hormones or affecting the action of the Sertoli cells or the functions of the epididymis, which are involved in sperm production and maturation, could lead to a reversible fertility control technique for males.

Much more emphasis needs to be given to these areas of investigation. In this regard, I am pleased to report that the Population Council's Center for Biomedical Research has recently reorganized its priorities to give primary attention to fundamental research in the physiology of the

male reproductive system with the goal of developing safe, effective, and efficient contraceptive methods for males. To lead this work, Dr. C. Wayne Bardin, formerly head of the Division of Endocrinology of the Department of Medicine at the Milton S. Hershey Medical Center, joined the Council in 1978.

Health and Safety

Many widely used contraceptives pose safety risks; others have not been studied sufficiently and are only presumed to be safe. Given their wide use, the seriousness of their suspected side effects, and widespread concern for their safety, too little is known about problems that are related to most contraceptive use. While the reasons for our ignorance are many and complex, three closely related parts of the explanation are apparent: methodological difficulties, too few trained investigators, and inadequate funding.

All three factors must be addressed more thoroughly in the necessary documentation of risks, but we must also remember that contraceptives bring significant benefits to their users. We need to assess the net impact on the health of those who use contraceptives and not dwell on either isolated safety risks or isolated benefits. Our goal should permit the development of risk/benefit comparisons that an individual can use when choosing one or more options so that he or she could enhance benefits and minimize risks and weigh all safety risks in the context of overall health and well-being.

IMPLEMENTING POLICIES THAT WILL ATTRACT PUBLIC SUPPORT FOR CONTRACEPTIVE RESEARCH

Having outlined the current levels of funding and the current state of contraceptive research, I turn now to increasing funds for this research and to developing policies that will engender public support to effect this.

Between 1965 and 1972, worldwide support for contraceptive research rose from $31 million to $110 million (L. Atkinson, personal communication, July 6, 1978). But since 1972, there has been no growth in such support when calculated in constant 1972 dollars. The future inclination of the political, industrial, and philanthropic leadership toward contraceptive research will determine the magnitude of total support and the speed at which progress will be made. The U.S. Government plays a key role in this because it influences and reflects public

attitudes, it accounts for the lion's share of research support, and it has both a domestic and a world role in regulating the way new contraceptives are developed and marketed. As in other areas of national policy, Government decisions affecting contraceptive research are not made in a political vacuum but emerge by a process of analysis, argumentation, and negotiation. Therefore, it is critically important that we begin to pay more attention to those factors that underlie and affect relevant public policies if we wish to accelerate contraceptive research. The principles and steps that I believe must be taken to accomplish this are stated below:

First, if support for contraceptive research is to become more widespread and effective, policymakers and consumers must receive better information, delivered in timely and imaginative ways, about the possibilities, payoffs, and problems involved. Greater expenditures will require greater justifications. A scanning of the field suggests that a new mechanism should be established to collect, analyze, and make available needed information on contraceptive research. In the absence of such information, it would be difficult to obtain and to present effective advocacy of the importance of increased funding for contraceptive research.

This same mechanism could provide a basis for engaging the interest of organizations in increasing these funds. These organizations include churches, labor unions, women's organizations, and consumer groups. Members of these organizations have a vital stake in the quality of contraceptives. If some members of the industrial sector have noted in recent congressional testimony that these and other pressure groups are uniformly abusive on such issues, that only underscores the importance of establishing better communication between those who develop contraceptives and those who use them. I am not suggesting a propagandistic approach to try to educate consumers; rather, I am suggesting a genuine dialogue with them to inform them about the direction and potential benefits of further contraceptive research, to listen to their concerns about the safety and use of contraceptives, and to open the windows to the interested world beyond the laboratory in exploring the central issues of contraception. The coming months, during which the media will be focusing on proposals for major revision of federal drug legislation, may offer opportunities to open and pursue this dialogue.

Second, regulatory requirements and research guidelines should support the most efficient use of research dollars that is consistent with adequate protection of human subjects and with clear and rigorous test-

ing standards. Present requirements of the U.S. Food and Drug Administration (FDA), when viewed from the perspective of those seeking rapid progress in contraceptive research and development, may sometimes seem too costly and burdensome. But we must keep in mind that consumers are entitled to expect that drugs and devices meet very high standards before they are made widely available and that prompt action will be taken to warn of dangers and side effects as they become known for drugs and devices already on the market. In my view, the national legislation now pending on this subject is in the right direction.

To reconcile the two essential public interests, rapid development of improved contraceptives and their safety, the FDA should have the flexibility necessary to make judgments about the adequacy of new product testing on a case-by-case basis. Issues of adequate and clear labeling, full physician and consumer information, honest obtaining of informed user consent, enhanced use of and reliance on scientific peer review, and transfer of uniformly high research standards and results across national boundaries for use in implementation and testing need to be promoted with vigor and commitment by scientists and all others involved in this endeavor.

Third, I believe that both scientists and policymakers should know more about consumer reactions to available contraceptives and that the process by which priorities for future contraceptive funding and development are set would be strengthened by giving greater attention to consumer needs. We must better understand and document the nature of consumer problems as well as their personal and social consequences. Investigation in this area can assist in setting effective targets for future research and development. The recent move by the FDA to establish a stronger and more active liaison with consumer groups may provide lessons for all of us in this field.

Fourth, I believe that a better appraisal of industrial needs and capabilities is required if public policy is to encourage a balanced research program and the maximum private sector contribution. There are rising concerns that industry's contribution to this field is being undercut by present federal regulatory and funding policies. Because the private sector's role is vital, these concerns merit serious attention.

If chances are poor for a significant commercial return on a high research investment in contraceptive development, especially when compared with returns from other drugs used against disease, then the private sector will curtail its important role in this field. The present picture is cloudy and offers no clear-cut solutions to the dilemmas of industry. Several important issues should be analyzed, including what

constitutes reasonable return on commercial investment in contraceptive development.

A better understanding of private and public interests and capabilities in this field could help governments and private donors encourage a division of research labors that would be optimally productive. The time may be right for establishing an *ad-hoc* joint public and private commission on contraceptive research to investigate the facts and to determine which steps should be taken next. Such a study could assure policymakers and the public that additional funds would be efficiently spent and give hope that they would be used in a manner that encouraged maximum private sector involvement. It would also be useful in the periodic reordering of research priorities.

CONCLUSION

In closing, let me affirm my belief that the time is right for taking the steps I have described. Scientists and consumers alike have much to gain by an expanded and efficient research program for developing safe, effective, and convenient contraceptives. The social needs warrant an immediate and continued expansion of our efforts. The basic scientific capacity exists and can be enhanced. There is a lack of widespread awareness and agreement that contraceptive research deserves higher public priority and a higher call on public and private funds.

Only when a broadened and deeper public understanding is achieved can the necessary and appropriate level of support be realized and sustained. Public involvement should be seriously and genuinely solicited, both as a worthwhile goal in itself and as a necessary element in the building of a sound foundation for our efforts.

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Discussion of Paper Presented by George Zeidenstein

FREDERICK S. JAFFE[1]

Mr. Zeidenstein has presented a concise summary of the major considerations that justify a substantial increase in the priority and attention that are given to research aimed at the development of improved methods of fertility control. His paper is noteworthy because it deals mostly with the considerations of personal health and welfare that support such a shifting of priorities, rather than those related to the rapid rate of population growth in less developed countries.

To some, this approach may be puzzling. During the past two decades, the principal private forces stimulating the growth of this field of science have been the population programs of the Ford Foundation, the Rockefeller Foundation, and the Population Council. Their principal governmental counterpart is the Center for Population Research (CPR) of the National Institute of Child Health and Human Development. One of the early efforts to assess the need for research in fertility control was completed just 25 years ago in *The Physiological Approach to Fertility Control*, a report published by a working group that was established by the Conservation Foundation (1953). This group included biomedical researchers like Frederick Hisaw, Leo Szilard, Caryl Haskins, and William Doering; social scientists like Kingsley Davis; and physicians like Alan Guttmacher and Howard Taylor. Its argument for a directed program of research in fertility control was based entirely on the rapid rate of population growth in developing countries. "The

[1]Deceased.

discovery of systemic, or physiologic, methods readily applicable under peasant conditions," the report argued, "divorced from the sexual act itself, lasting over an extended period, and requiring a minimum of expenditure, inconvenience and education, would enormously increase the likelihood of fertility control in the regions where it is urgently needed" (Conservation Foundation, 1953, p. 12). Since then, concern over population growth has been the principal stimulus for expansion of federal support. Given the criteria used by the National Institutes of Health (NIH) during the 1960's, there is little question that the field would be very small today if it had competed with disease-related research for funding without the urgency provided by population growth.

In my view, there is no essential contradiction between the two approaches, because more effective and acceptable methods of fertility control would make a significant contribution to both the reduction of population growth in developing countries and the improvement of health and well-being in both industrialized and less developed nations. The emphasis previously placed on demographic concerns may have obscured the equally important issues of safety, acceptability, and effectiveness that affect the lives of millions of Americans and define the stake that they have in this research enterprise. The extensive Ford Foundation review of the field (Greep *et al.*, 1976) concluded that "current contraceptive technology cannot be regarded as adequate to meet individual *or* societal needs in either industrial *or* developing nations."

The President's proposed budget for fiscal year 1979 asks for the first significant increase for the CPR since 1971. There is considerable evidence that three factors contributed to this: the Ford Foundation review itself, rising concern over the incidence of teenage pregnancy, and a feeling that better methods might reduce the need for abortion. Two of these factors apply exclusively to domestic issues.

Many will agree with Mr. Zeidenstein's major arguments, but there will be some differences. For example, dissatisfaction with the pill has certainly been increasingly verbalized, but the proportion of married couples using it in 1976 is only three percentage points smaller than it was in 1973 (Ford, 1978), and the proportion of teenage users doubled between 1971 and 1976 (Zelnik and Kantner, 1977). Consequently, the pill remains the most popular method. Use of the diaphragm increased by less than one percentage point—from 3.4% to 4.3%—between 1973 and 1976.

The discussion of male methods fails to mention the considerable body of research that associates fertility decline in 19th-Century West-

ern Europe and the United States with extensive male involvement in fertility control, that is, the use of withdrawal and the condom. Some of us believe that the role of abortion and infanticide is underestimated in these studies. It is historically important to note that female methods came into use primarily in this century as a consequence of the valid interest of leaders of the women's and birth-control movements in methods that women could control directly. Nonetheless, vasectomy has become an increasingly important method throughout the world today. I am puzzled also by the statement that 85% of CPR funds are "earmarked" for female contraceptive studies, since there is no such earmarking process in CPR for any of its research activities. CPR estimates that from 20% to 25% of its funds support male studies.

In regard to the health and safety issues, it is, of course, impossible to attain a technology of any kind that is entirely risk-free. We need to pay more attention to questions of risk with respect to contraceptives, but we should also make it clear that modern contraceptives have been subjected to closer and more continual evaluation than any other medication in large-scale use. As a result, we already have a framework for enabling individuals to assess risks and benefits that is superior to that available for other drugs. I am referring particularly to the studies of Tietze and his colleagues at the Population Council, who compared the risks from all contraceptive methods with those from childbearing (Tietze, 1977). These studies indicate that it is safer for women below the age of 35 to take the pill, even if they smoke, than to drive a car. As part of the dialogue with consumers that Mr. Zeidenstein calls for, it seems important to stress the considerable efforts that have been and continue to be made, not only to maximize safety, but to develop new techniques for evaluating risks and benefits.

Mr. Zeidenstein suggests that there is a need to build support for increased funding of contraceptive research. This is an especially important subject. The Ford review showed that this field, which had essentially no support from governments in 1960, reached 0.9% of governmental medical research expenditures in 1965 and then increased to 1.6% in 1974. The figures are interesting because the 1965–1974 decade was marked by very rapid expansion in the family planning/population field and a considerable increase in its political acceptability. This led to the first world population conference of governments in Bucharest. It was a decade in which changes in contraceptive technology stimulated a contraceptive revolution in industrialized nations and expedited the development and implementation of national family planning programs in less developed countries containing 92% of the Third World population.

The results of these processes were far-reaching. There were declines in unwanted fertility and in fertility levels in both industrialized and less developed nations and improvements in the health and social status of women. In the United States, technological change led to equalization of the use of modern contraceptives by the poor and the well-to-do and to a decline in differential fertility. These are no small achievements in sociohistorical terms—nor in scientific terms. Yet, these achievements have not been reflected in any significant increase in the priority that governmental decisionmakers assign to this field.

To be sure, other processes at work during this decade also affected the field. In the United States, the rapid expansion of the NIH budget came to a halt, and there was a general disillusionment with science. In the late 1960's, Kistiakowsky said that the age of science for the scientist's sake was over and that science would have to show demonstrable benefits to enjoy increasing public support. Moreover, there has been growing concern that not everything done in the name of science is necessarily beneficial. This is evident in the controversies over recombinant DNA and energy policy.

Yet, there remains another factor that we must face. The importance attached to reproductive research and contraceptive development by the scientific community appears to have changed very little. Referring to the diaphragm, Tietze (1958, p. 27) observed that "it is an amazing thing that a discipline reputedly as modern as this should have as its mainstay a method which was described, in essence, in a paper published in 1882. In most other fields of medicine, any method used in 1882 is now mentioned only in the course on the history of medicine."

Twenty years later, a significant factor underlying the continuing dissatisfaction among physicians and scientists about the pill is the persistent belief that the diaphragm, which has few method-related risks, is an acceptable substitute. Now, as then, this is true for some persons in some countries, but not for many others in the United States or in the developing nations. The implicit comparison of the safety of the diaphragm to the risks of the pill and the IUD, which underlies many current statements about the pill, ignores the experience of the last 15 years. In my view, this is poor science. One of its principal results is sensationalized press stories that have literally scared some people away from using modern methods and have led to more unwanted pregnancies, abortions, and births, particularly among teenagers.

The scientific community, as a whole, has had—and continues to have—a very inadequate understanding of the need for improved fertility methods among our own people, much less throughout the world. This is particularly problematic because government research priorities

are not determined solely by Congressmen and consumers. Through a diverse group of direction-setting bodies, the scientific community itself has an influence that may have more to do with the year-to-year priorities of NIH than either Congressmen or consumers. It is true that the Office of Management and Budget (OMB) establishes a budget level for NIH that limits how much can be spent on biomedical research. But it is also true that OMB and the relevant congressional committees pay at least some attention to the President's Science Advisor, the National Science Foundation, the National Academy of Sciences, and the NIH leadership, not to speak of the scores of scientific societies, beginning with the American Association for the Advancement of Science. If any of those bodies have pressed for expansion of this field in the last decade, they have been speaking very softly. Their influence appears to have been expended in other directions.

To be sure, the scientific community is pluralistic. Other groups have pressed their particular causes with much success, thereby limiting the funds remaining for fields like reproductive research. For example, passage by Congress of the National Cancer Act ensured that a disproportionate share of the NIH budget would go for cancer research. It is also true that the campaign for the National Cancer Act was led by influential laymen. But sharing the leadership was a group of distinguished scientists who were determined to make the case for expansion of cancer research and were willing to provide a more or less credible justification of how the money could be spent.

The expansion of the cancer research enterprise has been criticized, which was entirely predictable. But that criticism does not negate the key conclusion that an indispensable condition for increasing the priority for any field of research is the willingness of at least some of its scientists to stand up as forceful and effective advocates. Reproductive research as a field has been relatively timid in pressing its case, despite the evident fact that its findings affect literally everyone. Far from pressing for more funds, reproductive scientists have been more apt to say that the field needs better ideas rather than more money, although ideas can come only from persons, persons require money with which to live and work, and the probability of having more good ideas can be increased if the number of able persons capable of having them is increased.

In an interesting article in *Daedalus*, Harvey Brooks (1978) showed that there is no scientific framework for deciding how much should be spent on research—or on any specific branch of research. Science priorities cannot be set without taking account of considerations that are external to science in a political process in which the scientific com-

munity interfaces with the political community. It may be useful to build a constituency in support of reproductive research among consumers. However, it is probably more necessary to build a constituency of support among reproductive researchers. I suggest that this could be initiated by informing them about the key developments in Washington that affect the future of the field and by assisting them in taking the case to the direction-setting bodies of the scientific community, to governmental decisionmakers, and to the public at large. This would be at least a start toward giving this field some parity with its competitors. It may not require new mechanisms. Rather, activities and functions not presently being carried out systematically by existing groups need to be assigned and undertaken.

The case for greater priority for reproductive research and contraceptive development is, at bottom, part of a much larger debate about priorities within the field of biomedical research that has arisen in the last several years. For the first time, the emphasis placed on research that is related to diseases of middle and old age has been sharply challenged. If more reproductive researchers enter the debate and bring to it the vast amount of information documenting the urgent needs of the field and its enormous potential for improving human welfare in our own country as well as throughout the world, they will have the opportunity to influence the thinking of the scientific and political communities and to elicit the support of the public at large.

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Experience with Contraceptive Methods in Developed Countries

JANE MENKEN, JAMES TRUSSELL, KATHLEEN FORD, *and* WILLIAM F. PRATT

The contraceptive revolution that began among married couples in the United States during the 1960's shows every indication of continuing throughout the 1970's. A high proportion of married couples uses contraception, and this pattern is accompanied by an increasing proportion that uses the most effective methods: sterilization, the pill, and the intrauterine device (IUD). However, for an individual couple, fertility control may be far from perfect. Contraceptive use may still lead to an unwanted pregnancy or birth. Since there is more extensive information for the United States than for other developed countries, our intention in this brief report is to cover three major areas: current contraceptive practices, failures in the United States, and contraceptive practices in developed countries for which national level data are available. The extent of contraceptive use will be measured by the proportions of the population that are currently using a method, the distribution of methods used, and differentials in use by various segments of a population.

The ability of couples in the United States to use different methods can be thought of as the result of two components: the effectiveness of the method in preventing pregnancy during use and the satisfaction with the particular contraceptive, or at least the willingness to continue using it, which is reflected in continuation rates. Therefore, contraceptive methods will be assessed by examining both failure rates and continuation rates. Failure rates in this paper are defined as the proportions experiencing an unintended pregnancy during the first year

that a method is used, either for the first time or after interrupting earlier practice. Continuation rates measure the extent to which couples discontinue a method for reasons other than wanting to have a child.

The combination of contraceptive failures and nonuse will be summarized in estimates of the numbers of children whose births were reported as unintended, being either *unwanted* or *unplanned,* during 1970–1972, the most recent period for which we have estimates.

Finally, we would like to bring to your attention the problems that individual users face when they attempt to obtain reasonably good information on how effective a particular contraceptive will be for them—information on the extent to which they can rely upon a particular method to protect them from having an unintended pregnancy.

CONTRACEPTIVE USE IN THE UNITED STATES

In the United States we are fortunate in having a series of surveys from which to estimate levels and trends in the extent of contraceptive use. Representative national samples of women were interviewed in 1965, 1970, 1973, 1975, and 1976. The quinquennial surveys—the 1965, 1970, and 1975 National Fertility Studies (NFS)—were conducted by Charles Westoff and Norman Ryder of Princeton University. The 1973 and 1976 National Surveys of Family Growth (NSFG) are the first two of a series of surveys to have been conducted on a regular basis by the National Center for Health Statistics. The 1965 study included currently married women only. In 1970, women were included if they had *ever* been married. In the 1973 and 1976 surveys, never-married women who had at least one of their own children living with them were added to the sample. The 1975 study was designed to include interviews with a subsample of currently and continuously married white women who had participated in the 1970 study. Sample sizes varied from close to 5,000 in 1965 to over 6,000 in 1970, nearly 10,000 in 1973, and 9,000 in 1976. There were 3,400 in the subsample follow-up in 1975. They are all representative samples of American women under 45 in the respective target populations, at least within the limits of sampling variability.

The definition of a contraceptive user is comparable in all of these studies for all methods except sterilization. Since the reasons for sterilization may be wholly medical, the studies have attempted to determine whether contraceptive intent was involved. The studies prior to 1976 asked women who reported sterility if the operation was done at least partly so that they would have no more children. Only those who answered positively were classified as contraceptively sterile. In the 1976

TABLE 1 Percent Distribution of Currently Married U.S. Women Aged 15–44 by Current Contraceptive Practice, According to Race: 1973, 1970, and 1965[a]

Race	Distribution of Currently Married Women (%)							
	Using Contraception				Not Using Contraception			
	Wife Sterilized	Husband Sterilized	Other Methods	Total	Pregnant, Postpartum, Trying to Get Pregnant	Surgically Sterilized for Noncontraceptive Medical Reasons	Other Nonusers[b]	Totals
All races								
1973	8.6	7.8	53.2	69.6	14.2	6.5	9.6	30.3
1970	5.5	5.1	54.4	65.0	14.5	6.3	14.1	34.9
1965	4.5	3.3	56.1	63.9	14.2	7.6	14.3	36.1
Whites								
1973	8.2	8.4	54.0	70.6	14.2	6.6	8.6	29.4
1970	4.9	5.5	55.3	65.7	14.5	6.4	13.4	34.3
1965	4.1	3.5	57.3	64.9	14.0	8.2	13.0	35.2
Blacks								
1973	13.6	1.0	45.3	59.9	14.0	6.2	19.8	40.0
1970	11.4	0.6	47.2	59.2	13.9	6.3	20.6	40.8
1965	8.3	0.3	48.6	57.2	16.1	5.3	21.6	42.9

[a]From Westoff, 1976; Westoff, unpublished data; Ford, 1978; and 1965 and 1970 NFS public use tapes.
[b]Includes nonsurgically sterile, subfecund, and those who use no method.
NOTE: Figures may not add to 100 due to rounding.

NSFG, respondents were asked whether one reason that they elected to have the operation was that they had had all the children they wanted (Ford, 1978). Therefore, data on contraceptive use or on choice of method among users are not comparable with earlier material. Consequently, in the following discussion, the available information will not always allow us to describe trends over the entire 12-year period from 1965 through 1976.

In 1973, 70% of married women reported that they were currently using contraception (Westoff, 1976) (see Table 1). From 1965 to 1973, the proportion of whites using contraceptives rose from 65% to 71%, and the proportion of blacks from 57% to 60%. The noncomparable figures for 1976 are slightly lower, 68%, 69%, and 58% for the total, white, and black populations, respectively. Of the 30% of all married women who were nonusers in 1973, most were not at risk of accidental pregnancy; 45% were either pregnant or had delivered a baby less than 1 month before interview or were trying to become pregnant; and 35% considered themselves sterile or subfecund. Thus, only the remainder, constituting 9% of the total population of married women who were at risk of unintended conception (those fecund or contraceptively sterilized), were not using contraception. The 91% who were using at least one method reflects the proportion of married couples who were using some form of contraception to plan their births (Westoff, 1976).

In this general trend, social differentials in the proportion practicing contraception persist. Black married women use contraception less frequently than white at all ages (60% versus 71%), partly because of a higher prevalence of sterility and subfecundity, but mainly because a larger proportion are not using any method, although they are neither currently pregnant nor planning to become pregnant.

Regional variation is too small to be statistically significant.

Among married white couples, a higher proportion of Protestants (71%) compared with Catholics (67%) were practicing contraception in 1973, but the proportion in both cases was lower than that for Jews (85%). The Protestant–Catholic difference is narrowing, primarily owing to a sharp decline in nonuse among younger Catholics. In 1965, only 59% of Catholics compared with 70% of non-Catholics reported current use of any method (Westoff, 1976).

Sterilization

As Table 1 shows, there has been a sharp increase in contraceptive sterilization, from 8% of all couples in 1965 to 16% in 1973. Among once and continuously married white women, the 1975 NFS showed a con-

tinuation of the previously observed trend toward increased use of contraceptive sterilization (Westoff and Jones, 1977).

Sterilization is clearly the method of choice among married couples when the wife is between 30 and 44 years old. The proportion that was sterilized rose from 10% in 1965 to 23% in 1973. The figures represent 16% and 34% of all contraceptive practice in each of the 2 years. The overall proportions of married couples where at least one partner has been surgically sterilized increased throughout the period (Table 2).

The Pill

The use of the pill increased rapidly after its introduction. By 1965, 15% of all married women were using this method; by 1973, 25%, or just over one-third of all contraceptive users, were taking the pill. Between 1973 and 1976, pill use declined slightly. The latest figures show that 22% of all married women between 15 and 44 years of age use the pill. The pill, at least through 1976, has been the preference of younger women. In 1973, more than 53% of the contraceptive users under 30 had chosen the pill, compared with 21% of those between the ages of 30 and 44. Even in 1976, 35% of all married women under age 30 were pill users, a decline from 38% in 1973 (Ford, 1978).

IUD

Use of the IUD increased from less than 1% in 1965 to 7% in 1973 and declined to 6% in 1976. Collectively, the three most effective methods—contraceptive sterilization, the IUD, and the pill—have steadily increased in popularity, being used by 24% of couples in 1965, 38% in 1970, 48% in 1973, and remaining at 48%, even with the change of definition, in 1976. In the three earlier surveys, these methods accounted for 37%, 58%, and 69% of all use. Considering that these methods were virtually unknown in 1960, the change is indeed revolutionary.

Other Methods

Between 1965 and 1973, the use of all other methods had declined, except for foam, which increased from 2% to 3%. The percentage of couples using the condom declined from 14% to 9%. By 1973, only 2% were using the diaphragm. The rhythm method also declined, from 7% to 3% of all couples. The use of the douche declined sharply—from 3% to 1%. Since the proportion of couples who were using any method was increasing simultaneously, the decreases in percentage of users who

had selected these methods were greater than the absolute decreases just given. Both the 1975 and 1976 surveys show small increases in the use of the diaphragm and rhythm methods, although the changes may not be statistically significant. However, among blacks, there was an increase in the percentage using each of the traditional contraceptive methods. Although black couples were less likely than whites to use contraceptives prior to 1976, those who did were more likely to use the pill, IUD, or sterilization. In 1976, the proportion of users of contraception or sterilization who had chosen one of these three methods was for the first time lower for blacks than for whites.

Summary

Dramatic changes in contraceptive practice have taken place in the United States during the 1960's and 1970's. The pill was adopted rapidly after its introduction and increased in popularity until 1973. Only in the past few years has its use declined somewhat. During the same period there has been a marked rise in elective sterilization to control fertility. By 1976, more married women were sterile due to surgery than were using the pill. Among couples who intend to have no more children, the proportions who have chosen sterilization, and presumably have almost zero chance of bearing unwanted children, are truly remarkable. For the continuously married sample of the 1975 NFS, Westoff and Jones (1977) estimated that over 43% of contraceptors who intend no more children had been sterilized. The pill remains the most appealing method to wives under 30, while sterilization dominates the preference pattern among couples when the wife has passed age 30. Whether the observed slight trend away from the pill has continued or become steeper is an important question for future studies.

EFFECTIVENESS OF CONTRACEPTIVE USE IN THE UNITED STATES

How good are these methods at preventing women from experiencing an unintended pregnancy? The following data were taken exclusively from the 1973 NSFG. For each month between July 1970 and July 1973, respondents were asked whether or not they had become pregnant. They were also asked if they were using contraception and if their intention, while using it, was to *prevent* pregnancy or to *delay* it. "Preventers" are women or couples who do not want to have another child, while "delayers" use contraception to postpone conception although they plan to have at least one child in the future. In the first

TABLE 2 Surgical Sterilization and Contraceptive Status of Currently Married U.S. Women Aged 15–44, According to Race: 1976, 1973, 1970, 1965[a]

	Sterilization and Contraceptive Methods of Married Women (%)											
	Surgically Sterile			Contraception Other Than Sterilization								
Race	Noncontraceptive	Contraceptive	Total	Pill	IUD	Diaphragm	Condom	Foam	Rhythm	Withdrawal	Douche	Other
All races												
1976	9.0	19.3	28.3	22.3	6.1	2.9	7.2	3.0	3.4	2.0	0.7	0.9
1973	6.5	16.4	22.9	25.1	6.7	2.4	9.4	3.5	2.8	1.5	0.6	1.3
1970	6.3	10.6	16.9	22.3	4.8	3.7	9.2	3.9	4.1	1.5	2.1	2.9
1965	7.6	7.8	15.4	15.3	0.7	6.3	14.0	2.1	6.9	2.6	3.3	4.9
Whites												
1976	9.0	20.1	29.1	22.5	6.1	3.0	7.4	2.9	3.5	2.0	0.5	0.9
1973	6.6	16.5	23.1	25.1	6.6	2.5	9.9	3.5	2.9	1.6	0.5	1.3
1970	6.4	10.4	16.8	22.4	4.8	3.8	9.7	4.0	4.4	1.5	1.9	2.8
1965	8.2	7.6	15.8	15.6	0.7	6.8	14.5	2.0	7.5	2.7	2.7	4.8
Blacks												
1976	8.8	12.9	21.7	22.0	6.1	1.8	4.5	3.8	1.4	1.8	2.7	1.2
1973	6.2	14.6	20.8	26.3	7.6	1.2	3.2	3.0	0.7	0.4	1.8	1.0
1970	6.3	12.0	18.3	22.1	4.5	3.1	4.0	3.6	1.0	0.4	4.7	3.8
1965	5.3	8.6	13.9	12.4	1.7	2.9	9.7	3.5	1.4	1.2	10.0	5.8

[a]From Ford, 1978; Westoff, unpublished data; and 1965 and 1970 NFS public use tapes.

year that a method was used (whether it was the first attempt or a resumption after a period of nonuse), 3.7% of preventers and 7.3% of delayers failed to prevent an unintended pregnancy while using the contraceptive of their choice. If we exclude sterilization, the failure rate for preventers was 5.1% (Vaughan *et al.*, 1977). In the second year, for those who had not experienced failure in the first year, the failure rates were 2.4% for preventers and 5.2% for delayers.

The rates measure the effectiveness of a method in the general population of users who have selected one method from all those available to them at a particular time. These measures do not represent a magic number giving *the* effectiveness of a method. They may change over time, as the characteristics of the users change. Their advantage lies in the fact that the effectiveness of all methods can be estimated from comparable data on the general population of married contraceptors.

The failure rates presented here are all estimated by life table procedures. The figures are estimates of the percentage of couples who begin using a method and would experience an unintended pregnancy within 1 year, calculated under the assumption that there is no reason except pregnancy for discontinuing the use of that method. We strongly prefer this estimation procedure to the Pearl Index, which was commonly used in earlier studies. The Pearl Index is defined as 12 times pregnancies/couple-months of use. It is an adequate measure only when couples do not vary in fecundity or in effectiveness of contraceptive use. If they do, the Pearl Index *decreases* as the length of the follow-up study increases because, as the months go by, only the less fecund or the more effective users are left in the study population. They contribute months of use to the denominator, but few pregnancies to the numerator. The Pearl Index is, therefore, difficult or impossible to interpret as a useful statistic for comparing different methods (see the appendix).

Failure rates within the first year of contraceptive use vary greatly by method. For preventers, failure rates ranged from 0% (sterilization) to 13.1% (foam, jelly, cream). The failure rates for delayers were higher than those for preventers for all methods except the pill, which remained at 2% (see Table 3).

There are differentials in use and failure rates among various groups of the population. The age of the respondent might be expected to have a strong influence on the propensity to fail. First, fecundity is known to decline with age, and other things being equal, lower fecundity implies a lower proportion who will fail. Moreover, advancing age is one reason underlying a decision to curtail childbearing. One might expect,

TABLE 3 Percentage of Married Couples in the United States Who Fail to Prevent an Unwanted Pregnancy or to Delay Their Wanted Next Pregnancy within the First Year of Contraceptive Use, by Intention and Method, between 1970 and 1973[a]

Method	Failures by Intention (%)		
	Prevention	Delay	Total
All methods	3.7	7.3	5.5
Pill	2.0	2.0	2.0
IUD	2.9	5.6	4.2
Condom	6.6	13.7	10.1
Foam/cream/jelly	13.1	16.7	14.9
Other	8.5	20.4	14.5
Diaphragm	10.3	15.9	13.1
Rhythm	9.5	28.8	19.1
Remainder	6.5	15.1	10.8

[a]From Vaughan *et al.*, 1977. With permission from *Family Planning Perspectives*.

then, that age would be a more important determinant of failure rates for preventers than for delayers. Indeed, 1-year failure rates decline monotonically from a high of 7.1% for women aged 15–19 to a low of 1.1% for women aged 35–39. On the other hand, there is no systematic relationship between the woman's age and her failure to delay a pregnancy that is wanted.

Higher education has nearly always been found to be negatively associated with failure rates. Education may be a surrogate for contraceptive sophistication, or an educational opportunity may be lost because of an unintended pregnancy. Whatever the reason, higher education was indeed negatively associated with contraceptive failure for women in the United States between 1970 and 1973. Among delayers, 1-year failure rates averaged 8.6%, 7.2%, and 6.5% of women with fewer than 4 years of high school, 4 years of high school, and more than 4 years of high school, respectively; among preventers, the averages were 4.2%, 3.8%, and 2.9% of those in the same educational categories.

Parity may be expected to be positively associated with contraceptive failure because high parity implies, in part, previous contraceptive failure. In fact, we found that among preventers, parity is negatively associated with the propensity to fail, except for the very highest

parity, i.e., six or more births. We found no association among delayers.

As was mentioned earlier, blacks are less likely to be users of contraceptives. However, we find that their effectiveness is higher than that of whites when they want to postpone a pregnancy, primarily because they are more likely to be using the more effective methods. The failure rates for delayers were 3.8% for blacks and 7.4% for whites. When the intention is prevention, the failure rate for blacks (4.2%) is slightly higher than that for whites (3.7%). This difference could result from a differential tendency to report a pregnancy as *unwanted* (at the time of that pregnancy, the woman never wanted another child).

Catholics have increasingly used the more effective methods. Among married white couples, Catholics experience slightly higher failure rates than do non-Catholics (8.7% versus 6.7%) when they attempt to postpone a pregnancy and slightly lower failure rates (3.3% versus 3.8%) when they seek to prevent a pregnancy.

Thus, there are low, but not insignificant, failure rates associated with even the "best" methods. In use, rather than in the laboratory, sterilization is the only close to infallible method.

However, these failure rates present only part of the overall picture. They represent the unintended pregnancies that occur while the method is being used. We know that many women or couples experience difficulties with the use of some methods and discontinue their use. We therefore examined the continuation rates for each method for which sufficient data were available. The continuation rates numerically answer the following question: What proportion of women would still be using this method 1 year after they began use if the only reasons for stopping it were related to dissatisfaction with the method (as indicated either by switching to another method or by stopping for reasons other than wanting to become pregnant or marital dissolution). For all methods together (except sterilization), 77% of preventers and 71% of delayers would still be using the method at the end of 1 year, and 69% and 58%, respectively, at the end of 2 years. The continuation rates for the condom and for foam, cream, and jelly taken together are lower than those for the pill and IUD (after 1 year, for preventers, 64% and 58% versus 73% and 78%; for delayers, 67% and 57% versus 76% and 76%) (Vaughan *et al.*, 1978). In summary, even if accidental pregnancies are avoided, 25% or more discontinue use of a particular method within a year.

We believe that these failure rates are all too low. In the 1973 survey, almost no abortions were reported, although there were significant numbers recorded under the various systems in which abortions are

counted at the time they are performed. Therefore, a contraceptive failure that was followed by an abortion was not reported to the interviewers at all, so that our numbers of contraceptive failures *underestimate* the true ones.

Thus, no perfect contraceptive is yet available. Even with the overwhelming proportion of couples using methods of fertility control that seem to have fairly low failure rates, the problem of unintended childbearing is not solved. Even these small failure rates are important for the population considered in aggregate. Among married women, some 396,000 births per year (13% of all births in 1970–1972) resulted from unplanned or unwanted pregnancies of women who were using a method. Another 19% of all births were unplanned or unwanted and were conceived while the mother was not using a method (see Table 4). On the basis of the 1973 NSFG, nearly one-third of all legitimate births resulted from unintended pregnancy as recently as 1970–1972.

These numbers represent the experience of married women only; hence, few teenagers are included in any of these studies. Consequently, these figures, dramatic as they are, do not reflect the true magnitude of the problems of fertility control that remain in the U.S. population.

CONTRACEPTIVE USE IN DEVELOPED COUNTRIES

For no other countries are there data on levels and trends in use of contraceptive methods as extensive as those for the United States. Many developed countries have yet to publish or even collect data on a national level. This situation will change over the next few years as data suitable for transnational comparative studies become available. The World Fertility Survey (WFS) currently being conducted by the International Statistical Institute is sponsored by the United Nations and the International Union for the Scientific Study of Population. The WFS plans to conduct fertility surveys in more than 40 developing countries. Complementing and cooperating with this effort, about half as many developed countries will conduct their own fertility surveys designed to yield comparable information. Among the latter are Belgium, Bulgaria, Canada, Czechoslovakia, Denmark, Finland, France, Israel, Japan, the Netherlands, Norway, Poland, the United Kingdom, the United States, and Yugoslavia (Nortman, 1977).

For relatively recent data, we turned to the United Nations Economic Commission for Europe (ECE), which published a report (United Nations, 1976) analyzing results from national surveys that were conducted in the United States and European countries between 1966 and 1972. The data have been analyzed on the basis of comparable

TABLE 4 Average Annual Number of Unwanted and Unplanned Births to Married Women in the United States from 1970 to 1972[a]

Status of Birth	Births, Annual Average (thousands)				Percentage of All Births
	Intended	Unwanted	Unplanned	Total	
Intended births	2,060.3			2,060.3	67.8
Unintended births					
Conceived while using contraception		220.1	176.1	396.2	13.0
Conceived while not using contraception		307.0	277.5	584.5	19.2
TOTALS	2,060.3	527.2	453.5	3,041.0	100.0

[a]Tabulated from the 1973 National Survey of Family Growth public use tapes.
NOTE: Number may not add to total due to rounding.

definitions and with the important qualification that data on contraceptive sterilization were not collected in most of the countries. Therefore, the analysis has been restricted to users of methods of contraception other than sterilization. The study staff recognized that the period covered was one of rapid change in contraceptive practice. Table 5, which contains data from 11 countries, should be examined with these caveats in mind. The data for the United States are based on the 1970 NFS but do not agree with the information discussed earlier because sterilization is excluded from the definition of contraceptive use and the definition of current contraceptive use is slightly different. In all of the countries, fertility is relatively low and contraceptive use substantial, with close to 60% or more of married women reporting current use. However, as the United Nations' authors point out, "the two most significant things about the data on current use are the marked diversity in types of methods employed in the context of low fertility and the absence of any apparent correlation between levels of current fertility and reliance on the most effective methods" (United Nations, 1976, p. 149).

Figure 1 displays the percentage of users who rely on the pill and IUD (top panel), the condom and diaphragm, withdrawal, and rhythm. The United States has the highest percentage relying upon the most

TABLE 5 Total Fertility, Current Use, and Percent Distribution of Married Women of Reproductive Age, by Current Contraceptive Practice, in 11 Countries of the United Nations Economic Commission for Europe[a]

Fertility and Contraceptive Use	Finland (1971)	Hungary (1966)	Denmark[b] (1970)	Czecho-slovakia (1970)	Poland[c] (1972)	Yugo-slavia (1970)	France (1972)	United States (1970)	Belgium[c,d] (1966)	England and Wales (1967)	Nether-lands[e] (1969)
Total fertility rate in survey year	1.7	1.9	2.0	2.1	2.2	2.3	2.4	2.5	2.5	2.6	2.6
Current users											
Percentage of all respondents	77	64	67	66	57	59	64	56	76	69	59
Percentage of respondents exposed to risk of pregnancy[f]	83	70	84	—	—	62	71	67	83	84	—
Percentage distribution of users according to main method currently used[g]											

Intrauterine device	4	—	4	14	1	2	2	9	—	2	1
Pill	26	—	37	4	4	9	17	41	8	19	45
Condom	40	16	30	19	17	6	12	17	6	41	23
Diaphragm	—	7	9	—	—	—	1	7	—	6	2
Withdrawal	21	66	7	52	49	73	52	3	51	25	9
Rhythm	1	4	2	3	23	3	14	8	26	5	19
Other	8	7	11	8	5	8	2	16	8	2	1
TOTALS	100	100	100	100	100	100	100	100	100	100	100

[a]From United Nations, 1976, p. 151.
[b]Excluding central municipalities of Copenhagen.
[c]Delay of 18 months in field work.
[d]Women under 40 years of age.
[e]Marriage cohorts in 1958 and 1963 only.
[f]Excluding pregnant and sterile women; but for Yugoslavia, excluding only pregnant women.
[g]Women reporting multiple methods (excluding abstinence and sterilization) were assigned to the first of those multiple methods as they are ordered in this table.

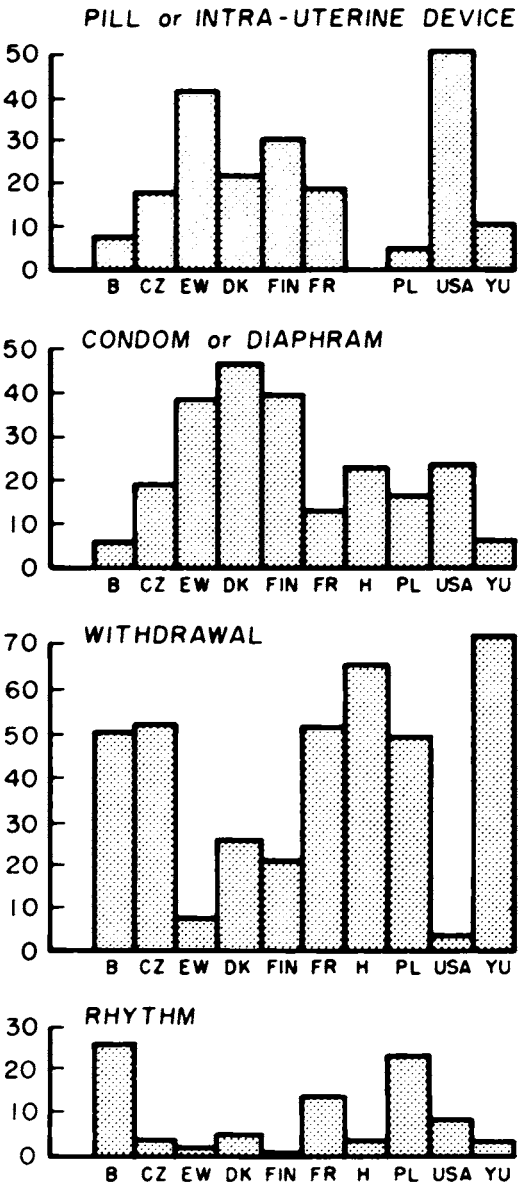

FIGURE 1 Percentage of current users, by method of contraception. B = Belgium, CZ = Czechoslovakia, EW = England and Wales, DK = Denmark, FIN = Finland, FR = France, H = Hungary, PL = Poland, USA = United States, and YU = Yugoslavia. From United Nations, 1976, p. 150.

effective methods (50%). The variation in use of these methods is large, ranging from the value just reported for the United States to 8% in Belgium, 5% in Poland, and nearly zero in Hungary. More recent data for Flemish Belgium show dramatic changes indicating that by 1975–1976, 41% of users were employing these methods (Nortman, 1977, p. 13). Around 1970, the condom and diaphragm were selected by over 30% of users in England and Wales, Denmark, and Finland but by considerably lower proportions elsewhere. By contrast, 52% of Japanese users in 1975 reported that the condom is their current method, 12% used the pill or IUD, and 4% used withdrawal (Nortman, 1977, pp. 12–13). The use of withdrawal in Europe around 1970 is surprisingly high. In two countries—Hungary and Yugoslavia—over 60% of the users depended upon this method, one that forms a miniscule fraction of contraceptive practice in the United States. In four additional countries—Belgium, Czechoslovakia, France, and Poland—fully one-half of the users still depended upon withdrawal. The rhythm method represented over 10% of users in France and over 20% in Belgium and Poland.

These very different patterns of contraceptive practice *all* resulted in low fertility, although any number of studies have shown that the effectiveness of the methods varies considerably. How, then, could low fertility be achieved? The ECE report concluded that the answer must be in the prevalence of induced abortion. Figure 2, taken from their study (United Nations, 1976), shows the relationship between the percentage of users depending upon withdrawal and the number of legal abortions per 1,000 women aged 15–44. Belgium and France are omitted because no legal abortions are reported. The Eastern and Western European countries tend to cluster at opposite ends. However, before drawing overly simplistic conclusions from this figure, it must be noted that in the United States and most Western European countries, the legal abortion rates were underestimates of the true prevalence of abortion. For example, the U.S. rate for 1975, when legal abortions were more readily obtainable, was 18 per 1,000 women (U.S. Department of Health, Education, and Welfare, 1977). The ECE reported that after the abortion laws changed in England, the abortion rate rose to 11.2 per 1,000 women in 1972. In addition, on the basis of assumptions that they consider to be quite conservative, they estimated that the prevalence of abortion in France was at least 29 per 1,000 women which, when combined with the fact that 52% of contraceptors use withdrawal, would place France quite close to Czechoslovakia in Figure 2 (United Nations, 1976, pp. 152–154).

In countries where couples depend on a method with high failure

rates, whether the dependence results from inaccessibility or a lack of variety of more effective methods, there is clear indication that the only way that low fertility can be achieved is by resort to induced abortion.

DISCUSSION

In the United States and other developed countries today, there is still a high incidence of unintended pregnancies despite the fact that the vast majority of couples use methods of fertility control that seem to have fairly low failure rates. A large proportion of couples has chosen sterilization, the only method that is a virtually perfect preventive of further childbearing. One view of this phenomenon is that people are more willing to accept responsibility for controlling their reproductive lives and to make the nearly always irrevocable decision to terminate reproduction. Another view is that the resort to sterilization is indicative of dissatisfaction with the currently available imperfect methods of contraception that cannot prevent significant numbers of their users from becoming pregnant and having an unintended child or making the often difficult decision to abort the pregnancy. Rather than living with this unpleasant prospect for the remainder of their naturally fecund years, couples may be forced to choose sterilization as the best of unsatisfactory alternatives before they are truly certain that they never want or never will want another child.

Couples who do not choose sterilization and no longer want to rely on the pill are faced with the very real difficulties resulting from dependence on less effective methods. Increased abortion or increased unintended fertility or both may be the consequence of changing from the pill to use of currently available alternatives.

The problems of fertility control in the developed countries call for action on two fronts. An intensive research effort is needed to develop and make available effective, safe, and easily used contraceptive methods. Concern and support for such research cannot be allowed to decline because of a mistaken assumption that all major problems of contraception are solved.

Another part of the problem may be that individuals have insufficient information at their disposal to make rational choices from among the available methods. There is need for continuing evaluation of the effectiveness of methods in normal use and for disseminating this knowledge to users, prospective users, and their advisors in the contraceptive decisionmaking process.

The U.S. Food and Drug Administration (FDA) recently made a

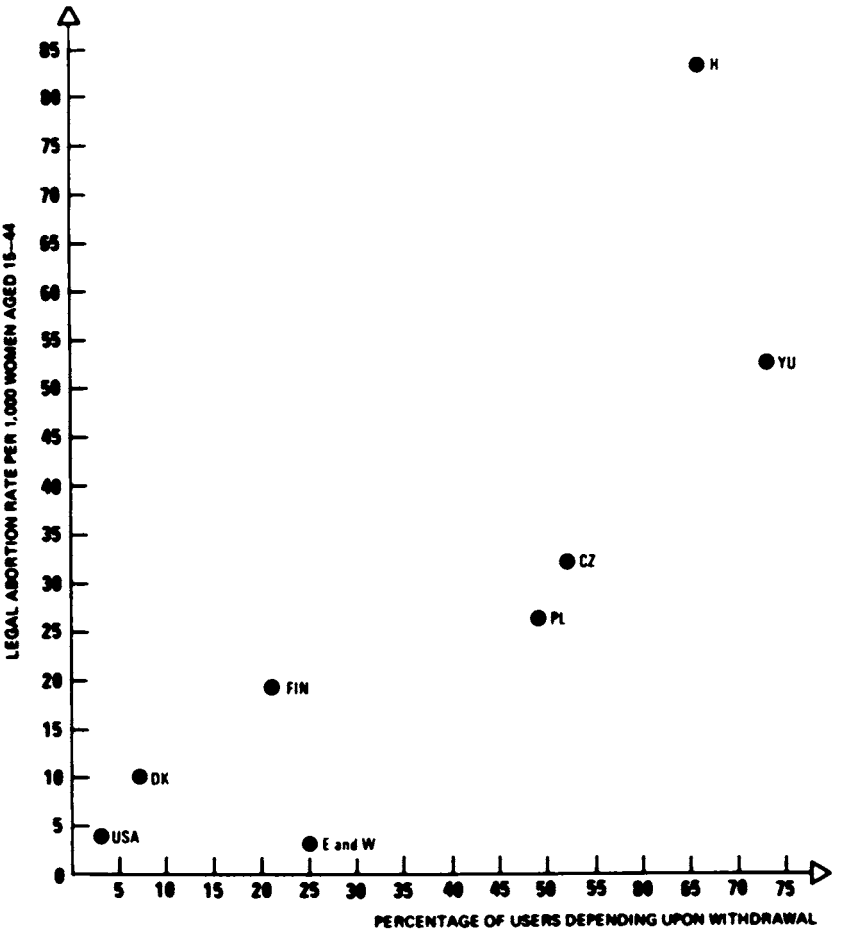

FIGURE 2 Legal abortion rates and proportion of contraceptive users depending upon withdrawal. USA = United States, DK = Denmark, FIN = Finland, EW = England and Wales, PL = Poland, CZ =Czechoslovakia, H = Hungary, and YU = Yugoslavia. From United Nations, 1976, p. 153.

laudable decision to require package inserts with the pill and IUD's. These inserts will provide information that is needed by women to make rational contraceptive choices. The FDA has been advised that the content of this information, especially with regard to effectiveness, needs to be improved. Unfortunately, it has decided that the failure rates listed in the inserts are sufficient, although they are based on an inadequate methodology (Pearl Index) and do not reflect the current

experience of American women. If improvements were made and a requirement that similar information be provided in over-the-counter contraceptive products was instituted, the ability to make an informed choice would be significantly improved.

The development of other mechanisms for evaluating the effectiveness of contraceptive methods and disseminating the resulting information would be welcome.

Although contraceptive practice is nearly universal, at least among married couples in the developed countries, we see much room for improvement in methods to help women and men achieve the numbers and spacing of children that they desire.

APPENDIX: THE PEARL INDEX

For at least the past decade, it has been well known that the Pearl Index conceals far more than it reveals. After investigating the properties of this measure, Sheps (1966) concluded that "the behavior of the index may become so erratic that it does not serve as an estimator of any quantity of interest and comparisons between groups may be impossible to interpret." Although her arguments were framed in complex mathematical terms, the reasoning underlying her conclusion is quite simple. The Pearl Index is defined as the number of failures (pregnancies) divided by the total number of months of exposure to pregnancy, multiplied by 12 (to convert from months to years) and frequently multiplied by 100 (to eliminate the decimal). The resulting statistic is then interpretable as the number of pregnancies per 100 woman-years of exposure to the risk of pregnancy. The Pearl Index (before it is multiplied by 1,200) is an unbiased estimator of the monthly probability of becoming pregnant if and only if the monthly probability is *constant* over both women and duration of use. However, two decades of research have demonstrated conclusively that monthly failure rates decline as the duration of use increases. This decline may be caused by two factors. First, couples may "learn by doing," so that the lucky ones who by chance do not become pregnant learn how to contracept more effectively as their experience increases. Second, the poorer (or less motivated) contraceptors or women with higher biological propensities to conceive are eliminated early, leaving a pool of either better contraceptors or less fecund women as time goes by. It is not possible to distinguish empirically between the two reasons; nor does it matter, for our current purposes, which of the two is more likely. That failure rates decline is quite incontrovertible. For example, the data collected in the 1973 cycle of the NSFG on women who sought

to prevent an additional pregnancy by using the IUD or condom yield the following Pearl Indices, depending on the maximum exposure that any woman is allowed to contribute:

Maximum Exposure	IUD	Condom
12 months	18/7,865 × 1,200 = 2.75	59/9,654 × 1,200 = 7.33
24 months	23/13,560 × 1,200 = 2.03	82/17,279 × 1,200 = 5.69

It can easily be seen that the Pearl Index can be unintentionally made to be nearly any number. Specifically, the longer that one runs a prospective study, the smaller the resulting Pearl Index will be (Potter, 1960).

One way to eliminate this problem is to cut off the study at 12 months by not permitting successful users to contribute more than 12 months of exposure. The comparisons between methods can be made with more validity. Unfortunately, the Pearl Index is still difficult to interpret. Many family planning clinicians infer that the index can be interpreted as the number of women out of 100 who would become pregnant within 1 year, regardless of when exposure is truncated. The inaccuracy of this interpretation can be most easily understood by considering the Pearl Index for those who use no method at all. The Pearl Index for women in their prime reproductive years (20 to 30) who use no method is approximately 240 pregnancies per 100 woman-years of exposure. Clearly, it is invalid to interpret this statistic as meaning that "240 women out of 100 will become pregnant within 1 year." How could the index logically be so high for these women? The answer lies in the often omitted and seemingly innocuous phrase "per year of exposure to the risk of pregnancy." Women who become pregnant are no longer at risk. Conceptually, the Pearl Index replaces each woman who becomes pregnant. Thus, the maximum attainable index would be 1,200, or 12 pregnancies per woman-year of exposure; this number would occur if each woman became pregnant during the first month of exposure.

The method known as the life table procedure can be used to calculate only the measure that most people find easiest to interpret. Detailed, comprehensive discussions of this method are available (Tietze and Lewit, 1973). Basically, a life table can be viewed as a column of numbers that specify the percentage of women who are still using a contraceptive after 3, 6, 9, 12, or any specified number of months since initiation of use. Clearly, there are many ways to exit from a contraceptive life table: one may fail (become pregnant) or

discontinue use for medical, aesthetic, or personal reasons. For the purpose of isolating events of interest, an associated single decrement life table may be computed from the information contained in the multiple decrement life table. Resulting pregnancy rates when all other causes of discontinuation have been eliminated are called gross rates, while those obtained from the multiple decrement table are called net rates. Gross rates convey the proper information to a couple seeking to know their *average* chances of a contraceptive failure. Similarly, if one is interested in removal of an IUD for medical reasons, all other causes of discontinuation should be eliminated.

The life table procedure gives clearly interpretable results, whereas the Pearl Index does not.

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Discussion of Paper Presented by Jane Menken *et al.*

LISE FORTIER

Dr. Menken has given a sophisticated view of contraception as practiced in developed countries from the point of view of effectiveness and universality, since it appears that only 8% of women at risk in the United States do not use contraception.

Her main conclusion is that individual fertility control systems are far from perfect because they still lead to unwanted pregnancies and that the known number of contraceptive failures is an underestimate of the real one. She makes her point strongly when she states that during 1970–1972, in the United States, a third of the legitimate births were unintended. I suspect that a number of those births have resulted from the neglect of physicians to inform their patients accurately.

In this discussion of contraception, abortion is mentioned only to point out that a couple depending on a method with high failure rates may resort to abortion. Consequently, their achieved fertility does not vary greatly from that of the couple who depends on more effective methods. Indeed, Tietze has shown that this combination of less dependable method and legal abortion is the safest means of fertility control in terms of health (Tietze and Murstein, 1975).

Contraception is defined as "the prevention of conception." This contradicts the etymological sense of the word, which is "against conception," and has no time-related value, so that abortive procedures should be included in contraception.

I think the narrowing of the meaning of contraception to exclude abortion is another symptom of prudishness and the unwillingness to

admit that abortion is one of the main avenues to fertility control that should sometimes be preferred.

Dr. Menken's very statistical approach to contraception challenged me to discuss the philosophy of contraception and the way it affects women especially. Although the *raison d'être* of contraception is to make sex more enjoyable by eliminating undesired consequences for both partners, some rationalize that being the breeder, the woman should be the contraceptor.

Yet, the first effective means of contraception, abortion excluded, were male-oriented methods, such as condoms and coitus interruptus. This contributed to the maintenance of the dominance of the male over the female, since *he* was free to decide when *she* would or would not become pregnant.

Since the advent of diaphragms, jellies, and pills, men have acted very often as if contraception was no longer their business. However, the women's liberation movement has made many women look suspiciously on female-oriented contraception, comparing it to the venereal disease control programs of the past, when infected females were imprisoned while the male partners were left to propagate the disease among other females.

Beyond the time of conception, birth control can only be female-oriented. But, why is contraception mostly female-oriented prior to conception? We have heard from Mr. Zeidenstein that monies available for research in contraception are directed mostly to female contraception. While this has been challenged by Mr. Jaffe, I would suspect that it is true.

It makes me wonder if this situation would have occurred had there been as many women physicians and scientists as there are male physicians and scientists. Contraception in developed countries is undergoing a subtle change with which many of us are still not too familiar. Women are becoming more and more self-reliant. They believe that they no longer need to submit to their biological destiny and be forced by laws or morals to produce cannon fodder for the nation or baptized souls for the church.

While some women's radical groups view most contraceptives as an exploitation of women and as an evidence of male irresponsibility, other women (and their number is growing) see the use of sterilization, the pill, or IUD's as a way to master their own destiny. Furthermore, male contraception protects women against activity with one male, but not against activities with others.

With male contraception, women must relinquish the control of their

reproductive function to a man. Although many women are still unable to verbalize the motivation behind their preference for female sterilization rather than the much simpler and safer vasectomy, there is no doubt that keeping the control of their reproductive function is one of the main reasons.

One could divide the history of contraception into eras. As was emphasized by Dr. Menken, the change in contraceptive practice is revolutionary. In 1976, 69% of those practicing contraception in the United States were using methods that were unknown in 1960. The pre-pill era was characterized by a willingness to face sexual restriction as being much better than no sex at all.

During that era, females even feigned sickness as a means of contraception. Nobody would have complained that a diaphragm or jelly was messy. If lucky enough to find a physician who would fit a diaphragm, women were so elated that they overlooked its disadvantages.

Then came the pill. It was a shining star. I remember being one of its high-pressure salesmen, singing its wonders, insisting on its innocuousness, and, most of all, asserting its 100% efficacy. Nothing could make me, who had lived in the pre-pill era, more irate than the young women, who after 2 or 3 years of being adequately protected, would complain that they were tired of using the pill.

One of the underestimated effects of the pill was its discrediting of many spiteful theories about women, such as the mental origin of vomiting during pregnancy or of functional dysmenorrhea. For that reason alone, the pill would have been worth its weight in gold.

Some people are terribly worried about the pill's health risks. For others, the pill's contraceptive efficacy is so important that they are ready to forego the safety of other methods. Some women would rather die than have another child. This is substantiated by the risks that they take with illegal abortion. They insist on a 100% efficacy that could be dangerous.

Telling them that it is better to risk a pregnancy than to risk one's life does not impress them. This situation applies especially to a number of women who should be taken off the pill because of their age or some other condition. They are the ones who will refuse an IUD because of its slight risk of failure.

One danger with which women have not been sufficiently concerned is the loss of fertility resulting from the use of IUD's. Many women will fear that after years of taking the pill they may not be able to conceive again or will bear abnormal children. The same fear has not reached

their consciousness as far as IUD's are concerned, although barrenness resulting from that method is much more in the realm of possibility.

IUD's are additionally disadvantageous in that they cause haphazard bleeding. In some religions, which, like all religions, degrade women, intercourse is often impracticable because women are considered impure when bleeding. Consequently, there is an ever-growing demand for sterilization, the only method that is nearly infallible.

Indeed, motherhood in our society must be quite a burden when so many women with one child or even none insist on sterilization and ignore the possibility of future regret. The only consideration that seems to make them hesitate is the possible failure of even tubal ligation.

The laws that impose delays before abortion are laws that have been elaborated for nonparenthood. Unfortunately, they do not protect a patient very much. No laws exist for parenthood. A very small minority of patients will derive advantages from those laws, while a large majority will have to fight their way through them. Delays guarantee more unwanted pregnancies than thoughtful decisions, and there are many more women deprived of the sterilization they want than there are women sterilized against their will.

Sterilization of severely mentally retarded people is still a subject of great controversy. The myth that childbirth is a normal, almost always desirable function ignores the fact that pregnancy and childbirth, even under the best of conditions, are a threat to the health of a normal person and more so to the physical and mental health of a mentally retarded person. If those people are not sterilized, they will be condemned to the use of pills, injections, and IUD's, which demand continuous medical surveillance and are not without risk. In the end, they are deprived of their capacity to bear the children they are unable to care for and are subjected to the dangers of these contraceptive methods.

More than one type of contraceptive is needed for each patient. Some of the methods of contraception that are in use are enjoyed because of their ease of application and their efficacy. Eventually, these may fall into disrepute. Some that have already fallen into disrepute will be rediscovered and will know new moments of glory.

The popularity in Japan of the colored, multishaped condom is a good example of that. As a woman, I wish that new methods would be developed that would interfere less with the female physiology and more with the male physiology or with the transfer process. But the ideal method of contraception, a method that is 100% effective, has no

side effects, does not interfere with the enjoyment of sex, and is reversible, is unlikely to exist, since perfection is foreign to this world.

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Tietze, C., and M. C. Murstein. 1975. Table 35, p. 61, in Induced Abortion: 1975 Factbook. Reports on Population/Family Planning. No. 14, 2nd ed. The Population Council, New York.

Experience with Contraceptive Methods in Developing Countries

W. PARKER MAULDIN

For convenience, the term contraceptive methods will be used to *include* induced abortion (although it is not strictly a contraceptive method), because it is assumed that the intent is to discuss experience with conscious efforts to control fertility. Coitus interruptus (withdrawal) is *excluded* because it needs neither information/instruction nor supplies and because there is a paucity of information about its use.

The issues addressed in this presentation are where have we been, where are we, how did we get there, and what were the problems along the way. I will address broadly what has happened, from around 1960 up to the present, in developing countries.

THE SITUATION IN DEVELOPING COUNTRIES

We choose 1960 as a starting point because governmental efforts were then just beginning, donors were confined to Sweden and a few foundations, and oral contraceptives and IUD's had been invented but were not yet in substantial use.

Policies and Programs

India had a policy that was designed to reduce rates of population growth dating from 1952, but its programmatic efforts were still rather small. Gopalaswami (1962) attributed the slow progress to the fact that:

. . . the work which we had undertaken was unprecedented. We had to find out by trial and error exactly what was the right thing to do and what was the right way of doing it. We had, therefore, to limit the number of places at which active work was started, allow time for trying out our provisional ideas regarding the organizational setup and methods of work: we have been engaged only on what must be regarded as pilot experimentation.

China gave some attention to fertility control starting in 1958, but the extent and nature of activities at that time are shrouded in generalities that have been manufactured from bits and pieces of information. Pakistan (including what has become Bangladesh) had just adopted a policy that was designed to reduce fertility and had developed a general plan for its implementation (Sharif, 1962), but programmatic activities were yet to begin. Voluntary family planning associations had small programs in a number of developing countries. These were important primarily for their policy rather than for their demographic effects.

In May 1958, the government of Ceylon (now Sri Lanka) accepted an offer from the Swedish government to give technical assistance to a Family Planning Pilot Project in two rural areas in Ceylon. It expected that the experiences in the rural areas could be extended to a nationwide scale (Kinch, 1962). These were the small beginnings of program activities at that time.

A conference held in October 1960 (Kiser, 1962c) summarized the major programs, pilot studies, and research then under way. Discussions centered on such topics as whether family planning programs should be concentrated in urban areas or be attempted in rural areas as well, how best to communicate with prospective clients, and other timely issues. Excerpts from that conference indicate the status of contraceptive technology in developing countries at that time:

- "The condom was not used in the Harvard Ludhiana study in part because it was thought not suitable and possibly because it was thought to be too expensive and was introduced in the Singur study only after the foam tablet, withdrawal, and rhythm had been tried" (Kiser, 1962a).
- In a survey on fertility and attitudes toward family formation in Santiago, Chile, "questions as to contraceptive practices were not asked, since it was thought the respondents might regard this as an inquiry of so intimate a nature as to be objectionable" (Tabah and Samuel, 1962).
- "Use-effectiveness studies of contraceptives included the condom, diaphragms, foam tablets, jelly alone, suppositories, withdrawal, and douche" (Tietze, 1962).

- Experience with the pill was limited, and its potential was viewed as follows: "Even at the present time, however, this method warrants recognition as an outstanding achievement in the control of fertility by physiological means" (Segal, 1962).
- "Brief reference was made to uterine rings, which are receiving a revived interest in certain countries" (Kiser, 1962b).

There are no data regarding the extent of use although it is known that use was extremely low in rural areas and, for the most part, was limited to the small upper classes of cities. Fertility was high and stable. Crude birth rates were estimated at 48 in Africa, 41 in the Americas, and 39 in Asia (or above 40 in Asia, excluding China).

In 1965 a similar conference was held. But the focus had shifted to action programs rather than research. Berelson (1966) described the major changes that occurred in the short period of 1962–1965 as follows:

> Family planning programs are successfully underway in South Korea, Taiwan, and Tunisia, and are currently in process of major expansion and intensification in India and Pakistan. Turkey, Malaysia, Singapore, Ceylon, and Egypt are embarking upon national efforts. A high-level seminar on population policy in Thailand was followed by a successful pilot project and that in turn by a seminar to consider extension of the program there. In the Philippines, the Health Department of Manila and a major university are beginning experimental efforts. In Latin America, the first Pan-American Assembly on Population Problems was held in summer, 1965; Peru and Venezuela have established population units within their Ministries of Health, and Colombia within its Association of Medical Faculties; and a national program is being established in Chile. The government of Mauritius is supporting family planning efforts there, and a technical assistance mission submitted its report to the government of Kenya in the summer of 1965, the first such mission to a country in sub-Saharan Africa.
>
> Within the United Nations, the World Health Organization in May 1965, authorized the development of an advisory program; the UNICEF Governing Council in June instructed the Director to prepare a statement on possible activities in the field; and the Economic and Social Council in July unanimously recommended "advisory services and training on action programs in population." Moreover, the United Nations sent an expert mission to India in the spring of 1965 to advise on that country's family planning program, and so did the World Bank.
>
> The Roman Catholic Church became engaged in a "wide and profound" study of its position on this matter, including the establishment of a Papal Commission. Several high prelates in the Ecumenical Council called for a searching re-examination of Church teachings.
>
> A major advance in contraceptive technology, the intra-uterine device, was developed and came into widespread use.

In the United States, the Agency for International Development extended its policy in the spring of 1965 to include the provision of technical assistance on family planning. Several universities have established centers for population study, typically in their schools of public health. Two great American foundations have included population studies prominently among their programs. The American Medical Association reversed a neutral policy dating from the 1930's; the National Academy of Sciences issued reports on world and United States population problems; the Supreme Court voided a state law against contraception on grounds of the right to personal privacy; federal, state, and local governmental agencies expanded their activities in family planning; and the President of the United States spoke out about the urgency of dealing with population problems.

Such programs were just beginning. At the 1965 conference, Freedman (1966) "hazarded" the prediction of really major fertility declines in the subsequent 5 years, at least in Taiwan, Korea, Singapore, and Hong Kong. He observed that:

In the 1960 Milbank-Population Council Conference, only five years ago, there were doubts that organized efforts could make a difference on a large scale anywhere soon. The four populations to which I refer were not even represented by scholars or reports at the 1960 conference. They were hardly mentioned.

Funding

The earliest summary of funding for activities pertaining to population control in developing countries is for 1962. At that time Sweden was the only government to provide assistance. Others involved in such activity included the Ford Foundation, the Population Council, and the International Planned Parenthood Federation (IPPF). Their combined budgets for population activities were less than $5 million (Harkavy *et al.*, 1969). In 1976, the comparable figure was $300 million ($214 million in constant 1970 dollars) (Gille, 1977).

CONTRACEPTION IN DEVELOPING COUNTRIES, 1976–1978

Policies and Programs

From a standing start approximately 15 years ago, 65 countries containing 92% of the population of the developing world have officially adopted family planning policies, for either demographic or health-related humanitarian reasons (Table 1). The programs have ranged from vigorous and continuous efforts under skilled management

TABLE 1 Number of Countries, Population, and Distribution of the Population in the Major Regions of the Developing World, by Government Position on Population Growth and Family Planning, 1977[a]

Government Position	All Developing Countries[b]	Northern Africa[c]	Balance of Africa	Western Asia[d]	Eastern Asia and Oceania[e]	Southern Asia	Latin America[f]
	Number of Countries[g]						
Official policy to reduce the population growth rate	35	3	5	2	11	5	9
Official support of family planning activities for other than demographic reasons	30	2	13	2	1	0	12
Government position unknown	1[h]	0	0	0	1[h]	0	0
Remainder: no policy to reduce the growth rate and no support of family planning activities	66	1	28	12	12	1	12
TOTALS	132	6	46	16	25	6	33
	1976 Population (in millions)						
Official policy to reduce the population growth rate	2,252	62	30	75	1,186	790	109
Official support of family planning activities for other than demographic reasons	422	36	169	31	3	0	183
Government position unknown	16[h]	0	0	0	16[h]	0	0
Remainder: no policy to reduce the growth rate and no support of family planning activities	209	2	113	36	45	1	12
TOTALS	2,899	100	312	142	1,250	791	304

	Percentage Distribution of Population						
Official policy to reduce the population growth rate	78	62	10	53	94.9	99.9	36
Official support of family planning activities for other than demographic reasons	14	36	54	22	0.2	0	60
Government position unknown	1	0	0	0	1.3	0	0
Remainder: no policy to reduce the growth rate and no support of family planning activities	7	2	36	25	3.6	0.1	4
TOTALS	100	100	100	100	100	100	100

NOTE: Data shown in this table are for developing countries that have official government population policy positions or that have estimated populations of 100,000 or more.

[a]From Nortman and Hofstatter, 1978.

[b]Development status is based primarily on stage of economic development.

[c]Includes Algeria, Egypt, Libya, Morocco, Tunisia, and Sudan.

[d]Excludes Israel (3.5 million), which has low fertility.

[e]Excludes Japan (112.5 million), Australia (13.7 million), and New Zealand (3.1 million), which have low fertility. Includes Melanesia, Polynesia, and Micronesia in Oceania (4.3 million).

Includes the Caribbean area plus Central and South America, but excludes Argentina (25.7 million) and Uruguay (3.1 million), both of which have low fertility.

[g]The count of countries with neither a policy to reduce the growth rate nor support of family planning excludes countries with high fertility having populations under 100,000.

[h]Democratic People's Republic of Korea.

to weak and spotty performance under indifferent administration. Similarly, the private provision of means of fertility control has been good in some countries and poor in others. Most countries with policies to reduce the population growth rate have developed stronger family planning programs than have other countries. The most effective programs are found principally in Southern and Eastern Asia. Other areas with such programs, in order of decreasing effectiveness, are Northern Africa, Western Asia, Latin America, and Black Africa.

Laws and Regulations

In 1976 the United Nations Fund for Population Activities (1976) published a survey of laws affecting contraceptive technology in 84 developing countries. This survey grouped the laws by severity in four major categories: import, manufacturing, sale or distribution, and advertising. By far, the largest number of countries with the most restrictions were located in Black Africa (Table 2).

Many countries have made significant changes in their laws within the past several years in order to make contraceptives more accessible to their people. The most common changes include: the development of a population program, often integrating family planning services into the existing health services; elimination of requirements for prescriptions of pills; and incorporation of paramedical personnel into the family planning delivery system in order to overcome the scarcity of medical doctors and pharmacies in rural areas. In many, perhaps most countries, there are divergences between law and practice. There is a lag in legal reforms, despite the official pronouncements and public opinion indicating their need. This lag results in nonenforcement of restrictive contraceptive laws. Nonetheless, restrictive laws act as barriers to the availability of information about and supplies of contraceptives.

During the past 10 years there has been some liberalization of laws relating to induced abortion in a number of developing countries; but in 12 of the 74 countries surveyed abortion is illegal with no exceptions, and in 29 of the countries it is legal only on narrow medical grounds when the life of the mother is endangered. Abortion is legal with no restrictions (except administrative regulations) in five countries: China, Viet Nam, Singapore, Tunisia, and Iran. Abortions are also legal on broad health grounds in 28 countries (Table 3). Thus, there is leeway in many developing countries for regulations that would make abortion available to a large proportion of women. However, with a few notable exceptions, facilities for induced abortion are limited largely to urban

areas and, probably, are available primarily to the relatively small proportions of the populations in the upper and upper middle classes.

Acceptors and Users

The reported number of new acceptors of fertility control methods in developing countries has increased dramatically in recent years. In 1965, 2.5 million new acceptors were counted; in 1970, 9.1 million; and in 1975, 17.4 million. In 1976, concurrent with India's strong sterilization drive, the number jumped to 23 million (Table 4). Preliminary figures for 1977 suggest there was a major decline in India but a modest increase in most other countries. For convenience, and with no great loss in accuracy, one may say that "new acceptors" in developing countries number about 20 million per year. Excluding China, as the above figures do, there are about 300 million married women in the reproductive ages; thus, new acceptors each year now amount to approximately 7% of married women in the reproductive ages.

The number of current "users" is less well known, but, as an order of magnitude, it is a little more than twice "new acceptors" or in the range of 40–50 million. A convenient figure is 45 million, or 15% of married women in the reproductive ages.

In India, the method of choice has been the condom and male sterilization, but elsewhere oral tablets and the condom are the methods of choice. These lead other methods by a factor of more than 2 to 1, with female sterilization and IUD's being equally popular. Estimates of condom use are less firm than the not-so-firm other figures, partly because they are derived from distribution figures and partly because condom users are counted among those in the "Other" category as opposed to a specific categorization such as the "Pill," "IUD," "Sterilization," or "Abortions." Among current users, percentages of sterilization and IUD users have increased little compared to acceptor percentages because the periods of their use are somewhat longer than those for pills and condoms.

The above figures are derived primarily from organized governmental and private family planning associations. The current user figures are a mix of acceptor data that are adjusted for dropouts or discontinuations based on follow-up studies and of survey data that include private sector as well as program users. New acceptor data tend to be overstated, in part because of "repeat" acceptors. However, that overcounting is offset, to some extent, by users in the private sector whose numbers are not reflected in the data. Thus, it is probably safe to generalize that there are somewhat more than 45 million users of

TABLE 2 Regional Frequencies of Contraceptive Laws and Regulations[a]

Contraceptive Laws and Regulations	Black Africa	North Africa	Latin America	Asia and Oceania	TOTALS
	Number of Countries Using the Pill				
Import					
Prohibited	10	1	1	3	15
Authorization required[b]	12	1	12	7	32
No restriction	6	1	1	3	11
N.A.	7	3	11	5	26
TOTALS	35	6	25	18	84
Manufacturing[c]					
Prohibited	12	1	0	1	14
Restricted[d]	8	1	11	8	28
No restriction	3	1	1	1	6
N.A.	12	3	13	8	36
TOTALS	35	6	25	18	84
Sale or distribution					
Prohibited	12	1	0	1	14
Prescription required	16	3	13	5	37
No restriction	0	0	1	1	2
Other[e]	7	2	11	11	31
TOTALS	35	6	25	18	84
Advertising					
Prohibited	18	2	2	2	24
Restricted	2	1	7	6	16
No restriction	0	3	4	5	12
N.A.	15	0	12	5	32
TOTALS	35	6	25	18	84
	Number of Countries Using IUD's				
Import					
Prohibited	11	1	1	3	16
Authorization required[b]	6	0	6	6	18
No restriction	5	1	2	1	9
N.A.	13	4	16	8	41
TOTALS	35	6	25	18	84
Manufacturing[c]					
Prohibited	12	1	0	1	14
Restricted[d]	1	0	7	4	12
No restriction	4	1	1	1	7
N.A.	18	4	17	12	51
TOTALS	35	6	25	18	84
Sale or distribution					
Prohibited	12	1	0	1	14
Prescription required	2	2	1	1	6
No restriction	4	3	2	0	9
Other[e]	17	0	22	16	55
TOTALS	35	6	25	18	84

TABLE 2
Continued

Contraceptive Laws and Regulations	Black Africa	North Africa	Latin America	Asia and Oceania	TOTALS
Advertising					
Prohibited	15	2	0	2	19
Restricted	2	0	5	4	11
No restrictions	0	3	4	3	10
N.A.	18	1	16	9	44
TOTALS	35	6	25	18	84
Insertion requirements	2	1	4	11	18
	Number of Countries Using Condoms				
Import					
Prohibited	10	1	1	3	15
Authorization required[b]	9	1	10	7	27
No restriction	4	1	1	2	8
N.A.	12	3	13	6	34
TOTALS	35	6	25	18	84
Manufacturing[c]					
Prohibited	12	1	0	0	13
Restricted[d]	1	1	7	4	13
No restriction	6	1	2	3	12
N.A.	16	3	16	11	46
TOTALS	35	6	25	18	84
Sale or distribution					
Prohibited	10[f]	1	0	1	12
Prescription required	3	1	0	0	3
No restriction	8	1	5	4	18
Other[e]	15	3	20	13	51
TOTALS	35	6	25	18	84
Advertising					
Prohibited	16	2	0	3	21
Restricted	2	1	6	4	13
No restrictions	2	3	4	5	14
N.A.	15	0	15	6	36
TOTALS	35	6	25	18	84

[a]Derived from the United Nations Fund for Population Activities, 1976.
[b]Besides authorization, includes other restrictions such as quotas, customs duties, and currency restrictions.
[c]Nigeria also provides financial inducements for the manufacture of pills, condoms, and IUD's.
[d]Includes quality control restrictions.
[e]Includes countries with restrictions on distribution sites and display as well as those for which no information is available.
[f]In all these cases the condom is forbidden as a contraceptive, but available for health reasons, or actual practice differs from the law.

TABLE 3 Legal Status of Abortion by Level of Development, 1978[a]

Legal Status	Number of Countries		
	Developed (N = 35)	Less Developed (N = 74)	TOTALS (N = 109)
Illegal (no exceptions)	3	12	15
Legal (grounds not specified)	10	5[b]	15
Legal (on specified grounds)	21	57	78
Medical			
Narrow (life)	3	29	32
Broad (health)	18[c]	28[d]	46
Eugenic (fetal)	11	10	21
Juridical (rape, incest, etc.)	13	13	26
Social-medical	12	2[e]	14

[a]From Tietze, 1979.
[b]China (1957), Viet Nam (1971), Tunisia (1973), Singapore (1974), Iran (1974).
[c]Most states of Australia allow abortions for health and eugenic reasons; however, two states allow abortion only when the life of the mother is endangered.
[d]Nigeria: Southern states only; in Northern states abortion is legal only to preserve life.
[e]India (1971), Zambia (1972).

fertility control methods in developing countries, excluding China. Estimates for China range from approximately 45 million to double that number!

A tremendous amount of effort has gone into the collection and analysis of family planning service statistics and research relating to acceptors and their characteristics, method continuation rates, person continuation use rates, etc. Thus, family planning statistics are often of moderately good quality. At one level, we know quite a lot about the dynamics of selected programs. But there are many weaknesses and gaps in the data. Attempts such as this to add the pieces and come up with global numbers and percentages can be only approximate at best.

Abortion

There is no dearth of estimates of the numbers of abortions in various parts of the world. Such estimates range from 30 million (Klinger, 1969) to 55 million (International Planned Parenthood Federation, 1974). The IPPF estimates that 20 million abortions of their 55 million total occur in developed countries (Table 5). The recorded number of abortions comes to fewer than 4 million per year, and in developing countries the recorded number is less than 0.5 million per year. That number is clearly

TABLE 4A Family Planning Acceptors by Region, 1965–1976[a]

Region	Number of New Acceptors (in thousands)				
	1965	1970	1974	1975	1976
South Asia	1,823	6,068	5,708	9,668	15,855
East/Southeast Asia	602	1,623	4,089	4,537	4,680
Latin America/Caribbean	36	705	1,816	2,020	1,834
West Asia/North Africa	20	639	839	962	1,016
Sub-Saharan Africa	3	83	194	198	279
Developing world total	2,484	9,118	12,646	17,385	23,663

TABLE 4B Family Planning Acceptors by Method, 1975

Region	Percentage of New Acceptors				
	Sterilization	IUD	Pill	Abortion	Condom/Other
South Asia	28	9	7	2	54
East/Southeast Asia	5	20	54	0.4	21
Latin America/Caribbean	3	34	47	7	10
West Asia/North Africa	1	17	73	2	7
Sub-Saharan Africa	0.1	12	71	0.1	17
Developing world total	18	15	28	2	37

NOTES: Where figures for the number of new acceptors were not available for a given year, reported figures for an earlier year were used.

The distribution of 1976 acceptors was not used because the number of sterilizations in India for that year was abnormally high.

[a]From Watson, 1977, and Nortman and Hofstatter, 1978.

too low because it does not include abortions in China, where abortions are legal and reportedly readily available and frequently obtained. Nor do the recorded figures include illegal abortions. Moreover, survey techniques, although often ingenious, are not equal to the task.

Estimates can be very useful when they are appropriately described and have a reasonable base, but it is difficult to accept the estimate of 2.36 abortions per live birth in the USSR (about 12 million per year), or the implied estimate of almost 20 million abortions in China. Recent evidence on the abortion rate in Moscow indicates that there are 1.7 abortions per live birth in that city (Tietze, 1979). The rate for the entire

TABLE 5 Abortions per Year by Geographic Area: Estimated by IPPF and Number Actually Reported[a]

Region	1971 Population (millions)	Crude Birth Rate, 1971	Estimated Number of Abortions per 1,000 Live Births	Estimated Number of Abortions (thousands)	Recorded Number of Abortions (Most Recent Year Available) (thousands)
Eastern Europe	172	23	429	1,697	1,108
Western Europe	329	17	550	3,076	452
USSR	245	21	2,355	12,116	U[b]
Japan	105	18	1,122[c]	2,120	664
North America	229	21	271	1,303	1,222
Oceania[d]	16	20	362	118	U
Developed countries	1,096	20	932	20,430	3,446
Black Africa	268	48	16	206	U
North Africa and Middle East	178	46	95	778	20[e]
South Asia	712	44	278	8,709	274[f]
Southeast Asia	293	42	45	554	16[g]
East Asia (excluding China)	66	31	339	694	U
Latin America	287	39	346	3,873	121[h]

Developing countries	1,804	43	191	14,814	431
TOTALS (excluding China)	2,900	34	357	35,244	3,877
TOTALS (including China)[i]	3,687	35	427	55,102	3,877

[a]Columns 1–3 are from IPPF, 1974. Populations were given for 3 separate years, and no year was given for the crude birth rates; however, it is implied that 1971 was the year used. Column 4 has been calculated from columns 1–3. Column 5 is from the following unless otherwise noted: Tietze and Murstein, 1975, 1977, and Tietze, 1979. For the purposes of this exercise, geographic areas given by IPPF have, in several cases, been reaggregated.

[b]U = Unknown.

[c]A range of 1.122–1.496 was given by IPPF.

[d]Australia and New Zealand only.

[e]Tunisia (1976).

[f]India (1976). Nortman and Hofstatter, 1978.

[g]Singapore (1976).

[h]Cuba (1976).

[i]IPPF did not give an abortion rate for China; however, its world total rate of 427 abortions per 1,000 live births implies an abortion rate of 701 for China.

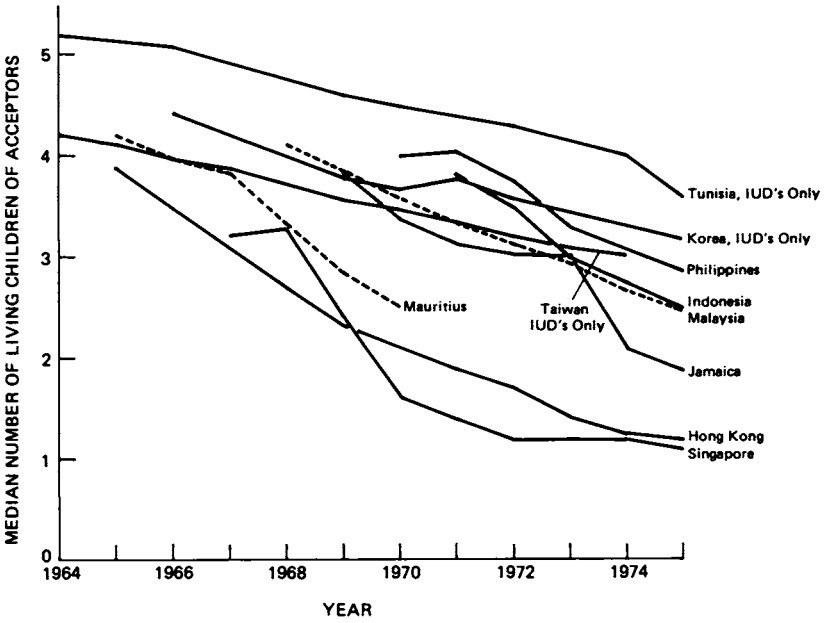

FIGURE 1 Median number of living children of acceptors by year. From Ross and Potter, 1979.

country is likely to be somewhat lower. This suggests an upper limit of about 6 million abortions. For the purpose of this paper, perhaps it is adequate to say that the magnitude of induced abortions in developing countries is unknown except in a few instances. Even in countries where abortion is legal, services are not widely available and are not much used, except in Cuba, where the ratio of abortions to live births is approximately 660 per 1,000 live births, and probably in China. Informed sources believe that induced abortions are infrequent in Black Africa and in much of the Muslim world, but frequent in Latin America and in much of Asia. The frequently quoted statement that abortion is the leading method of fertility control in the world has no factual basis, and, in my opinion, is almost surely wrong.

Characteristics of Acceptors

The common sense view is that when organized family planning programs first start, new acceptors are primarily older, high parity women. As the program matures there is a shift to younger, lower

parity women. Acceptance rates and indices increase with age to 30–34 years, when programs first begin in most countries. After that time they start to decline (Sirageldin and Ross, 1977). Most acceptors are between 25 and 34 years of age, although at the same time appreciable proportions are younger than 25 and older than 34. Pill acceptors are typically younger than are IUD acceptors, and they in turn are younger than women who accept sterilization—and they are younger than men who choose vasectomy.

Ross (1977) has compiled information on acceptors by age and by number of living children for 23 countries (Figures 1 and 2, and Tables 6 and 7). Figure 1 shows the median number of living children for selected countries by calendar year. The downward trend over time is striking. Moreover, the decline is remarkably regular year by year. Many of the lines are almost straight, and with the exception of the two advanced cities at the bottom, the slope of the decline is similar for countries whose median number of living children per acceptor is quite different.

The trends by age are equally consistent within countries (Figure 2),

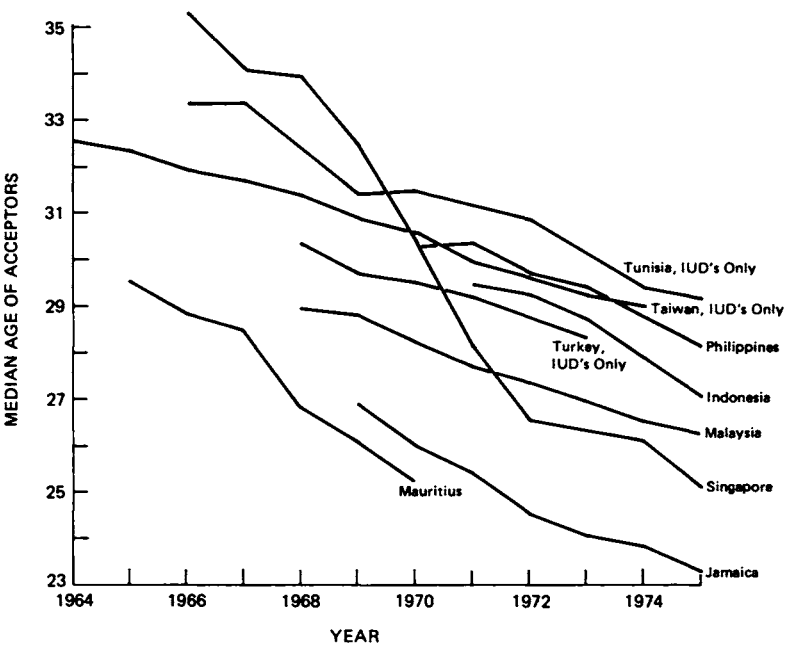

FIGURE 2 Median age of acceptors by year. From Ross and Potter, 1979.

TABLE 6 Acceptors by Method and by Age of Wife: Percent Distribution for 30 Countries that Support Family Planning Programs[a] (Percents May Not Add to 100 Because of Rounding)

Country and Method	Acceptor Sample		Percentage in Wife's Age-Group								Wife's Median Age
	Acceptor Period (month/year)	Number (in thousands)	Total	Under 20	20–24	25–29	30–34	35–39	40 & Over	Unknown	
Bangladesh											
Orals[b]	4/1976	0.7	100	5.0	13.9	20.5	29.6	23.9	7.1	0	31.8
Bolivia											
All methods	1976	2.5	100	10.7	17.6	28.7	14.9	23.3	4.8	0	28.8
IUD's	1976	1.1	100	7.5	28.6	31.3	18.8	11.1	2.7	0	27.2
Orals	1976	0.8	100	8.1	24.4	31.1	18.0	13.9	4.4	0	27.8
Brazil											
All methods	1974	15.4	100	13.1	32.0	25.6	15.6	9.1	4.1	0.5	25.9
IUD's	1974	1.0	100	3.6	22.5	31.5	22.5	12.6	6.8	0.5	28.7
Orals	1974	13.6	100	14.0	32.8	25.3	15.0	8.8	3.7	0.4	25.5
Colombia											
All methods	1–6/1972	15.8	100	13.9	32.8	24.3	15.4	9.1	4.2	0.2	25.7
All methods	1975	174.1	100	12.6	31.4	24.8	15.0	10.1	4.3	1.8	26.0
IUD's	1–6/1972	6.7	100	11.3	31.7	25.4	16.7	10.0	4.6	0.3	26.4
IUD's	1975	62.9	100	11.0	32.0	26.7	15.2	9.5	4.0	1.6	26.1
Orals	1–6/1972	8.1	100	17.2	35.8	23.5	13.3	7.1	3.1	0.2	24.6
Orals	1975	90.0	100	15.8	35.1	24.1	12.3	7.7	3.0	2.0	24.7
Sterilization	1974	6.6	100	0.3	4.7	19.3	32.5	27.5	14.3	1.4	33.8
Sterilization	1975	11.4	100	0.7	4.5	21.1	32.5	28.9	11.4	0.9	33.6
Costa Rica											
All methods	1974	12.6	100	18.3	32.2	21.5	13.2	7.3	4.7	2.7	24.7

All methods	1975	31.0	100	20.0	33.2	21.5	12.2	7.1	4.6	1.4	24.4
IUD's	1974	1.0	100	12.5	28.3	24.1	17.1	8.6	6.7	2.7	26.6
IUD's	1975	2.1	100	11.0	28.5	24.7	17.9	9.8	6.8	1.3	27.0
Orals	1974	8.3	100	21.6	35.8	21.2	10.9	5.0	2.6	2.9	23.8
Orals	1975	20.5	100	23.5	37.1	20.9	9.9	4.7	2.4	1.5	23.5
Dominican Republic											
All methods	1976	58.2	100	18.3	33.2	25.7	12.8	7.2	2.8	0	24.8
IUD's	1972	7.3	100	11.0	34.2	26.7	16.3	8.7	2.8	0.2	25.9
IUD's	1976	6.0	100	10.1	30.9	27.3	16.5	10.4	4.8	0	26.6
Orals	1972	8.6	100	17.6	39.2	23.4	11.9	5.9	2.0	0	24.1
Orals	1976	41.7	100	20.4	39.4	23.4	10.0	5.1	1.7	0	23.8
Ecuador											
IUD's	1973	5.1	100	8.8	33.0	29.0	17.5	8.5	2.8	0.4	26.4
IUD's	1974	14.4	100	8.0	30.0	30.0	17.0	10.0	4.0	1.0	26.9
Orals	1–8/1971	0.9	100	5.3	24.6	30.3	23.8	10.9	3.9	1.2	28.2
Orals	1974	16.2	100	9.3	32.6	25.6	18.3	9.3	4.4	0.5	26.5
El Salvador											
All methods	3/1971–8/1972	4.0	100	9.2	31.6	27.8	16.9	9.2	3.9	1.4	26.5
Sterilization, female	1–6/1976	5.5	100	1.1	20.3	36.5	23.7	15.7	2.7	0	28.9
Ghana											
All methods	1976	11.1	100	5.4	29.2	27.8	19.3	12.4	5.9	0	27.8
IUD's	1973	2.6	100	2.9	16.3	27.1	25.6	18.3	9.8	0	30.7
IUD's	1976	1.3	100	2.7	18.6	28.4	24.8	16.3	9.2	0	30.1
Orals	1973	17.6	100	4.9	24.2	27.2	22.1	13.2	8.4	0	28.8
Orals	1976	9.3	100	6.0	31.6	28.0	18.4	11.2	4.8	0	27.2
Guatemala											
All methods	2–12/1976	9.6	100	0.1	56.8	25.3	11.1	4.7	2.0	0	24.4
IUD's	2–12/1976	1.3	100	0.1	44.5	35.2	12.6	5.4	2.2	0	25.8
Orals	2–12/1976	6.4	100	0.0	64.5	21.8	8.9	3.5	1.3	0	23.9
Injectables	2–12/1976	0.5	100	0.1	23.3	30.7	26.7	13.4	5.8	0	29.3

TABLE 6 *Continued*

Country and Method	Acceptor Sample: Acceptor Period (month/year)	Acceptor Sample: Number (in thousands)	Percentage in Wife's Age-Group: Total	Under 20	20–24	25–29	30–34	35–39	40 & Over	Unknown	Wife's Median Age
Hong Kong											
All methods	1970	30.5	100	3.4	31.4	26.4	17.2	14.4	7.2	0	27.9
All methods	1976	25.5	100	7.0	41.1	34.4	8.5	4.6	4.2	0.2	25.3
IUD's	1968	3.0	100	[c]	15[c]	22	27	23	14	0	32.4
IUD's	1976	0.3	100	0	9.4	29.2	22.5	22.2	16.8	0	32.5
Orals	7/1966–6/1968	1.5	100	[c]	27.9[c]	28.2	22.9	16.1	4.9	0	28.9
Orals	1976	16.8	100	8.1	45.6	35.0	6.8	2.9	1.3	0.2	24.6
Injectables	1975	0.2	100	0	4.7	14.5	20.6	26.6	33.2	0.4	36.9
Injectables	1976	0.2	100	0	4.6	11.3	18.5	22.0	43.6	0	38.5
India											
IUD's	3/1965–5/1969	2.3	100	2.4	[d]	47.0[d]	44.8[e]	[e]	5.8	0	30.1
IUD's	4/1975–3/1976	521.2	100	3.8	20.2	31.3	26.3	14.0	4.4	0	29.2
Sterilization, male	7/1970–1/1971	2.8	100	[c]	6.0[c]	15.5	28.2	30.2	20.1	0	35.0
Sterilization, male	4/1975–3/1976	1,002.4	100	1.3	9.4	22.1	29.5	25.9	11.8	0	32.9
Sterilization, female	7/1970–1/1971	2.1	100	[c]	3.0[c]	21.7	31.3	24.8	19.2	0	34.0
Sterilization, female	4/1975–3/1976	765.5	100	0.4	7.9	29.6	34.7	22.0	5.4	0	31.7
Indonesia											
All methods	4–9/1972	27.8	100	5.1	21.0	28.6	25.2	16.1	3.9	0.1	29.2
All methods	9–12/1974	36.7	100	7.1	25.9	29.1	22.2	12.7	3.0	0.1	27.9
IUD's	4–9/1972	10.2	100	3.7	18.5	29.3	27.5	17.1	3.9	0	29.7
IUD's	10–12/1976	8.1	100	6.6	28.0	30.3	20.0	12.5	2.6	0	27.5
Orals	4–9/1972	15.8	100	6.2	22.9	28.2	23.9	15.2	3.6	0	28.7
Orals	10–12/1976	20.6	100	10.5	31.0	27.9	17.5	10.7	2.4	0	26.5
Injectables	10–12/1976	0.2	100	3.1	29.4	31.4	19.6	12.4	4.1	0	27.8

Iran											
IUD's	9–10/1972	0.4	100	6.6	21.4	22.9	22.9	20.0	6.3	0	29.8
IUD's	5/1975	1.0	100	10.7	32.9	22.3	18.5	11.6	4	0	26.4
Orals	9–10/1972	0.6	100	7.0	21.5	18.0	23.6	19.4	10.5	0	30.7
Orals	1974	2.3	100	12.1	30.2	22.8	17.1	11.9	5.8	0	26.7
Jamaica											
All methods	1970	19	100	14	31	24	15	8	8	0	26.0
All methods	1975	24	100	26	36	17	10	6	5	0	23.3
Orals	11/1968–12/1971	44.0	100	14.6	32.9	26.0	14.6	7.9	3.9	0.1	25.5
Kenya											
All methods	1974	40.6	100	10	34	25	15	8	3	5	25.7
All methods	10–12/1976	10.8	100	12	36	26	14	8	4	0	25.4
IUD's	1970	4.8	100	[c]	25[c]	29	21	14	11	0	29.3
Orals	1970	8.5	100	[c]	33[c]	28	17	12	9	0	28.0
Orals	4–6/1971	1.1	100	10.1	35.0	24.8	14.2	9.6	3.3	3.0	25.7
Korea, Repubic of											
IUD's	1966	218.4	100	[c]	0.3[c]	6.5	22.3	28.9	42.0	0	38.6
IUD's	1–6/1975	203.3	100	0.1	6.4	25.6	31.0	25.5	11.4	0	32.9
Orals	1969	7.6	100	[c]	3.5[c]	19	35	30	13	0	34.0
Orals	1971	5.0	100	[c]	5.2[c]	21	34	27	13	0	33.5
Sterilization	1972	4.0	100	[c]	2.2[c]	17	37	32	11	1	34.2
Sterilization, male	1–6/1975	22.4	100	0.0	2.3	24.4	40.0	26.3	7.0	0	32.6
Sterilization, female	1–6/1975	3.2	100	0.0	1.2	16.5	37.3	32.2	12.8	0	34.3
Abortion	1–6/1975	3.0	100	0.2	4.0	17.7	32.2	30.7	15.2	0	34.4
Malaysia, Peninsular											
All methods	1969	70.6	100	4.8	23.8	27.9	24.2	13.4	5.9	0	28.8
All methods	1976	75.2	100	8.9	34.2	29.0	14.5	9.3	4.1	0	31.2
IUD's	1972	1.1	100	1.6	18.5	29.9	24.5	17.2	8.3	0	30.0
IUD's	1976	1.1	100	1.3	21.2	32.7	22.3	13.4	9.1	0	29.2
Orals	1972	48.9	100	7.6	33.2	27.3	18.0	10.0	3.9	0	26.7
Orals	1976	65.0	100	10.0	37.2	28.7	13.0	7.9	3.2	0	25.5
Sterilization	1972	3.9	100	0.1	4.9	18.8	37.8	28.2	10.2	0	33.5
Sterilization	1976	4.0	100	0.1	5.7	27.8	31.2	24.8	10.4	0	32.6

TABLE 6 *Continued*

Country and Method	Acceptor Sample: Acceptor Period (month/year)	Acceptor Sample: Number (in thousands)	Percentage in Wife's Age-Group: Total	Under 20	20–24	25–29	30–34	35–39	40 & Over	Unknown	Wife's Median Age
Mauritius											
Orals	1974	2.0	100	13.7	37.4	23.7	14.6	7.4	3.2	0	24.9
Orals	1976	2.0	100	18.8	38.9	24.1	10.2	5.7	1.8	0.5	24.0
Injectables	1976	0.2	100	3.0	13.6	25.1	25.1	15.6	17.1	0.5	31.6
Mexico											
IUD's	1972	12.1	100	4	25	30	23	15	3	0	28.5
IUD's	1973	18.8	100	7.9	26.9	27.0	20.4	12.9	4.9	0	27.8
Orals	1972	17.7	100	8	31	27	19	12	3	0	27.0
Orals	1973	23.1	100	8.0	27.0	26.9	19.9	13.2	5.0	0	27.8
Injectables	1973	8.9	100	8.0	27.1	27.1	20.0	12.8	5.0	0	27.7
Morocco											
All methods	1966–67	8.3	100	2.4	14.9	28.9	28.3	18.9	6.6	0	30.7
All methods	1971	18.6	100	3.7	14.8	23.1	28.5	22.3	7.6	0	31.5
IUD's	1969	7.7	100	2.8	13.6	23.6	27.7	22.8	8.6	0.9	31.7
Orals	1969	4.8	100	3.7	16.5	26.2	27.0	19.1	6.5	1.0	30.6
Nepal											
IUD's	7/1972–7/1973	0.2	100	3	17	31	23	17	9	0	29.8
IUD's	1975–76	0.4	100	4.2	25.6	27.6	25.0	10.8	6.8	0	28.7
Orals	4–6/1970	1.9	100	5.3	22.8	26.6	25.5	12.5	6.6	0.6	29.1
Orals	1975–76	2.7	100	4.2	20.6	23.6	27.8	16.6	7.2	0	30.3
Sterilization, male	7/1972–7/1973	1.7	100	0	2	13	25	25	35	0	37.0
Sterilization, male	1975–76	1.3	100	0.7	11.2	28.6	32.4	19.3	7.8	0	31.5
Sterilization, female	1975–76	0.6	100	0.4	5.8	28.7	34.9	20.9	9.3	0	32.2

Philippines											
All methods	4–6/1972	149.2	100	3.9	21.0	25.6	23.8	17.3	8.2	0.2	29.9
All methods	7–12/1975	347.3	100	6.4	25.9	27.5	19.0	14.3	6.7	0.2	28.2
IUD's	10–12/1970	1.4	100	2.8	17.9	26.4	28.1	17.8	6.0	1.0	30.5
IUD's	1976	43.1	100	24.7	23.5	17.0	11.9	8.4	5.3	9.3	24.4
Orals	10–12/1970	3.3	100	3.3	19.7	27.4	24.4	17.6	7.2	0.4	29.9
Orals	1976	282.4	100	29.9	22.5	15.3	11.6	8.0	5.1	7.6	23.6
Sterilization, male	7–12/1975	4.1	100	0.4	7.2	22.0	31.5	26.7	12.1	0.2	33.2
Sterilization, male	1976	10.3	100	1.9	13.5	20.2	19.2	16.3	12.5	16.3	31.6
Sterilization, female	7–12/1975	13.4	100	0.3	6.8	27.6	32.2	25.4	7.5	0.1	32.4
Sterilization, female	1976	37.6	100	0.5	6.6	18.3	23.9	19.4	12.2	19.1	33.1
Puerto Rico											
All methods	1974–75	38.8	100	21.5	31.9	22.4	13.2	6.9	4.1	0	24.5
IUD's	1974–75	2.4	100	5.8	21.8	29.1	21.9	12.6	8.8	0	28.8
Orals	1974–75	20.2	100	23.9	35.5	22.5	10.7	4.9	2.5	0	23.7
Singapore											
All methods	1972	17.7	100	8.6	37.9	29.7	12.5	6.0	3.5	1.8	25.5
All methods	1976	27.5	100	4.8	28.8	35.5	17.1	9.7	3.3	0.8	27.3
Orals	7/1967–3/1968	3.0	100	2.1	19.8	31.8	25.7	12.0	8.0	0.5	29.4
Orals	1976	9.0	100	9.6	44.9	33.2	8.1	3.1	1.1	0	24.5
Sterilization, male	1976	0.4	100	1.6	17.1	29.1	30.9	13.1	7.7	0.5	30.3
Sterilization, female	1975	9.2	100	0.2	8.9	31.3	32.9	20.2	6.1	0.4	31.5
Sterilization, female	1976	9.5	100	0.5	8.3	32.2	30.1	20.7	5.8	2.4	31.3
Sri Lanka											
All methods	1970	55.3	100	2.3	22.0	29.0	21.6	14.0	3.8	7.1	28.8
All methods	1973	95.9	100	2.5	23.0	28.9	21.8	12.6	3.9	7.3	28.6
IUD's	1974	29.7	100	4.3	33.0	30.6	17.0	9.0	2.5	3.6	26.8
IUD's	1–9/1975	24.3	100	5.1	34.7	31.1	16.3	8.8	2.4	1.6	26.5
Sterilization, female	1974	34.9	100	0.1	7.6	26.0	31.9	23.0	9.6	1.7	32.4
Sterilization, female	1–9/1975	24.9	100	0.2	9.6	31.0	32.5	20.6	4.3	1.8	31.3

TABLE 6 *Continued*

Country and Method	Acceptor Sample: Acceptor Period (month/year)	Acceptor Sample: Number (in thousands)	Percentage in Wife's Age-Group: Total	Under 20	20–24	25–29	30–34	35–39	40 & Over	Unknown	Wife's Median Age
Taiwan											
IUD's	1968	123.7	100	[c]	10.4[c]	30.1	30.5	18.8	9.3	0.9	31.6
IUD's	1975	173.4	100	[c]	20.5[c]	37.0	21.0	13.3	7.9	0.3	29.0
Orals	1967–68	59.0	100	1.0	10.6	31.4	30.7	18.5	7.8	0	31.1
Orals	1975	54.4	100	5.0	31.4	31.1	16.5	9.2	5.0	1.8	27.0
Thailand											
IUD's	1971	1.2	100	2.7	24.1	27.8	23.2	15.8	5.9	0.5	29.2
IUD's	1976	1.2	100	6.7	34.3	28.0	17.0	9.4	4.3	0.3	26.6
Orals	1971	3.8	100	3.9	23.8	24.7	22.9	16.2	7.8	0.7	29.5
Orals	1976	6.3	100	9.9	32.5	25.3	14.2	11.1	6.4	0.6	25.4
Sterilization	1974	1.1	100	1.1	14.7	33.4	26.8	18.1	5.6	0.3	30.1

Sterilization, male	1976	2.1	100	0.0	3.8	18.2	28.7	28.2	20.1	1.0	34.8
Sterilization, female	1976	1.5	100	1.4	17.9	33.9	27.9	14.1	4.3	0.5	29.5
Injectables	1976	1.1	100	5.8	26.6	28.4	17.4	13.5	7.7	0.6	28.0
Tunisia											
IUD's	1966	7.0	100	0.7	8.9	20.4	29.7	29.1	11.2	0	33.4
IUD's	1975	13.5	100	2.2	23.1	29.4	21.5	16.8	6.5	0.5	29.2
Orals	1/1969–8/1972	0.9	100	2.7	19.3	24.0	25.6	17.5	7.9	3.0	30.5
Orals	1975	11.6	100	2.6	24.7	29.6	20.2	15.5	7.0	0.4	28.8
Sterilization, female	1975	8.0	100	0.0	0.9	9.7	26.8	43.6	19.0	0	36.4
Abortion	1975	10.2	100	1.6	14.9	24.5	24.2	23.0	10.8	1.0	31.8
Turkey											
IUD's	7–12/1968	26.4	100	3.3	19.5	24.8	25.2	19.9	6.3	1.0	30.4
IUD's	1973	28.3	100	5.1	27.0	26.8	20.3	15.5	5.3	0	28.3

[a]From Nortman and Hofstatter, 1978.
[b]Prevalence of contraceptive use in Matlab Thana.
[c]Percent shown in the "20–24" category includes the "under 20" category.
[d]Percent shown in the "25–29" category includes the "20–24" category.
[e]Percent shown in the "30–34" category includes the "35–39" category.

TABLE 7 Acceptors by Method and by Number of Living Children: Percent Distribution for 29 Countries that Support Family Planning Programs, Recent Data[a] (Percents May Not Add to 100 Because of Rounding)

Country and Method	Acceptor Sample		Percentage, by Number of Living Children								
	Acceptor Period (month/year)	Number (in thousands)	Total	0 or 1	2	3	4	5	6 or more	Unknown	Median Number of Living Children
Bangladesh											
Orals[b]	4/1976	0.7	100	5.5	5.9	8.5	13.8	13.8	52.5	0	5.5
Bolivia											
All methods	1976	2.5	100	37.2	22.7	18.9	9.5	5.2	6.5	0	2.1
IUD's	1976	1.1	100	20.1	29.3	24.6	11.5	7.2	7.3	0	2.5
Orals	1976	0.8	100	61.6	12.8	10.8	7.0	3.4	4.4	0	<1
Brazil											
All methods	1974	15.4	100	33.5	21.3	13.4	27.2[c]	[c]	[c]	4.6	2.2
IUD's	1974	1.0	100	19.7	23.3	17.9	37.2[c]	[c]	[c]	1.9	2.8
Orals	1974	13.6	100	34.4	21.5	13.2	26.5[c]	[c]	[c]	4.4	2.1
Colombia											
All methods	1–6/1972	15.8	100	24.3	21.4	15.2	11.5	8.0	18.9	0.8	2.8
All methods	1975	174.1	100	27.4	22.0	14.9	10.6	7.5	16.2	1.4	2.5
IUD's	1–6/1972	6.7	100	17.6	22.2	16.5	12.7	9.0	21.1	0.7	3.1
IUD's	1975	62.9	100	25.1	25.0	16.1	10.6	7.2	14.9	1.1	2.5
Orals	1–6/1972	8.1	100	31.2	21.8	14.0	10.4	6.9	14.8	0.9	2.4
Orals	1975	90.0	100	32.4	22.3	14.0	9.3	6.6	13.6	1.8	2.2
Sterilization	1974	6.6	100	1.2	4.6	14.8	19.6	15.7	43.0	1.1	5.1
Sterilization	1975	11.4	100	0.9	4.4	15.8	21.1	17.5	40.4	0.9	4.9

Costa Rica											
All methods	1974	12.6	100	39.1	20.7	12.2	7.6	5.4	13.1	1.9	2.0
All methods	1975	31.0	100	41.4	20.6	12.2	7.4	5.3	11.8	1.3	1.9
IUD's	1974	1.0	100	27.3	20.6	13.1	9.4	8.9	19.1	1.6	2.6
IUD's	1975	2.1	100	27.3	21.5	17.3	9.6	6.3	16.9	1.1	2.5
Orals	1974	8.3	100	44.8	22.3	11.7	6.4	4.4	8.3	2.0	1.7
Dominican Republic											
All methods	1976	61.5	100	28.0	22.0	15.7	10.8	7.5	16.0	0	2.5
IUD's	1972	7.3	100	11.5	19.6	18.6	14.2	11.2	24.8	0.2	3.5
IUD's	1976	6.0	100	16.8	21.0	18.2	13.7	9.7	20.6	0	3.2
Orals	1972	8.7	100	23.8	22.1	17.5	11.6	8.6	16.3	0.1	2.7
Orals	1976	41.7	100	32.0	23.1	15.4	10.0	6.6	12.9	0	2.3
Ecuador											
All methods	1974	35.1	100	17.3	20.6	18.3	12.9	11.2	18.4	1.8	3.1
IUD's	1–8/1971	1.0	100	9.3	17.0	16.1	16.7	13.7	25.4	1.7	4.0
IUD's	1973	5.9	100	11.4	18.9	15.9	16.2	11.2	24.3	2.2	3.7
Orals	1–8/1971	0.9	100	15.6	18.6	19.4	17.0	9.7	17.9	1.8	3.3
Orals	1973	1.2	100	25.0	24.3	17.6	11.9	7.1	13.5	0.6	2.5
El Salvador											
All methods	3/1971–9/1972	4.0	100	23.4	21.0	16.2	11.7	8.7	19.0	0	2.8
Ghana											
All methods	1976	11.1	100	23.5	19.2	15.7	14.0	10.0	17.6	0	3.0
IUD's	8/1970–11/1972	10.6	100	5.9	10.6	11.7	13.1	11.0	47.7	0	5.3
IUD's	1976	1.3	100	13.8	17.2	17.0	16.8	13.0	22.2	0	3.6
Orals	8/1970–11/1972	24.2	100	15.5	15.1	12.2	12.7	10.3	34.2	0	4.1
Orals	1976	9.3	100	25.6	20.0	15.7	13.6	9.3	15.8	0	2.8
Hong Kong											
All methods	1975	21.4	100	66.3	16.2	7.6	4.2	2.4	3.2	0	<1
All methods	1976	25.5	100	68.2	16.5	7.2	3.8	2.0	2.2	0.1	<1
IUD's	1968	3.0	100	[d]	29.0[d]	19.0	19.0	34.0[e]	[e]	0	3.6
IUD's	1976	0.3	100	13.7	35.2	25.4	14.1	6.2	5.4	0	2.5

TABLE 7 *Continued*

Country and Method	Acceptor Sample: Acceptor Period (month/year)	Acceptor Sample: Number (in thousands)	Percentage, by Number of Living Children: Total	0 or 1	2	3	4	5	6 or more	Unknown	Median Number of Living Children
Hong Kong (Continued)											
Orals	7/1966–6/1968	1.5	100	23.6	[f]	14.8[f]	31.6[e]	[e]	[e]	0	2.7
Orals	1976	16.8	100	74.5	15.7	5.4	2.3	0.9	1.0	0.1	<1
Injectables	1975	0.2	100	4.6	15.4	17.8	17.8	14.5	29.9	0	4.2
Injectables	1976	0.2	100	4.1	12.3	21.0	19.0	17.9	25.6	0	4.2
India											
IUD's	3/1965–5/1969	2.3	100	4.9	14.0	20.2	21.5	17.3	22.0	0	4.0
IUD's	4/1974–3/1975	6.7	100	14.5	26.7	23.7	17.0	9.1	8.8	0.2	2.9
Sterilization, male	7/1970–1/1971	2.8	100	3.7	11.3	23.7	23.7	37.6[e]	[e]	0	4.0
Sterilization, male	4/1974–3/1975	6.8	100	0.9	18.1	28.1	24.9	14.3	13.6	0.1	3.6
Sterilization, female	7/1970–1/1971	2.1	100	1.9	11.0	15.0	23.7	48.4[e]	[e]	0	4.4
Sterilization, female	4/1974–3/1975	4.9	100	0.3	5.7	23.6	30.5	20.3	19.4	0.2	4.2
Indonesia											
All methods	1971–1972	38.7	100	10.6	15.6	17.8	17.4	14.2	23.6	0.7	3.8
All methods	9–12/1974	36.7	100	23.8	21.8	17.7	13.4	10.5	12.6	0.2	2.7
IUD's	7–9/1973	6.3	100	11.3	19.6	19.7	17.3	13.5	18.6	0	3.5
IUD's	10–12/1976	8.1	100	21.6	25.6	18.6	13.1	9.4	11.6	0.1	2.7
Orals	7–9/1973	13.7	100	20.6	20.1	18.4	15.3	11.2	14.4	0	3.0
Orals	10–12/1976	20.6	100	29.8	21.8	17.2	12.3	8.6	10.2	0.1	2.4
Iran											
IUD's	9–10/1972	0.4	100	5.5	14.5	15.7	11.4	16.0	36.9	0	4.7
IUD's	1973	0.3	100	7.0	18.6	19.8	21.5	15.8	17.3	0	3.7

Orals	9–10/1972	0.6	100	7.2	14.8	15.7	18.7	15.2	28.4	0	4.2
Orals	1974	2.3	100	14.0	23.1	18.0	17.1	11.9	15.8	0.1	3.2
Jamaica											
All methods	1970	19	100	18	18	16	13	10	25	0	3.4
All methods	1975	24	100	42	21	12	9	5	11	0	1.9
Kenya											
All methods	1974	40.6	100	22	18	14	12	11	23	0	3.2
All methods	10–12/1976	10.8	100	22	19	15	12	10	22	0	3.1
IUD's	1970	4.0	100	[d]	16[d]	14	14	16	41	0	4.8
Orals	1970	8.5	100	[d]	26[d]	15	14	13	32	0	4.1
Orals	4–6/1971	1.1	100	17.3	17.6	11.8	12.9	12.2	27.7	0.7	3.7
Korea, Republic of											
IUD's	1966	218.4	100	1.6	8.2	17.5	24.8	24.9	23.0	0	4.4
IUD's	1–6/1975	203.3	100	8.5	21.9	24.9	21.4	14.3	8.9	0.1	3.3
Orals	1969	7.5	100	[d]	17[d]	23	27	34[e]	[e]	0	3.9
Orals	1971	5.0	100	6	14	25	25	17	14	0	3.7
Sterilization	1972	4.0	100	1	14	30	27	16	11	1	3.7
Sterilization, male	1–6/1975	22.4	100	2.0	30.0	37.4	19.8	7.3	3.2	0.3	3.0
Sterilization, female	1–6/1975	3.2	100	3.3	16.0	34.2	27.1	12.2	6.8	0.5	3.4
Abortion	1–6/1975	3.0	100	4.6	16.7	26.0	24.9	16.4	10.4	1.0	3.6
Malaysia, Peninsular											
All methods	1972	56.4	100	21.5	19.2	14.6	12.1	9.9	22.7	0	3.1
All methods	1976	75.2	100	31.4	22.1	13.9	10.3	7.5	14.8	0	2.3
IUD's	1971	0.9	100	5.9	12.3	13.3	18.4	14.1	36.0	0	4.5
IUD's	1976	1.1	100	13.9	25.6	19.2	14.3	9.9	17.0	0	3.0
Orals	1971	47.8	100	21.5	19.5	15.3	12.2	9.6	21.9	0	3.1
Orals	1976	65.0	100	33.9	23.3	13.8	9.6	6.6	12.8	0	2.2
Sterilization	1971	4.0	100	0.4	2.6	6.8	11.7	16.3	62.3	0	>6
Sterilization	1976	4.0	100	0.8	5.3	13.4	19.8	19.5	41.2	0	5.0
Mauritius											
Orals	1974	20.0	100	34.5	20.1	15.1	10.5	8.5	11.3	0.0	2.3

TABLE 7 *Continued*

Country and Method	Acceptor Sample: Acceptor Period (month/year)	Acceptor Sample: Number (in thousands)	Percentage, by Number of Living Children: Total	0 or 1	2	3	4	5	6 or more	Unknown	Median Number of Living Children
Mauritius (Continued)											
Orals	1976	2.0	100	42.1	22.7	14.0	7.9	5.4	7.7	0.2	1.8
Injectables	1976	0.2	100	8.5	8.5	15.1	14.6	13.6	39.7	0.0	4.7
Mexico											
IUD's	1972	12.1	100	[d]	31[d]	[g]	25[g]	9	35	0	4.0
IUD's	1973	18.8	100	12	18	17	13	40[e]	[e]	0	3.7
Orals	1972	17.7	100	[d]	32[d]	[g]	29[g]	10	29	0	3.7
Orals	1973	23.1	100	13	17	17	13	40[e]	[e]	0	3.7
Injectables	1973	8.9	100	5	10	20	22	43[e]	[e]	0	4.2
Morocco											
All methods	1969	14.3	100	5.5	8.1	10.1	13.5	15.4	46.8	0.5	5.3
All methods	1971	18.6	100	7.3	10.4	11.9	13.9	14.7	40.8	0	4.9
Nepal											
IUD's	7/1972–7/1973	0.2	100	5	19	20	23	14	20	0	3.8
IUD's	1975–76	0.4	100	8.6	23.2	25.0	16.6	12.1	14.5	0	3.2
Orals	4–6/1970	1.9	100	15.6	15.8	21.7	17.2	12.8	16.9	0	3.4
Orals	1975–76	2.7	100	12.3	17.5	23.1	17.6	13.5	16.0	0	3.4
Sterilization, male	7/1972–7/1973	1.7	100	0	6	19	22	20	33	0	4.7
Sterilization, male	1975–76	1.3	100	0.2	5.3	21.7	24.2	19.8	28.8	0	4.4
Sterilization, female	1975–76	0.6	100	0.9	3.4	20.5	25.9	25.2	24.1	0	4.5
Philippines											
All methods	4–6/1972	149.2	100	12.9	17.3	16.2	13.9	21.4	17.7	0.6	3.8

All methods	7–12/1975	347.3	100	24.3	20.0	15.6	12.8	9.4	17.9	0	2.9
IUD's	10–12/1970	1.4	100	7.3	13.2	16.6	16.1	46.0[e]	[e]	0.7	4.3
IUD's	7–12/1975	21.9	100	21.0	23.7	16.9	13.7	7.8	16.9	0	2.8
Orals	10–12/1970	3.3	100	9.8	15.8	15.7	15.0	42.9[e]	[e]	0.8	4.1
Orals	7–12/1975	163.5	100	27.3	21.4	15.6	12.2	8.3	15.2	0	2.6
Sterilization, male	7–12/1975	4.2	100	2.4	11.9	19.0	21.4	16.7	28.6	0	4.3
Sterilization, female	7–12/1975	13.2	100	0.8	6.0	16.7	24.2	18.2	34.1	0	4.6
Puerto Rico											
All methods	1974–75	38.8	100	50.0	[f]	31.9[f]	10[h]	[h]	7.6	0.4	1.0
IUD's	1974–75	2.4	100	23.5	[f]	45.8[f]	15.7[h]	[h]	14.4	0.6	2.6
Orals	1974–75	20.2	100	54.5	[f]	31.1[f]	8.3[h]	[h]	5.6	0.4	<1
Singapore											
All methods	1973	19.1	100	67.6	16.2	5.9	2.9	1.7	3.3	2.5	<1
All methods	1976	27.5	100	49.9	16.1	16.4	8.5	4.0	4.2	0.9	<1
Orals	7/1967–8/1968	3.0	100	23.4	18.6	15.4	11.6	10.0	20.7	0.3	3.0
Orals	1976	9.0	100	78.5	14.0	3.3	1.4	0.7	1.0	1.1	<1
Sterilization	1975	9.6	100	1.5	14.9	34.3	22.9	11.2	14.8	0.4	3.5
Sterilization, male	1976	0.4	100	1.3	45.9	27.2	12.3	12.0[e]	[e]	1.3	2.6
Sterilization, female	1976	9.5	100	1.7	17.5	39.2	21.4	19.8[e]	[e]	0.4	3.3
Sri Lanka											
All methods	1970	55.3	100	[d]	26.2[d]	[g]	29.5[g]	35.7[e]	[e]	8.6	3.8
All methods	1973	95.9	100	13.9	18.1	17.1	13.9	10.5	18.7	7.8	3.3
IUD's	1974	29.7	100	18.9	25.1	18.3	12.4	8.0	12.5	4.8	2.7
Sterilization	1974	42.2	100	0.9	6.9	20.8	22.0	17.6	29.8	2.0	4.5
Sterilization, male	1–9/1975	4.6	100	1.8	17.9	24.6	19.7	13.2	20.1	2.8	3.7
Sterilization, female	1–9/1975	24.9	100	0.4	4.2	20.6	22.5	18.9	31.8	1.7	4.6
Taiwan											
IUD's	1968	123.7	100	3.9	14.9	25.2	24.0	14.9	15.9	1.9	3.7
IUD's	1975	173.4	100	11.6	24.3	29.4	18.8	8.6	5.8	1.5	3.0
Orals	1967–68	59.0	100	3.8	15.2	27.4	25.2	14.8	13.6	0.0	3.6
Orals	1975	54.4	100	23.9	25.1	24.0	14.2	6.6	5.1	1.1	2.5

TABLE 7 *Continued*

Country and Method	Acceptor Sample: Acceptor Period (month/year)	Acceptor Sample: Number (in thousands)	Percentage, by Number of Living Children: Total	0 or 1	2	3	4	5	6 or more	Unknown	Median Number of Living Children
Thailand											
IUD's	1971	1.2	100	11.0	19.2	18.8	16.9	12.6	21.4	0.1	3.6
IUD's	1976	1.2	100	21.9	29.4	20.2	9.7	8.8	9.7	0.3	2.5
Orals	1971	3.8	100	14.7	19.6	17.6	15.5	11.9	19.9	0.8	3.4
Orals	1976	6.3	100	33.4	22.6	14.6	9.8	7.3	11.1	1.2	2.2
Sterilization	1974	1.1	100	0.9	11.4	31.4	23.8	13.2	19.3	0	3.8
Sterilization, male	1976	2.1	100	0.9	23.4	23.0	20.6	11.5	17.8	2.8	3.6
Sterilization, female	1976	1.5	100	2.2	16.9	31.5	21.6	12.6	14.2	1.0	3.5
Injectables	1976	1.1	100	25.3	27.3	17.5	10.5	8.8	10.3	0.3	2.4

Tunisia											
IUD's	1966	7.0	100	2.3	7.0	12.0	18.0	18.6	42.2	0	5.1
IUD's	1975	13.3	100	11.7	18.6	17.2	17.1	13.2	22.1	0.1	3.6
Orals	1/1969–8/1972	0.9	100	9.0	14.0	14.6	17.4	15.3	28.2	1.5	4.2
Orals	1975	11.6	100	17.6	19.0	16.4	15.4	11.6	19.2	0.8	3.3
Sterilization, female	1969	1.9	100	0.4	2.0	4.1	12.8	21.9	53.0	5.8	>6
Sterilization, female	1975	6.3	100	1.6	2.1	5.2	16.0	24.6	45.1	5.4	5.4
Abortion	1975	10.2	100	12.6	11.4	12.8	15.9	14.0	29.2	4.1	4.2
Turkey											
IUD's	7–12/1968	26.0	100	6.3	17.2	21.2	20.1	15.6	19.6	0	3.8
IUD's	1973	28.5	100	10.5	23.8	22.7	17.8	11.9	13.3	0	3.2

[a]From Nortman and Hofstatter, 1978.
[b]Prevalence of contraceptive use in Matlab Thana.
[c]Percent shown in the "4" category includes categories "5" and "6 or more."
[d]Percent shown in the "2" category includes the "0 or 1" category.
[e]Percent shown in the "5" category includes the "6 or more" category.
[f]Percent shown in the "3" category includes the "2" category.
[g]Percent shown in the "4" category includes the "3" category.
[h]Percent shown in the "4" category includes the "5" category.

but there are more differences in ages among countries, which is not unexpected given the variation among countries in mean age at childbearing. Countries vary a good deal in age at marriage, and other influences, such as difference in lactation practices and their effect upon birth intervals, disturb the regularity of age patterns. Beyond that, decisions concerning family building and behavior almost surely are more closely related to the number of children than to the wife's chronological age.

These findings also apply to specific methods. Both age and family size decreased with time for acceptors of IUD's, pills, and sterilization. Indeed, the method-specific trends are often sharper than those shown for all methods inasmuch as they avoid the averaging that comes from a shifting mix of methods through time.

Continuation Rates

The number of users of contraceptive methods is a function of the length of use as well as the number of new acceptors. Figure 3 illustrates the mathematical relationship between continuation rate and years of use. It is strikingly apparent that with continuation rates of less than 60% per year, the average period of use is 2 or fewer years. However, with continuation rates above 70%, the average period of use rises sharply, for example, to 10 years with 90% continuation. The average period of use is calculated simply. It is the reciprocal of the 1-year discontinuation rate with no allowance made for early dropouts.

The relationship between the crude birth rate and the percentage of users of contraceptive methods is shown in Figure 4. Countries with fewer than 10% users have high crude birth rates, e.g., 40 or more per 1,000. As the proportion of users approaches 30%, crude birth rates drop to the range of 30–35. When there are 50% or more users, the crude birth rates drop to the low 20's or into the teens. The variations in the percentage of users for a given crude birth rate are due partly to the mix of methods, i.e., the proportion using efficient methods such as sterilization, IUD's, and pills (when taken regularly) versus those using less efficient methods; regularity of use; impairment of fecundity among users; and the degree of accuracy of the figures, both percentages of users and crude birth rates.

In my judgment, the record of continuation rates of nonpermanent contraceptive methods is poor. In quantitative terms, 1-year continuation rates tend to range from 70% to 80% for the IUD, from 50% to 60% for pills, and probably somewhat less for condoms, although data on continued use of methods such as condoms are not readily available.

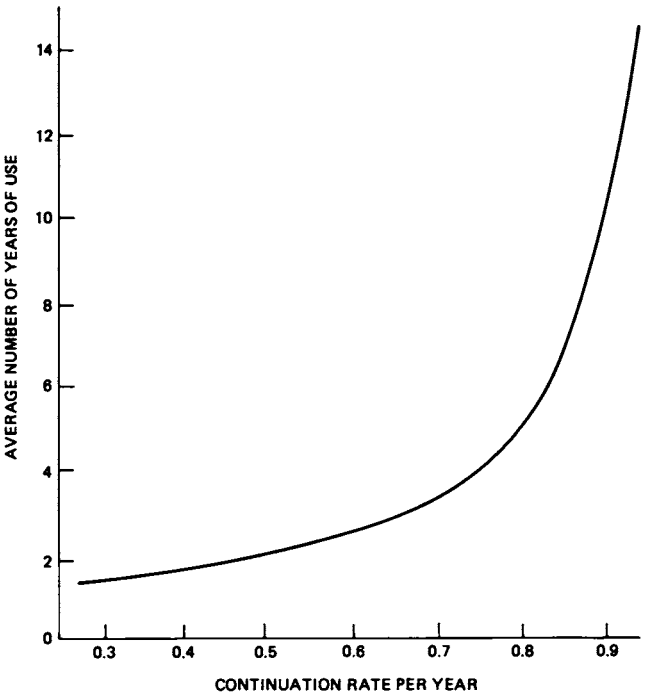

FIGURE 3 Contraceptive methods: Average period of use as a function of continuation rates. This is a mathematical relationship derived from the decay curve $R = ae^{-rt}$, where R is retention rate (or proportion) at time, t; a is a constant (with a value of 1 in this example); e is the natural logarithm; r is the annual rate of discontinuation; t is time expressed in years; and a/r is the average number of years of use.

Indonesia has a better record with the IUD than does the average country. It has an approximately 85% 1-year continuation. Interestingly, India's reported figures for continuation of IUD use were as good as those in Taiwan. However, India's IUD program was judged to be a failure, and IUD's fell more or less into disrepute, whereas Taiwan's family planning program, strongly based on the IUD, is considered to be an overwhelming success. The relative success of Taiwan's program is generally attributed to early efforts to familiarize Taiwan's gynecologists and obstetricians with IUD's, to offer training in insertion techniques to those who wanted it, and to involve leading obstetricians and gynecologists in both research and referral of cases involving medical complications. Taiwan experimented with different

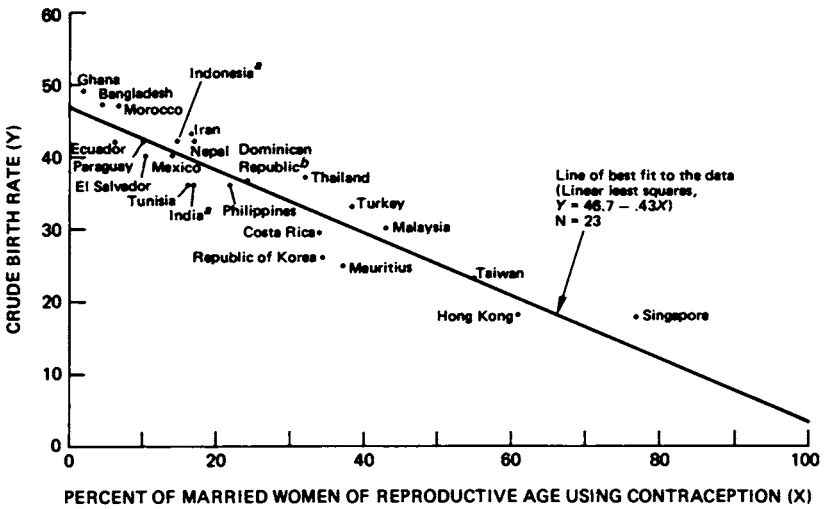

FIGURE 4 Contraceptive use and birth rates. From Nortman and Hofstatter, 1976. [a]Program users only. [b]In this country there is considerable out-migration of husbands of married women of reproductive age.

models of the Lippes loop, and the physicians encouraged patients to have another IUD inserted in cases of expulsion and, to some extent, in cases of removals. In addition, program personnel had "wearers" report to prospective and actual clients that they, too, had experienced some bleeding and pain, but in time had adjusted to the IUD. India, with a much weaker health and administrative infrastructure, either could not deal with medical complications and various side effects or did not adequately handle them. In addition, the Hindu view that a woman is "unclean" when bleeding was an important factor in the limited acceptance of IUD's.

The importance of reducing dropouts to a relatively low level is illustrated in Figures 5, 6, and 7. Figure 5 shows that with 7.5% new acceptors per year (a typical figure for a moderately good program) and continuation rates of only 60% per year (an all too frequent figure for acceptors of oral pills), the maximum percentage that users would ever reach is 18.75%. Figure 6 shows that a more vigorous program that recruited 10% new acceptors per year would achieve 25% users among married women of reproductive age with the same 60% continuation. Alternatively, 25% use could be obtained with 7.5% acceptors if continuation could be increased to 70%. In both figures one can combine various percentages of new acceptors and continuation rates to

achieve the 15% and 25% maximum for users. Figure 7 extends the illustration to show various combinations of 25%, 50%, and 70% users. These figures were selected because a country in which 50% of the women or couples of reproductive age use contraception will have crude birth rates in the mid to low 20's and will be well on the way to low fertility. User rates of 70% are typical of today's developed countries and produce fertility rates approaching replacement. South Korea and Taiwan have had acceptance rates around 10%, and, as

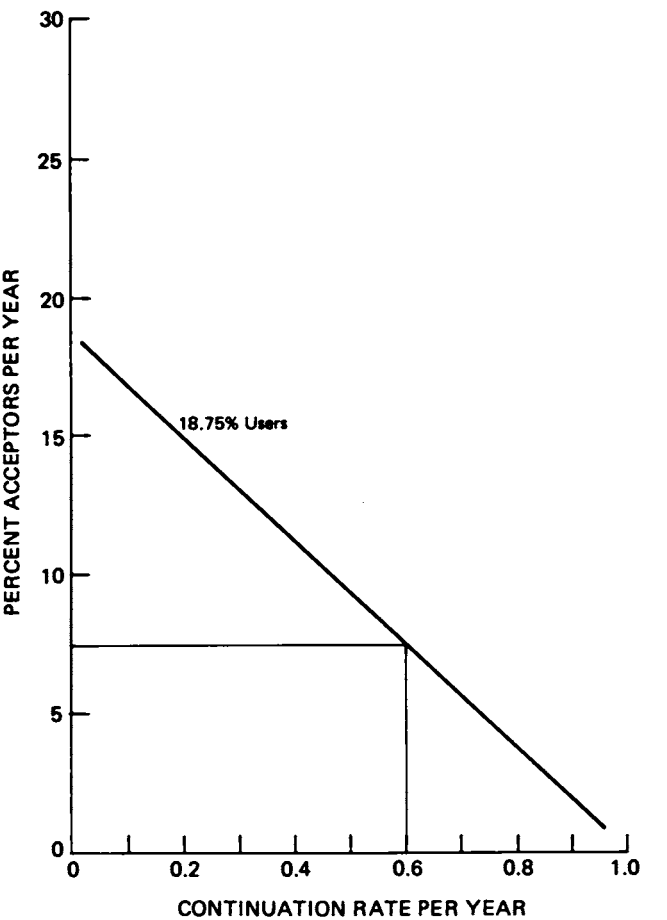

FIGURE 5 Contraceptive users with 7.5% annual acceptance and 60% continuation per year.

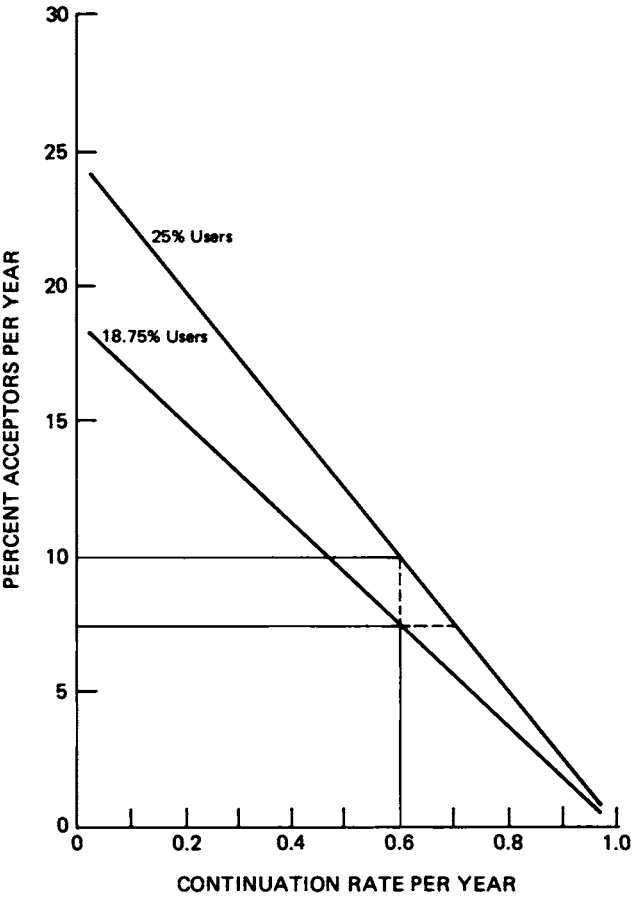

FIGURE 6 Contraceptive users with 7.5% and 10% annual acceptors.

shown in Figure 4, Taiwan has more than 50% users. This suggests that continuation rates must be 80% per year or higher.

There is an extensive literature on the methodology of calculating continuation and discontinuation rates of methods. For IUD's, the technical jargon includes such terms as first segment, second segment, all segments, etc. The first segment is the length of time that the first IUD was worn before termination for whatever reason. The second segment would be the length of time a second IUD was worn, etc. A little more than 10 years ago, two colleagues and I (Mauldin *et al.*, 1967) speculated that the average length of IUD use could be estimated by

using the simple exponential decay curve of $C = ae^{-dt}$, in which C is the proportion continuing, a is a constant that makes an allowance for early dropouts, e is the natural logarithm, and d is the rate of discontinuation expressed in the same units as t, time. In the examples that I have given, d and t have been expressed in units of a year.

Avery (1973) has shown that experience is better than the above formula suggests, at least in Taiwan. He found that the 6-month termination probability decreased from approximately 16% to 5% after

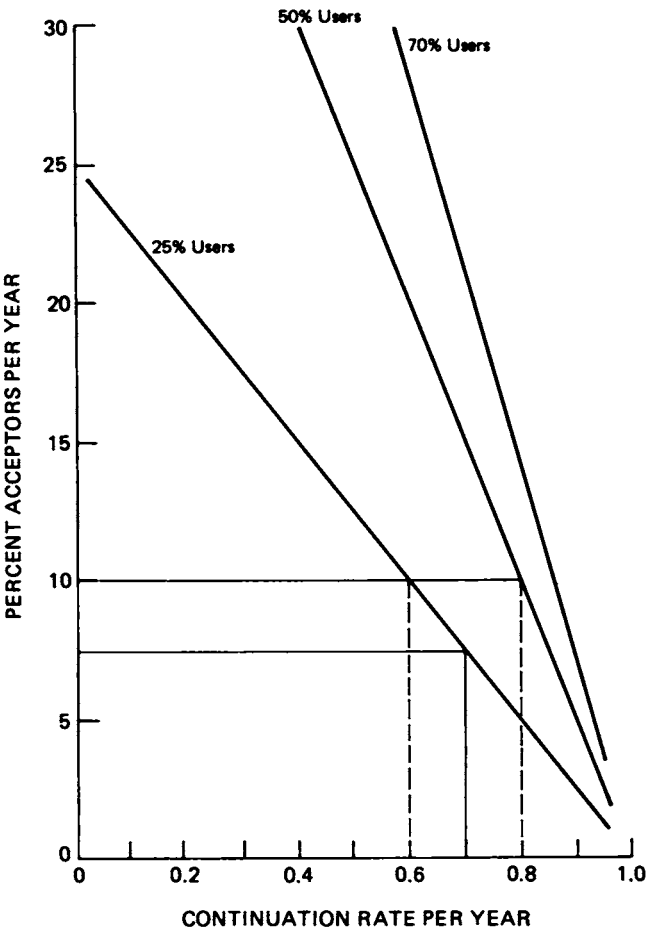

FIGURE 7 Annual acceptors required to achieve 25% to 70% contraceptive users.

5 to 6 years and suggests that this may be attributed to two classes of acceptors—one that tends to expel the IUD and to have it removed when side effects are experienced and a second group that has better tolerance to the IUD and its side effects. At the time that Nortman, Stephan, and I introduced the simple negative exponential to estimate IUD retention time (Mauldin *et al.*, 1967), we speculated that a two-stage model would be a better predictor. However, at that time we did not have data for a sufficiently long period to test such a model. Subsequently, Liu *et al.* (1972) tested such a model, which does fit the data better than the simpler model. But, alas, the single-stage model is the one most frequently used because of its simplicity!

REASONS FOR TERMINATION OF METHOD

Oral Contraceptives

Commonly reported side effects resulting from the use of oral contraceptives are nausea and vomiting, headaches, dizziness, nervousness, bleeding, and weight change. Other side effects include decreases in milk and chloasma. Among women who report discontinued use of oral contraceptives because of side effects, nausea and vomiting are most frequently mentioned, followed by headaches, dizziness, and nervousness (Jones and Mauldin, 1967).

Typical reasons for discontinuation include accidental pregnancy, planned pregnancy, medical or side effects, personal reasons, and method change. The two most frequent reasons for termination are medical and personal (Table 8). There is great variation in the frequency with which these two broad reasons are mentioned. But over a large series of studies, medical and personal reasons are mentioned about equally (Kreager, 1977). Method change is the next most frequently cited reason. Accidental pregnancies are reported by approximately 5% of initial acceptors during the first year of use.

Not all reports of side effects are attributable to oral contraceptives, but the perception that an unpleasant condition is caused by (or associated with) the taking of oral contraceptives often leads to a shift to another method or to complete discontinuation of contraceptive use. Moreover, the frequency with which various physical conditions are associated with the taking of oral contraceptives suggests strongly that an improved product would lead to a reduction in the number of complaints and a decrease in dropouts, or discontinuation.

TABLE 8 Oral Contraceptive and IUD Discontinuation Rates, by Reason, for Selected Developing Countries: Median Percentages and Ranges[a]

Reason for Discontinuation	Medians and Ranges (Number of Studies in Parentheses)			
	Oral Contraceptives		IUD's	
	12 Months	24 Months	12 Months	24 Months
Pregnancy	3.5 (9) 0.5–7.0	5.3 (5) 3.6–9.1	2.3 (20) 0.4–7.8	3.6 (13) 1.7–8.2
Expulsion	—	—	8.3 (19) 1.8–20.9	10.4 (12) 1.8–16.4
Planned pregnancy	5.2 (8) 3.8–12.2	6.6 (5) 4.8–8.0	1.1 (8) 0.2–1.9	2.6 (6) 2.0–5.1
Medical and side effects	30.6 (8) 8.2–49.8	35.9 (4) 19.0–48.5	18.3 (19) 4.0–34.2	19.3 (8) 5.0–49.7
Personal or others	18.7 (10) 9.4–29.2	19.2 (4) 12.8–24.1	2.9 (12) 0.2–6.1	4.6 (8) 0.8–9.0
All reasons	54.7 (10) 30.8–79.1	71.3 (5) 57.6–73.4	33.8 (20) 14.8–61.3	43.5 (13) 25.0–62.7

[a]Adapted from Kreager, 1977.

IUD's

Medical removal because of intermenstrual bleeding, cramps, and pain is the primary cause of termination of IUD use. But during the first 6 months after insertion, expulsions are also frequent, occurring in 10% to 12% of cases (Avery, 1973; Sivin, 1974). In Taichung, the 6-month termination probability of expulsion was 8.7% in the first 6-month period, 4.6% in the second, 2.4% in the third, and continued to drop until it was less than 0.5%. Medical removals also decrease with time, dropping from 10.5% in the first 6-month period to 3%–4% after several years. Other studies produced different levels of termination rates, but the relative order of cause of termination is about the same (Table 8). Other serious side effects of IUD's are pelvic inflammatory disease and perforations of the uterus, although these are less frequent than the other symptoms just mentioned.

ASPECTS OF THE EXPERIENCE

Medical and Biosocial Aspects

The medical profession largely determines which new contraceptive methods will be legalized in a given country and with what restrictions. The IUD is a good example of the desirability, indeed the near necessity, of involving the medical profession in testing, developing personal experience, and undertaking research on a new product. When the IUD was introduced in Taiwan in the Taichung experiment, great care was taken to involve the leading obstetricians and gynecologists. With their involvement, the IUD became a very popular method in that country. The situation was similar in South Korea. However, I believe that less attention was given to involving the medical profession in a number of other countries. Where the medical infrastructure is weak, more problems appear to have been encountered with the IUD.

In Singapore, initial experience with the IUD included a number of perforations or translocations. This, along with reports of excessive bleeding in a number of cases, gave the IUD a negative image:

> Women with IUD's fitted were frightened by the somewhat lurid tales which circulated freely in the clinics where unrestricted mingling of women awaiting fittings, women attending for routine check-ups and women attending with demands for removal took place daily. The result of this was a steep fall in insertions, and a steep rise in removals . . . (Wolfers and Ratnam, 1970, p. 116).

The translocation rate was 1 in 96.5 insertions or an incidence of 10.4 per 1,000 (Ratnam and Tow, 1970), a much higher rate than reported by other investigators.

> [A] sample study of 4,003 consecutive insertions made at or later than 4 weeks after delivery revealed that less experienced doctors and certain individuals had a significantly higher incidence. . . . While no senior member is exempt for having had a perforation, house officers and part-time general practitioners had higher perforation rates. One of the general practitioners in particular had a very much higher rate than the others (Ratnam and Tow, 1970, p. 146).

In that sample study, there were 20 perforations of which 12 were among the 1,949 insertions of a single doctor. In Singapore, apparently, both the medical profession and clients and prospective clients decided that the IUD was not an acceptable method. Those interested in contraceptive methods outside Singapore continue to wonder how the IUD would have been received if only the better trained professionals had been

allowed to make the insertions, at least initially, and if satisfied users had been in the habit of discussing their experiences with other clients.

Local experience is needed on ethical, personal, professional, and political grounds. Lack of familiarity with the characteristics of a product, how it will be used, how it will be perceived, what the associated side effects may be, etc., are barriers to the adoption of all new products, including the contraceptives. The pill was not accepted in India until 1975, and then not with enthusiasm. In the early 1960's objections were raised on two grounds—namely, cost and the nature of the steroids that are used in oral contraceptives. A few years later, after some experimentation with oral contraceptives, doubts about their nature were largely removed, but cost and logistic considerations remained as substantial barriers. In 1965, Segal (1967) estimated that a moderately successful pill program in India was likely to produce 100 million clinic visits per year and that the foreign exchange cost would be more than 10 times the hard currency allocation to the Ministry of Health for all drugs.

Adaptation of Technology

There is a need for local modification of products that have been developed and tested in the West, or, more generally, for assessment of whether these products would be more effective, more acceptable, and less prone to as many side effects if some modifications were made. Examples that have received some attention include smaller IUD's for smaller Asian women and smaller dosage levels of oral contraceptives for smaller women in developing countries. Are smaller dosages as effective in controlling fertility? Would smaller dosages lead to fewer side effects?

A Program for the Introduction and Adaptation of Contraceptive Technology (PIACT) (United Nations Fund for Population Activities Newsletter, 1978) has been formed to act as a "bridge" between biomedical research in fertility control technology and national family planning service programs. As a part of its activities, PIACT seeks to increase the availability, acceptance, continued use, and improved safety of family planning methods. To serve these ends, it has formed a Product Reference Service to respond to requests for information on the cost, use, repair, and local manufacture of fertility control equipment.

In recent years, other groups have become interested in this area, but adaptations to date have been mostly in the field of marketing—giving locally appealing names to existing products and packaging them

appropriately. This may be a more important adaptation than it first appears. In the United States there are more than 100 different contraceptive products sold under more than 600 different brand names (Table 9). This degree of market segmentation is not necessary to meet the preferences of the consumers, but all studies support the idea that a wide range of contraceptive methods is needed.

Sterilization techniques have been greatly improved in recent years,

TABLE 9 Contraceptive Products Marketed in 1976[a]

Contraceptive Method	Number of Brands	Number of Different Products
Cervical caps	13	2
Diaphragms	10	3
SUBTOTALS	23	5
Condoms		
Dry	92	2
Lubricated	120	1
Shaped	63	1
SUBTOTALS	275	4
Spermicides		
Creams and jellies	45	4[b]
Aerosols	8	2[b]
Suppositories	26	2[b]
Foaming tablets	21	2[b]
SUBTOTALS	100	10[b]
Hormonal contraceptives		
Combined	175	43
Sequential	31	18
Continuous	22	7
Injectable	15	4
SUBTOTALS	243	72
IUD's	24	18
TOTALS	665	109[b]

[a]This table was compiled by S. B. Schearer of the Population Council. It is based on products listed in the *Directory of Contraceptives* (International Planned Parenthood Federation, 1976).
[b]Approximate.

and these developments have been stimulated by needs in developing countries. Laparoscopy is now performed with only local anesthesia. The U.S. Agency for International Development (USAID) has purchased nearly 1,200 laparoscopes for distribution to trained gynecologic surgeons in 64 countries (Green, 1978). Laparoscopy requires a skilled surgeon and expensive equipment and is accompanied by problems of supply and repair:

> A newer technique, mini-laparotomy, is becoming widely used as an outpatient procedure. Mini-lap permits tubal occlusion through a very small suprapubic incision. . . . inserted through the vagina, to push the uterine fundus against the anterior abdominal wall. First described by H. Uchida and colleagues in 1961 in Japan, mini-laparotomy was pioneered in Thailand by Vitoon Osathanondh in 1973. Since then, it has been widely and successfully used in Colombia, El Salvador, the Philippines, and many other countries (Green, 1978).

Ravenholt (1976) has estimated that 80 million couples control fertility by voluntary sterilization. His figures include 16 million sterilizations in more developed countries, 35 million in China, 22 million in India, and 7 million in other developing countries. The figure for China is speculative. But that aside, sterilization remains an important method of fertility control, and its popularity is increasing.

Religious and Cultural Aspects

Religious The Catholic elite and hierarchy in Latin America opposed family planning programs and the use of contraceptive methods in the 1960's. This acted as a barrier to the availability of contraceptive methods and to information programs relating to such methods. In Asia, analysis of the interrelationships between economic development and rates of population growth in the late 1950's and early 1960's was a major factor in the decision of governments to seek policies and programs that would slow population growth. But in Latin America, where the Church prevented the adoption of population policies and where prevailing economic thought was of a different brand, it was the physicians who influenced policy. They were greatly concerned about the large number of women who, of necessity, came to hospitals for treatment following poorly performed abortions. However, the masses were relatively uninfluenced by the attitude of the Church and of the elites. Individuals in Catholic countries have reacted to knowledge

about and availability of contraceptive methods as much as other groups.

Conservative Muslim religious leaders, primarily at the village level, have often opposed the use of fertility control methods, but these attitudes are a reflection of their cultural heritage rather than of the Muslim religion itself. A Fatwah that was issued in 1936 by religious leaders at Al Azhar University in Egypt was favorable to family planning, as were subsequent Fatwahs. Abortion was the only method of fertility control that was specifically prohibited. Muslim fertility remains high, but not because of theological doctrine as much as from subordination of women.

Cultural Cultural factors are very important to an understanding of fertility levels and trends. In peasant societies, cultural factors support high fertility, partly because of tradition, partly because large families provide status and security. In Hindu societies, women are viewed as "unclean" during their menstrual period. This leads to unpopularity of contraceptive methods that cause bleeding, such as the IUD. This may well be an important factor in the ready acceptance of vasectomy among Hindus. The Chinese tend to reject vasectomy, but are more tolerant of female sterilization.

Almost everywhere injections and vaccinations are viewed positively because of past experience with smallpox vaccinations and injections of many kinds. It seems likely that women would accept vaccination that would protect against pregnancy, but, unfortunately, no such product is yet available. The experience with injectables, principally Depo-Provera®, is highly promising, but its disapproval as a contraceptive by the U.S. Food and Drug Administration has had a highly negative impact on its use abroad.

Perhaps the best known program using Depo-Provera® is at the McCormick Hospital in Chieng Mai, Thailand, where Dr. Edwin McDaniel has been a strong proponent of family planning and of Depo-Provera®. About 10,000 women have received Depo-Provera® injections (Jones, 1977). Although two-thirds of the women have some irregularity in their periods, 80% are reported to continue use after 1 year, 70% after 2, and 60% after 3. The total fertility rate declined by almost 50% in that area from 1960 to 1975 (Pardthaisong, 1978), and it seems likely that the availability of Depo-Provera® accelerated the fertility decline that started in the mid-1960's.

Programmatic Aspects

Statistics quoted earlier indicate that prior to 1960 family planning programs were barely existent, but since then many countries have adopted population policies and implemented programs that range from the weak and inefficient to the vigorous, widespread, and apparently efficient.

Trained Personnel There are far too few strategically located physicians to implement mass programs of oral contraceptives, IUD's, sterilization, and abortion. In Thailand, this situation has been appreciably improved for oral contraceptives, initially by authorizing paramedical personnel to use a checklist of symptoms to determine whether a given client could receive pills (Hemachidha and Rosenfield, 1975) and later by relaxation of regulations requiring a prescription for pills. Paramedical personnel have also been trained for insertion of IUD's and, in some instances, have been permitted to make insertions under loose medical supervision. However, paramedical personnel are not generally used much for IUD insertions and virtually not at all for sterilization or abortion. Thus, the shortage of physicians in developing countries constitutes a major bottleneck to the ready availability of a variety of fertility control methods.

Trained nonmedical personnel are also an essential part of an effective family planning program. The problems of what the characteristics of such personnel should be, what training they should receive, how they should be supervised, where they should be located, etc., must be solved in order to develop a good program. Solutions range from multipurpose health workers to a family planning organization that is separate from the health infrastructure.

Organizational Issues The World Health Organization's philosophy has been that family planning must be a part of the health program and, typically, a part of the Maternal and Child Health Program. Health infrastructures are very weak in most developing countries, and to tie family planning efforts exclusively to existing health networks is to assign a lower priority to such activities than to malaria or smallpox, for example, for which special-purpose workers were hired, trained, and assigned in the field. Several countries have followed an analogous plan with family planning workers with marked success, notably in South

Korea and Taiwan. Another pattern is to establish a coordinating body, such as those in Egypt and Indonesia, which has responsibility for involving many ministries in the overall program. The Ministry of Health continues to have a central role in such schemes, but ministries such as those for communications, agriculture, education, labor, defense, etc., are more likely to be involved than in situations where the Ministry of Health has overall responsibility.

One of the themes of the 1974 World Population Conference was the integration of population measures and programs into comprehensive social and economic plans and programs (United Nations, 1974). This theme is reflected repeatedly in current United Nations' documents. At a recent meeting of the Economic and Social Commission for Asia and the Pacific, it was recommended that major policy-oriented studies and research on integration of family planning with other development programs should be associated with the planning office in order to give them the scope, objectivity, and access to other agencies that would be required (United Nations Economic and Social Commission for Asia and the Pacific, 1977).

Logistics The marked increase in the number of family planning acceptors in organized programs during the past 10 to 15 years, along with the increase in proportion of users of fertility control methods among couples in the reproductive years, indicates that there is a ready availability of methods. In an earlier study I have shown that there is a strong relationship between the availability of fertility control methods and declines in crude birth rates (Mauldin, 1975). That study also indicated that fertility control methods are not generally available to large proportions of populations in developing countries, at least not within a short distance at reasonable cost.

A recent publication of the World Fertility Survey (Rodríguez, 1977) listed the average "time of travel to perceived nearest outlet" for methods of fertility regulation (Table 10). There are many indications that fertility control methods are not readily available at a reasonable cost, with a reasonable degree of anonymity, and within easy travelling distance.

The vasectomy camps held in Ernakulam and Gujarat in India are cited as examples of what a highly organized program with intensive publicity (and some positive incentives, e.g., gifts and money with a value of 65–110 rupees, plus a lottery with a large sum) can accomplish. In Ernakulam, 11% of couples in the reproductive ages were sterilized, and in Gujarat, 5%—both substantially above previous performance

TABLE 10 Time of Travel to Perceived Nearest Outlet for Methods of Fertility Regulation[a]

	Time (minutes)		
	India	Panama	Turkey
Medians			
Urban	15	15	10
Rural	30	30	30
Means			
Urban	26	19	13
Rural	51	31	57

[a]From Rodríguez, 1977.

and notable for what was accomplished in a very short period of time (National Institute of Family Planning, 1973; Soni, 1971).

The cost of modern contraceptives is important, and sometimes prohibitive, to low-income countries. In the mid-1960's the commercial price for IUD's ranged upwards from 35¢ each to more than $1.00. The Population Council had public sector rights to the Lippes loop in developing countries and was able to purchase IUD's for about 6¢ each. It was later able to authorize others to make purchases at similar prices. In addition, the Council aided a number of countries (including South Korea, Taiwan, India, Indonesia, Hong Kong, Pakistan, and Turkey) in the establishment of a local manufacturing capability.

Around 1963 the wholesale price of oral contraceptives was $1.60 per cycle. The first major drop in prices was negotiated by the Egyptian pharmaceutical industry, which brought the price down to 42¢ per cycle. Over the years the price has continued to drop. USAID, a very large purchaser of oral contraceptives, is able to obtain them for about 20¢ per cycle. But even this sum, which translates to about $3 per woman-year of use, including some allowance for shipping and distribution, looms very large in the foreign exchange budget of a developing country. USAID has had a generous policy of supply for countries that it assists, but in time, countries will be expected to buy their own supplies. The United Nations Fund for Population Activities has recently developed a policy of making contraceptives easily available to developing countries. Thus, supplies are becoming more easily available, for the time being, although the number of distribution points is still far from adequate.

Commercial and Community-Based Distribution Systems

Nonclinical delivery systems have developed primarily because of the inability to expand clinic-based systems. Such systems vary considerably in their modes of operations, as is suggested by the terms used to describe them, e.g., commercial distribution, community-based, village-based, contraceptive retail sales programs, inundation, household distribution, and saturation. For convenience, one may classify these systems into commercial distribution and community-based systems or projects. The latter can be divided into village and household distribution. Since 1962, at least 83 nonclinical projects have been initiated in 36 developing countries, but perhaps no more than two had been established prior to 1970. Eleven programs were inaugurated between 1970 and 1973, and 70 were established between 1974 and the early months of 1978 (Foreit *et al.*, 1978).

In commercial distribution systems, contraceptives are made available to the distribution network at no cost or at subsidized low price so that the contraceptives can be sold to the consumer at a low price. Some of the money that is generated from sales is typically returned to the program to lessen program costs. Such programs usually attempt to locate commercial firms that handle other products. But in some instances a special force of distributors is established, such as those used in Bangladesh. According to Foreit *et al.* (1978), there are 27 commercial programs in operation that sell oral contraceptives and/or condoms. Small pilot projects to test the use of vending machines and mail orders as inexpensive means of distributing contraceptives have also been initiated.

In a number of countries, community-based distribution systems utilize local personnel and resources for distribution. The cooperation of local leaders is sought, and prospective canvassers are identified, contacted, trained, and supplied with contraceptives. A simple map of the district is constructed, and households are visited in order to identify clients and prospective clients. Repeat visits are often made, and contraceptives are sold at the home of the local distributor. Arrangements are made for supervision and also for the referral of complications.

A study in the Philippines (Laing, 1977) shows that prevalence of use of contraceptives decreases regularly as distance from family planning clinics increases. For example, the prevalence of use was 26% among those who lived within 1 km of the clinic, 21% for those living approximately 2 km away, 15% for those living 4 to 5 km from the clinic, and 10% for those living more than 8 km from the clinic.

Ready availability of contraceptive methods in terms of cost, distance, time, anonymity, knowledge of effectiveness, safety, and ease of use are expediting factors in the adoption and continued use of contraceptives. Thus, programs designed to make contraceptive methods more easily available are likely to lead to an increase in acceptance and use. In one area of Brazil such programs have increased the number of distribution points from 11 to more than 600. In Colombia, the urban and rural Profamilia projects added more than 1,600 distribution points. In Indonesia, the number of distribution points has been increased by more than 100,000.

Both the number and variety of village, household, and commercial projects have increased rapidly during recent years. Currently, most projects serve small populations, although large-scale programs do exist in Bangladesh, Taiwan, India, the Philippines, South Korea, Sri Lanka, Thailand, Colombia, Brazil, and Jamaica. There are preliminary indications that this approach leads to major increases in the proportion of users of contraceptive methods at a reasonable cost. For example, a household delivery program in the Matlab area of Bangladesh led to an increase from 1.1% to 15% use by married women in their reproductive ages. Comparable figures were from 18% to 31% in Egypt (Kahn and Huber, 1977).

Demographics

Prior to 1965 fertility was high in almost all developing countries. Declines in fertility were relatively small and were limited to few countries. However, after 1965 there have been major declines of more than 20% to 40% in 19 countries with a combined population of just over 1 billion and declines of between 10% and 19% in 9 countries, again with a combined population of more than 1 billion. Declines have been largest in Asia, amounting to about 17% in the decade from 1965 to 1975, and to approximately 12% in Latin America. Fertility is declining little or not at all in Black Africa.

Although there is controversy as to the cause of these declines, it is increasingly perceived that both socioeconomic development and organized family planning programs have contributed to the declines. Where strong programs and relatively good socioeconomic status are combined, declines have been much greater than elsewhere. The details of that controversy need not concern us here other than for us to note that an important mechanism for reducing fertility has been the increased use of contraceptive methods and that organized programs have aided the flow and availability of such methods.

To increase the proportion of users of contraceptive methods, developing countries need more trained personnel, better management, and a much expanded supply system that would provide each of the principal methods of fertility control conveniently and at small cost. Beyond that, there is a need for new contraceptive methods, including injectables and immunization, that have two characteristics: attractiveness to the poor, to the uneducated, and to those with limited continuous motivation; and high continuation rates, because, as we have seen, low continuation rates effectively place a low ceiling on the proportion of users. I have not included effectiveness as a primary consideration, taking it for granted that new methods will be as effective as the IUD or even the condom, when used with moderate care. An increase in the effectiveness beyond that of the current models of the IUD would have little demographic effect.

The Indian subcontinent can be used to illustrate this point. The combined populations of Bangladesh, India, and Pakistan total more than 760 million. The litany of indices of underdevelopment is long and has changed but little in decades. The civil administrative structures are weak and so far have not been able to mobilize local resources. Village or community structures are fragmented, unlike those in China and Indonesia, and provide small promise of providing local leadership and peer group pressure to change reproductive norms and behavior. It is difficult to imagine fertility control programs that would sharply reduce fertility and growth rates in short periods without the widespread use of sterilization and/or abortion. Other available fertility control methods require more continuous motivation than is likely to be forthcoming in those social and economic settings. But the availability of relatively long-lasting methods, such as injectables or the dreamed-of immunization, could make a difference, even in that setting.

The need seems clear, and the need is now. Although fertility has begun to decline in many developing countries, it remains high in many and relatively high in most. Rates of population growth are still uncomfortably high, and we are likely to see the addition of 2 billion persons to the earth's numbers by the year 2000.

CONCLUSION

In the past decade and a half, a major new industry, population planning and family planning programs, has developed. It involves tens of millions of people and hundreds of millions of dollars. This development coincided with the introduction of two modern methods of

contraception, oral contraceptives and the IUD, and these methods are very important in current programs. Beyond that, suction abortion and improvement in sterilization techniques have widened the array of methods, although there remain barriers to the widespread utilization of these latter two methods.

The increase in new acceptors in organized programs from about 2.5 million in 1965 to more than 10 times that number in 1976 is impressive and heartening, but the low rate of continuation is almost as disheartening as the earlier statistic is encouraging. The frequency of side effects of modern methods of fertility control is impressively large. It is a constant reminder of the many limitations that characterize today's catalog of contraceptive methods.

The constraints to enabling all women and couples to control their fertility if they wish to do so and the constraints to lowering fertility in developing countries are many—low socioeconomic setting, high illiteracy, low education, low income, high mortality, inadequate food supplies, poor housing, etc. There are major political problems and some ethical ones that I have not dealt with, but they are real, nonetheless. Problems of obtaining trained personnel, of improving management, and logistical problems, etc., are all too apparent, although some progress has been made in recent years along these lines.

The needs for improved contraceptive technology are clear—and such improvements would make a large demographic difference, if they were available in the very near future. We need more methods that are acceptable to the poor and uneducated and that have high continuation rates!

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Discussion of Paper Presented by W. Parker Mauldin

LESLIE CORSA

I find myself remarkably in tune with most of what Mr. Mauldin has said. This may not be so remarkable when we consider the similarities of our sources of information and of our processes of looking at the issues. I like his intention of examining all forms of effective birth planning, including induced abortion, in all less developed countries, including China, the home of one-third of the two-thirds of the world's people who live in less developed countries. I share his frustrations concerning the paucity of information on induced abortion in developing countries and on contraceptive technology in general in China, which add an order of magnitude of uncertainty to our understanding of the status of this field. I agree with his estimates of the prevalence of contraceptive use in the less developed countries during 1960 and now, and, like him, thank Ms. Nortman and the International Planned Parenthood Federation (IPPF) for their latest efforts to compile such data throughout the world from the best available sources. I also concur with him on most of the factors that he believes need action to improve contraceptive use in developing countries.

In this situation I find it most useful to talk about some things Mr. Mauldin did not say, because of the lack of time or because he disagrees. First, I would like to extend his comments on sources of data on contraceptive use. There are basically three sources: sample surveys of population at risk (cohabiting women of reproductive age); service data from organized family planning programs, both public and private; and distribution and sales data from the private sector. There

is not much of the last, and where it is available, the information is usually very limited. Our best data on contraceptive use in the private sector come from surveys like the early ones in the United States, which were described by Dr. Menken, despite the problems of obtaining accurate data on contraception and, particularly, on illegal abortion, from household interviews. One solid contribution of technological transfer from more to less developed countries has been application of the sample survey to measurement of birth and death rates and of reproductive behavior including use of all methods of birth planning. Its application has been uneven, but with the latest systematic efforts of the World Fertility Survey we should have more complete coverage and more accurate data about this aspect of development than about most others. Similarly, despite valid questioning of family planning program (service) statistics, their coverage and accuracy provide data that are better than most other program data from developing countries. We should continue to qualify our analyses with caution and to improve these family planning data. We should also qualify and improve the data on other variables that we use in trying to understand the processes of overall development.

I would make a strong case for ceasing to consider "acceptors" as a measure of contraception in favor of adopting current users as much more meaningful. I studied these matters in Pakistan, during the early 1960's and intermittently thereafter, and in Malaysia, where several of us from Michigan have been closely involved since 1965. Malaysia is unusual among developing countries in the extent of coverage and quality of its records of birth and family planning programs. Moreover, for some time it has provided a unique identification number for each individual. Since 1967, each woman's identity number has been included on the records of birth and family planning programs, making computer cross-matching reasonably simple and accurate.

The national program in Malaysia checks new acceptors periodically to determine how many were previously registered. The percentage of "acceptors" who had already been recorded at an earlier date rose from 3.5% in the first year to 4.7% in the second, 7.1% in the third, and 9.3% in the fourth. Given Malaysia's well-controlled record system and negligible incentives for false or inaccurate registration of acceptors, these duplication rates are probably the lowest in the world.

This data system also provides unusual opportunities to compare the effectiveness of extended contraceptive use for various populations, e.g., cohorts of users of family planning programs compared to cohorts of nonusers of programs that are similar in age, parity, date of last birth, ethnic group, and duration of marriage, from which can be

derived the impact of the national program on the national birth rate. We have done that for program cohorts in Malaysia in 1968, 1970, and 1972, and have demonstrated the substantial effect on the birth rate of the contraceptive use provided by the program (Johnson *et al.*, 1978). We have also shown that similar results are obtained by translating current program contraceptive use data (e.g., cycles of pills distributed to users by the program in a given year) into prevented births by assuming that users would have had national average age-specific fertility rates in the absence of the program. In this aspect of evaluation, Malaysia is clearly more developed than the United States.

To expand a little on Mr. Mauldin's consideration of the limiting effect of the insufficient numbers of doctors and nurses on availability and use of modern contraception and abortion in developing countries, I concur with his conclusion that new kinds of health and family planning personnel are the answer. Experience of the past 10 years in various developing countries and in the United States is encouraging. China's barefoot doctors with their varied capabilities to insert IUD's and to perform vasectomies and vacuum abortions are part of a well-developed and highly publicized program. However, many other countries, starting with Bangladesh and Barbados in the mid-1960's, have shown that specially trained young women can insert IUD's as well as physicians. In addition, effective new cadres of specially trained women and men now working with people in many rural villages of the world have demonstrated their ability to initiate and maintain oral contraceptive use.

Two continuing American misconceptions merit mention in this connection. First, too many Americans still believe that the way we practice medicine (and family planning) in the United States is ideal and that anything else is second rate. Those views are being changed by experience with misapplication of modern Western medical practice in less developed countries and by the U.S. infant mortality rate which has ranked for years behind those of 15 other countries where trained midwives deliver babies, in or out of the hospital, instead of physicians who perform most deliveries in the United States. Fortunately, the United States is now expanding the use of trained nurse–midwives to deliver babies and of trained family planning nurse–practitioners to provide contraceptive services. Their performance is speaking for itself in terms of client satisfaction, increased continuation rates, and fewer side effects.

A second misconception is that safety standards in the United States and other more developed countries are not applicable in most of the less developed countries, simply because the latter's risks of maternal

death and disability are enormously greater. Responsible officials in developing countries make decisions on contraceptive practice (e.g., who may insert IUD's or distribute oral contraceptives and what precautions are required before initial use) on the basis of alternative risks of their own people, just as we do. They arrive at different decisions because of the different risks. We must be careful not to misapply our conclusions to their situations.

Sterilization deserves far more attention and support than it has received. It makes enormous sense that people turn to an easy, highly effective method once they have all the children that they want and are reasonably certain that these children will survive. Dr. Menken has shown us the great growth in use of surgical sterilization, particularly vasectomy, in the United States in recent years. Similar growth in use of sterilization is occurring in some developing countries, but others persist in the untested belief that men will not use vasectomy. In addition, people everywhere are concerned about possible involuntary misuse of this method. In the absence of new technological breakthroughs in contraception and in the presence of safeguards against misuse, we should expect, facilitate, and welcome a continued expansion of male and female sterilization in all countries.

Lactation should also receive greater attention for its contraceptive effects. The prevalence of breast-feeding and its significance in modifying national birth rates remains an important difference between more or less developed countries. We tend to forget this in a culture where breast-feeding is little used. Actions are being taken by some developing countries, and should be taken by more, to prevent the decline of breast-feeding that historically accompanies development and has already occurred in many of their urban areas. It is also essential to remember that lactation is not a highly effective contraceptive method. It must be supplemented by other methods of contraception as a part of birth planning programs everywhere. It is also important to remember that as births decrease in any country, so does breast-feeding, which must be replaced in the reproductive lifetime of each woman by some form of effective contraception. This places increased demands on birth-planning services that are not always foreseen.

I intended to close with a few words about two highly interrelated elements of culture and development of great import for contraception: the status of women and the value of sons. However, Dr. Fortier has just said it far better than I possibly could. Despite the need to find better contraceptives, nothing will increase effective birth planning more than improving the status of women. This will automatically

equalize the value of sons and daughters at the same time. I urge you to heed her words.

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The Health Effects of Fertility Control

HOWARD W. ORY

Current methods of fertility control can be used with reasonable safety; however, an even greater safety can be attained. This paper first discusses the number of women using fertility control and then the number of women who become ill and die as a result of this use. It also describes the medical benefits of oral contraception. Throughout this report, emphasis is placed on ways that risks of fertility control can be minimized by applying knowledge that is gained from epidemiologic surveillance to the practice of medicine.

Annual estimates during the early and mid-1970's indicate that approximately 14 million women were using a highly effective method of fertility control (Table 1). The most popular method was the oral contraceptive (OC), which approximately 9.7 million women used. The other three primary methods and estimated usage are: intrauterine devices (IUD's), 3.2 million; abortions, 0.7 million; and tubal ligation, 0.6 million. The risks that are inherent in these methods are described below. Another 5.7 million women used less effective (when used singly) methods of fertility control—namely, the diaphragm, condom, foam, jelly, rhythm, withdrawal, and douche. The Association for Voluntary Sterilization estimates that about 0.6 million vasectomies were performed in 1977 (B. Gonzales, unpublished data).

At least 25.3 million American women have at some time used one of the highly effective methods of fertility control (Table 2). From an epidemiologic viewpoint, these women have been exposed to whatever

TABLE 1 Estimated Number of Women Exposed to Certain Methods of Fertility Control Annually in the United States

Method of Fertility Control	Number of Women (millions)
Oral contraception (1973)[a]	9.7
Intrauterine device (1973)[b]	3.2
Abortion (1972–1975 annual average)[c]	0.7
Tubal ligation (1974)[d]	0.6
Subtotal	14.2
Other (1973)[e]	5.7
TOTALS	19.9

[a]From U.S. Department of Health, Education, and Welfare, 1976. Adjusted for oral contraceptive use by unmarried teenagers based on Zelnik and Kantner, 1977. Also adjusted for oral contraceptive use by 20-year-old and older women who are not currently married (Bureau of Census, 1973), assuming that this group used oral contraceptives at one-half the rate of married women of the same age.
[b]From Kahn and Tyler, 1975.
[c]From Cates *et al.*, 1977b.
[d]From 1972–1973 Mortality Tapes, Commission on Professional and Hospital Activities, Ann Arbor, Michigan, unpublished data.
[e]Includes diaphragm, condom, foam, jelly, rhythm, withdrawal, and douche. From William S. Pratt, National Center for Health Statistics, personal communication. Estimate for ever-married women based on unpublished data from the 1973 National Survey of Family Growth.

turns out to be the long-term complications or benefits of the method of fertility control that they use.

Because of the possibility of long-term effects in these women, we must continue searching for long-term risks and benefits from fertility control. Currently, we suspect four long-term effects of OC use: it increases the user's chance of developing benign liver tumors and gallbladder disease, and it apparently prevents some rheumatoid arthritis and a substantial amount of benign breast disease. However, it is what we do not know that concerns me. At the moment, the most important unanswered question is: What is the effect of OC's, if any, on a woman's risk of developing breast cancer? While the results of almost a dozen epidemiologic studies of women have been encouraging, breast cancer is known to be affected by hormones, and, in some cases, these effects do not show up for 10 to 30 years. Thus, while existing data are reassuring, it is essential to maintain surveillance on the health effects of OC's for no less than 10 and, perhaps, as many as 30 years.

TABLE 2 Estimated Number of Women Who Have Ever Been Exposed to Certain Methods[a] of Fertility Control in the United States

Method of Fertility Control	Number of Women (millions)
Oral contraception (1973)[b]	16.6
Abortion (1971–1976)[c]	3.8
Tubal ligation (1973)[d]	4.9
TOTAL	25.3

[a]Estimates are available only for the three methods shown in this table.
[b]From William S. Pratt, National Center for Health Statistics, personal communication. Estimate for ever-married women based on unpublished data from the 1973 National Survey of Family Growth.
[c]From Sullivan *et al.*, 1977.
[d]Estimate for currently married women under 45 years of age, 1975. From Westoff and Jones, 1977.

Table 3 contains estimated rates and numbers of deaths for users of IUD's, OC's, abortions, tubal ligations, and, for comparison, pregnancy-related deaths in the United States.

Currently, death rates associated with use of OC's are not known with certainty. The OC users' death rates in Table 3 are those estimated by Tietze (1977). They are based on data prior to Beral's report (Beral and the Royal College of General Practitioners, 1977), which shows that all cardiovascular diseases, not just myocardial infarction, appear to be associated with OC use. If Beral's results are used instead, the excess annual death rates would be 10 for OC users who are nonsmokers and 30 for OC users who are smokers. Beral's rates are not included in Table 3, because her estimates may not be directly applicable to those in the United States.

Applying the age-specific death rates from Beral's report to U.S. women, I estimate that 6,000 of the approximately 8,000 cardiovascular disease deaths occurring annually in the United States to women of reproductive age would be attributable to OC use. This does not seem possible. U.S. vital data (U.S. Department of Health, Education, and Welfare, 1950–1974) show that death rates from cardiovascular disease have been falling nearly equally and steadily for men and for women of reproductive ages since 1950. If OC's were as powerful a cause of cardiovascular disease as Beral's results suggest, death rates from these for men and women should diverge.

On the other hand, Beral's results strongly confirm that users of OC's who smoke suffer substantial mortality from cardiovascular diseases. The number of cases in her study was not large enough to allow her to look separately at the effects of OC's, smoking, and age. As her study gets larger, she will probably be able to separate the effects of OC's, age, and smoking.

Table 3 shows variation of death rates for specific methods. Annually the death rate per 100,000 women is 3.7 for OC users and 0.3 for IUD users. For every 100,000 women who have an abortion, 4 will die, and for every 100,000 women undergoing surgical sterilization, 16 will die. Of 100,000 women who become pregnant and elect not to have an abortion, 21 will die from events that are related to pregnancy and childbirth.

Not shown on the table is Tietze's estimate of the miniscule death rate for women who use barrier methods and, if the barrier method fails, abortion (Tietze, 1977). This combination is 100% effective and provides the safest available method of fertility control. Also, in the United States, vasectomy appears to be free of mortality. I say "appears" because vasectomy has not been subjected to the systematic surveillance that has been given to other methods. We do not know with certainty whether the zero or near zero mortality that we are observing is correct or whether it represents an artifact of no systematic surveillance.

Even more striking than the difference in risk among methods is the difference in risk within a method by characteristics of the various subgroups. The annual number of deaths among women (Table 3) indicates that if OC users stopped smoking, a substantial proportion—about one-half—of their estimated annual number of deaths would be eliminated. If all women chose to have their abortions prior to the 12th week of gestation, the number of deaths due to abortion would decrease by approximately one-half. If women and physicians followed the implications of these data, I estimate that approximately one-half of the deaths that are associated with fertility control in the United States could be prevented. This is a major public health achievement that is within our reach.

Prevention of deaths and control of complications from fertility control is achieved by first learning what types of complications occur for specific categories of women. That information must then be given to the women and physicians so that fertility control can be applied rationally and safely.

Table 4 shows the major harmful effects of OC use. It highlights the variation in risk of complications from OC that results from the

TABLE 3 Estimated Numbers and Rates of Deaths for Users of Certain Methods of Fertility Control in the United States[a]

Method of Fertility Control	Estimated Death Rate	Estimated Number of Deaths Among Women Annually
Oral contraception[b]		
Smokers	6.5	252
Nonsmokers	1.8	105
TOTALS	3.7	357
Intrauterine device[c]	0.3	10
Abortion[d]		
Before 12 weeks	1.8	11
After 12 weeks	14.9	15
TOTALS	3.7	26
Tubal ligation		
Laparotomy[e]	20.0	78
Laparoscopy[e]	7.5	14
TOTALS	16.1	92
Maternal mortality[g]	20.6	472

[a]Death rates expressed per 100,000 women per year for oral contraceptive and IUD users, per 100,000 procedures for abortion and tubal ligation, and per 100,000 births for maternal mortality. The estimated numbers of deaths are derived from applying the death rates to the estimated number of contraceptive users shown in Table 1.

[b]From Tietze, 1977. The death rate shown has been age-standardized to the estimated distribution of users of oral contraception in the United States during 1973. The annual number of deaths among women was obtained by applying the death rates in each smoking category to the proportion of oral contraceptive users that were smokers (40%) and nonsmokers (60%), respectively.

[c]From Kahn and Tyler, 1975.

[d]From Cates *et al.*, 1977b.

[e]From 1972–1973 Mortality Tapes, Commission on Professional and Hospital Activities, Ann Arbor, Michigan, unpublished data.

[f]Phillips *et al.*, 1975.

[g]Data concern maternal mortality exclusive of abortion. Death rate is the number of deaths per 100,000 live births in the United States during 1971. The number of women is an average for the United States, 1971–1975. The rates are standardized to the age distribution of U.S. women using oral contraceptives.

presence or absence of controllable factors. For example, venous thrombosis is clearly related to the dose of estrogen in the oral contraceptive. Another example is that myocardial infarction is twice as likely to occur with an OC user with no associated risk factors than it is for a nonuser. However, women who have three risk factors for myocardial infarction, such as OC use, smoking, and high cholesterol, have nearly 80 times the risk of myocardial infarction as a woman who has none of these three factors.

Hemorrhagic stroke occurs about twice as often in OC users and is strongly related to smoking and hypertension. Against this background, Beral reported that of the nine deaths from subarachnoid hemorrhage that occurred in the Royal College of General Practitioners' cohort, every one of them was an OC user or former user. This finding strongly suggests that OC's are a risk factor for hemorrhagic stroke and, particularly, for subarachnoid hemorrhage. (This has been confirmed by Petitti and Wingerd, 1978.) It appears likely that an OC user who has hypertension or who smokes is particularly at risk for this calamitous event.

Table 5 shows an interesting facet of OC safety—namely, that the incidence of at least four diseases is apparently reduced by OC use. Women who use OC's are one-fourth as likely to develop benign breast lumps as are nonusers. Likewise, they are one-fourteenth as likely to develop ovarian cysts, two-thirds as likely to develop iron deficiency

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It is difficult to combine into one table information about several methods of fertility control that have been gathered from various sources. The denominators vary. Death rates that are associated with OC use are expressed as number of deaths per woman-years at risk. On the other hand, abortion-related death rates are expressed as number of deaths per number of procedures. In addition, the respective age distributions of women using OC's, abortion, or tubal ligation are not comparable. Because of these differences, comparisons are difficult. For example, tubal ligations are most common after the age of 30, but pregnancies are most common under the age of 30. The use of oral contraceptives is relatively more common over the age of 30 than are pregnancies but relatively less common than tubal ligation. Thus, the distribution of women using OC's is intermediate between those having tubal ligations and those delivering babies. Where possible, I have standardized rates to the distribution of women using OC's. Doing this has led to an age-standardized maternal mortality rate of 20.6 for 1971, which is higher than the usually quoted figure of about 16 per 100,000. Standardizing the death rate that is related to pregnancy and childbirth to the distribution of women using OC's tends to emphasize the deaths in the older gravida more than if maternal deaths are standardized to the distribution of women in the United States, as is usually done. So little is known about death rates from sterilization that only crude rates are available. Because women having sterilizations are older and because age itself increases one's risk of death, comparison with the other methods probably exaggerates the risk that is associated with sterilization as compared to the other methods.

TABLE 4 Major Harmful Effects of Oral Contraceptives: Modification of Those Effects by Other Factors

Complication	Modifying Factor	Risk of Complication in Oral Contraceptive User with Special Risk Factor Compared to Nonuser Without (Risk) Factor
Venous thrombosis[a]	Low-dose estrogen	4:1
	High-dose estrogen	10:1
Myocardial infarction[b]	None	2:1
	Cigarette smoker	5:1
	Any three risk factors combined	78:1
Thrombotic stroke[c]	None	3:1
	Severe hypertension	14:1
	≥1 pack/day smoker	6:1
Hemorrhagic stroke[c]	None	2:1
	Severe hypertension	26:1
	≥1 pack/day smoker	8:1
Gallstones[d]	<2 years oral contraceptive use	1:1
	≥2 years oral contraceptive use	2:1

[a]From Stolley *et al.*, 1975.
[b]From Mann *et al.*, 1975.
[c]From Collaborative Group for the Study of Stroke in Young Women, 1975.
[d]From Royal College of General Practitioners, 1974.

anemia, and one-half as likely to develop rheumatoid arthritis. For every 100,000 OC users, there are 270 fewer surgeries for ovarian cysts and benign breast diseases than there would be if these 100,000 women did not use OC's.

The major harmful effects of IUD's, as they are used in the United States, are shown in Table 6. The risk depends on the biological characteristics of the woman and on the type of IUD. Septic spontaneous abortion is a clear example of disease prevention through epidemiologic surveillance. Table 6 shows that pregnant women wearing an IUD are 50 times more likely to have a septic spontaneous abortion than pregnant women not wearing an IUD. In the middle of 1974, the Food and Drug Administration (FDA) and the American College of Obstetrics and Gynecology launched a major campaign to

TABLE 5 Major Noncontraceptive Beneficial Effects of Oral Contraception in the United States

Disease Prevented	Risk of Disease in Oral Contraceptive User Relative to Nonuser
Benign breast lumps[a]	1/4
Ovarian cysts[b]	1/14
Iron deficiency anemia[c]	2/3
Rheumatoid arthritis[d]	1/2

[a]From Ory *et al.*, 1976.
[b]From Ory and the Boston Collaborative Drug Surveillance Program, 1974.
[c]From the Royal College of General Practitioners, 1974.
[d]From Wingrave and the Royal College of General Practitioners, 1978.

inform physicians and women that if a woman becomes pregnant while wearing an IUD, the IUD should be removed. This combination of publicity was effective. Up to the middle of 1974, 17 deaths from spontaneous abortion that were related to IUD use were reported to the Center for Disease Control (CDC) (Cates *et al.*, 1977a). Since then, the CDC has maintained surveillance and has discovered only two such deaths. While the number of deaths that has been prevented is

TABLE 6 Major Harmful Effects of IUD's in the United States

Harmful Effect	Risk-Modifying Factor	Risk in IUD User Compared to Nonuser
Septic spontaneous abortion[a]	None	50:1
	Dalkon shield	75:1
	All other IUD's	25:1
Pelvic infection[b]	None	3:1
	≤20 years of age	4:1
	≥26 years of age	2:1
	Nulliparous	7:1
	Multiparous	2:1
Ectopic pregnancy[c]	None	6:1

[a]From Cates *et al.*, 1976.
[b]From Ory, 1978.
[c]From Cates and Ory, 1979.

small, this is a persuasive example of the beneficial effects that epidemiologic surveillance can have on identifying a preventable cause of mortality and then monitoring its near elimination.

Table 6 also presents a summary of the results of eight analytic epidemiologic studies that have examined the relationship between IUD use and acute pelvic inflammatory disease (PID) (Eschenbach *et al.*, 1977; Faulkner and Ory, 1976; Lippes, 1975; Noonan and Adams, 1974; Targum and Wright, 1974; Vessey *et al.*, 1976; Weström *et al.*, 1976; and Wright, 1968). These studies used various methods, were conducted by different investigators, and were performed in three different countries; yet, their results are consistent. The consistency provides a strong indication that the association between PID and IUD use is one of cause and effect. Each study has its strengths and weaknesses, but these eight studies taken as a group have accounted for and dismissed nearly every major source of bias as a possible reason for observing the association.

Over and above the basic association, there are several interesting facts concerning PID and IUD use. In the first place, there does not appear to be any statistically significant difference between IUD users and nonusers regarding the percentage of women with PID who have positive cultures for gonorrhea (Eschenbach *et al.*, 1977; Weström *et al.*, 1976). Moreover, the epidemiologic data suggest that copper IUD's do not protect against gonococcal infection (Weström *et al.*, 1976), as suggested by some earlier laboratory data. The wide variety of infectious agents that cause IUD-associated PID is probably no different from that found for PID that is not associated with IUD's (Eschenbach *et al.*, 1977). Finally, there is the interesting finding that a sterile inflammatory process occurs in the tubes of nearly one-half of the women who use IUD's (Smith and Soderstrom, 1976). Whether this sterile inflammation produces acute symptoms on its own or potentiates the susceptibility of the tubes to microbial invasion is not known.

Clinically, the relationship between IUD's and ectopic pregnancy is highly relevant. About 5% of pregnancies that occur with an *in-situ* IUD are ectopic (Tatum and Schmidt, 1977). This makes the evaluation of amenorrhea in a woman using the IUD a matter of clinical urgency.

Whether or not IUD's have increased the overall incidence of ectopic pregnancies remains an interesting question. Trends in England (Beral, 1975) and Los Angeles (Hallatt, 1976) indicate that the incidence of ectopic pregnancy has been increasing since the 1960's, when IUD's were first introduced as a method of contraception. In England, the age and regional trends in ectopic pregnancy correlated more closely with IUD use than with acute PID. At Kaiser Hospital in Los

Angeles, patients with IUD-associated ectopic pregnancies were 11 times less likely than non-IUD cases to have acute PID documented at surgery. The latter trend has also been shown in Finland (Erkkola and Liukko, 1977).

Little has been published about comparative rates of complications of various methods of female surgical sterilization. The CDC is currently embarking on a hospital-based surveillance of surgical sterilizing operations. In addition, it is instituting a surveillance in search of deaths that are related to surgical sterilizations. Since female sterilization is a surgical procedure, the CDC expects to find analogous results to its study of abortion: (1) different procedures done at different times will have different death and complication rates; and (2) these rates will be low, but ways can be found to eliminate deaths and lower rates of other complications.

SUMMARY AND CONCLUSIONS

Available methods of contraception are effective and relatively safe. This is important because at least 14 million women are using a modern and highly effective method of fertility control and are, therefore, at risk of suffering a complication. Moreover, at least 25 million women have at some time used a method of fertility control and, if there are long-term effects, these women are at risk. Given the widespread use of modern and highly effective fertility control, it is incumbent on us to make their use as safe as possible. These are medicines and surgical methods being used by women, not to cure disease, but to prevent an unwanted pregnancy.

To make available methods of fertility control safer than they already are, we should increase the surveillance of the safety of existing methods of fertility control and disseminate widely and effectively the knowledge gained in this surveillance to both the potential user and her physician so that together they can carefully select the method of fertility control that is best suited to her current health and circumstances.

The example of the near elimination of IUD-related spontaneous abortion deaths clearly demonstrates the impact of the course that I have outlined. Likewise, avoidance of the particularly harmful effect of smoking on the health of OC users and the harmful effect of delayed abortion are relatively simple ways to make these methods of fertility control safer. If women and physicians follow the implication of the data, at least one-half of all morbidity and mortality that are related to fertility control could be prevented.

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Discussion of Paper Presented by Howard W. Ory

HENRY W. FOSTER, JR.

All of us who share a concern for improving the quality of contraceptive methods are indebted to the Family Planning Evaluation Division of the Center for Disease Control (CDC). The value of this unit is aptly demonstrated by the virtual elimination of deaths from spontaneous abortion that are related to the use of intrauterine devices (IUD's).

Dr. Ory is correct in that we constantly hear pleas for safer contraceptives when very clearly the ones that are in existence could be used more safely. However, the *theoretical* safety and effectiveness of these agents well exceed their actual safety and effectiveness in use. Since the Family Planning Evaluation Division seeks to eliminate the mortality and to control the morbidity that are associated with contraception by applying knowledge gained from epidemiology, I must ask: What is the limit beyond which we can expect to enhance safety given the limitations imposed by our inadequate understanding of human behavior? What role or relationship should or do behavioral scientists play in meeting the objectives of the Family Planning Evaluation Division? How many of the 50 staff members are strictly behavioral scientists? I will be keenly interested in Dr. Warren Miller's presentation on "Psychosocial Aspects of Contraception."

In examining the health effects of fertility control, Dr. Ory has labeled as highly effective the methods of oral steroid contraception, the intrauterine device, abortion, and tubal ligation, which are used by 16 million women in the United States annually. His table of methods also lists 5.7 million women who use other, less effective methods.

However, his table does not list hysterectomy. What is the speculated contribution of this procedure to contraception in this country? I do appreciate the difficulty in determining whether or not the procedure is performed solely for the purpose of sterilization or ostensibly for some medical indication. In some centers, hysterectomies are performed expressly for the purpose of contraception.

The widespread use of oral contraceptive hormones and their potential long-term risk has stimulated concern for contraceptive safety. The single most important unanswered question regarding steroid contraceptives is: Do they increase the risk of cancer? But, as pointed out by Dr. Ory, the period of observation has not been long enough to make this judgment. To date, the production of breast tumors by steroid contraceptives has been limited to specific strains of rats and mice. High doses of estrogen have not produced breast tumors in a variety of other laboratory animals including monkeys. Although diethylstilbestrol (DES) is not a steroid hormone, the recent report by Bibbo *et al.* (1978) on females who received this drug more than 25 years ago shows a 4.6% incidence of breast cancer for users of DES as opposed to an incidence of 3.1% for nonusers. Although this difference is not statistically significant, it is unsettling and shows the need for more answers.

There now seems to be less concern regarding the effects of steroid contraception upon the endometrium than on other genital organs. In fact, a protective result may accrue to the endometrium from combination birth control pills.

As pointed out by Dr. Ory, the published data by Beral (1975) cannot as yet be considered fully applicable to women in the United States, but without question, they probably have some applicability to this country. These data show that all cardiovascular diseases appear to be increased in users of oral contraceptives. By applying her data to Tietze's data, which show excess annual death rates (Tietze, 1977), Dr. Ory has shown that in addition to the significant difference in death rate between nonsmokers and smokers, the base rate for nonsmokers is higher than his data showed independently. I cannot question this extrapolation. As he has emphasized, firm conclusions remain yet unsubstantiated for this country.

I agree with Dr. Ory that information regarding benign liver tumors needs further explanation. However, preliminary data on the subject indicate that the practice of medicine has already been influenced favorably—few practitioners now routinely prescribe more than 50 μg doses of estrogen for contraceptive purposes. There is one unanswered question: Is the relationship of hepatoma formation with the use of

mestranol stronger than that with the use of ethinyl estradiol, or was this artifact caused by the disproportionate use of mestranol over ethinyl estradiol in contraceptive formulae? This question and others have been addressed by Rooks *et al.* (1979).

I should like to emphasize the continued need for the requirement of prescription renewal for steroid contraceptives. This practice will afford the opportunity for continued screening for genital malignancy and other possible estrogen-related disorders.

Dr. Ory has presented a table showing the major harmful effects of IUD's, excluding death. Of these harmful effects, reference has already been made to septic spontaneous abortion. It is interesting to note the increased risk to IUD users as compared to nonusers, which is caused by the risk-modifying factors of an age of less than 20 years and nulliparity. Does this increased morbidity reflect biological differences that are not inherent in multiparous, older patients? Or is the difference in risk attributable to the dissimilar lifestyles of the two groups, e.g., greater and more varied social and sexual exposure of the younger nulliparous women, with a greater risk for contracting venereal disease? Dr. Ory also does not mention the progesterone-bearing IUD's. This is a bit unusual inasmuch as he, I, and others devoted the greater part of a recent meeting discussing this topic.

On two occasions during his presentation, Dr. Ory pointed out that little is known about complication rates of surgical sterilization. Recently, CDC has embarked upon an in-depth surveillance program. Such a response by CDC cannot be more timely in view of the fact that the 1975 National Fertility Study (Westoff and Jones, 1977) found that sterilization is now the contraceptive method of choice for couples of reproductive age married 10 years or more and that 25% of all once and currently married white couples under 45 have selected sterilization as their contraceptive method (14% female, 11.1% male). According to the National Center for Health Statistics (U.S. Department of Health, Education, and Welfare, 1976), the election of sterilization has doubled since 1965 to nearly 25% among married couples of reproductive age in the United States, thus indicating a new trend in public and personal acceptance of this contraceptive procedure.

Just over 2 years ago, we began to perform the interval minilaparotomy sterilization procedure at the gynecology service at Meharry Medical College in Nashville, Tennessee, and more recently as an ambulatory procedure performed with local anesthesia at the Planned Parenthood Affiliate of Nashville. Shortly after instituting this new surgical procedure, I reviewed the literature in an effort to gain some insights as to advantages and disadvantages of interval minilaparotomy

over other forms of surgical sterilization. Some crude comparative outcomes for these two procedures were made between the health effects of uterine perforation, bladder injury, intestinal injury, bleeding, infections, deaths, and subsequent pregnancy rates. When making these comparisons, I am fully aware that no well-structured prospective study between the laparotomy sterilization and minilaparotomy has been conducted using standardized definitions and uniformity of reporting. What I have done, however, is to compare some outcomes of several laparoscopic studies with the only available minilaparotomy study, which was conducted by Dr. V. Osathanondh of the Ramathibodi Hospital in Thailand (Osathanondh, 1974, 1976).

Table 1 compares uterine perforation, bladder injury, intestinal injury, bleeding, and infection of minilaparotomy with laparoscopic sterilization. Uterine perforation occurred almost twice as often with laparoscopy. Bladder injuries sustained during the minilaparotomy were more frequent in one and less frequent in another laparoscopic study. Intestinal injuries were less with the minilaparotomy than with all three laparoscopy series. Bleeding occurred more often with the minilaparotomy in one study and less often in another than with the laparoscopic approach.

Infections from minilaparotomies occurred more often than in any of the laparoscopic studies. However, the Ramathibodi study (Osathanondh, 1974, 1976) subdivided the infections into grossly infected (2 cases) and skin inflammation (24 cases). Four hundred sixty-six cases (16%) of the 2,786 procedures from this study were conducted in outpatient centers in rural Thailand by nonphysicians. No mortality figures were given in this study.

Table 2 presents the subsequent pregnancy rate from five laparoscopy studies. The pregnancy rate in these studies ranges from a low of 0.6% to a high of 2.8% in a study of women who used the spring clip exclusively. There is no specified time period or cutoff point by which pregnancy in these studies was measured. The question of subsequent pregnancies did not appear in the Ramathibodi study. However, Garb (1957) reported 22 pregnancies in 5,477 Pomeroy procedures yielding an overall pregnancy rate of 0.4%. Based on 10 major studies from three continents, Tietze found that 34 failures occurred with 20,000 surgical sterilizations (0.17%). In these studies, no distinction is made as to the time of the procedure, i.e., postpartum or during the interval state. With regard to any type of sterilization procedure, there remains the unclarified issue of menstrual irregularity subsequent to the sterilizing procedure and, of course, psychological sequelae, which are difficult to evaluate.

TABLE 1 Complications from Minilaparotomy Compared with Those from Laparoscopic Sterilization

	Laparoscopic Sterilization				Minilaparotomy			
			Complications				Complications	
Complication	Study	Total in Study	Number	%	Study	Total in Study	Number	%
Uterine perforation	Corson and Bolognese, 1972	1,545	9	0.58	Ramathibodi (Osathanondh, 1976)	2,786	9	0.32
Bladder injury	Corson and Bolognese, 1972	1,545	1	0.06	Ramathibodi (Osathanondh, 1976)	2,786	5	0.18
	Georgy *et al.*, 1974	800	2	0.25				
Intestinal injury	Corson and Bolognese, 1972	1,545	3	0.19	Ramathibodi (Osathanondh, 1976)	2,786	3	0.11
	Peterson and Behrman, 1971	186	1	0.53				
	Thompson and Wheeless, 1973	3,600	11	0.3				
Bleeding	Corson and Bolognese, 1972	1,545	1	0.06	Ramathibodi (Osathanondh, 1976)	2,786	10	0.36
	Peterson and Behrman, 1971	186	5	2.6				
Infection	Corson and Bolognese, 1972	1,545	9	0.58	Ramathibodi (Osathanondh, 1976)	2,786	26	0.93
	Peterson and Behrman, 1971	186	0	0				

TABLE 2 Pregnancies After Interval Minilaparotomy Compared to Those Following Laparoscopic Sterilization

Laparoscopic Sterilization				Minilaparotomy			
		Subsequent Pregnancies				Subsequent Pregnancies	
Study	Number of Sterilizations	Number	%	Study	Number of Sterilizations	Number	%
Corson and Bolognese, 1972	1,545	3	0.19	Garb, 1957	5,477	22	0.4
Thompson and Wheeless, 1973	4,200	31	0.73	Tietze (Hellman and Pritchard, 1971)	20,000	34	0.17
Peterson and Behrman, 1971	186	1	0.53				
Kessel *et al.*, 1976	876	20	2.28				

TABLE 3 Complications of Abortion Patients, July 1, 1970 to June 30, 1971[a]

Patients	Complication Rates per 100 Women Obtaining Abortions			
	Total Complications		Major Complications	
	Total Patients	Local Patients with Follow-Up	Total Patients	Local Patients with Follow-Up
All patients				
≤12-weeks gestation	5.2	7.8	0.6	1.1
≥13-weeks gestation	22.2	26.1	2.2	3.0
Patients *without* pre-existing complications, by procedure				
Suction [b]	4.2	6.1	0.4	0.6
D&C[b]	6.0	8.2	0.5	0.8
Saline[b]	23.4	27.2	1.7	2.4
Hysterotomy[c]	33.4	32.9	6.7	6.9
Hysterectomy	49.9	50.9	14.3	15.6
Patients *without* complications *or* sterilization				
≤12-weeks gestation	4.2	6.2	0.4	0.6
≥13-weeks gestation	20.6	26.0	1.6	2.1
Patients *with* pre-existing complications, *without* sterilization				
≤12-weeks gestation	12.7	17.1	1.4	2.0
≥13-weeks gestation	29.9	35.1	4.6	6.7
Patients *without* pre-existing complications, *with* sterilization				
≤12-weeks gestation	25.9	28.0	6.1	7.2
≥13-weeks gestation	35.8	35.4	8.2	8.0
Patients *with* pre-existing complications *and* sterilization				
≤12-weeks gestation	43.0	46.2	14.9	17.1
≥13-weeks gestation	56.5	60.4	13.8	17.4

[a]From Tietze and Dawson, 1973.
[b]Without tubal sterilization.
[c]With tubal sterilization.

To reemphasize a point made by Dr. Ory concerning abortion, particular attention should be given to health effects of multiple variables, the effect of time (length of gestation), and the relationship of the two to each other as they affect abortion-related mortality and morbidity. The following data are taken from a study by the Institute of Medicine, *Legalized Abortion and the Public Health,* which was published in May 1975 (Institute of Medicine, 1975).

Table 3 examines abortion and the variables of preexisting disease, no preexisting disease, associated sterilization, no associated sterilization, and relates these variables to gestational age of greater than 13 weeks or less than 12 weeks. The best outcome was achieved in patients who had no preexisting disease, no associated sterilization procedure, and were less than 12-weeks pregnant. The opposite is true for poorest outcome, i.e., patients had preexisting disease, associated sterilization procedure, and were more than 13-weeks pregnant.

Table 4 shows an increasing mortality and morbidity with advancing pregnancy, by weekly increments. It also depicts the decreased morbidity and mortality that are associated with suction procedures and

TABLE 4 Reported Deaths Associated with Legal Abortion in the United States, by Weeks of Gestation and Method of Abortion, 1972 and 1973[a]

Length of Gestation and Abortion Method	Number of Abortions	Number of Deaths	Mortality Ratio (Deaths per 100,000 Abortions)
Weeks of gestation [b]			
≤ 8	421,896	2	0.5
9–10	361,885	6	1.7
11–12	212,981	9	4.2
13–15	87,573	6	6.9
≥16 or more	118,228	19	16.1
Method of abortion			
Suction/D&C	1,065,338	17	1.6
Saline	123,684	19	15.4
Hysterotomy/ hysterectomy	8,161	5	61.3
Other	5,380	1	18.6

[a]From U.S. Department of Health, Education, and Welfare, 1978.
[b]Distribution of abortions based on gestation of pregnancy known for 449,709 abortions reported during 1972 (77% of the total for that year) and for 453,535 abortions reported for 1973 (74% of the total for that year).

in increased mortality and morbidity with surgical procedures. Figure 1 illustrates this increasing mortality with advancing fetal age.

Legalized abortion is rather new to the American scene. Consequently, some long-term complications are unresolved. I will close, therefore, by simply listing these long-term complications, which are associated with legalized abortion, and offering Dr. Ory and others a challenge to help us formulate a better understanding of these entities which are sterility, prematurity, spontaneous abortion, ectopic pregnancy, Rh isoimmunization, specific effects on teenagers, and psychological sequelae. The World Health Organization has already begun to seek some of these answers in a structured manner. I hope that the Family Planning Evaluation Division will also play a pivotal role in the process.

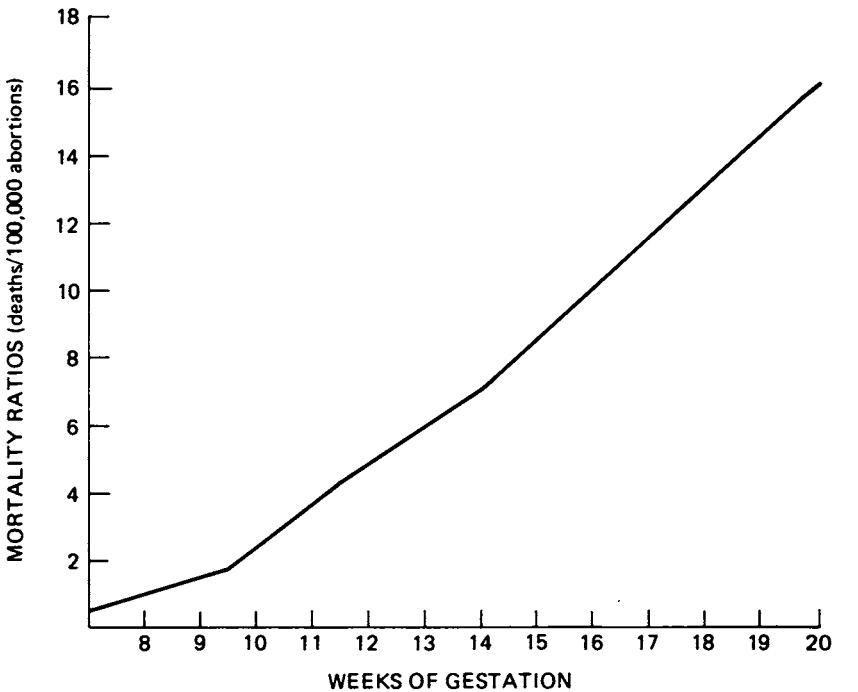

FIGURE 1 Abortion mortality ratios by weeks of gestation, United States, combined 1972–1973 data. From Institute of Medicine, 1975.

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NEW METHODS AND RESEARCH HORIZONS IN CONTRACEPTION

ROY HERTZ
Session Chairman

Methods of Fertility Regulation in Clinical Trial

SHELDON J. SEGAL

Contraceptive research is a complex process that includes development of research methodology, enhancement of the understanding of basic biological processes, identification of vulnerable links in the reproductive chain of events, establishment of appropriate animal models for the particular events being studied, and attempts at chemotherapeutic, hormonal, immunological, or surgical intervention with specific physiological events. Only then can the various phases of clinical investigation begin. They involve comprehensive and detailed Phase I toxicity studies in few subjects, followed by Phase II studies with scores of volunteers, and, finally, Phase III studies of effectiveness, which involve larger numbers of subjects.

Over the past 20 years, there has existed the paradox of health officials throughout the world appealing for methods of fertility regulation that are better suited to their countries' conditions, while most contraceptive research, initiated by pharmaceutical companies, has been directed toward modifying the formula of the existing oral contraceptive—"the pill"—as firms have vied to gain a share of this lucrative hard currency market. The success of this strategy is evident. Three oral contraceptive products were approved by the U.S. Food and Drug Administration (FDA) prior to 1965. In 1968, there were 20 oral contraceptive products marketed in the United States. By 1975, the list had grown to 42, and it is still growing.

A cost of $6.8 to $18 million is estimated (Djerassi, 1970) for developing a new drug product for female contraception. On this basis,

the 42 new products represent an investment of $285 to $760 million by industry to win a share of a proven market. In fact, the actual investment undoubtedly was lower since many of the products are based on the use of the same compounds. Nevertheless, it is evident that this field has received a high priority in industrial research and development budgets.

A few companies have attempted to open completely new markets in the chemical abortifacient field. For several years, the Ortho Company, Cutter Laboratories, William S. Merrill Company, and the Upjohn Company have had an interest in a series of compounds with structural similarity (triphenyl-ethylene derivatives), which acted as postcoital antifertility agents in the rat. However, this work, when taken to preliminary clinical investigation, proved disappointing and has essentially been abandoned (Morris, 1977). By far the largest research investment in abortifacients has been that of the Upjohn Company in prostaglandin. By 1970, with more than 10 years of work and a very strong patent position behind the effort, Upjohn had a multimillion dollar investment in prostaglandin for a variety of uses, including possible abortifacient activities. This work has led to the development of an abortifacient product to be used in mid-trimester abortion and to clinical investigations, still under way, for the use of prostaglandins or derivatives of the natural prostaglandins as vaginally administered preparations for earlier abortion.

As a general rule, scientists in university, hospital, or government research centers are dependent on corporate policy and company initiatives to obtain experimental drugs and devices for testing in all fields of chemotherapy. In 1970 there was an exception in the contraceptive field. The Population Council provided scientists with experimental models of intrauterine devices for clinical evaluation. This program played a major role in the development of all intrauterine devices now used by an estimated 10 to 20 million people throughout the world (see paper by Mr. Mauldin).

By 1970, a number of novel approaches to contraception were evident, but had not been tested adequately or had lost the support of their commercial sponsors. For example, the use of Silastic® subdermal implants for long-term contraception had been proposed (Segal, 1967). Preliminary clinical tests by scientists in Brazil, Chile, and India had established the feasibility of this method, but a major development effort was required. A contraceptive vaginal ring, using the Upjohn-patented progestin, medroxyprogesterone acetate, had undergone one clinical trial (Mishell *et al.*, 1970), which was sponsored by the Upjohn Company. With no particular interest in testing the possible advantages of other progestins, which were owned by other companies, Upjohn carried the program no further at that time.

The potential of using the progestational compounds of the pill in a novel manner such as a once-a-month pill had been shown by Nygren *et al.* (1972), but the commercial patent holders did not choose to test the compound for this use. Clinical trials of a once-a-week pill (Mora *et al.*, 1974) were sponsored by Roussell Uclaf, but the company was not prepared to test variations in dosages.

For an objective evaluation of these scientifically feasible leads and many others that were untested, programs were required that could work effectively with private industry while remaining independent of industry for determining priorities of work to be undertaken. These considerations led to various programmatic approaches to accelerate applied contraceptive research that would be supplementary to the efforts of private industry. They include the Contraceptive Development Branch of the Center for Population Research at the National Institute of Child Health and Development (NICHD), the Population Council's International Committee for Contraception Research (ICCR), the World Health Organization's Special Program on Human Reproduction, the U.S. Agency for International Development's university-based Program for Applied Research in Fertility Regulation, and its International Fertility Research Program.

These programs have now had several years of work behind them, and some efforts have reached either an early or an advanced stage of clinical investigation. Any new method that is going to be ready for use in the next 3 to 5 years has to be at a very advanced stage of testing now, including clinical trials with human subjects. Any project not yet in the clinical stage will take much longer to develop.

VACCINATION AGAINST THE PREGNANCY HORMONE

Researchers in several countries are working to develop a long-term, safe, and effective contraceptive vaccine. The focus of the work is human chorionic gonadotropin (hCG), the hormone secreted by the fertilized egg that signals the corpus luteum to continue producing the progesterone that is necessary for the continuation of the early pregnancy. The objective is to develop a vaccine that would influence the body's immune system to form antibodies to hCG. Such antibodies would then intercept the crucial message, should the egg indeed have been fertilized, and the corpus luteum would regress, progesterone levels would decline, and menstruation, accompanied by the disappearance of the fertilized egg, would occur. In this way, each cycle would end with menstruation, whether or not fertilization had occurred.

A number of issues need to be studied before the vaccine can move beyond the preliminary testing state. The pregnancy hormone, hCG, is

similar in structure to a pituitary hormone—the luteinizing hormone (LH). The formation of antibodies that would cross-react with LH could be hazardous and could interfere with normal ovarian and menstrual cycles. An approach to minimizing this risk has been to use only one part of the hCG molecule, a part that is not fully shared by the LH molecule. However, this contributes to a second problem: The part of the hCG used, the beta subunit, is quite small and does not serve as a good antibody stimulant. To overcome this, the hCG-β molecule has been linked with the familiar tetanus toxoid, which is widely used by humans. To date, results in tests with volunteers show that the vaccine causes the production of antibodies that neutralize the activity of hCG without interfering with ovarian and menstrual cycles (Talwar *et al.*, 1976). Clinical chemistry studies have not revealed any toxicity or abnormalities in liver and kidney function, but more work needs to be done on both the safety and reliability issues before the substantial promise of the method is realized.

Still at the animal level is similar work in the United States, the United Kingdom, and Australia, using a fragment of the beta subunit of hCG.

PHARMACOLOGIC SUPPRESSION OF THE CORPUS LUTEUM

Also in progress are studies in animals to identify a compound that would directly suppress the progesterone function of the corpus luteum—a process referred to as luteolysis. The principle is to eliminate the only source of progesterone that can prevent the expected menses in a fertile month. The action would probably be based on inhibiting a specific enzyme in progesterone production, but there are other possible mechanisms. If a proper compound could be identified, the high degree of specificity, affecting only the corpus luteum, would reduce the chances of side effects or complications beyond its intended effect: the prevention of pregnancy. The only thing required of the woman would be to know that she was expecting a menses on a given day. On the three or four occasions a year when she is 1 or 2 days late, she could take a pill that would bring about menstruation. Others might prefer to use the pill on a regular monthly basis to induce menstruation without knowing if there was any question of being "late." So far, the search for a purely luteolytic agent has turned up a few substances: an extract called Zoapatle from the Mexican plant *Montanoa tuberosa;* a synthetic nonsteroidal drug made in India named Centchroman; a few steroid inhibitors of progesterone synthesis; and a synthetic prostaglandin (Segal and Nordberg, 1977). Other approaches to luteolysis (described below) are at even earlier stages of fundamental investigation and must

await more information about the control of progesterone synthesis and the role of cell receptors in the action of hormones.

Closely related to this field of research is work with a chemical substance extracted from an herb that is used in China to induce abortion. The tuberous roots of *Trichosanthes kirilowii maxim* are the source of the substance. The protein extracted is called trichosanthin. It is believed to be effective as an abortifacient through its cytotoxic effect on cells that produce chorionic gonadotropin (Shanghai Institute of Experimental Biology, 1976).

LONG-ACTING FORMS OF CONTRACEPTIVE STEROIDS

To overcome some of the disadvantages of the pill, such as the need to remember to take it daily and the sudden absorption into the bloodstream (and directly to the liver) of the synthetic sex hormones, better forms of steroidal contraception are sought. Ease of administration, the medical preference for constant dosage levels in the system, and the acceptability of injections by women who are accustomed to them for disease control are factors influencing this research. The attempts to find an effective and long-acting steroid take the forms listed below. Most are based on the same principle as the pill.

Injection

Injections of progestins, given at lengthy intervals, are being tested clinically. The injection of Depo-Provera® every 3 months is widely used for contraception throughout the world, but this use is not approved by the FDA. The synthetic progestin, which is the active ingredient of Depo-Provera® has not performed well in long-term toxicity studies in beagle dogs. This fact, plus clinical experience suggesting a post-treatment loss of fertility, has contributed to a cautious interpretation by the U.S. regulatory agency of the compound's risk/benefit ratio. The concern over safety has been reinforced by recent findings in rhesus monkeys. On the other hand, in South America, the Caribbean Islands, and in many Asian and African countries, Depo-Provera® is used regularly as an injectable contraceptive in spite of the safety issues and its serious disruption of menstrual bleeding patterns.

An international team of scientists is studying another injectable progestin, called norethindrone enanthate (World Health Organization, 1978). It is a close chemical relative of the progestin in one of the most popular contraceptive pills. So far, the effort has not been very

successful, due to irregular bleeding and frequent unplanned pregnancies.

Implants

To avoid the need for return visits to a clinic and to assure the constant and gradual release of steroids, various implants have been tested. These are tubes or rods made of a rubberlike compound containing the synthetic steroids that are implanted, with a small incision, under the skin—usually in the arm or the buttocks. One implant regimen that would last for 1 or 2 years uses a new progestin, norgestrienone; another uses norgestrel, a popular drug when used in pill form, which could last for as long as 6 years. Also being tested, but at a much earlier stage of research, are biodegradable implants or steroids coated with biodegradable substances like those used in absorbable surgical sutures. The advantage of this development is that the implants would not need to be removed, but would simply disintegrate under the skin as they progress through their effective lifetime. The 6-year implant of norgestrel is highly effective in terms of pregnancy prevention. However, it causes bleeding irregularity, a side effect that makes the method unacceptable for about 18% of those who use it (Coutinho *et al.*, 1978). This particular form of the implant method is ready for use and will probably be introduced for use during 1980 or 1981. This timetable assumes the absence of unforeseen safety issues, which might develop in chronic animal studies or after extensive use.

Vaginal Ring

Steroids can be absorbed through the vaginal mucosa. Taking advantage of this property, researchers have incorporated progestins into a plastic ring, which is similar to but smaller than the rim of a diaphragm. This ring is introduced into the vagina behind the cervix. The woman can insert the ring herself and leave it in place for 3 weeks before removing it, thereby precipitating a menstrual flow. The schedule of 3 weeks in and 1 week out is similar to the contraceptive pill regimen. The advantage is that the user does not have to remember to take the pill every day. The steroids are released at a more constant level, a feature which may avoid significant side effects of the pill. The ring needs to be replaced with a new one about once every 6 months when the supply of steroids is exhausted. This method shows clinical promise and could be in general use by 1981 (Mishell *et al.*, 1978).

PHARMACOLOGIC CONTRACEPTION FOR MALES

For centuries, contraception was the purview of males through the use of coitus interruptus and the condom. Attention to chemical methods for men began in earnest with clinical trials only as recently as 1971. A difficulty in research on contraception for the male is the small number of links in the reproductive chain of events in the male, compared to the number of vulnerable points that have been identified in the female system. The focus has been on suppressing the production of sperm through the action of synthetic male hormones in a manner that is analogous to the suppression of egg production and ovulation in the female with the pill. The problem, as with pill use by females, is to achieve a dosage of steroids that would stop sperm production but not cause unacceptable side effects.

Combinations of the male sex hormone, testosterone, and a progestin have been used to stop sperm production. They are reversible, and they do not introduce unacceptable hazards (Schearer *et al.*, 1978). The main problem with the compounds and dosages that have been tested is their inability to maintain low sperm counts for a protracted period. In too many cases, sperm production breaks through after a few weeks or months. It appears to be a problem of proper compound identification and the establishment of proper dose. A contraceptive for males, like contraceptives for females that are still under investigation, could take the form of a pill, an implant, or an injection. From China there have been reports of successful clinical trials in men with a compound extracted from cottonseed oil (National Coordinating Group for Male Contraceptives, Shanghai, 1978). The studies were undertaken on the basis of reports of a high incidence of male infertility in a region where cottonseed oil is used widely in the diet. A known toxic substance, gossypol, was extracted from the cottonseed oil, tested in animals, and found to suppress sperm production. It was subsequently introduced into clinical trials. The cumulative toxicity of gossypol in certain animal species, including humans, is a cause for concern with this drug, although the Chinese studies are being conducted with low doses of the substance. The published report of nearly complete effectiveness is encouraging. However, the toxicological potential of gossypol makes the establishment of an acceptable pharmacologic ratio of toxic dose to effective dose a critical issue (Berardi and Goldblatt, 1969).

In addition to these new types of methods, investigation is continuing on refinements of other methods discussed earlier: improved IUD's, better techniques of female sterilization, and reversible vasectomies.

NEW AREAS OF RESEARCH

In the long process of development of practical methods of fertility control, a number of new areas of possibility are still "at the bench" in the laboratory.

Many of these have come about through major breakthroughs in methodology, e.g., radioimmunoassay, amino acid sequencing, and peptide synthesis. These fundamental methodological advances and other discoveries in protein chemistry, neuroendocrinology, and molecular biology have great potential for a future generation of contraceptives. In some cases, we know enough to have reached certain levels of application already touched on in this paper. In other cases, knowledge is still at such an early stage that we do not even know how the basic processes work in detail. Nevertheless, we now know much more about what we do not know—the "gaps" in our information base—and can identify fundamental areas of laboratory research that hold implications for fertility control.

Influencing the Brain

The luteinizing hormone release hormone (LHRH) is a protein that is produced in the brain. It triggers the production and release by the pituitary of the hormones that stimulate the ovary and the testis (see paper by Dr. Guillemin). It is now possible not only to synthesize LHRH, a decapeptide, but to make agonistic or antagonistic compounds (Rivier and Vale, 1978). One possible application of this would be an antagonist to suppress ovulation. A second application would be to stimulate ovulation on a predictable basis, administering the synthetic protein as a pill, a tablet absorbed under the tongue, a nasal spray, or a vaginal tampon. The message would reach the brain, LHRH would cause the production of LH, and ovulation would occur at a precise time, allowing a woman to use the rhythm method with greater certainty. Since such a method would affect only the cells in the pituitary that produce LH, it would avoid the more general side effects of less specific compounds, such as the steroid pill. In the male, analogues of LHRH could be used to prevent sperm production (Labrie *et al.*, 1978).

Occupying the Binding Sites

The binding of gonadotropins to specific cells of the ovary requires the presence of the molecule's carbohydrate component. The naked pro-

teins bind onto their special target cells but move off so quickly that they have minimal biological activity. This suggests that inactive molecules could occupy the binding cells in place of the native hormone and act as a competitive antagonist (Bahl *et al.*, 1974). With hCG competitors, this "first-come-first-bind" process could lead to a chemical abortifacient.

Identifying the Receptors

Work is proceeding to learn more about the chemistry of the receptors for the gonad-stimulating hormones on the surface of cells of the ovary or testis. Altering the binding capacity of these cells might also inhibit gonad function (Dufau *et al.*, 1974).

Understanding the Intracellular Action of Steroids

A very important field is the biology of steroid hormones at the level of the target cell (see paper by Dr. Jensen). In the last 10 years we have learned that cells of the reproductive system are regulated by a complex chain of events starting with the entry into the cell of the steroid hormone. The hormone attaches to receptors in the cytoplasm of the cell, which carry it into the nucleus of the cell (Talwar *et al.*, 1964). There, interaction with the chromatin determines the pattern of gene activity. This new knowledge implies that we might be able to allow the ovarian cycle to continue normally but then interfere with the action of the steroids on the cells of the endometrium so that the uterus does not prepare properly for pregnancy. Different impact points in the normal steroid-receptor interaction are possible: the formation of the receptors in the cytoplasm; the rate of degeneration of the receptors; the binding process of the steroid to the receptor; and the binding of the steroid-receptor complex to the chromosomes.

Affecting the Membranes of Egg or Sperm

When the first sperm touches the egg in the fallopian tube, changes in the membrane of the egg block the entry of more sperm. This block to polyspermy is essential for egg survival. If it is penetrated by more than one sperm, it would not develop and would be sloughed off in menstruation. Research on marine invertebrates, such as the sea urchin, suggests that the first sperm chemically alters the egg membrane so that the remaining sperm receptors on its surface are inactivated (see paper by Dr. Metz). Therefore, one approach would be to develop a way to induce this change in the egg membrane and block the penetration of

active sperm. Another possibility would be to encourage polyspermy and the subsequent passing of the nonviable egg with menses.

Interfering with Sperm and Egg Development

In a process that is not very well understood, sperm mature after leaving the testis but before entering the fallopian tube of the female. Important changes occur during the journey through the male epididymis, including alterations in structure, metabolism, pattern of motility, and fertilizing capacity (Prasad *et al.*, 1973). Once more is learned about the biochemical nature of this process, the epididymis may serve as a site for interrupting capacitation so that the male ejaculate would contain inactive sperm (see paper by Dr. Fawcett).

In the human female, the egg is in a state of arrest for a number of years, a condition apparently caused by a maturation inhibitor produced by the follicles. When certain follicular maturation factors are applied to the ovary of marine organisms such as the starfish, the eggs in the ovary will start to develop (Kanatani, 1973). Work is under way to determine whether a natural or chemical agent can be used to inhibit or stimulate egg maturation in the follicles of mammalian ovaries (see paper by Dr. Channing). This development would have the greatest usefulness in fertility control application because of its specificity to the reproductive process.

CONCLUSION

The future of contraceptive technology, as well as the management of infertility and other aspects of reproductive medicine, depend to a great extent on how much is invested in fundamental research in reproductive and developmental biology. It is vital to recognize that the ongoing work and study in laboratories is doing more to advance the state of the science than much of the applied work that attracts public attention.

The process is basic to science. Improvements that are applicable to the regulation of human fertility begin with fundamental studies of the reproductive system and extend to applied product development. It is a task that engages chemists, biologists, physicians, and a host of other professionals. Seldom has there been such an opportunity to use science for the benefit of all humanity as there is in this area now.

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Follicular Maturation and Ovulation

CORNELIA P. CHANNING

The development of new approaches to contraception must come out of a better basic knowledge of reproductive processes. Areas that have shown promise are follicular maturation, follicular rupture, oocyte maturation, corpus luteum formation, and regulation of implantation.

FOLLICULAR MATURATION

Advances in the regulation of follicular maturation, oocyte maturation, luteinization, and follicular rupture have recently been reviewed by Channing and Tsafriri (1977) and Channing *et al.* (1978a,b). As shown diagrammatically in Figure 1, the ovarian follicle grows beyond the antral stage and matures under the influence of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and intraovarian steroidal and nonsteroidal substances. Basal levels of LH occur throughout the primate menstrual cycle except for the preovulatory period (Figure 2). In the human and the monkey, the follicle matures during the follicular phase of the menstrual cycle. Some follicular growth begins during the end of the luteal phase of the previous cycle. In the rhesus monkey (*Macaca mulatta*), a useful primate model for the human, a follicle is "chosen" on or about day 5 of the menstrual cycle (Clark and Dierschke, 1975). This follicle grows to between 10- and 12-mm diameter in the monkey and to approximately 20-mm diameter in the human. It ovulates at midcycle. Shortly prior to ovulation, under the influence of the preovulatory LH/FSH surge, the oocyte within the

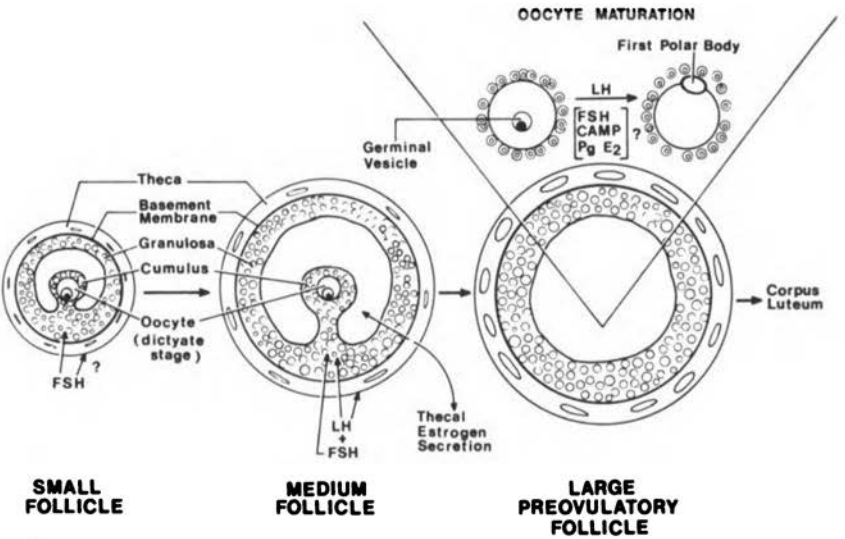

FIGURE 1 Schematic diagram of follicular growth, oocyte maturation, and follicular rupture. The small follicle at the left represents a follicle on day 1 of the menstrual cycle. The follicle grows during the follicular phase of the cycle (the first 12 days of the menstrual cycle) and by midcycle the follicle reaches its full size (1 to 2 cm). This full-size follicle is shown at the far right of the figure. In the 2 days before follicular rupture, the oocyte matures (insert at top of page). After follicular rupture, the follicle transforms to a corpus luteum which secretes progesterone. From Channing and Tsafriri, 1977, with permission.

mature preovulatory follicle completes its first meiotic division and extrudes the first polar body. This division must be completed for the oocyte to become fertilizable. Completion of the second oocyte meiotic division occurs after fertilization.

During the follicular maturation that accompanies the increase in follicular size, there is an increase in the number of granulosa cells within the follicle. These cells increase in number in response to FSH or estrogen (Bradbury, 1961; Richards and Midgley, 1976) or to a combination of both. Thanki and Channing (1976, 1978) have been able to stimulate growth of granulosa cells in culture with the addition of both estradiol-17β and purified human FSH. In further support of FSH stimulation of granulosa growth, Ryle (1972) and her colleagues have observed that addition of FSH stimulates granulosa cell uptake of tritiated thymidine in organ cultures of mouse ovaries.

As the follicle matures, there are decreases in granulosa cell FSH receptors and in the ability of FSH to stimulate accumulation of both cyclic adenosine monophosphate (AMP) (Lindsey and Channing,

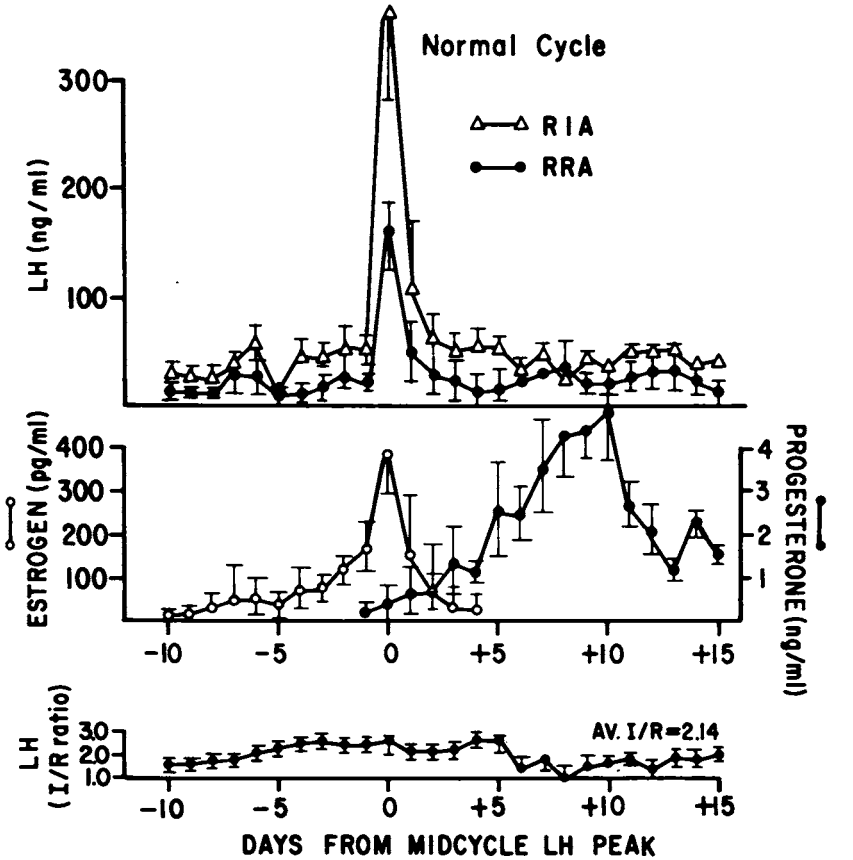

FIGURE 2 Changes in serum pituitary luteinizing hormone estrogen and progesterone throughout the menstrual cycle of five rhesus monkeys using a radioimmunoassay (RIA) and a radioreceptor assay (RRA). (I/R ratio = Immune/Receptor ratio) Adapted from Sakai and Channing, 1979.

1979a,b) and progesterone by cultured granulosa cells (Thanki and Channing, 1978) (Figure 3). In contrast, granulosa cell LH/human chorionic gonadotropin (hCG) receptors increase 50 to 100 times (Channing and Kammerman, 1973, 1974), and the ability of LH to stimulate granulosa cell cyclic AMP accumulation (Lindsey and Channing, 1979a,b) and progesterone secretion (Channing, 1970a,b) increases 10 to 15 times. When cultured, the granulosa cells from small and medium follicles of the pig (Channing, 1970a), monkey (Channing, 1970b), and human (Channing, 1969; McNatty and Sawers, 1975) do

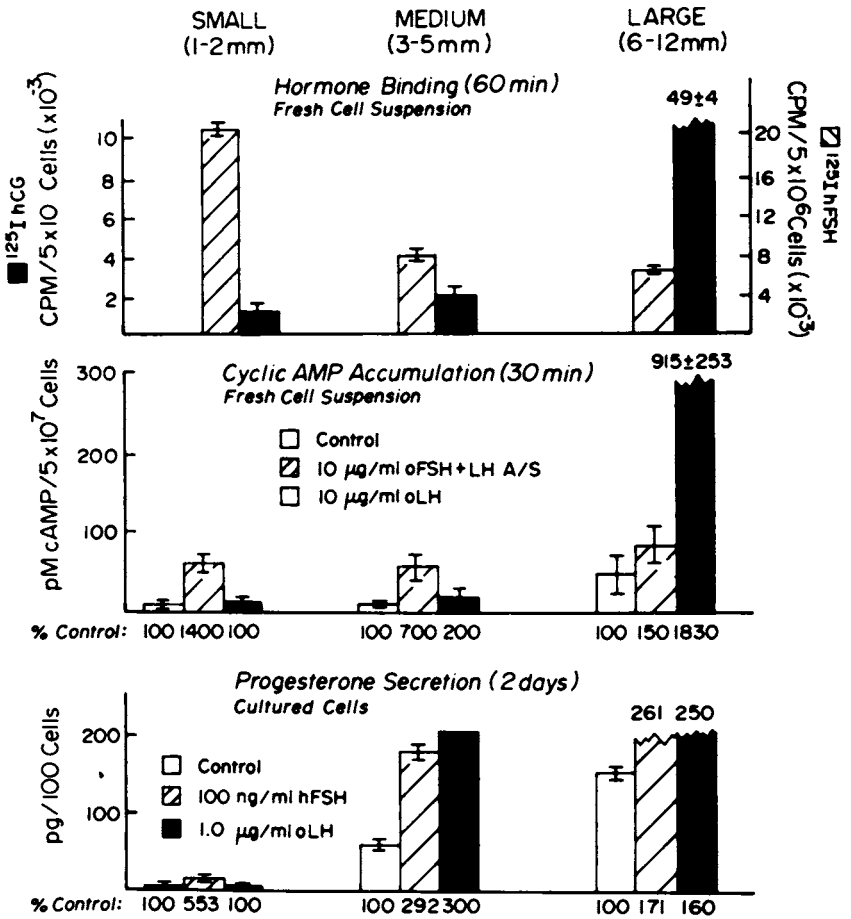

FIGURE 3 Changes in LH and FSH responsiveness in porcine granulosa cells during follicular maturation. Data on FSH binding are taken from Nakano *et al.* (1977). Data on hCG binding, which are taken from Channing and Kammerman (1973, 1974), are the means of 6 to 10 observations. Data on the ability of FSH and LH to stimulate intracellular cyclic AMP accumulation are taken from Lindsey and Channing (1979a,b, and unpublished observations). Data represent mean ± SE of 6 to 11 observations. Data on the effect of FSH upon progesterone secretion in cultured cells, from Thanki and Channing (1978) and Channing and Kammerman (1973), are the mean of 6 to 9 observations. Observations on the effect of ovine LH upon progesterone secretion by cultured porcine granulosa cells were taken from Channing (1970a and unpublished observations).

not have the potential to luteinize in culture. In contrast, granulosa cells that are harvested from large preovulatory follicles during or immediately after the LH surge can luteinize spontaneously in culture (Channing, 1969, 1973; McNatty and Sawers, 1975).

The use of cultured granulosa cells from small porcine follicles has enabled investigators to determine which hormones may be required for induction of luteinization. Addition of a mixture of insulin (1 mU/ml), thyroxin (10^{-7}M), and cortisol (0.01 μg/ml) to 5% pig serum and 0.5% bovine serum albumin, along with 0.1 μg/ml of purified human FSH and LH, can stimulate progesterone secretion manyfold (Channing *et al.*, 1976; Channing and Ledwitz-Rigby, 1975). Addition of all of these hormones minus the LH stimulates the accumulation of LH/hCG receptors (Anderson and Channing, 1978; Channing *et al.*, 1978a).

In the pig, as the follicle matures the ability of the thecal layer to secrete estrogen increases (Stoklosowa and Channing, unpublished observations). Concurrent with the increase in LH/hCG receptors (Channing and Kammerman, 1973, 1974), the ability of the granulosa layer to aromatize testosterone increases as the follicle progresses from 1–2 mm to 3–10 mm diameter (Anderson *et al.*, 1979). The control of thecal estrogen secretion during follicular maturation has not been studied rigorously. The thecal layer of the preovulatory follicle in the monkey is probably the principal source of ovarian venous estrogen, since removal of the granulosa and follicular fluid from the preovulatory follicle does not alter estrogen levels in the ovarian vein after a 2-hour period (Channing and Coudert, 1976).

INTRAOVARIAN FOLLICULAR INHIBITORS

Nonsteroidal ovarian regulators, which control the events occurring during follicular maturation, include a follicular fluid oocyte maturation inhibitor (OMI), a follicular fluid luteinization inhibitor (LI), a follicular fluid inhibin (folliculostatin), and a luteinizing hormone binding inhibitor (LHRBI) in the corpus luteum. All of these substances are potential contraceptive agents and have the advantage of being naturally occurring substances.

Granulosa cells normally fail to luteinize until after ovulation or only start to do so immediately prior to ovulation. However, if granulosa cells are removed from large follicles of a number of species and are then cultured (see review by Channing and Tsafriri, 1977), they luteinize spontaneously. Addition of 50% follicular fluid from small- and medium-sized porcine follicles prevents their morphological

luteinization, ability to secrete progesterone, and ability to accumulate cyclic AMP in response to LH (Bernard, 1973; Kraiem and Lunenfeld, 1976; Ledwitz-Rigby, 1974; Ledwitz-Rigby *et al.*, 1977). By the time that the porcine or human follicle is preovulatory, this ability of follicular fluid to inhibit luteinization is lost.

The cellular origin of the luteinization inhibitor is under investigation. Thus far its mass appears to be greater than 10,000 daltons, although it may also have a small molecular weight component (Channing and Hillensjo, unpublished observations). LI may inhibit induction of LH receptors in porcine granulosa cells of small follicles because it can decrease LH/hCG receptors after 2 to 4 days in culture, and its inhibitory action is overcome by FSH (Anderson and Channing, 1978; Channing *et al.*, 1978a). However, it does not block LH/hCG receptor sites on short-term exposure (Anderson and Channing, unpublished observation; Ledwitz-Rigby and Rigby, 1978).

An oocyte maturation inhibitor, which is a polypeptide of about 2,000 daltons, has been isolated from the follicular fluid of pigs (Stone *et al.*, 1978; Tsafriri *et al.*, 1976), cattle (Gwatkin and Andersen, 1976), and humans (Channing *et al.*, 1978b; Hillensjo *et al.*, 1978). This inhibitor can prevent the resumption of meiosis of cultured cumulus-enclosed oocytes of pigs (Tsafriri *et al.*, 1976), hamsters (Gwatkin and Andersen, 1976), and rats (Tsafriri *et al.*, 1977). Its effects are reversible (Stone *et al.*, 1978). Furthermore, they can be overcome by the addition of LH to the culture media (Tsafriri and Channing, 1975; Tsafriri *et al.*, 1976). It is synthesized by the granulosa cells of the porcine and rat follicle (Tsafriri *et al.*, 1977; Tsafriri and Channing, 1975). The low molecular weight fraction of porcine follicular fluid that inhibits porcine oocyte maturation also inhibits cumulus cell progesterone secretion (Channing *et al.*, 1978b) (Figure 4).

Theoretically, OMI should be an ideal contraceptive method. Its only target cell should be the oocyte. Moreover, by keeping the oocyte immature, it would permit normal ovulation of an immature oocyte, which would be nonfertilizable.

Charcoal-treated porcine follicular fluid has been shown to inhibit serum FSH levels in both the intact and castrated female rat (Marder *et al.*, 1977; Schwartz and Channing, 1977). The active inhibin is a proteinaceous substance (trypsin labile). It is greater than 10,000 daltons. The concentration per milliliter of fluid from small porcine follicles (1 to 2 mm) is greater than that found in fluid from large (6 to 12 mm) ones (Lorenzen and Schwartz, 1979; Lorenzen *et al.*, 1978). Serum LH levels were not altered by the follicular fluid treatment, except when high doses of fluid or a high molecular weight fraction were used.

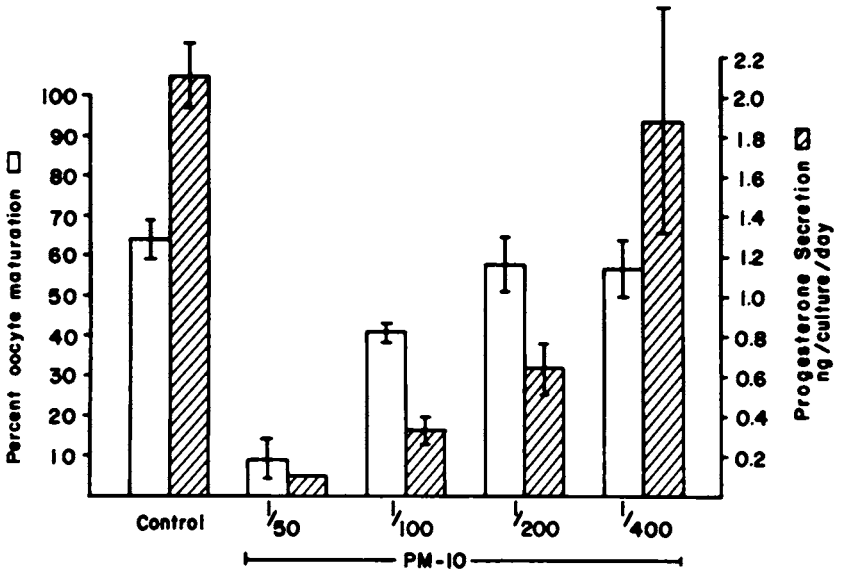

FIGURE 4 Effect of various doses of the low molecular weight fraction of porcine follicular fluid (PM-10 filtrate) upon porcine oocyte maturation and cumulus cell progesterone. Each value in the mean ± SE of four cultures containing 12 to 15 cumulus-enclosed oocytes per culture. The cells were harvested from medium-sized (3 to 5 mm) porcine follicles and cultured for 42 to 44 hours as outlined previously (Tsafriri *et al.*, 1976). Oocytes were fixed and stained with aceto-orcein and examined microscopically. Oocytes were considered immature if they still had an intact germinal vesicle. Oocytes that had progressed beyond this stage (the majority to metaphase II) were considered to be mature. Less than 10% of the oocytes were degenerated regardless of treatment group. Progesterone was measured by radioimmunoassay in the culture medium at the end of the culture period using the method of Channing *et al.* (1976), which employs direct radioimmunoassay of dilute-nonextracted culture medium. The PM-10 fraction did not in itself affect the progesterone assay (Hillensjo, unpublished observations).

Observations by Channing *et al.* (1979) indicated that charcoal-treated porcine follicular fluid can inhibit serum FSH levels in the long-term female castrate and intact female rhesus monkey. They also observed that treatment of monkeys with follicular fluid early in the menstrual cycle could lead to diminished follicular growth and that at midcycle the follicle contained fewer granulosa cells than untreated monkeys or those that were treated with pig serum (Channing *et al.*, 1979).

An inhibitor of LH/hCG binding has been isolated from aqueous extracts of the corpus luteum of rats (Yang *et al.*, 1976, 1977) and pigs (Sakai *et al.*, 1977; Tucker *et al.*, 1979), but not from nonluteal

tissue. The material that has been isolated from extracts of the rat corpus luteum is primarily a low molecular weight polypeptide, whereas the porcine material is mostly of higher molecular weight. The porcine material is present in higher concentrations in older corpus luteum extracts compared to extracts of young corpus luteum (Tucker *et al.*, 1979).

When crude extracts of porcine corpus luteum that have been treated with charcoal to remove steroids are injected into rats that have been given pregnant mare serum gonadotropin (PMSG), there is diminution of follicles. This indicates that the treated extracts may be antagonistic to the stimulation of follicular growth by gonadotropin (Batta and Tucker, 1978). Further purification of the LHRBI will be necessary to gain a better understanding of its physiological action. Extracts of pig corpus luteum, but not nonluteal tissue, also inhibit progesterone secretion by cultured porcine granulosa cells (Kumari and Channing, 1978).

Steroids as well as nonsteroidal agents can act as intraovarian regulators of follicular function. Estradiol-17β stimulates granulosa cell growth in small porcine follicles. At the same time, it causes a decrease in progesterone secretion (Thanki and Channing, 1976, 1978). In addition to the follicular fluid luteinization inhibitor, this would prevent granulosa cell luteinization from occurring too early and permit continued cell division. Ross and his colleagues postulated that androgens cause follicular atresia (Louvet *et al.*, 1975; Ross and Lipsett, 1978).

SUMMARY

Follicular maturation has been described in terms of an increase in follicle size, an increased ability to secrete estrogens, and a potential to secrete progesterone. Granulosa cells proliferate, and they demonstrate a greater ability to respond to LH/hCG and LH as indicated by stimulation of cyclic AMP accumulation. At the same time, there is a decrease in FSH responsiveness. Intrafollicular nonsteroidal regulators, such as a follicular fluid oocyte maturation inhibitor, luteinization inhibitor, and a corpus luteum luteinizing hormone binding inhibitor, play a role in the regulation of follicular maturation. These substances have potential as new contraceptive agents.

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The Organization of the Seminiferous Epithelium, Its Relevance to Fertility Control

DON W. FAWCETT

For many years the prospect for development of antifertility agents that act upon the testes was viewed with pessimism. To interrupt spermatogenesis, a continuous process yielding tens of millions of gametes daily, seemed a more formidable challenge than preventing ovulation—a single event that occurs once a month. There was also the fear of mutagenesis. The male germ cells in the early stages of their development spend several days in meiosis—a special form of cell division during which there is a reorganization and exchange of segments between paired chromosomes—which affects the genetic constitution of the spermatozoa. During this period, the genetic material is believed to be especially vulnerable to chemical mutagenesis. A number of drugs are known to arrest sperm development. Several of them are alkylating agents that are related to some of the potent cancer chemotherapeutic drugs that have considerable potential for chromosomal damage. There was the fear that if a drug were not completely effective in arresting spermatogenesis, it might produce genetic alterations that could result in abnormal offspring. This possibility was so alarming that funding agencies for many years have been reluctant to support research involving the action of drugs on the testes. This position may now need to be reconsidered.

During the past decade, there has been great progress in our understanding of the structural organization and physiology of the testis. It has become apparent that development of the germ cells and release of spermatozoa are dependent upon the activities of a support-

ing population of Sertoli cells. These cells have now emerged as a promising target for antifertility drugs because it seems likely that selective suppression of one or more of their essential functions would interrupt spermatogenesis without the danger that is inherent in the action of drugs directly upon the germ cells. The mood of discouragement that was long a deterrent to progress in the quest for antispermatogenic agents has now given way to one of considerable optimism. This paper reviews some of the findings that have made the prospect of safe antifertility drugs for the male seem more promising.

The testis is made up of hundreds of meters of minute convoluted tubules. These are lined by one of the most complex epithelia in the body—one that is still poorly understood. In the golden era of microscopic anatomy around the turn of the century, when the cellular organization of all organs was being studied in considerable detail, the seminiferous tubules proved unusually difficult to analyze. The patterns of cell association in their lining did not conform to that of any of the accepted categories of stratified epithelia. The form and limits of the individual cells could not be defined because of their overlapping and superimposition in the relatively thick histological sections that were studied and because of the inability of the light microscope to resolve the cell membrane. The many empirical methods of chemical fixation then in use resulted in variable patterns of nuclear chromatin, and the staining of cytoplasmic organelles was difficult and capricious. Consequently, the several cell types in the epithelium could not always be identified accurately. Routine histopathological examination of the human testis is still largely limited to description of relatively gross, far-advanced disorders of tissue architecture because study of biopsy and autopsy specimens continues to rely heavily upon those traditional methods of tissue preparation in which problems of resolution and identification prevent the detection of subtle early alterations in individual cell types.

Endocrinology has dominated research on the testis since the 1930's and has contributed much to our understanding of the hormonal requirements for initiation and maintenance of spermatogenesis. However, it has become increasingly evident that this approach alone cannot explain the cyclic nature of the process, the cytological events in sperm development, the synchrony of germ-cell differentiation, or the mechanism of sperm release. These challenging problems require a detailed analysis of the organization of the seminiferous epithelium and of the functional interactions of its several cell types. The rapid progress in this area during the past 15 years is largely attributable to three technological advances—the development of radioautographic

methods, which made possible a careful analysis of the duration of the cycle and the kinetics of germ cell proliferation (Clermont, 1967; Huckins, 1971); the widespread use of the electron microscope to clarify the complex topographical relationships among the cells and to reveal the ultrastructure of their organelles (Burgos and Fawcett, 1955; Fawcett, 1970); and the recent introduction of a method for dissociating the seminiferous epithelium and recovering, by unit gravity sedimentation, relatively pure fractions of its constituent cell types (Romrell *et al.*, 1976). Segregation of individual germ cell types from the heterogeneous cell population now makes spermatogenesis accessible to biochemical analysis to a degree hitherto impossible. The key to further progress now lies in exploiting these and other methods to probe further the cell biology of the testis.

ORGANIZATION OF THE SEMINIFEROUS EPITHELIUM

To make understandable the extraordinarily confusing appearance of the lining of seminiferous tubules (Figure 1), it is helpful to review first the organization of simpler epithelia that cover surfaces and line cavities elsewhere in the body. These coherent sheets of cells are held together by small complementary specializations of the membranes of neighboring cells called desmosomes (Figure 2A). These plaques are scattered along the cell boundaries and are sites of cell-to-cell adherence. Near the free surface of the epithelium, the cells are more firmly attached by circumferential bands of membrane specialization called occluding junctions (*zonulae occludentes*) (Farquhar and Palade, 1963). In these bands, proteinaceous strands within the opposing membranes are in register and are bonded to one another (Staehelin, 1974) (Figure 2C). The intercellular clefts are thus obliterated in the juxtaluminal region by circumferential bands of membrane fusion that form an effective barrier to permeation of the epithelium from the lumen. Another physiologically important membrane specialization of epithelial cells is the communicating or gap junction (Goodenough and Revel, 1970; Revel and Karnovsky, 1967). At these sites the intercellular space, as seen in electron micrographs, is narrowed to a 2-nm slit, which is traversed by regularly spaced, periodic densities. In membranes that are cleaved by the freeze-fracture method, these junctions appear as plaquelike aggregations of closely packed particles of membrane protein (Figure 2B). The apposition and bonding of particles in register in the two cell membranes make gap junctions another site of very firm attachment of cells. More important is the fact that hydrophilic pores traverse the apposed junctional particles and permit

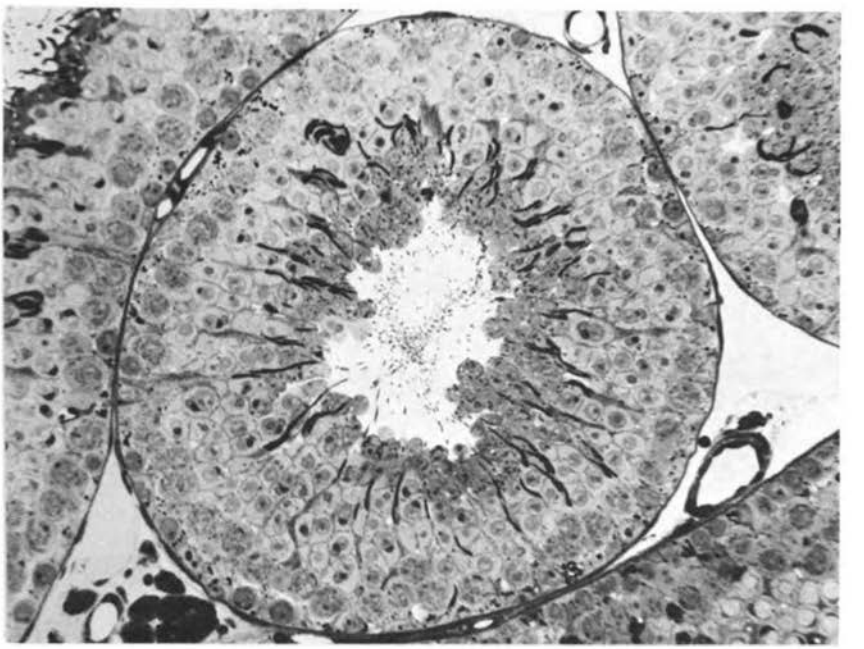

FIGURE 1 Photomicrograph of a seminiferous tubule from guinea pig testis, illustrating the complexity of the lining epithelium and the difficulty of resolving the relationship between germ cells and their supporting cells.

passage of ions and small molecules from cell to cell. These communicating junctions are the structural basis for electrical and metabolic coupling of cells throughout an epithelium.

Occasional wandering lymphocytes cross the basal lamina of simple columnar epithelia in the body and are found in intercellular clefts between the principal cells (Figure 3A). These cells are not integral parts of the epithelium but are transient invaders that establish no enduring attachments to neighboring cells. By analogy, the amoeboid primordial germ cells in the embryonic testis invade intercellular spaces among the precursors of the Sertoli cells that form the epithelial seminiferous cords (Figure 3B). Like the lymphocytes in other epithelia, these primordial germ cells are not firmly attached to the neighboring epithelial cells. They remain a quiescent resident population until shortly before puberty. They then move to the base of the epithelium where they divide and are transformed into spermatogonia, the stem cells from which spermatozoa develop. With the onset of spermatogenesis, their progeny rapidly increase, eventually outnum-

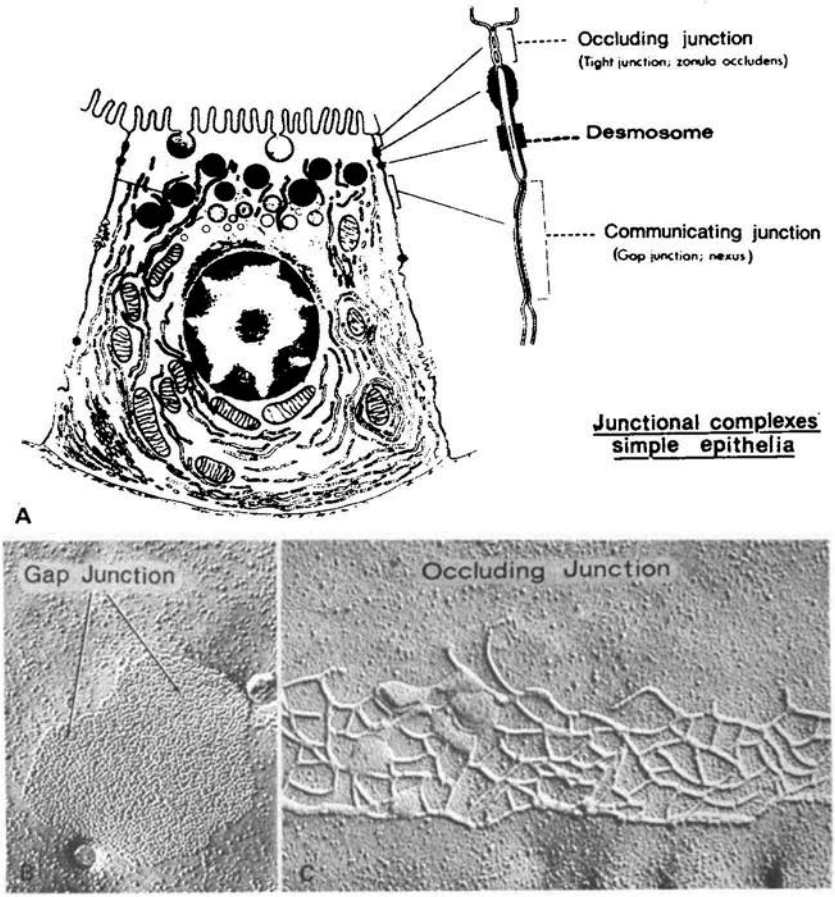

FIGURE 2 (A) Diagrammatic representation of the surface specializations of simple epithelia for cell attachment and cell-to-cell communication. (B) The appearance of a gap junction in a freeze-fracture preparation. Hydrophilic channels in the aggregated intramembrane particles permit passage of ions and small molecules from cell to cell. (C) Freeze-fracture appearance of an occluding junction from intestinal epithelium. Bonding between intramembrane strands that are in register in adjoining cell membranes results in obliteration of the intercellular cleft. These junctional complexes are a barrier to extracellular diffusion of substances across the epithelium. From Fawcett, 1979, with permission.

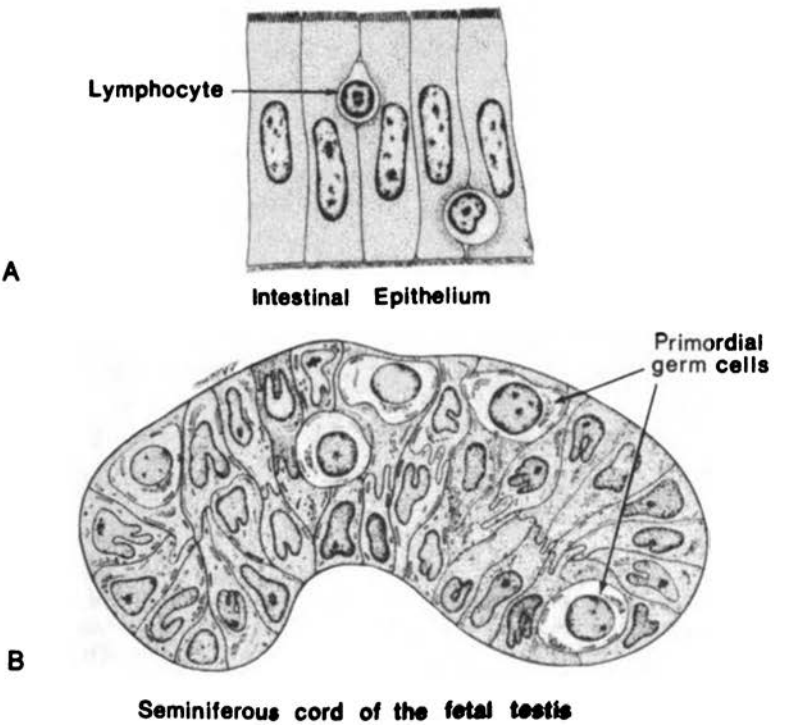

FIGURE 3 (A) Drawing of a simple columnar epithelium with wandering lymphocytes in the intercellular spaces between the principal cells. (B) In the fetal testis the amoeboid primordial germ cells invade the seminiferous cords and occupy intercellular spaces between the Sertoli cell precursors. From Fawcett, 1979, with permission.

bering the supporting epithelial cells. Reduced to simplest terms, the lining of the seminiferous tubules in the adult can be visualized as consisting of a population of proliferating and differentiating germ cells occupying greatly expanded intercellular spaces in a simple columnar epithelium of Sertoli cells (Figure 4). The seminiferous epithelium, therefore, consists of two distinct categories of cells—a fixed population of nondividing Sertoli cells, which extend from base to lumen, and a mobile population of germ cells, which proliferate near the base and move slowly upward in the epithelium as they develop, in turn, into spermatocytes, spermatids, and, finally, spermatozoa.

The Sertoli cells are remarkably elaborate in their shape as they extend processes into all of the interstices of the clusters of developing

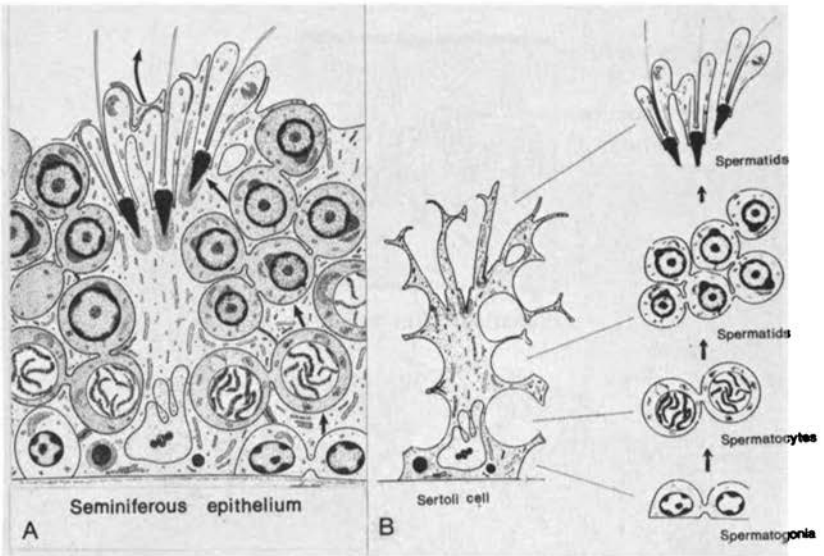

FIGURE 4 (A) Schematic representation of the seminiferous epithelium. The Sertoli cells extend from the basement membrane to the lumen. The developing germ cells occupy expanded intercellular spaces between neighboring Sertoli cells and slowly move toward the lumen as they develop into spermatozoa. (B) Schematic dissociation of the germ cells from the deep niches and recesses that they normally occupy in the supporting Sertoli cells. The germ cells are a proliferating and mobile population while the Sertoli cells are a nonproliferating fixed population. Adapted from Fawcett, 1974, with permission.

germ cells. They were long regarded as nurse cells for the spermatogenic cell line, but it was believed that their supportive role was mainly mechanical and that they were relatively inert metabolically. This interpretation now appears to have been quite incorrect. Recent evidence suggests that the survival and development of the germ cells depends largely upon a special microenvironment created by the surrounding Sertoli cells.

To create a unique fluid and electrolyte environment for any population of cells, a barrier to diffusion must isolate them from the general extracellular compartment of the body. The nurse cell relationship of the Sertoli cells to the germ cells is roughly analogous to that of the glial cells for the neurons in the central nervous system. To maintain the optimal environment for neural activity in the brain, a blood-brain permeability barrier isolates the neurons, a phenomenon that was discovered around the turn of the century. Intravascularly injected vital dyes rapidly escaped into most tissues and organs but

were excluded from the brain. Similar morphological experiments (DeBruyn *et al.*, 1950; Kormano, 1967) suggested that dyes were also excluded from the seminiferous tubules, but the significance of these observations was not appreciated until about a decade ago when Setchell *et al.* (1969) presented compelling physiological evidence for the existence of a blood-testis barrier. It was possible to collect the outflow of fluid from the seminiferous tubules by cannulating the rete testis in rams and, at the same time, to sample the general extracellular fluid compartment of the testis by collecting the testicular lymph through a cannula that was inserted into a lymphatic vessel of the spermatic cord (Figure 5). A variety of dyes and other test substances that were injected into the bloodstream rapidly appeared in the lymph

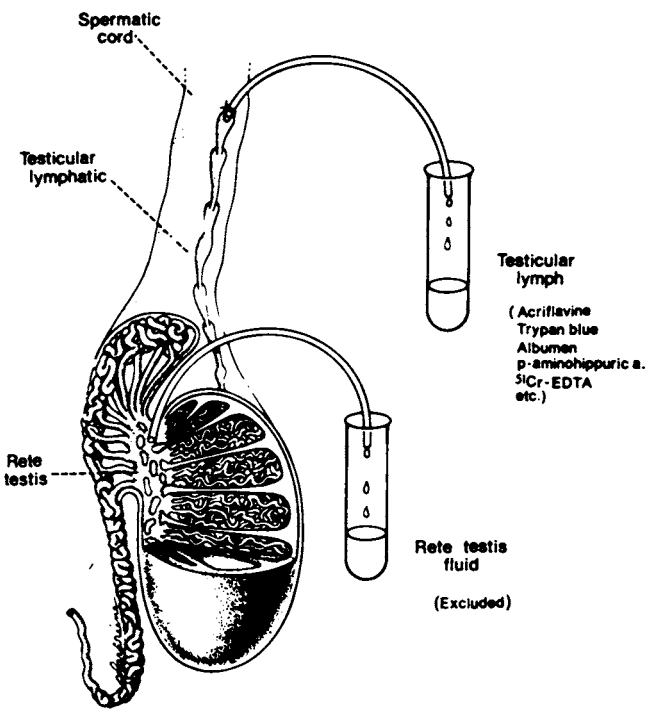

FIGURE 5 Schematic representation of the physiological experiments establishing the existence of a blood-seminiferous tubule permeability barrier. Vital dyes and other substances administered intravenously appear rapidly in the testicular lymph, but not in the fluid that is collected from the rete testis. Based on Voglmayr *et al.*, 1966.

but were absent or detectable only in trace amounts in the rete testis fluid. These results clearly demonstrated the presence of an effective blood-testis barrier.

It could be inferred from the rapid appearance of the test substances in the lymph that the barrier was not in the wall of the testicular capillaries, but somewhere in or immediately around the wall of the seminiferous tubules. To establish the structural basis and precise localization of the permeability barrier, we undertook studies of the junctional complexes between cells in the boundary tissue of the tubules and within the epithelium itself, using electron microscopy, freeze-fracturing, and electron-opaque probes of the extracellular space (Dym and Fawcett, 1970; Fawcett *et al.*, 1970; Gilula *et al.*, 1976).

As stated above, the cells of epithelia elsewhere in the body are firmly attached to one another both by desmosomes and gap junctions on their lateral surfaces and by occluding junctions in the juxtaluminal region. In these epithelia, the position of any cell in relation to neighboring cells is relatively constant. On the other hand, a unique feature of the seminiferous epithelium is the fact that the differentiating germ cells move upward slowly from the base to the lumen along the sides of the fixed population of columnar Sertoli cells. Any enduring attachment between the supporting cells and the germ cells would prevent their upward translocation and ultimate release as spermatozoa. Consistent with this requirement for upward mobility, no juxtaluminal occluding junctions, no gap junctions, and no typical desmosomes are found on the interface between Sertoli cells and germ cells either by conventional electron microscopy or in replicas of freeze-fracture preparations (Fawcett, 1974; Gilula *et al.*, 1976).

However, the supporting cells are a fixed population and, as we have indicated, they were originally cells of a simple columnar epithelium that was invaded by primordial germ cells in fetal life and further distorted at puberty by increasing numbers of germ cells proliferating in the intercellular spaces between them. Near the base of the epithelium, the Sertoli cells maintain contact with one another, and at these sites they are firmly attached by a unique type of membrane specialization, the Sertoli–Sertoli junctions (Fawcett, 1974; Flickinger and Fawcett, 1967). These are circumferential bands of membrane fusion that bear some resemblance to the occluding junctions of other epithelia. However, they differ in their basal location and in having associated cytoplasmic components that are not found in occluding junctions of other epithelia (Figure 6). In freeze-fracture preparations, instead of a narrow band of intramembrane strands, these junctions have up to 50 parallel rows of particles (Gilula *et al.*, 1976; Nagano and

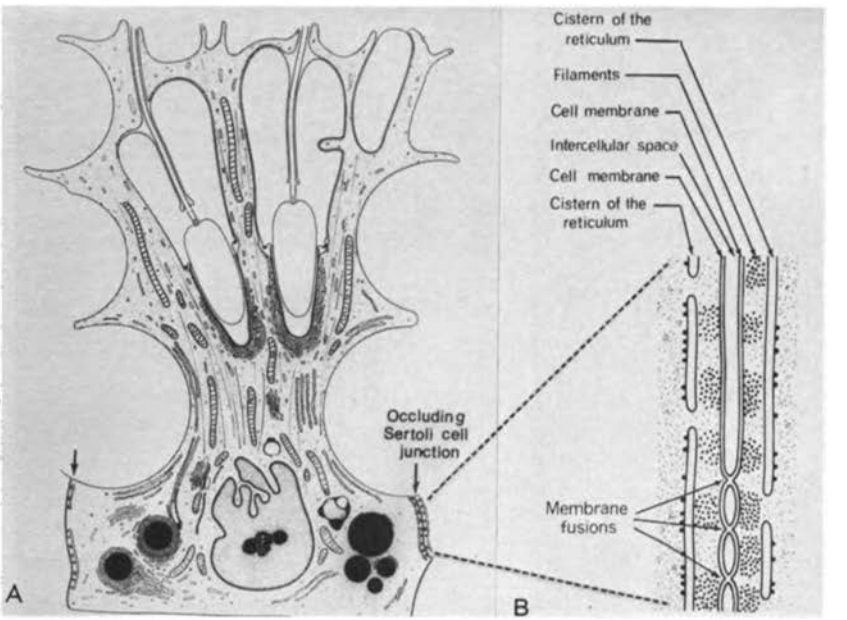

FIGURE 6 (A) Drawing of a Sertoli cell showing the location of the occluding junctions with adjacent supporting cells. (B) Enlarged drawing of the components of the specializations of the adjoining cells that constitute the junctional complex. From Fawcett, 1975, with permission.

Suzuki, 1976), many of which are in register with, and fused to, particle rows in the opposing membrane (Figure 7). In addition, circumferential bundles of filaments, which have been identified as actin (Toyama, 1975), are interposed between this specialized region of the surface membrane and an underlying fenestrated cistern of the endoplasmic reticulum (Figure 6).

When electron opaque probes of the extracellular space, such as lanthanum nitrate or horseradish peroxidase, are injected intravascularly or interstitially, they readily traverse the boundary tissue and basal lamina of the tubules. They penetrate the intercellular clefts at the base of the epithelium outlining the spermatogonia and start into the interspace between abutting Sertoli cells. There, adluminal advance of the probe is abruptly stopped by the occluding Sertoli cell junctional complexes (Aoki and Fawcett, 1975; Dym and Fawcett, 1970). Thus, these junctional specializations were identified as the structural basis for what is commonly called the blood-testis permeabil-

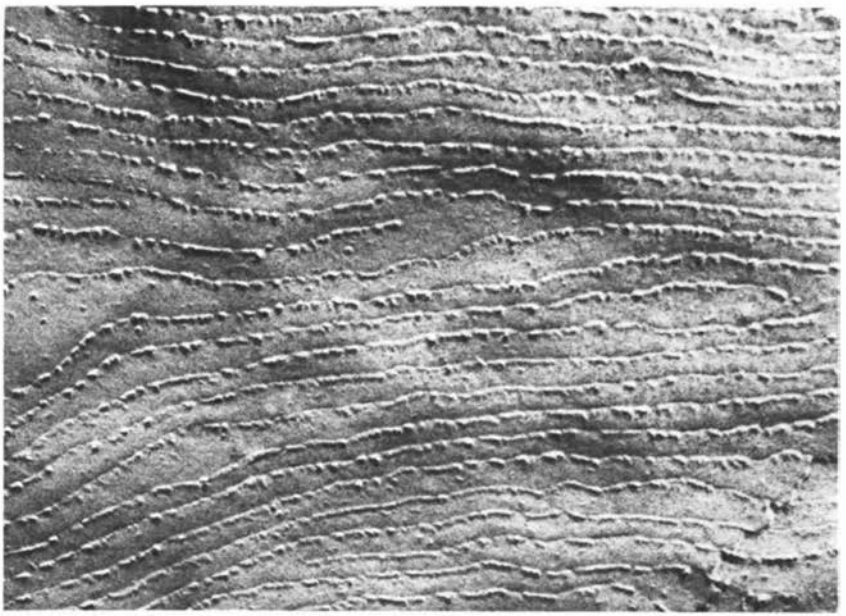

FIGURE 7 An electron micrograph of a portion of a Sertoli junction as seen in a freeze-fracture preparation. Up to 50 parallel rows of closely opposed intramembrane particles are found on the E-face of the cleaved Sertoli cell membrane. These junctional specializations within the membrane underlie the circumferential bands of membrane fusion that constitute the structural basis of the blood-seminiferous tubule permeability barrier. From Gilula *et al.*, 1976, with permission.

ity barrier. It would be more appropriately designated the blood-seminiferous tubule barrier.

The unusual location of the occluding junctions in this epithelium has some significant physiological consequences. Since the junctions are usually located between the Sertoli cell processes that overarch the spermatogonia and preleptotene spermatocytes, the permeability barrier is so situated that it divides the epithelium into two concentric compartments—a basal or peripheral compartment, outside of the barrier, and an adluminal or central compartment, which is isolated from the general extracellular space of the testis (Figure 8). The stem cells of spermatogenesis and their immediate progeny occupy the peripheral compartment, which is freely in communication with the perivascular interstitial spaces of the testis. Spermatocytes undergoing meiosis and the postmeiotic stages of germ cell development are isolated in the adluminal compartment. The Sertoli cells forming the

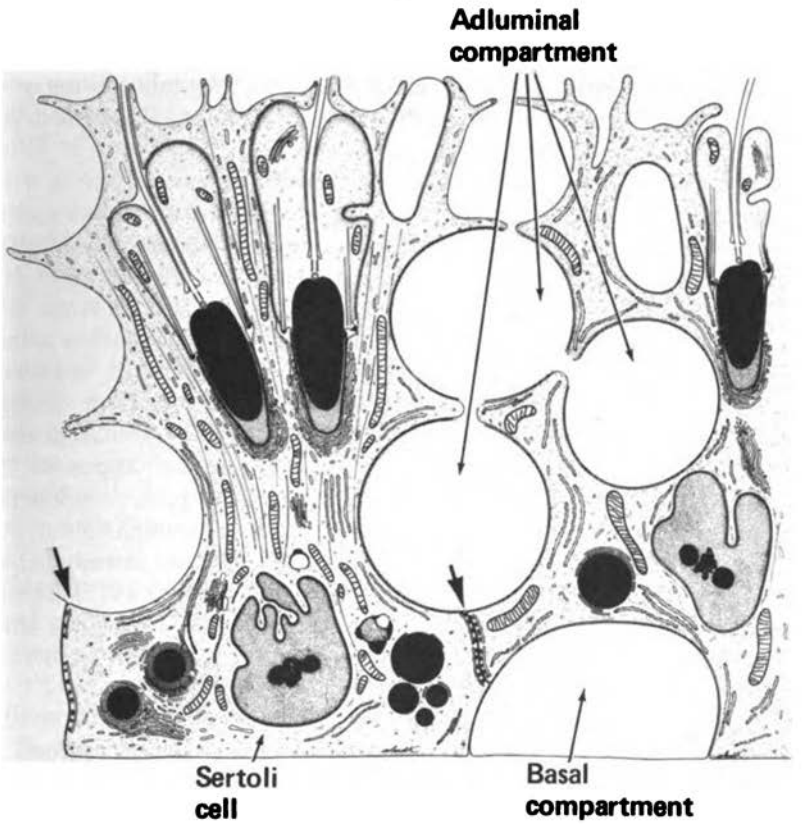

FIGURE 8 Occluding Sertoli junctions (at arrows) divide the seminiferous epithelium into a basal (or peripheral) compartment outside the permeability barrier and an adluminal (or central) compartment inside the barrier. From Fawcett, 1975, with permission.

walls of this compartment maintain in it a highly unusual fluid and electrolyte environment. Samples obtained by micropuncture of the lumen of the seminiferous tubules are high in potassium, low in sodium, rich in inositol, ascorbic, and glutamic acid, and also contain an androgen-binding protein (Tuck *et al.*, 1970). These and other constituents of the fluid that bathe the differentiating germ cells are believed to be essential for their development.

Awareness of the existence of this barrier has forced us to modify our views concerning hormonal effects on germ cell differentiation. The lipid-soluble androgenic steroids are not excluded and can diffuse throughout the tubules, but autoradiographic studies have shown that

the glycoprotein hypophyseal hormones are denied access to the meiotic and postmeiotic germ cells (Orth and Christensen, 1977). Therefore, any influence of gonadotropins on the tubules must be exerted on the Sertoli cells or on the earliest stages of germ cells in the basal compartment.

Why this unusually tight epithelial permeability barrier has evolved in the testis is not obvious, but at least some of its physiological consequences are apparent. As stressed above, it permits the maintenance of a local environment that is uniquely suited for germ cell development. But, possibly of equal biological significance is the fact that it confines antigenic products of germ cell differentiation within the central compartment of the seminiferous tubules. It has been known for some 40 years that injection of spermatozoa or homogenates of testis into guinea pigs results in autoimmune aspermatogenesis (Freund *et al.*, 1953). Recent studies on isolated cell types of the spermatogenic series have demonstrated that the antigenic components are not present on the cells that reside in the basal compartment, but are first synthesized and incorporated into the surface membrane of cells in the adluminal compartment (Millette and Bellvé, 1977). Therefore, a competent barrier may be necessary to retain within the tract the antigenic products of advanced germ cells that might otherwise reach the bloodstream and induce autoimmune infertility.

The existence of a barrier to diffusion from the blood into the tubules has obvious implications for the development of antifertility agents acting upon spermatogenesis. To be effective, drugs must either be able to act primarily upon the Sertoli cells, to traverse the barrier, or to act upon the stem cells and their immediate progeny, which are accessible in the peripheral compartment.

Concern over possible mutagenesis by drugs acting upon meiotic or postmeiotic germ cells must be reconsidered in light of the discovery of the blood-seminiferous tubule barrier. Some of those drugs that were hitherto believed to arrest spermatogenesis by a direct action on the spermatocytes and spermatids may, in fact, have been denied access to these cells by the interposed permeability barrier. It is possible that germ cell depletion, which was observed after administration of these drugs, may have been secondary to an effect upon the Sertoli cells—a nondividing population that is immune to mutagenesis. Research is now needed to localize various antifertility drugs within the tubules in order to ascertain whether their arrest of spermatogenesis is due to a direct effect upon the germ cells or is secondary to impaired Sertoli cell function.

CELL DYNAMICS IN THE SEMINIFEROUS EPITHELIUM

The contractile and motor functions of nonmuscle cells and the mechanisms for coordination of their activities are now burgeoning areas of research in cell biology. However, reproductive biologists have given little attention to the dynamics of cell movement and interaction within the seminiferous epithelium, although these have important implications for spermatogenesis. It may be relevant to describe some of these challenging problems in the hope of stimulating their investigation.

It is common knowledge that the spermatogonial stem cells give rise at regular intervals to type A_1 spermatogonia, which initiate a new cycle of spermatogenesis. A_1 spermatogonia are believed to be irreversibly committed to develop into spermatozoa. But before differentiating into spermatocytes, they first undergo a series of divisions to expand the germ cell population (Huckins, 1971). These and all subsequent divisions in spermatogenesis are atypical in that cytoplasmic division is incomplete. Thus, proliferation of the germ cells results in the formation of long, branching chains ultimately consisting of hundreds of cellular units that are joined together by intercellular bridges (Dym and Fawcett, 1971; Fawcett *et al.*, 1959) (Figure 9). Protoplasmic continuity within these chains insures synchrony of differentiation throughout the entire cohort of germ cells.

The germ cells themselves show little evidence of active shape change. Their upward movement in the epithelium is, in part, a consequence of proliferation of new cohorts of germ cells below them, but it no doubt depends also upon motor activities of the Sertoli cells. When spermatocytes reach the leptotene stage of meiotic prophase (Dym and Cavicchia, 1978), the neighboring Sertoli cells extend undermining processes between them and the basal lamina, displacing them upward. Where these processes meet they form new occluding junctions below the chain of spermatocytes while, at the same time, the preexisting junctional specializations between the overarching Sertoli processes break down (Figure 10). The germ cells are thus moved from the basal to the adluminal compartment without creation of even a transient break in the permeability barrier. The gradual upward movement of more advanced germ cells also requires active movements and changes in disposition of the Sertoli cell processes that extend into the interstices of the germ cell clones.

The long chains of conjoined cells extend through the domains of several supporting cells. Therefore, the motor activities of the Sertoli

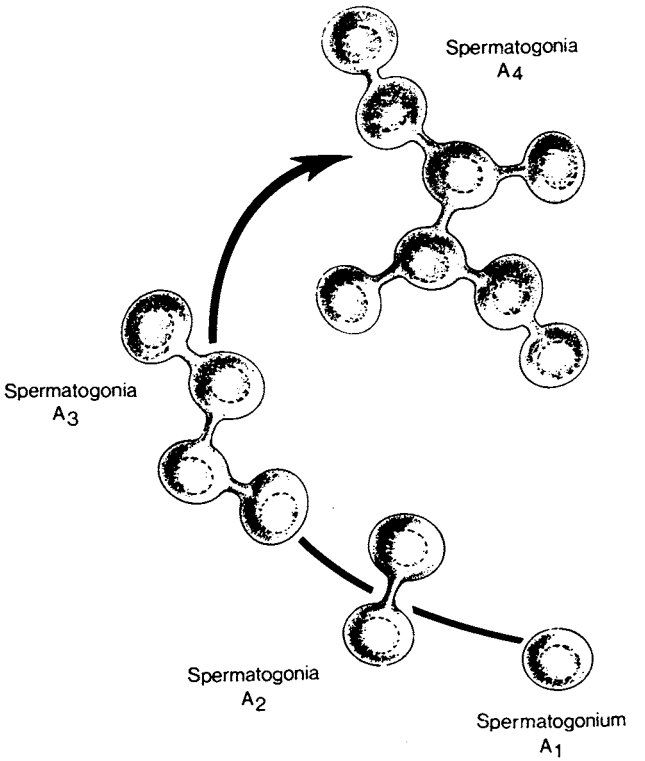

FIGURE 9 Incomplete cytokinesis in dividing germ cells creates long chains of interconnected cells that ultimately number in the hundreds. Cytoplasmic continuity through the intercellular bridges insures synchronous development of the entire clone of germ cells.

cells must be coordinated to achieve a smooth upward transition of germ cell clones and synchronous release of spermatozoa. The germ cells also appear to be passive in the process of spermiation. The Sertoli cells carry out complex maneuvers that gradually expel the nascent spermatozoa into the tubule lumen while their excess cytoplasm, held by enveloping Sertoli cell processes, is retained in the epithelium (Figure 11). As the tail and body of each spermatozoon are displaced farther into the lumen, a slender stalk connecting its neck region with the spermatid cell body becomes more and more attenuated and finally gives way, thereby freeing the spermatozoon from its residual cytoplasm (Fawcett and Phillips, 1969). Motor activities of the Sertoli cells are therefore responsible for separation of individual

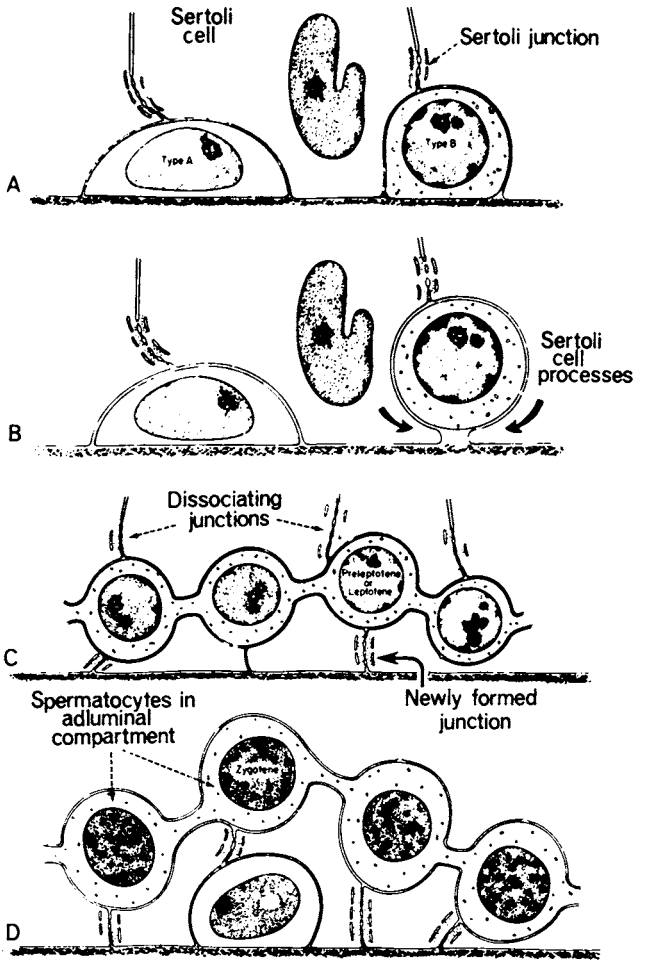

FIGURE 10 Successive stages in the transition of germ cells from the basal (A) to the adluminal compartment. Undermining processes of Sertoli cells elevate type B spermatogonia from the basement membrane (B). The cells divide to form preleptotene spermatocytes. The preexisting occluding junctions become dissociated while new Sertoli junctions form beneath them (C). The spermatocytes are thus transferred to the adluminal compartment (D) without any break in the permeability barrier. Adapted from Dym and Cavicchia, 1977, with permission.

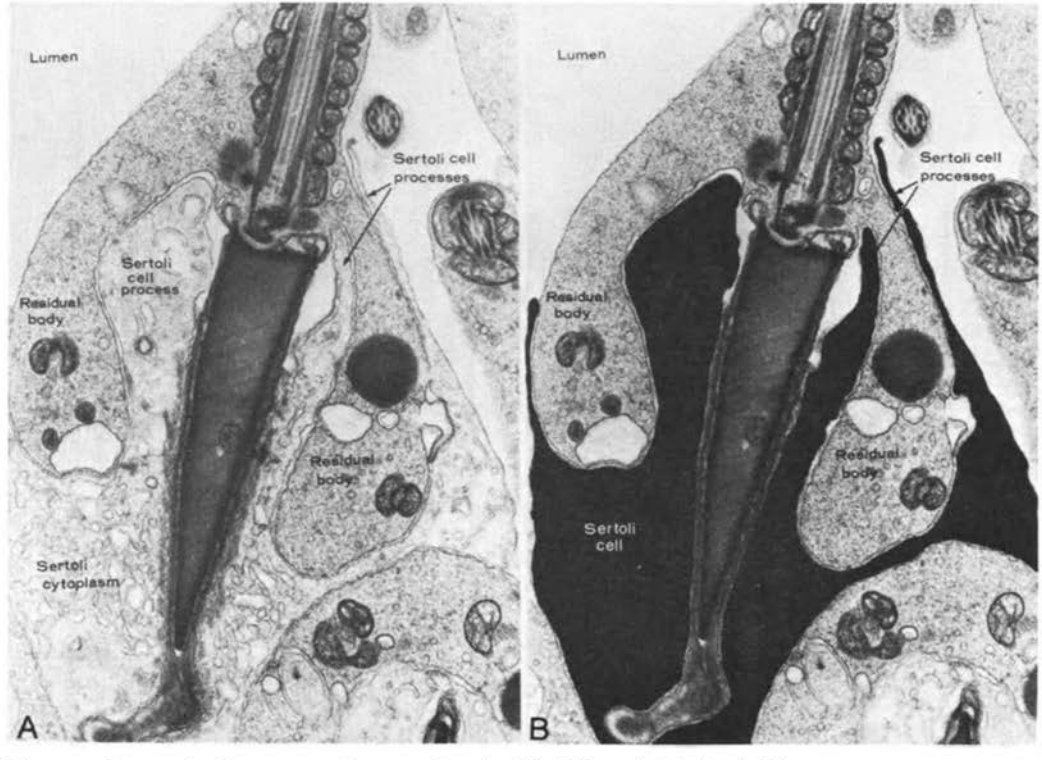

FIGURE 11 (A) Electron micrograph of the process of sperm release in chinchilla testis. The head of the nascent spermatozoon is extruded into the lumen of the seminiferous tubule, while the excess spermatid cytoplasm is retained by enveloping processes of the Sertoli cell. These complex maneuvers require the coordinated motor activity of large groups of supporting cells. (B) Same micrograph with Sertoli cell cytoplasm opaqued to facilitate interpretation of the relationship of the cells. Adapted from Fawcett and Phillips, 1969, with permission.

spermatozoa from the syncytial chains of spermatid cell bodies. Since this process involves not just two spermatids, as depicted in the simplified diagram (Figure 12), but chains consisting of scores or even hundreds extending over the territories of many supporting cells, it is evident that the activities of large groups of Sertoli cells must be coordinated to insure simultaneous release of all spermatozoa of the same cohort. Their coordination appears to be achieved by communicating or gap junctions, as in other epithelia. However, close contacts between adjacent Sertoli cells are largely limited to those same regions near the base of the epithelium where the cells form occluding junctions. The gap junctions of Sertoli cells are not the usual large plaques of intramembrane particles, but are small, elongated particle aggregations that are intercalated between the lines of membrane fusion in the Sertoli–Sertoli junctional complexes (Figure 13).

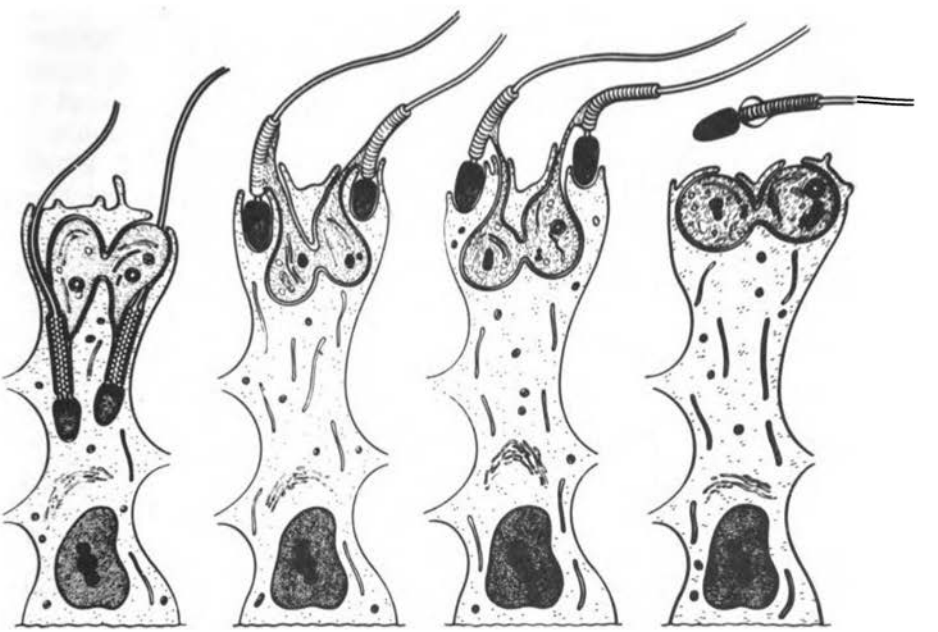

FIGURE 12 Schematic representation of successive stages in sperm release. The spermatids appear to be passive in the process. The Sertoli cells move the spermatids toward the surface and slowly extrude the nucleus and flagellum into the lumen (B, C). The conjoined cell bodies containing the excess cytoplasm are retained in the epithelium by Sertoli cell processes. A slender stalk connecting the residual cytoplasm to the neck region of the nascent spermatozoon is attenuated and finally gives way (C, D). Spermatozoa are thus released from their interconnected cell bodies, which are retained and degraded in the epithelium. From Fawcett, 1970.

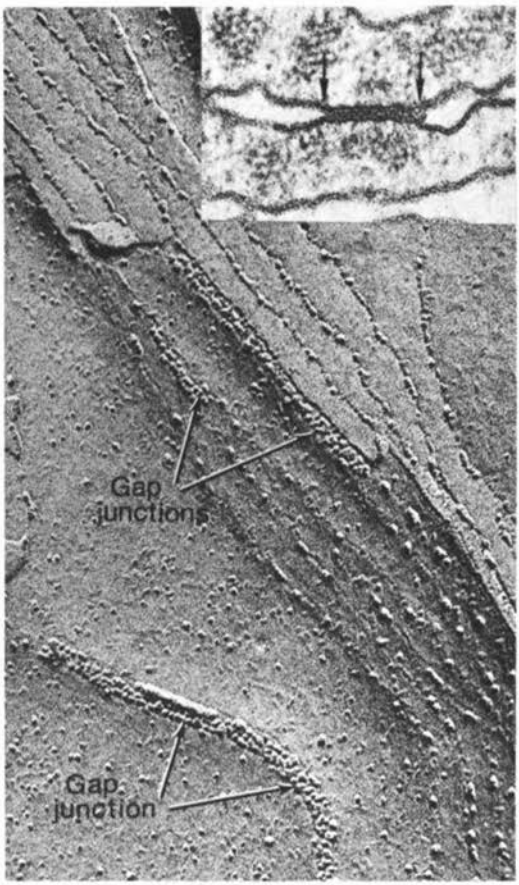

FIGURE 13 Electron micrograph of a freeze-fracture preparation showing atypical elongated gap junctions on the P-face of the Sertoli membrane between the rows of membrane particles in the occluding Sertoli junctions. The inset shows the appearance of one of these communicating junctions in a thin tissue section. These are believed to be responsible for coordination of the motor activities of groups of Sertoli cells. Adapted from Gilula *et al.*, 1976, with permission.

Therefore, these specialized regions of the Sertoli cell surface have the dual role of maintaining a barrier to diffusion of substances into the epithelium from the interstitium and of maintaining metabolic coupling and lateral communication between large groups of supporting cells.

CONCLUSION

Research in recent years on the seminiferous epithelium has focused attention upon the key role of the Sertoli cells in spermatogenesis. We now know that they possess specific receptors for follicle-stimulating hormones (FSH) and respond to testosterone; they synthesize an androgen-binding protein that may be required to maintain a high intratubular concentration of androgen; they probably produce inhibin to regulate hypophyseal release of FSH; they are responsible for movement of the clones of germ cells toward the lumen and are the agents of germ cell release and residual body degradation; they maintain the blood-seminiferous tubule permeability barrier; and they create in the adluminal compartment a unique microenvironment that is favorable for germ cell differentiation. This broad repertoire of functions, which is necessary for spermatogenesis, now makes the Sertoli cell an attractive target for antifertility drugs. Selective suppression of one or more of its essential functions promises to be an effective strategy for development of male contraceptives.

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Immunological Inhibition of Sperm and Egg Function: Prospects for an Antifertility Vaccine from Gametes

CHARLES B. METZ

Two major systems that regulate the internal affairs and environment of the body are the endocrine system and the immune system. In the reproductive process, the endocrine system is extremely pervasive and spectacular contraceptive results can be achieved by manipulating it. The immune system is equally notable, but for the opposite reason: it is extraordinarily permissive and is relatively refractory to manipulation that would effect contraception in spite of rational expectations.

The bases for these expectations, the permissiveness, and the refractoriness of the immune system are summarized in two simplistic but fundamental points of biological logic:

- The immunological machinery of the individual develops prenatally and is functional at birth (Jones, W. R., 1976a), whereas the gametes and their cell-specific macromolecules first differentiate to functional maturity at puberty, years after the maturation of the immune system. Therefore, at puberty the humoral and cellular immune systems of the individual should be able to recognize that gametes are foreign and mount destructive immunological defenses against them, resulting in almost immediate sterility. Likewise, the products of conception—the fertilized egg and developing blastocyst, fetus, and placenta—are similar to allografts because of their genetic differences from the mother and should shortly be rejected like skin or organ grafts from an unrelated individual.

• The second point is even more obvious, namely, that during millions of years of evolution through natural selection, vertebrates have developed very efficient mechanisms to ensure that such immunological sterility does not occur. Consequently, to develop an effective contraceptive based on immunity to gametes and the products of conception, the logical problem is to identify and understand the mechanisms that prevent auto- and isoimmune responses and to find means to circumvent them. Ultimately, control of fertility, like control of disease, should result from use of an appropriate vaccine.

In this paper, I consider mechanisms that normally prevent auto- and isoimmune responses to gametes, some approaches to contraception in the context of autoimmunity to gametes in the male and female, and especially isoimmunity to sperm in the female.

ACTION OF IMMUNE EFFECTOR SYSTEMS ON GAMETES

The two major immunological effector systems are the humoral system and the cellular system. The former includes circulating antibodies and the components of complement (C′) normally present in blood; the latter consists of immune effector cells including thymus-dependent (T) lymphocytes. The cellular system has importance in autoimmune aspermatogenesis (Tung, 1977) and is a major consideration in the allograft concept of placentation (Beer and Billingham, 1977). Cellular immunity has received relatively little attention as a factor in other aspects of immunoreproduction, although cellular immune responses are known to follow apparent auto- and isoimmunity to seminal antigens in clinical and experimental material (Erickson, 1977; Mancini, 1969). Consequently, humoral immunity will be the primary consideration in this paper. Brief accounts of the roles of immune systems in reproduction have been presented by Gowland (1976) and Metz *et al.* (1976b).

Antibodies combine specifically with the reactive sites of the antigen to which they are directed. In so doing, they can have several effects on those antigens and any cells, including eggs and sperm, of which they are components. The primary effect is blocking of the specific complementary reactive site of the antigen to which the antibody is directed. Due to its physical size, the bound antibody may also sterically block regions adjacent to the antigen and neighboring cell surface. Both direct and steric blocking can interfere with the antigen's biological function, e.g., at antigenic sites with enzymatic, hormonal, or specific receptor function. Secondary physical effects of antibody

can result from cross-linking of antigens because of antibody multivalency. Examples include precipitation of soluble antigens from solution and in gels, including cell surface gels (Metz *et al.*, 1968). In addition, cross-linking of surface antigens on different cells can result in cell agglutination. Finally, tertiary effects can follow combination of C′ with antigen–antibody complexes involving the IgG and IgM immunoglobulin (Ig) classes.

Sperm Agglutination

Antibody agglutination of sperm has been studied intensively, especially in clinical material (Boettcher *et al.*, 1977). By virtue of its restrictive action on sperm movement (Figures 1 and 2), sperm

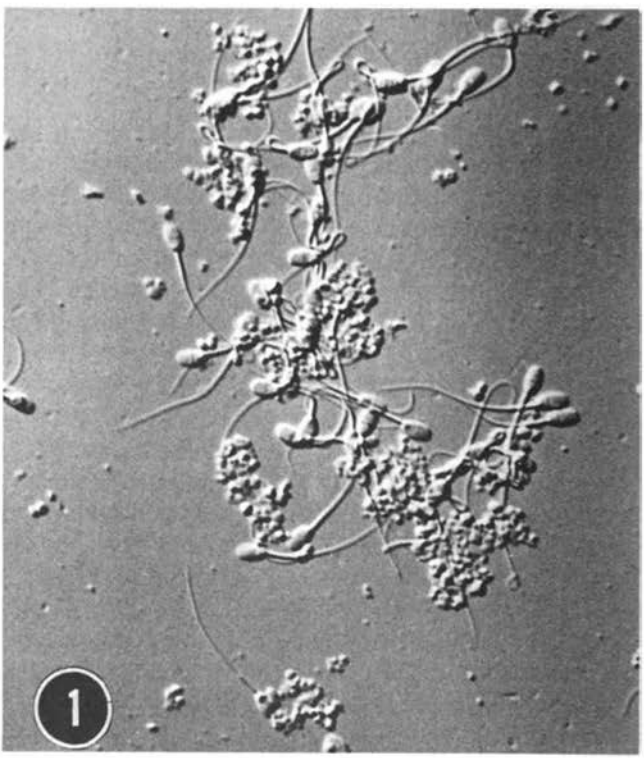


FIGURE 1 Rabbit sperm agglutinated by isoantiserum from female rabbit immunized with rabbit semen.

agglutination should interfere with normal sperm behavior and function including cervical passage, penetration of egg envelopes, and sperm–egg interaction. The degree to which sperm agglutination actually affects fertility in experimental and clinical situations is uncertain. Antisera to rabbit seminal plasma agglutinate rabbit sperm but do not impair fertility (Menge and Protzman, 1967). This implies that agglutination does not impair sperm function. However, some, if not all, seminal plasma antigens that are shared with sperm are sperm-coating antigens adsorbed to ejaculated sperm. Most of these antigens are lost during sperm capacitation (Johnson and Hunter, 1972; Oliphant and Brackett, 1973). Such loss either prior to or during capacitation should reverse the agglutination. Agglutination of sperm occurs in the semen

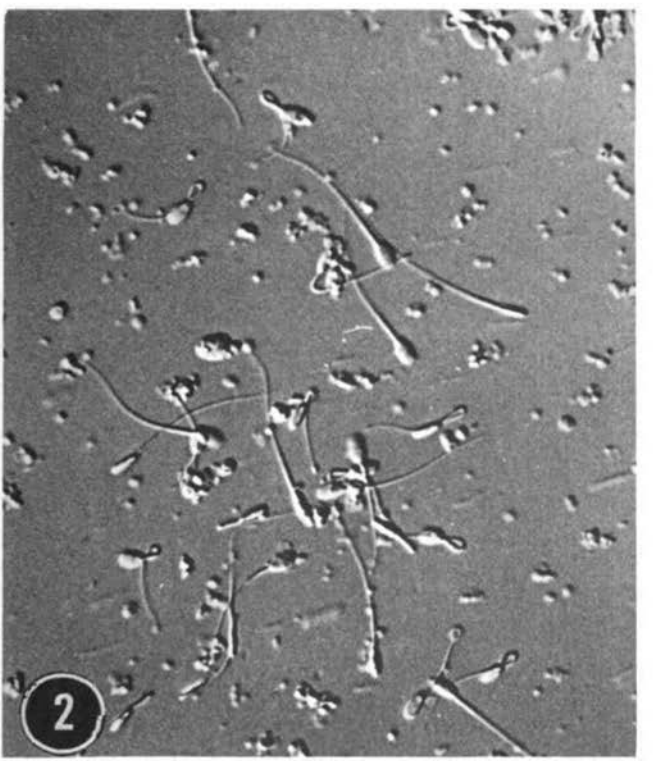
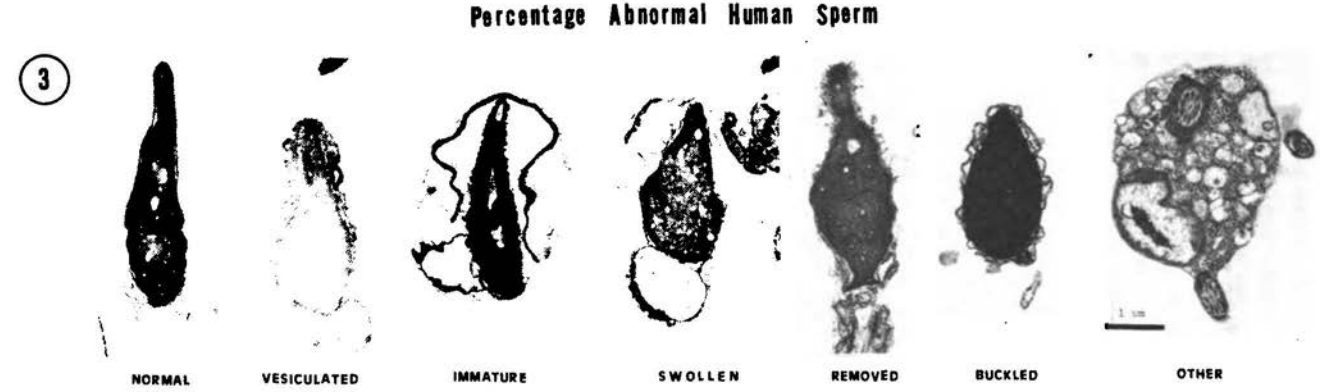


FIGURE 2 Rabbit sperm in control (preimmune) female rabbit serum. Photographs of living sperm, electronic flash and Nomarski optics (approx. 500x). From Metz, 1972, with permission.



								n
Un	**45**	14	14	4	12	12	—	78
♂'	12	21	7	15	21	8	15	110
C'	—	11	5	**59**	9	6	11	93

FIGURE 3 Ultrastructure of sperm in a single human semen sample. Data give frequencies of the different morphologies in untreated semen (UN); semen plus heated complement and rabbit antihuman semen serum (C'); and semen plus unheated complement and rabbit antihuman semen serum (C'). Sperm in the C' sample were immobilized. In a second experiment, the "vesiculated" rather than the "swollen" class predominated (Metz *et al.*, 1976a).

of some fertile men. Similarly, circulating sperm agglutinins in women are not always associated with infertility. In any event, to establish a causal relationship between agglutination and infertility *in vivo* would require elimination of blocking of essential sperm antigens and of C′-dependent immobilization of sperm. Accordingly, sperm agglutination by sera and reproductive tract fluids is as yet of interest primarily as a diagnostic tool that is indicative of auto- and isoimmune responses to sperm antigens (Boettcher *et al.*, 1977).

Sperm Immobilization

Products of complement-immune complex interaction can have a destabilizing effect on cell membranes causing cell lysis (e.g., hemolysis), cell immobilization, and cell death. In the rabbit (Russo and Metz, 1974c; Russo *et al.*, 1975), guinea pig (LeBoutillier *et al.*, 1975), and rhesus monkey (Alexander, 1975), sperm immobilization is associated with striking cell membrane damage in the acrosomal region. In the rabbit, this results in massive lesions of the cell membrane and an apparent "rolling back" of the cell membrane to the equatorial segment, rupture of the outer acrosomal membrane, and loss of the acrosomal contents. The acrosomal membrane damage, although striking, is not necessarily the primary cause of the immobilization of rabbit sperm, because isolated "headless" rabbit sperm tails are immobilized by antisperm antibodies with C′ (Metz and O'Rand, 1975).

In view of the apparent morphological specificity of the immobilization-associated damage and its prominence, e.g., it is demonstrable by immunofluorescence in the rabbit (Russo *et al.*, 1975), immunologically immobilized human sperm were examined for comparable phenomena. Such damage, if specifiable by morphology and immunofluorescence as it is in the rabbit, could be a valuable tool for identifying immunologically immobilized human sperm in, for example, cervical mucus as an adjunct to the postcoital test. Examination of immunologically immobilized human sperm (Metz *et al.*, 1976a) by transmission electron microscopy confirmed the well-known spectrum of sperm morphology in single ejaculates. Figure 3 shows that comparison of control (motile) and immunologically immobilized human sperm from the same ejaculate reveals no unique immobilization-related changes in sperm morphology. However, comparison of frequencies of arbitrarily established morphological types indicates a marked reduction in "normal" sperm and an increase in "abnormal" sperm following immobilization. In one experiment, an increase in frequency was particularly striking in "swollen-head" sperm. Evidently, morphological

changes occur in the acrosome region following immunological immobilization of human sperm. However, the changes indicated by these limited data are hardly striking or specific enough to have practical diagnostic value.

As remarked by Cabot and Oliphant (1978), the membrane damage that is associated with immunological immobilization resembles membrane alterations of the acrosome reaction (a normal event in sperm–egg interaction), at least to the extent that the plasma membrane over the acrosome and the outer acrosome membrane are involved in both immobilization and the acrosome reaction. These two effects could be related since C′ components may be involved in both. However, the natures of the membrane alterations in the two phenomena are quite different, except possibly in the guinea pig (LeBoutillier *et al.*, 1975). The membrane damage that is associated with immunological immobilization results in true lesions, a loss of integrity of the cell membrane, and cell death, whereas the acrosome reaction involves "orchestrated" multiple fusion events between the cell membrane and outer acrosomal membrane. These events release the acrosomal contents but at no time destroy the integrity of the cell membrane system during the acrosome reaction.

For clinical application, sperm immobilizing action is the most conservative diagnostic serum test of infertility resulting from immunity to sperm (Jones, W. R., 1976b; Isojima, 1973).

Antibody Action on Eggs

In addition to effects on sperm, antibodies have precipitating, agglutinating, and cytotoxic action on eggs. These have been especially well studied in sea urchins (Metz, 1972) and amphibians (Metz, 1967). Among mammals, the precipitation of the surface of the zona pellucida by antibodies is of special interest. This action is discussed below. The sensitivity of the rabbit egg to immunological damage is demonstrated by specific lysis of the fertilized but not the unfertilized egg following exposure to sperm-specific autoantibodies and C′ (O'Rand, 1977). Evidently, the autoantibodies react with sperm membrane antigen(s) that are incorporated into the egg plasma membrane at fertilization.

Antibody Fragments and the Mechanism of Antibody Action

As described above, antibodies can have several effects on gametes, any one or combination of which should impair gamete function and result in reduced fertility. For contraceptive purposes, it may be

immaterial which of these effects are involved if the practical result is achieved. However, to understand the functions of antigens in reproduction and infertility, it is important to resolve the mechanism of antibody action. Fortunately, advances in immunochemistry during the past 20 years have provided methods for distinguishing between primary (blocking), secondary (cross-linking), and tertiary (C′-dependent) antibody action with considerable precision. The most important methods involve enzymatic digestion of antibodies.

IgG is the most abundant antibody class. The IgG molecule is tripartite, consisting of two Fab and one Fc component. The two Fab components each terminate in a combining site that is specific for the antigen to which it is directed. The Fc component interacts with C′ and also serves as the attachment site to Fc receptors on some cell surfaces including some spermatozoa. Finally, the Fc component functions in transplacental passage of IgG.

Since each Fab component terminates in a single antigen combining site, isolated Fab fragments have only primary or blocking capability. They cannot agglutinate (cross-link) or combine with C′ components. Such isolated Fab fragments are readily prepared by digesting native IgG with papain (Porter, 1959). This splits the heavy protein chains of the IgG in the hinge region separating the two Fab components from each other and from the Fc. The Fab fragments can be secondarily cross-linked by appropriate antiglobulin to produce agglutinating systems. A bivalent, agglutinating antibody component $(Fab')_2$ lacking the Fc is obtained by pepsin digestion. The $(Fab')_2$ component can be separated into univalent Fab′ fragments by simple reduction. These are functionally similar to the Fab (papain) fragments. The $(Fab')_2$ bivalent fragments have primary (blocking) and secondary (cross-linking), but not tertiary (Fc-dependent), action including attachment to Fc receptor and C′-dependent effects such as cell lysis. I have used Fab (blocking) antibody fragments in many of my studies, some of which are described below.

Immunoglobulins and C′ in Genital Tract Fluids

To affect gamete function and thereby fertility, antibodies must necessarily be present, especially in genital tract fluids.

IgG and IgA are present in seminal plasma of men in varying amounts, i.e., 7–22 mg/ml and 0–6 mg/ml, respectively (Friberg and Tilly-Friberg, 1976). IgM is not present. The IgG may derive by diffusion from blood, but much of the IgA of seminal plasma is secretory IgA (SIgA), which is probably synthesized locally in one or more of the male accessory

glands. Immunoglobulins in seminal plasma can include antisperm autoantibodies, which are usually IgA. Such antibodies can agglutinate spermatozoa in the ejaculate. In some but not all cases, this correlates with male infertility. The presence of sperm agglutinins in the seminal plasma also correlates with high serum sperm agglutinin levels. Since the seminal plasma antibodies are ordinarily predominantly SIgA and the serum agglutinins are IgG or IgM, the seminal plasma and serum sperm agglutinins would appear to be synthesized by different, unrelated populations of bursa-equivalent (B) lymphocytes. Therefore, the correlation between sperm agglutinating antibody titers of seminal plasma and serum must be at least partially fortuitous and reflect the intensity of a generalized immune response to one or more antigens on the sperm surface (Husted and Hjort, 1975). Seminal plasma does contain one of the nine components of hemolytic complement (C'_3), but it also contains anticomplementary factors (Boettcher and Gruszynski, 1978), which should limit C′ action in seminal plasma.

Immunoglobulin levels in cervical mucus and in uterine, oviducal, and follicular fluids have been examined in some detail (Jones, W. R., 1976b; Cinedar and deWeck, 1976; Edwards, 1976; Schumacher, 1973; Shulman, 1977). Midcycle cervical mucus in humans contains SIgA, IgA, IgG, and trace amounts of IgM. The ratio of IgG to IgA ranges from 1:1 (Schumacher, 1973) to 3.7:1 (average of 66 samples) (Shulman, 1977). IgG is presumably transudated from serum, but much of the IgA is locally synthesized secretory SIgA. This is consistent with the appearance of antibodies to locally infecting organisms and to toxins that have been introduced into the female tract, either naturally or experimentally (Cinedar and deWeck, 1976). Human cervical mucus also contains the full hemolytic system of C′ components (Boettcher and Gruszynski, 1978).

The uterine fluid of humans contains IgG, IgA, and IgM. In the rabbit, local immunization (intrauterine immunization of doubly ligated uteri) with foreign antigen (sea urchin sperm) results in the appearance of antibodies in the uterine fluid of the injected organ, the serum, and the doubly ligated contralateral control uterine fluid (Metz, unpublished). In related experiments by Menge and Lieberman (1974), intrauterine isoimmunization with rabbit sperm regularly resulted in serum antisperm isoantibodies and, in some cases, uterine fluid isoantibodies with disproportionately high SIgA levels implying local SIgA synthesis. Incubation of sensitized sheep erythrocytes in rabbit uteri followed by examination of flushings revealed no hemolysis (Metz, unpublished). Evidently, the uterine fluid of rabbits has vanishingly low complement levels at most. Oviducal fluid contains IgG, IgM, and IgA in variable but

lower amounts than those in serum, depending on the time of cycle (Lippes *et al.*, 1972; Oliphant *et al.*, 1977). Follicular fluid contains essentially the components of serum except for fibrinogen (Shivers *et al.*, 1964). These include immunoglobulins and the complete hemolytic complement system at least in the cow and rabbit (Cabot and Oliphant, 1978). The existence of specific antisperm isoantibodies in the follicular fluid of isoimmunized females is inferred from the fact that ova from sperm-isoimmunized female rabbits (Table 1; Russo and Metz, 1974b) and mice (Tsunoda and Chang, 1976) have reduced fertility *in vitro*.

One can conclude, then, that the female tract fluids, especially the cervical mucus, oviducal fluid, and follicular fluid, contain major components of the humoral immune system although in reduced amounts compared to those in serum, and that a significant contribution is made by local secretory antibodies in tract fluids. The complete hemolytic complement system has been demonstrated only in cervical mucus and follicular fluid.

Autoimmunity to Sperm, Aspermatogenesis, and Male Fertility

The absence of spontaneous autoimmunity to the germinal tissue and spermatozoa in the male is explained by the blood-testis barrier, so

TABLE 1 Cleavage of Ova from Isoimmunized Females Following *In-Vitro* Insemination with Capacitated Sperm[a]

	Immune Ovum	Normal Ovum		
Experiment Number	Donor Inseminated	Donor Inseminated	Donor Uninseminated	Capacitator Ova[b]
1	1/10	1/4	0/3	6/6
2	7/38	3/15	0/4	7/7
3	3/20	0/6	0/3	7/10
4	0/3	6/8	0/7	4/7
5	0/10	5/8	0/1	3/4
TOTALS	11/81	15/41	0/18	27/34
PERCENT CLEAVED	13.6	36.5	0	79.4

[a]From Russo and Metz, 1974b, with permission.
[b]Ova from the female providing the capacitated sperm. Cleavage, i.e., fertilization of these eggs, confirms capacitation of sperm in the capacitated female.
[c]Cleaved ova from capacitator female/total ova.

elegantly described by Fawcett and coworkers (Dym and Fawcett, 1970; Gilula *et al.*, 1976), and by the duct systems of the male reproductive tract. The latter evidently isolate the germinal tissues, the spermatozoa, and their autoantigens from the immune systems of the individual. Moreover, they prevent access of immunoglobulins and, apparently, lymphocytes to the lumen of the duct systems of the testis and epididymis (Johnson, 1973; Jones, R. C., 1977). Nevertheless, in laboratory animals autoimmunization of the male with testis homogenate or semen, especially in an adjuvant emulsion, can result in autoimmune responses, including the appearance of immune effector lymphocytes (T cells) and sperm agglutinating and cytotoxic (sperm immobilizing) antibodies in serum. Likewise, examination of pre- and postvasectomy sera in laboratory animals and in men (the closest practical approach to a controlled experiment in men) shows that sperm agglutinating and/or immobilizing antibodies appear in at least 50% of cases following the operation (Alexander, 1977).

Cellular immune responses following vasectomy in humans are not dramatic (Alexander, 1977; Hess *et al.*, 1977). However, lymphocyte sensitivity to sperm antigens has been reported in 17% of 126 infertile men with nonobstructive azoospermia. In one study, 38% of the positive patients had a history of testicular trauma or biopsy (El-Alfi and Bassili, 1970). Some of these patients developed significant sperm counts following corticoid immunosuppressive treatment (Bassili and El-Alfi, 1970). However, Ansbacher and Gangai (1975) failed to find circulating antisperm antibodies in men following testicular biopsy. In one group of men, infertility (obstructive azoospermia) correlated with circulating antisperm antibodies and parasitic infection (*Schistosoma haematobium*) of the male tract (Abdel Aal *et al.*, 1975).

The immune response may be attributed to the rupture of the blood-testis barrier. Similarly, autoantibodies to sperm can be found following various other insults to the reproductive system of men including gonorrheal epididymitis and mumps orchitis in addition to physical injury (Rümke, 1969). Cellular immune responses can follow orchitis that is associated with leprosy (Wall *et al.*, 1977).

The studies reviewed briefly above show unequivocally that cellular and humoral autoimmune responses to sperm result from exposure of the immune system to seminal components by direct injection or through other bypass of the blood-testis barrier. Such autoimmune responses can affect male reproductive function. The autoimmune agents, especially the cellular immune system, can specifically attack the germinal tissue of the testis, thereby producing an autoimmune orchitis leading to aspermatogenesis in a number of animals. The

response is particularly dramatic in the guinea pig (Figures 4 and 5), in which a single injection of testis homogenate in Freund's adjuvant emulsion results in complete, and in extreme cases permanent, sterility in 6 weeks without side effects. Leydig and Sertoli cells are not affected (Mancini, 1976). Autoimmunization of young guinea pigs with testis homogenate produces no testicular response, but testicular reactions occur at maturity (Bishop *et al.*, 1961). This is consistent with an autoimmune response to sperm-specific autoantigen expression at maturity.

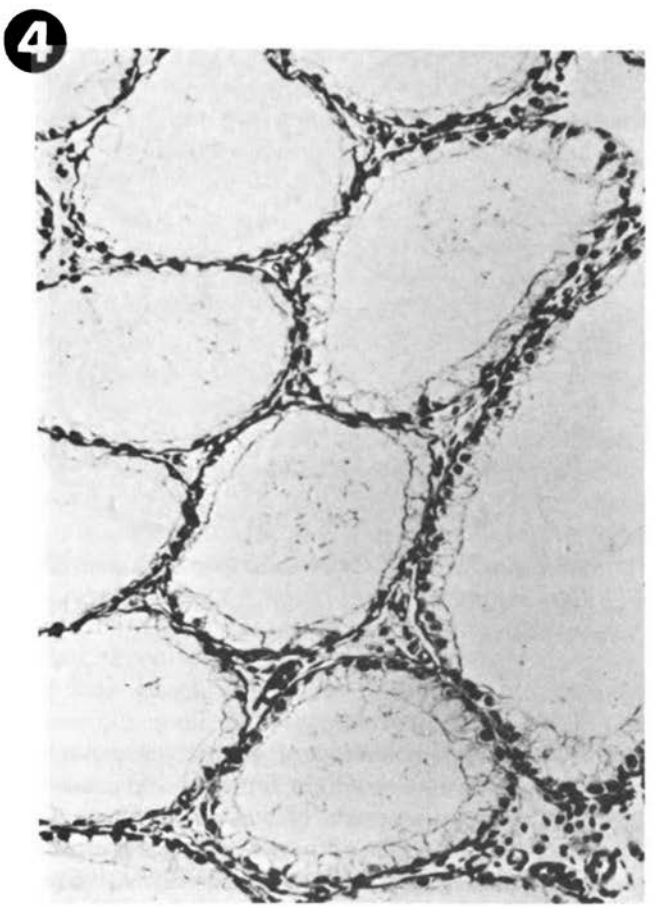


FIGURE 4 Section of guinea pig testis from an animal autoimmunized with guinea pig testicular extract in Freund's adjuvant. Provided by Dr. Seymour Katsh.

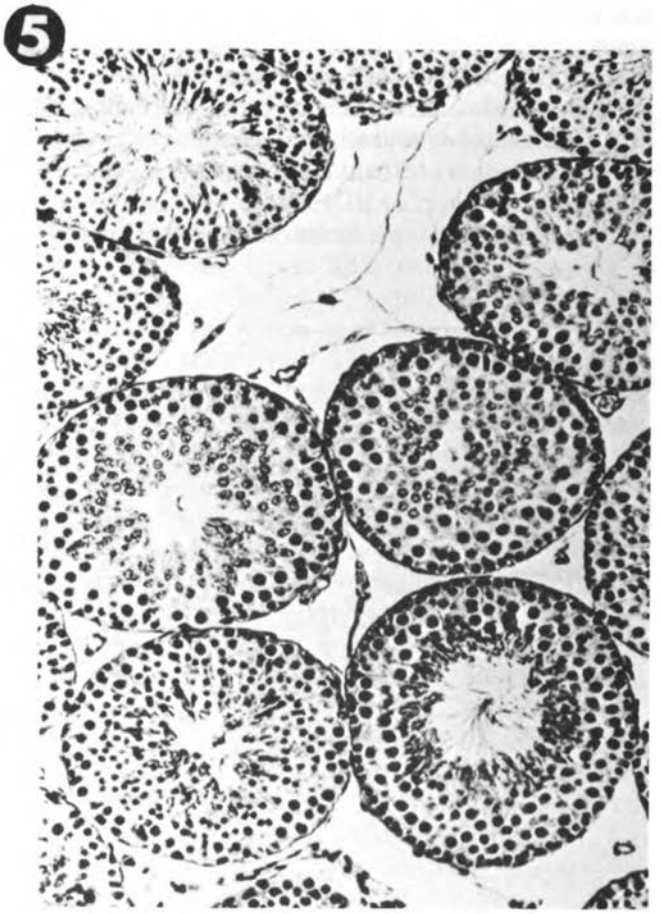


FIGURE 5 Section of control guinea pig testis. Provided by Dr. Seymour Katsh.

Characterization and purification of guinea pig aspermatogenesis antigens using aspermatogenesis as a bioassay have achieved some success. Since microgram amounts of purified antigens can produce aspermatogenesis, the "criterion of the purity of . . . presumed antigens becomes more stringent" (Tung, 1977). One highly active glycoprotein has been isolated from the guinea pig testis by Katsh *et al.* (1972) and one by Brown *et al.* (1965). Four active materials have been specified by Voisin *et al.* (1975), three of which have been at least partially characterized

(two as glycoproteins, one as protein). Eyler's group (Hagopian *et al.*, 1975; Jackson *et al.*, 1975) specified three active materials—one protein and two glycoproteins—of high purity as evidenced by single bands in acrylamide gel and immunoelectrophoresis. At least one of the antigens is not species-specific: guinea pig antigen produces orchitis in rabbits (Tung and Woodroffe, 1978). It is difficult to evaluate these purification and isolation products in terms of separate, distinct, native sperm macromolecules because of the rather harsh procedures used, e.g., 5% trichloroacetic acid (TCA) extraction, except in the case of the "T" autoantigen of the sperm surface (Voisin *et al.*, 1975). Another exception is sorbitol dehydrogenase, the sperm-specific isoenzyme and autoantigen reported to produce aspermatogenesis in guinea pigs (Bishop, 1970).

To examine for autoimmune responses of the testis in men, Mancini (1976) injected prostatic carcinoma patients with autologous and homologous sperm in adjuvant and also applied thermal injury to the testis unilaterally. He observed humoral antibodies, positive skin tests, multifocal testicular lesions, and immunofluorescent germ cell reactions in some patients following these treatments, thereby demonstrating the potential for autoimmune aspermatogenesis. In this context, it is of clinical importance that, unlike guinea pigs (Bishop, 1970) and to a lesser extent rabbits (Alexander and Tung, 1977; Flickinger, 1975), men incur only modest changes in the germinal tissue of the testis following vasectomy (Alexander, 1977).

Autoimmunization as a contraceptive procedure in men, in which antibodies are directed against one or more germ cell antigens to inhibit spermatogenesis, seems to be of limited promise. There is no obvious means for inducing restricted secretion of antisperm antibodies into semen via the male accessory glands. If autoimmunization followed the sequence of lower animals, it would have little appeal as an alternative to vasectomy, even if effective as a contraceptive procedure, for three reasons. First, even in the guinea pig, adjuvants that can produce undesirable side effects are required to achieve aspermatogenesis, unless an heroic immunization regimen is used (Bishop, 1961). Second, the blood-testis barrier and/or the efferent ducts must be breached to permit entrance of antisperm antibodies and/or lymphocytes to the germinal tissue. This should enable the spermatozoa to escape, which might reinforce and broaden the specificity of the total immune response, possibly resulting in the destruction of spermatogonial cells and permanent sterility. Third, the released sperm antigens could react with antibodies in the bloodstream. The resulting immune complexes could produce arteriosclerotic damage to the circulatory system, as may

occur following vasectomy, at least under extreme conditions (Alexander, 1978).

This sequence of events might occur even if the individual were autoimmunized against a single autoantigen appearing "late" in spermatogenesis. It should be noted that normal sperm counts return to 40%–90% in vasectomy patients following vasovasotomy, but that the fertility rate is only 20%–25%. As emphasized by Alexander (1977), this reduced fertility may have an immunological basis.

AUTOIMMUNITY TO OVARY AND OVA

The ovary lacks an obvious barrier separating germinal tissue from blood in a manner that is comparable to the blood-testis barrier in the male. But like other organs, the ovary does contain tissue-specific antigenic material, notably in the zona pellucida surrounding the ovum (Ownby and Shivers, 1972; Sacco and Shivers, 1973a,b). Antisera prepared in rabbits against hamster or mouse ovaries have the following effects on the zona, even after absorption of the serum with somatic tissue: precipitation of the zona surface, inhibition of digestion by proteolytic enzymes including trypsin and pronase (Gwatkin *et al.*, 1977; Ownby and Shivers, 1972), inhibition of sperm attachment to the zona and penetration of the ovum *in vitro* (Figure 3; Dunbar and Shivers, 1976; Shivers, 1979; Shivers and Dudkiewicz, 1974), blocking of fertilization *in vitro*, and temporary inhibition (for three cycles) of *in-vivo* fertilization following passive immunization (Jilek and Pavlok, 1975; Oikawa and Yanagimachi, 1975; Tsunoda and Chang, 1978; Yanagimachi *et al.*, 1976). In addition, antiovary or antizona sera prevent zona shedding and blastocyst hatching in the oviduct and implantation in the uterus, respectively (Glass and Hansen, 1974; Shivers, 1974).

These striking effects result from heteroantisera to the zona pellucida. The question then arises, is the zona antigen an autoantigen (e.g., is it capable of inciting autoimmune responses in the female), which could produce infertility by antibody action on the zona either before or after fertilization? Shivers and Dunbar (1977) suggested that the zona should have autoantigenic potential because it apparently forms late in development. Autoimmunization of female mice with mouse ovary homogenate in Freund's adjuvant significantly reduced fertility (litter size, fertilized ova). In comparable experiments with rats, the proportion of fertilized ova that was recovered following mating was reduced, although litter size at term was normal (Tsunoda and Chang, 1976).

Gwatkin *et al.* (1977) failed to detect an autoimmune response

(inhibition of fertilization *in vitro*) in female hamsters injected with isolated, heat-solubilized (65°C) hamster zonae. Similarly, autoimmunized mice produced only a very weak autoimmune response (immunofluorescence). However, female mice that were immunized with isolated, solubilized hamster zonae produced antisera that reacted strongly with hamster and mouse zonae (immunofluorescence), inhibited mouse fertilization *in vitro*, and rendered the immunized mice temporarily sterile. Zonae from the ova of these immunized mice gave positive immunofluorescence with antimouse IgG and antimouse C_3, indicating binding of antizona autoantibody and complement. The stronger "autoimmune" effect in mice that were immunized with hamster as opposed to mouse zonae is explained by assuming one or more common antigenic structures ("determinants") in mouse and hamster zonae but one that is attached to macromolecular structures in the hamster that are sufficiently different immunologically to produce an enhanced immune response in the mouse. Three of four rabbits that were immunized with solubilized bovine zonae also failed to conceive following mating (Gwatkin and Williams, 1978).

These results indicate that species-specificity of zona antigens is an important consideration. Early reports suggested virtually complete species-specificity among antiovary sera and zonae components (Garavagno *et al.*, 1974; Shivers, 1974). More recently, a number of cross-reactions have been reported. The most interesting are primate zonae and antisera to ovaries or zonae of mice (Gwatkin *et al.*, 1977) and pigs (Sacco, 1977; Shivers and Dunbar, 1977). These last results include strong reciprocal cross-reactions between pig and human ovary with appropriately absorbed antisera prepared in rabbits (Table 2).

These cross-reactions indicate that pig and human zonae share a common antigenic determinant(s) and provide a basis for a simple clinical test for autoantibodies to zona pellucida antigen(s) in women, namely, exposure of pig ova to a patient's serum followed by fluorescein-conjugated antihuman IgG and examination for fluorescence. Using this method Shivers and Dunbar (1977) examined sera from 22 infertile women selected from the World Health Organization Serum Reference Bank. As seen in Table 3, 32% of the sera produced very strong fluorescence and six were negative. Two "zonae-positive" women subsequently conceived. Sera from an unspecified number of fertile women were negative. Obviously, much additional study is required, but the data obtained so far strongly indicate autoantigenicity of zona antigen(s) in some women. The results also have other biomedical implications. They may provide a test for one type of possible immunological infertility in women, a possible relation of such autoimmunity

TABLE 2 Antigens in Pig and Human Ovaries and Pig Ova[a]

Antisera	Antigens		
	Pig Ovary[b]	Human Ovary	Pig Ova[c]
Antiserum to pig ovary			
Unabsorbed	8 to 12	4 to 6	2
Absorbed with pig kidney and spleen	4	2	2
Antiserum to human ovary			
Unabsorbed	2 to 4	9 to 12	2
Absorbed with pig kidney and spleen	2	3	2

[a]From Shivers and Dunbar, 1977, with permission. Copyright 1977 by the American Association for the Advancement of Science.
[b]The results are expressed as the maximum numbers of precipitin bands formed in agar gel double diffusion tests. Whether the common antigens between pig and human ovaries are identical cannot be determined from these experiments.
[c]Saline homogenates of zona-coated eggs were tested against antisera. Approximately 200 eggs were used per well in diffusion tests.

TABLE 3 Autoantibodies in the Zona Pellucida in Sera from 22 Infertile Women. These Sera were Tested on Pig Ova by the Immunofluorescent Antibody Technique[a]

Strength of Reaction[b]	Number of Samples	Individual Sample Numbers[c]
++++	7	1,3,4,20,35,36,42
+++	9	9,12,13,14,22,24,27, 33, 43
++ to 0	6	6,7,8,10,23,24

[a]Shivers and Dunbar, 1977, with permission. Copyright 1977 by the American Association for the Advancement of Science.
[b]Symbols: ++++, strong reaction; +++, moderate to weak reaction; ++ to 0, no reaction.
[c]Patient numbers assigned by the World Health Organization Serum Bank.

to oocyte atresia and menopause, and the potential for development of a contraceptive vaccine from purified zona antigens from other species (Shivers and Dunbar, 1977).

ISOIMMUNITY TO SPERM AND FEMALE INFERTILITY

Attempts to produce an isoimmune response to semen followed by female infertility date from experiments on guinea pigs (Savini and Savini-Castano, 1911). There were also early human trials, notably one with 20 women, some of whom developed immune responses and apparent temporary infertility following intramuscular injections with human semen (Baskin, 1932; reviewed by Jones, 1974). However, more consistent immune responses and reduced fertility were obtained with the advent of Freund's adjuvant in 1957 (Tyler, 1961; Tyler and Bishop, 1963). It is now accepted that isoimmunization of guinea pigs, mice, rabbits, sheep, and cattle with homologous testis, semen, or sperm in Freund's adjuvant emulsion produces an isoimmune response and reduced female fertility. Clinical evidence indicates that isoimmunity to sperm causes infertility in some otherwise normal women (Jones, 1974). Therefore, development of a vaccine from sperm for effective control of female fertility should be practical. To do so, the following studies should be conducted, preferably in an animal model first:

1. isolation, characterization, and ultimate synthesis of the effective isoantigen(s) from sperm;
2. elucidation of the immunological mechanism of antifertility action including essential step or steps in reproduction blocked;
3. development of a more effective, benign adjuvant;
4. development of a reliable secondary test for monitoring immunity in relation to infertility, preferably circulating antibody titers;
5. development of a means for reversing or bypassing the immunological infertility; and
6. a thorough examination for immunological and other possible side effects.

In our laboratory, we have used the rabbit as a model system to examine the first three of these requirements.

As outlined above, antibodies have the potential for adverse action on sperm function at various points in the female genital tract. Such action could result from sperm agglutination, C′-dependent sperm immobilization, sperm receptor blocking, or a combination of these. In an attempt to distinguish among these possibilities, Metz and Anika (1970) initiated

TABLE 4 Cleavage of Rabbit Eggs after Intravaginal Artificial Insemination with Semen Treated with Fab Goat Antirabbit Semen Globulin[a]

Experiment Number[b]	Fab Immune Globulin-Treated Semen			Fab Control Globulin-Treated Semen		
	Cleaved/ Total Eggs	Percent Cleaved	Number of Corpora Lutea	Cleaved/ Total Eggs	Percent Cleaved	Number of Corpora Lutea
1a	0/5	0	10	5/5	100	8
1b	0/7	0	7	9/9	100	8
2a	0/6	0	7	5/6	83	5
2b	0/7	0	8	6/6	100	6
TOTALS	0/25	0	32	25/26	96	27

[a]From Metz, 1972, with permission.

[b]Experiment designation: In "a" experiments, globulin was dialized with Hanks solution; in "b" experiments, globulin was dialized with saline; 1 and 2 experiments indicate different pooled semen suspensions.

a systematic study of the effects of antibody fragments on sperm function in the female tract. Rabbit semen was pretreated with Fab antisperm antibodies of guinea pig (Metz and Anika, 1970) or goat (Metz, 1972) origin and then artificially inseminated into female rabbits.

The pretreated sperm showed markedly reduced fertility in intravaginal artificial insemination experiments (Table 4). This reduced fertility is explained by failure of antibody-treated sperm to pass through the cervix. Fiftyfold fewer sperm treated with Fab antibody were recovered from the upper tracts (uteri, oviducts) of inseminated rabbits than were Fab-exposed control sperm (Table 5). This apparent failure of cervical passage by sperm pretreated with Fab antibodies implies an immunological block to cervical passage, possibly by inhibition of a sperm enzyme that normally depolymerizes cervical mucus to provide passage for the sperm. In this case, the use of Fab antibody clearly eliminates sperm agglutination and complement-dependent sperm immobilization, two mechanisms that have been invoked to explain immunological inhibition of sperm passage through the cervix in certain infertile women.

To examine for additional steps in sperm functions that are vulnerable to Fab antibody inhibition, the cervix was bypassed by intrauterine insemination. Again, sperm pretreated with Fab antibody had reduced fertility compared to controls (Table 6). This demonstrates a second immunological block to conception in addition to cervical passage. The nature of this block is unknown. Possibilities include inhibition of uterotubal passage, inhibition of capacitation or of the acrosome reaction, and blocking of essential sperm enzymes or receptors involved in sperm–egg interaction. Clearly, sperm–egg interaction is vulnerable to antibody inhibition, for when capacitated sperm that have been pretreated with Fab antibodies are brought to the normal site and time of sperm–egg interaction by intratubal insemination of ovulated females, conception is again reduced (Table 7; Metz, 1973).

The effects of Fab antisperm antibody described above were obtained by using antisperm antibodies that were prepared in heterologous species (guinea pig, goat). Therefore, they do not necessarily reflect possible isoantibody action. Unfortunately, all of the experiments have not been repeated with isoantisera. However, Menge (1971) obtained reduced sperm numbers in uterine flushings following intravaginal artificial insemination of rabbits with native antirabbit sperm isoantibody-pretreated semen. Whether the apparent failure of cervical passage of sperm resulted from mechanical trapping (e.g., sperm agglutination), complement-dependent immobilization, or antibody blocking of a specific sperm receptor(s) is uncertain. Morphologi-

TABLE 5 Total Number (×100) of Spermatozoa Recovered from Rabbit Oviducts and Uteri after Artificial Insemination with Fab Guinea Pig Antirabbit Semen Antibody-Pretreated Semen[a]

	Number of Immune Fab, by Experiment Number					Number of Control Fab, by Experiment Number				
Recovery Site	1	2	3	4	5	1	2	3	4	5
Oviducts	0	52.8	23.7	12.8	0	50.4	27.9	16.8	1.1	114.4
Uteri	28	39.6	45	0	19.5	2,173	2,370	78.8	563.8	6,780
TOTALS, each rabbit	28	92.4	68.7	12.8	19.5	2,223.4	2,397.9	85.6	564.9	6,894.4
TOTALS, experiments 1–5			211.4					12,176.2		
AVERAGE, experiments 1–5			42.3					2,435.2		

[a]Data from Metz, 1972, with permission.

TABLE 6 Cleavage of Rabbit Eggs after Intrauterine Artificial Insemination with Semen Treated with Fab Goat Antirabbit Semen Globulin[a]

Experiment Number	Immune Globulin-Treated Semen		Control Globulin-Treated Semen	
	Cleaved/ Total Eggs	Percent Cleaved	Cleaved/ Total Eggs	Percent Cleaved
1	0/11	0	6/8	75
2	0/4	0	2/2	100
3	3/7	43	3/3	100
4	1/12	8	3/5	60
5	0/5	0	0/3	0
6	2/14	14	5/7	70
TOTALS	6/53	11	19/28	68

[a]From Metz, 1972, with permission.

cal or immunofluorescence examination of recovered sperm could provide insight (Russo *et al.*, 1975) into immunological immobilization. Apart from possible effects on sperm transport, it is clear that Fab isoantibodies to whole sperm can inhibit fertilization rather directly, as demonstrated by inhibition of fertilization in *in-vitro* insemination experiments (Table 8) (Russo and Metz, 1974a).

TABLE 7 Cleavage of Rabbit Eggs Following Intratubal Artificial Insemination with Capacitated Sperm Treated with Fab Guinea Pig Antirabbit Semen Globulin[a]

Treatment	Number of Oviducts	Number of Cleaved/ Total Eggs	Percent Cleaved
Guinea pig globulin			
Immune Fab	10	0/34	0
Control Fab	10	18/27	66.6
Saline			
Capacitated sperm	9	16/33	48.8
Uncapacitated sperm	6	0/28	0

[a]From Metz, 1973, with permission.

TABLE 8 Cleavage of Normal Rabbit Ova *In Vitro* Following Exposure to Capacitated Spermatozoa Pretreated with Fab Antiepididymal Sperm Isoantibody[a]

Experiment Number	Immune Globulin[b]	Control Globulin[c]	Saline[d]	Uninseminated Ova[e]	Capacitator Ova[f]
1	0/9[g]	3/7	4/8	0/5	4/4
2	0/2	2/7	2/8	0/2	6/6
3	0/2	1/3	1/1	0/3	6/10
4	1/14	3/8	2/5	1/5	3/3
5	0/3	3/6	5/8	0/1	3/4
TOTALS	1/30	12/31	14/30	1/16	22/27
PERCENT CLEAVED	3.3	39	47	6	81

[a]From Russo and Metz, 1974a, with permission.
[b]Ova inseminated with capacitated sperm pretreated with Fab antiepididymal antibody.
[c]Ova inseminated with capacitated sperm pretreated with Fab control globulin.
[d]Ova inseminated with capacitated sperm and saline.
[e]Uninseminated ova cultured in synthetic medium as controls for parthenogenic cleavage and ova fragmentation.
[f]Ova from the female providing the capacitated sperm. Cleavage, i.e., fertilization of these ova, confirms capacitation of sperm in the capacitated female.
[g]Cleaved ova from capacitator female/total ova.

Such inhibition by Fab isoantibodies implies a direct or indirect blocking of some specific sperm isoantigenic substance that is essential for fertilization. Among possible essential substances, three sperm acrosomal enzymes rank high. The three enzymes, *hyaluronidase, acrosomal esterase(s),* and *acrosin,* are believed to act sequentially to create a passage for the sperm through the three extracellular coats of the egg: the cumulus oophorous, the corona radiata, and zona pellucida, respectively. Because these enzymes are easy to study and apparently play an essential role in reproduction, two of them (hyaluronidase and acrosin) have been examined extensively in several laboratories.

Hyaluronidase

The cumulus-dispersing action of hyaluronidase and its inhibition by antisera (Figures 6–11) have long been known (Metz *et al.,* 1972). Hyaluronidase can be autoantigenic in guinea pigs (Katsh, 1960) and probably in rabbits, rhesus monkeys (Metz, 1973), and men as evi-

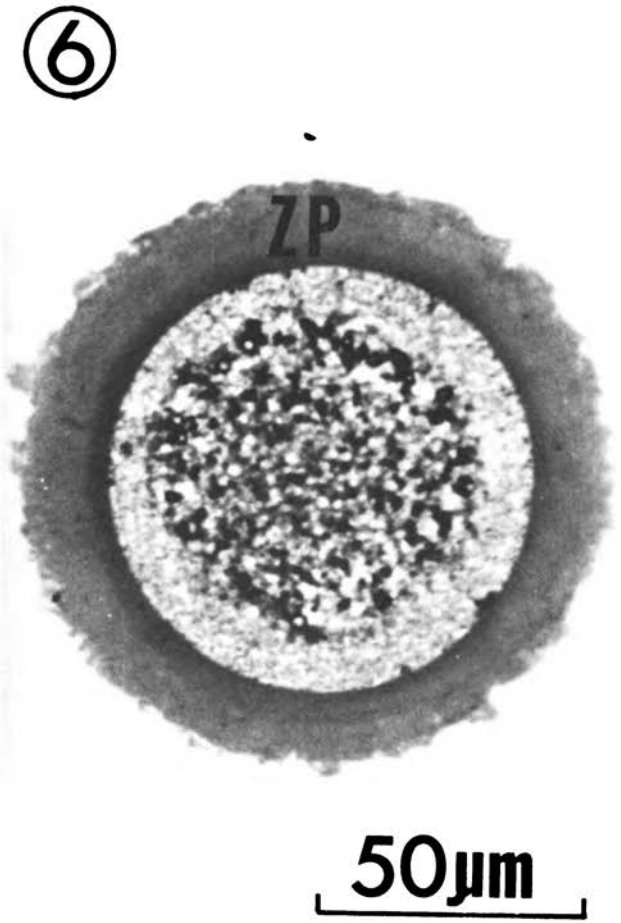


FIGURE 6 Section (1 µm) of human egg pretreated with rabbit antipig zona globulin and inseminated with human semen. Discussed in Shivers, 1979.

denced by appearance of hyaluronidase-inhibiting activity in sera following vasectomy in some men (Metz and Mumford, unpublished). Accordingly, it is not surprising that isoantisera to rabbit sperm inhibit sperm hyaluronidase (Metz *et al.*, 1972). Auto- and isoantigenicity of sperm hyaluronidase imply a sperm-specific isozymic form of the enzyme. This is confirmed by biochemical studies that show im-

FIGURE 7 Section (1 μm) of human egg pretreated with control rabbit globulin and inseminated with human semen. ZP = zona pellucida. Discussed in Shivers, 1979.

munological and pH optima differences between hyaluronidases of testicular and somatic origin (DeSalegui *et al.*, 1967; Katsh, 1960). Thus, antihuman semen rabbit serum inhibits human sperm hyaluronidase activity but not human serum hyaluronidase (Castro and Metz, 1972). Finally, antibody inhibition of sperm hyaluronidase activity is highly species-specific. As seen in Table 9 (Metz, 1973), such

specificity obtains even between human and chimpanzee hyaluronidases, although not between sheep and goats (Morton, 1977).

From the above it is clear that sperm hyaluronidase is a sperm-specific isoenzyme and an auto- and isoantigen. Moreover, isoantibodies to hyaluronidase inhibit the hydrolytic activity of the enzyme and its apparently essential biological function in reproduction, namely, sperm penetration of the cumulus (Metz *et al.*, 1972). These properties of sperm hyaluronidase fulfill the logical requirements for an antifertility vaccine from sperm.

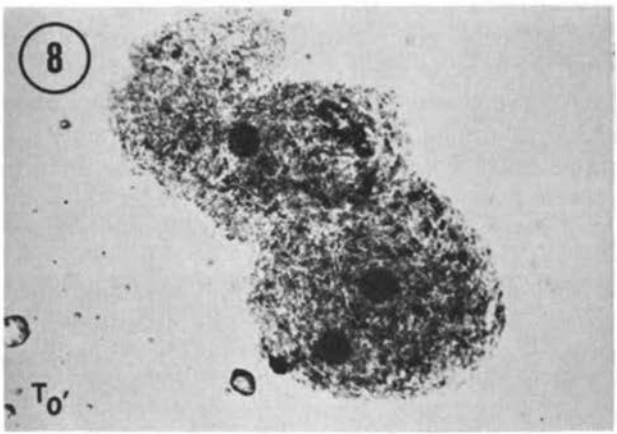
To test for such action, three types of experiments were performed using isoantibodies to purified rabbit sperm hyaluronidase: *in-vitro* insemination of eggs from normal females with capacitated sperm pretreated with Fab antihyaluronidase IgG isoantibody; intravaginal artificial insemination of normal females with sperm pretreated with Fab antihyaluronidase IgG; and intravaginal artificial insemination of females actively isoimmunized with purified rabbit sperm hyaluronidase. As seen in Table 10, capacitated sperm pretreated with Fab antihyaluronidase IgG antibody yielded markedly reduced fertilization *in vitro* (Dunbar *et al.*, 1976). This inhibiting action correlated with failure of cumulus dispersion.

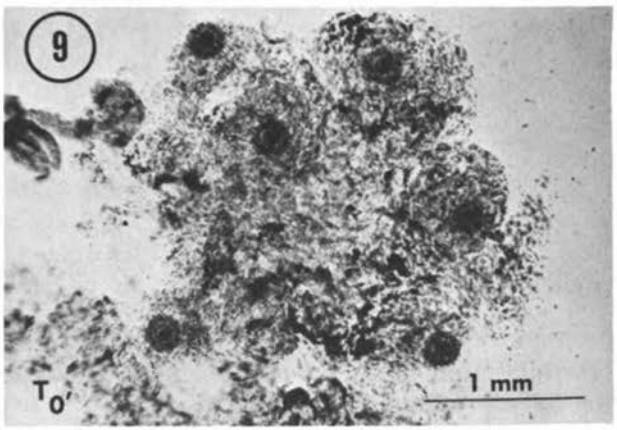
In spite of such marked inhibition of fertilization *in vitro, in-vivo* conception was not significantly inhibited (Metz, O'Rand, and Suarez, unpublished). Table 11 presents data from experiments in which normal virgin female rabbits were artificially inseminated intravagi-

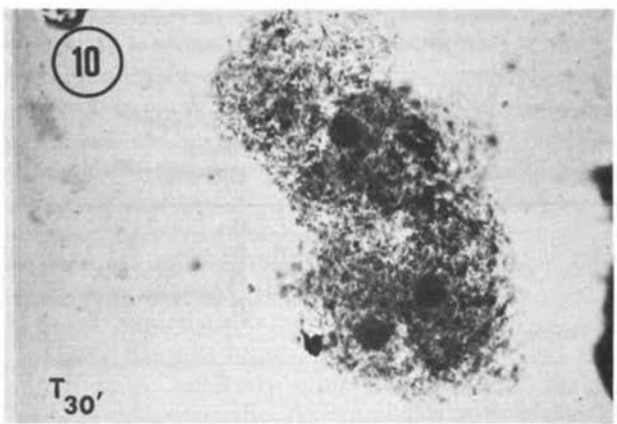
TABLE 9 Inhibition of Cumulus-Dispersing and Hyaluronidase Activity by Rabbit Antihuman Semen Antibody[a]

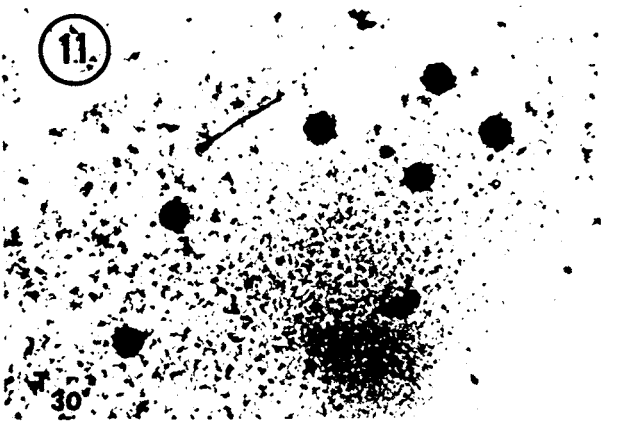
	Cumulus Dispersion		Hyaluronidase TRU's[b] Inhibited per Milligram of Rabbit Globulin	
Sperm or Hyaluronidase	Rabbit Antihuman Semen Globulin	Control Rabbit Globulin	Rabbit Antihuman Semen Globulin	Control Rabbit Globulin
Human	–	+	0.1	0
Chimpanzee	+	+	0	0
Rhesus	+	+	0	0
Rabbit	+	+	0	0
Commercial bovine	+	+	—	—

[a]From Metz, 1973, with permission.
[b]TRU = turbidity-reducing units.


8
$T_{0'}$


9
$T_{0'}$
1 mm


10
$T_{30'}$



FIGURES 8, 9, 10, and 11 Inhibition of rabbit sperm cumulus-dispersing action by Fab antirabbit globulin. Figure 8 shows cumulus in sperm-Fab antisperm globulin at time of mixing (T_0'). Figure 9 shows cumulus in sperm-Fab control globulin at time of mixing (T_0'). Figure 10 is the same as Figure 8 after 30 minutes of incubation (T_{30}'). Figure 11 is the same as Figure 9 after 30 minutes of incubation (T_{30}'). (From Metz *et al.*, 1972.) Figures reproduced with permission.

nally with ejaculated sperm that had been pretreated with Fab anti-hyaluronidase IgG. Failure to obtain reduced fertility in this *in-vivo* insemination experiment could be explained by the fact that only approximately 50% of the readily extractable hyaluronidase is accessible to Fab antibody (Metz *et al.*, 1972). Moreover, strongly bound hyaluronidase (O'Rand and Metz, 1976) may also be inaccessible. Furthermore, most or all of the Fab antihyaluronidase Ig could be bound to the hyaluronidase that is released from sperm prior to the acrosome reaction (Talbot and Franklin, 1974). Then, following sperm passage and before or after capacitation in the female genital tract, most or all of the Fab antibody–hyaluronidase complexes could be lost from the sperm. Clearly, no excess antihyaluronidase Ig would be expected at the normal site of sperm–egg interaction in this experiment. However, females actively isoimmunized with purified sperm hyaluronidase would be expected to have antihyaluronidase Ig of tract and follicular fluid origin (Cabot and Oliphant, 1978) near ovulated eggs.

Such antihyaluronidase Ig should inhibit some if not all essential hyaluronidase activity of the very few sperm (10^3 in the rabbit) that are

TABLE 10 Cleavage of Rabbit Eggs Inseminated *In Vitro* with Capacitated Spermatozoa Pretreated with Fab Antihyaluronidase Isoantibody[a]

Experiment Number	Groups					
	I (Spermatozoa + Anti-hyaluronidase)	II (Spermatozoa + Preimmune Ig)	III (Spermatozoa + Adjuvant Control Ig)	IV (Spermatozoa + Culture Medium)	V (Partheno-genesis Control)	VI (Eggs from Capacitators)
1	0/15 (±)	10/10 (+++)	—	8/12 (+++)	0/5 (−)	11/12
2	1/12 (++)	5/11 (+++)	—	3/5 (+++)	0/3 (−)	11/11
3	1/11 (±)	5/7 (+++)	7/11 (++)	4/5 (+++)	0/2 (−)	8/8
	0/6 (±)	1/3 (++)	3/6 (++)	0/4 (+++)	0/1 (−)	1/1
TOTALS	2/44	21/31	10/17	15/26	0/11	31/32
PERCENT CLEAVED	5	68	59	58	0	97

[a]From Dunbar *et al.*, 1976, with permission.

[b]Symbols in parentheses indicate degrees of cumulus dispersion at time of scoring for cleaved eggs: −, no cumulus dispersion; +++, complete dispersion.

TABLE 11 Fertility of Normal Rabbits Intravaginally Inseminated with Semen Pretreated with Fab Antihyaluronidase Isoantibody Globulin[a]

Fertility	Immune Fab	Control Fab
Total	24/43[b]	30/49
Percent cleaved eggs	56	61

[a]Metz, O'Rand, and Suarez, unpublished data.
[b]Cleaved/total eggs. Six females were inseminated with Fab antihyaluronidase globulin and six with Fab control globulin (from a female rabbit that was injected with Freund's adjuvant-saline). Excess antihyaluronidase globulin was demonstrated in treated semen supernatant.

normally present near the egg at fertilization (Austin, 1965; Metz and Anika, 1970). In addition, rabbits isoimmunized with purified hyaluronidase in FCA (Freund's complete adjuvant) can develop rabbit sperm immobilizing activity (Russo *et al.*, 1975). This could have a deleterious effect on fertility. Nevertheless, a significant reduction in fertility was not obtained in 15 female rabbits that were isoimmunized with purified rabbit epididymal sperm hyaluronidase.

Data from one experiment are given in Table 12. Females were immunized to high antihyaluronidase antibody titer and artificially inseminated after injection with 75 IU of human chorionic gonadotropin (hCG). Twenty-five to 30 hours later, oviducts were flushed and ova scored for cleavage. As seen in Table 12, both the rabbits immunized with hyaluronidase and the controls injected with Freund's adjuvant saline had comparable high fertilization rates. Morton (1977) also failed to obtain an antifertility effect in female sheep that had been isoimmunized with homologous sperm hyaluronidase.

It seems clear that hyaluronidase is not an effective antifertility vaccine, at least in rabbits and sheep. Sera from some "immunologically infertile" women inhibit human sperm hyaluronidase activity (Metz, 1973), but the low incidence (Boettcher *et al.*, 1977) indicates that isoantibodies to human sperm hyaluronidase are not significantly involved in infertility in women.

Acrosomal Esterase, the Corona-Dispersing Enzyme

Sperm penetration of the rabbit corona radiata is mediated by a "corona-dispersing enzyme," an esterase that is inhibitable by a

TABLE 12 Fertility (Cleaved Eggs) of Rabbits Isoimmunized with Purified Rabbit Sperm Hyaluronidase Following Artificial Insemination[a]

Immunized Females				Control Females			
Rabbit Number	Cleaved/ Total Eggs	Precipitin Band	Hyaluronidase Inhibition	Rabbit Number	Cleaved/ Total Eggs	Precipitin Band	Hyaluronidase Inhibition
2	6/10	+	+	1	7/7	–	–
4	9/11	+	+	3	0/8	–	–
6	8/8	+	+	5	6/6	–	–
8	2/2	–	+	7	8/8	–	–
TOTALS	25/31				21/29		
PERCENT FERTILIZED EGGS	81				72		

[a]From Metz, O'Rand, and Dunbar, unpublished data. Female rabbits (four) were immunized with purified rabbit sperm hyaluronidase to high circulating antibody titers; controls (four) were injected with Freund's adjuvant-saline. Twenty-five to 30 hours after hCG injection and artificial insemination, oviducts were flushed and recovered eggs scored for cleavage. Sera were tested for hyaluronidase-inhibiting and immunodiffusion-precipitating activity.

decapacitation factor (Bradford *et al.*, 1976). Immunobiological properties of the esterase have not been reported as yet. Possible involvement of corona-dispersing esterases in some species, including the human, which lack an identifiable corona radiata structure, remains problematical.

Acrosin and Penetration of the Zona Pellucida

Sperm penetration of the zona pellucida is achieved by the action of acrosomal proteinases, notably acrosin. Acrosin is released by the acrosome reaction during corona penetration (Barros *et al.*, 1967; Morton, 1977). After the acrosome reaction, enough acrosin apparently remains bound to the inner acrosomal membrane of the sperm to digest a path through the zona (Stambaugh and Smith, 1976).

Acrosin is inhibited by natural inhibitor(s) in seminal plasma, in the female genital tract, and by trypsin inhibitors (McRorie and Williams, 1974). In rabbits, some successful studies have been conducted on the contraceptive action of acrosin inhibitors in vaginal jellies (Zaneveld *et al.* 1970). However, their effectiveness is probably limited because the main functional acrosin is not exposed until the acrosome reaction occurs at an early step in sperm-egg interaction, a factor that may explain why incubation of ejaculated and capacitated boar sperm with antiacrosin serum did not reduce "halo formation" in the gelatinolysis test (Dietl *et al.*, 1978).

An early immunological study showed inhibition of rabbit sperm protease activity by antisperm sera prepared in goats (Metz, 1972). Apparently, this inhibition was a gross steric effect since Fab antibody was ineffective when TAME (*p*-tosyl-L-arginine) was used as the substrate. Zaneveld and Schlumberger (1972) reached a similar conclusion from other evidence. Tests for isoantigenicity of acrosin are positive, and isoantisera inhibit the enzymatic activity (Morton, 1977). Female sheep that have been actively immunized with ram acrosin may have impaired fertility (Morton, 1977). However, an effect approaching sterility has not been reported.

Lactate Dehydrogenase-X (LDH-X)

Apart from acrosomal enzymes, mammalian sperm possess additional isoenzymes. Among these, lactate dehydrogenase-X (LDH-X) has been examined for isoantigenicity and antifertility vaccine potential. LDH-X ($LDH\text{-}C_4$) consists of four identical sperm-specific "C" subunits, which are different than the subunits of somatic LDH types (Goldberg, 1974).

LDH-X is located intracellularly and on the sperm surface. Sperm surface LDH-X must be intimately associated with the cell membrane because antisera to crystalline LDH-X agglutinate and immobilize (C' present) sperm (E. Goldberg, personal communication, 1978). Unlike sperm hyaluronidase, immunological cross-reactions occur between antisera and LDH-X preparations of distantly related species.

Extensive trials for antifertility vaccine action showed that mice that were immunized with purified LDH-X suffered a significant reduction in fertility (Erickson *et al.*, 1975; Goldberg, 1974), but not complete sterility.

In summary, the sperm-specific isoenzymes, LDH-X, hyaluronidase, and acrosin, have been less than spectacular as potential contraceptive vaccines in females. In practical terms this is disappointing. In scientific terms it is interesting, and it becomes important to establish why, despite the impeccable logic for their predicted success, these vaccines have failed to meet expectations. Although lacking in glamor, studies to answer these questions would almost certainly be rewarding in terms of understanding sperm transport, sperm–egg interaction, and the immunobiology of the female tract.

Although a number of additional sperm-specific isoenzymes are known, they have not been examined for antifertility vaccine action in the female. The list includes sorbitol dehydrogenase, which is known to produce autoimmune aspermatogenesis in the guinea pig (Bishop, 1970).

Remarkably, none of the aspermatogenesis antigens appear to have been seriously tested for antifertility vaccine action in the female, although the one prepared by Katsh *et al.* (1973) produces high titer antibodies (passive hemagglutination reaction) in females.

Isolation of Isoantigens by Direct Fractionation

From the limited antifertility vaccine action of specific sperm enzymes, it appears necessary to fractionate sperm and test components for antifertility action in order to specify the most effective isoantigen(s). A major advance was made by Menge and Protzman (1967), who showed that antibodies to seminal plasma failed to inhibit the fertilizing capacity of rabbit sperm in artificial insemination experiments. More recently, Kummerfeld and Foote (1976) obtained virtual sterility (5% fertilized eggs) following artificial insemination of female rabbits isoimmunized with washed ejaculated sperm, epididymal sperm, and sperm that was pretreated with β-amylase. The antifertility vaccine action of β-amylase-treated sperm is of interest because β-amylase removes some antigenic material, presumably "coating antigens," and at least partially

"capacitates" the sperm (Johnson and Hunter, 1972). Thus, the effectiveness of the β-amylase-treated sperm as an antifertility vaccine suggests that capacitated sperm possess at least one antifertility isoantigen.

The experiments of Menge and Protzman (1967) and Kummerfeld and Foote (1976) imply that the antifertility vaccine antigen(s) of rabbit sperm is an intrinsic sperm antigen. At least one such antigen is likely to be an intrinsic plasma membrane glycoprotein and sperm-immobilizing auto- and isoantigen that is identical or similar to the antigens isolated by O'Rand and Metz (1976) and O'Rand and Porter (1979). However, complement-dependent sperm-immobilizing capability is not a requirement for an antifertility antigen because Fab antisperm antibodies inhibit sperm function effectively but do not immobilize sperm (Metz and Anika, 1970).

For effective purification, isolation, and identification, the antifertility vaccine antigen from sperm must first be solubilized in an antigenically active form. The direct approach should be solubilization and fractionation of the antigen using antifertility vaccine action as the bioassay. Using this approach, Bell and McLaren (1970) obtained reduced fertility in mice that had been isoimmunized with a 30,000-g supernatant of disrupted mouse sperm. More recently, Muñoz and Metz (1978) produced virtual sterility (< 5% cleaved eggs) in female rabbits by isoimmunization with a soluble fraction of sperm that had been disrupted with magnesium chloride ($MgCl_2$) (Table 13). The infertility correlated with high circulating sperm agglutinating, immobilizing, and hyaluronidase-inhibiting antibody titers and with up to five easily resolved precipitin bands in immunodiffusion. The effectiveness of the soluble sperm fraction (98,000-g sperm extract supernate) as an antifertility vaccine implies that this fraction contains one or more antifertility isoantigens or an effective combination of two or more isoantigens.

It should now be relatively easy to isolate at least one antifertility isoantigen from the soluble fraction of rabbit sperm by conventional purification procedures including affinity chromatography (O'Rand and Porter, 1979) and using antifertility vaccine action as a bioassay. Following such isolation, chemical characterization and cellular localization of the antigen should be established, and the mechanism of antifertility action and identification of the steps in reproduction inhibited by immunization should be identified. Comparison of the properties of the rabbit antifertility isoantigens with sperm antigens of other species, especially with respect to species-specificity, e.g., as with the zona antigen (Dunbar and Shivers, 1976), should be undertaken. Comparison with aspermatogenesis autoantigens and with human sperm

TABLE 13 Percentage of Cleaved Ova Recovered from Rabbits that Were Immunized with Different Sperm Extracts[a]

Immunizing Antigen	Percent of Cleaved Ova Recovered	Number of Cleaved Ova/ Total Ova Recovered
Group I, whole sperm	4.4	3/68
Group II, soluble fraction	0.0	0/61
Group III, insoluble fraction	1.6	1/61
Group IV, adjuvant control	96.5	55/57

[a]From Muñoz and Metz, 1978, with permission. Soluble and insoluble sperm fractions were prepared by 0.05M $MgCl_2$ disruption, homogenization, and 98,000-g centrifugation. Only one cleaved ovum among a minimum of nine eggs was recovered from any one female isoimmunized with sperm antigen. In controls, the uncleaved ova were among a minimum of eight cleaved ova. Thus, no isoimmunized female was completely fertile and no control was completely infertile. Each group contained eight females.

auto- and isoantigens, which are now being isolated in several laboratories (Boettcher, 1977), should be of special interest.

SUMMARY

1. Mammalian spermatozoa and ova possess cell-specific autoantigens. These can incite autoimmune responses in the male and female, respectively.

2. Spermatozoa possess several cell-specific isoantigens that can incite immune responses in the female.

3. Auto- and isoantibodies can interfere with gamete function by several mechanisms, both *in vitro* and *in vivo*. These mechanisms include blocking antigenic sites with essential functions (e.g., enzymes, specific receptors), antigen cross-linking producing mechanical trapping (sperm agglutination) or physical barriers (zona precipitation), and complement-dependent cytotoxicity (sperm immobilization, ovum lysis).

4. Purified sperm autoantigens can produce complete male sterility, especially in guinea pigs.

5. Solubilized zona pellucida autoantigen can produce female infertility. It has considerable promise as an antifertility vaccine.

6. Isoantibodies can interfere with sperm function at several levels in the female genital tract.

7. The sperm-specific isoenzymes, hyaluronidase, acrosin, and LDH-X, are effective isoantigens. They incite isoantibodies, which inhibit enzyme activities. However, they are not highly effective as contraceptive vaccines.

8. Isoimmunization of rabbits with a 98,000-g supernatant of disrupted rabbit sperm produces virtually complete infertility. In view of this action of the soluble sperm fraction, one or more specific sperm antifertility antigens should be readily obtained in purified form by appropriate fractionation procedures and using antifertility vaccine action as a bioassay.

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Mechanisms of Hormone Action

ELWOOD V. JENSEN

It has long been known that the growth and function of the reproductive organs are controlled biochemically by steroid sex hormones, which are produced chiefly, but not exclusively, by the ovary in the female and the testis in the male. Gonadal synthesis of sex hormones is stimulated by protein hormones known as gonadotropins, which are produced in both sexes by the anterior pituitary gland. More recently, it has been established that the secretion of gonadotropins is regulated in turn by releasing factors originating in the hypothalamus. Our knowledge of the nature and interrelationship of these various hormones is well advanced and has provided the first rational approach to fertility control by chemical means through the feedback inhibition of gonadotropin secretion by the products of their action on the ovary. In contrast to our knowledge of what the reproductive hormones are and what they do, our understanding of how they do it is more primitive. Still, the last two decades have seen remarkable progress toward the elucidation of biochemical mechanisms of hormone action, suggesting the eventual possibility of achieving fertility control through modulation of processes by which the hormones exert their biologic effects in target cells.

The mechanism by which the steroid sex hormones act in target tissues differs from that of the gonadotropins. As shown in Figure 1, the gonadotropins, like many protein hormones, bind to receptor substances in the plasma membrane of the target cells, an interaction that leads to activation of an adenylate cyclase enzyme system convert-

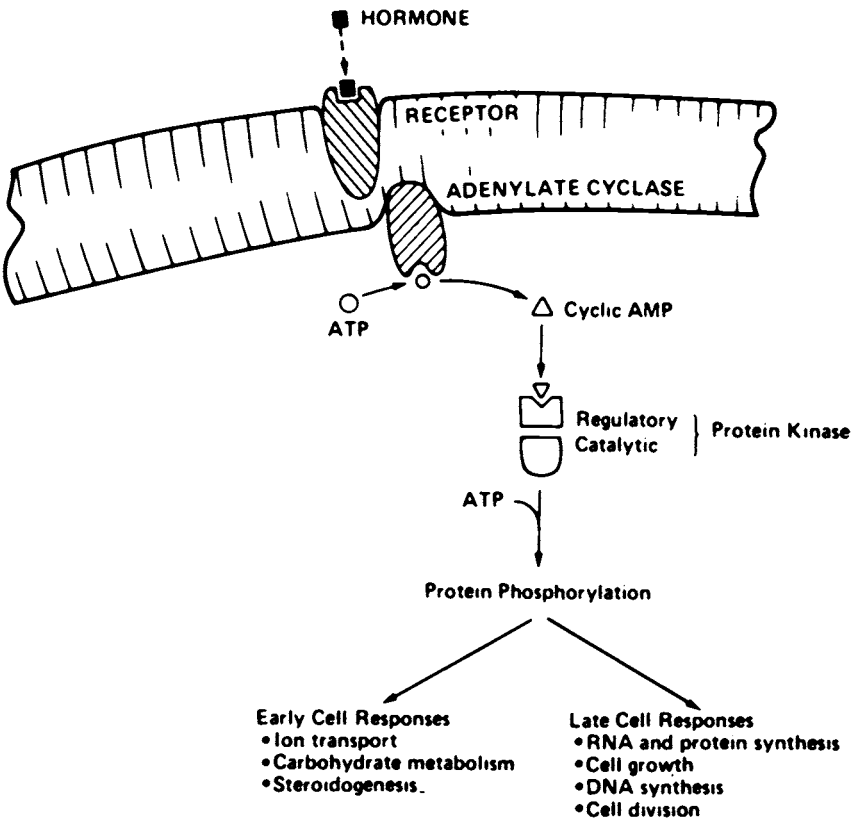

FIGURE 1 Action of gonadotropins on steroidogenic target cells of testis and ovary. Protein hormone interacts with receptor in the plasma membrane, thereby inducing the formation of a second messenger that serves as the intracellular effector of processes that lead to enhanced steroidogenesis. Courtesy of Dr. K. J. Catt.

ing adenosine triphosphate (ATP) to adenosine 3′,5′-monophosphate (cyclic AMP) (Catt and Dufau, 1978). This cyclic nucleotide serves as a "second messenger" within the cell, stimulating the degradation of cholesterol to pregnenolone, presumably through the activation of phosphorylating enzymes. In the case of the steroid sex hormones, the steroid enters the target cell and binds to an extranuclear receptor protein to form a hormone–protein complex, which then delivers the regulatory signal to the cell nucleus where biologic action is initiated (Figure 2). The translocation of the hormone–receptor complex to the nucleus appears to result from the ability of the steroid, through its

binding to the receptor protein, to induce the conversion of the receptor to an activated form that has a strong tendency to bind in the chromatin and in some way enhance processes involved in RNA production.

This paper, which is limited to considerations of steroid sex hormones (estrogens, progestins, androgens), will summarize the experimental observations leading to current concepts of hormone–receptor interaction, discuss the influence of hormone–receptor complexes on RNA synthesis in the nucleus, and, finally, describe our recent success in preparing antibodies to the estrogen receptor protein, which should provide new insight into unresolved questions concerning receptor-mediated hormone action, using the techniques of immunochemistry. In this brief overview, no attempt will be made to include complete documentation of the variety of contributions from many investigators.

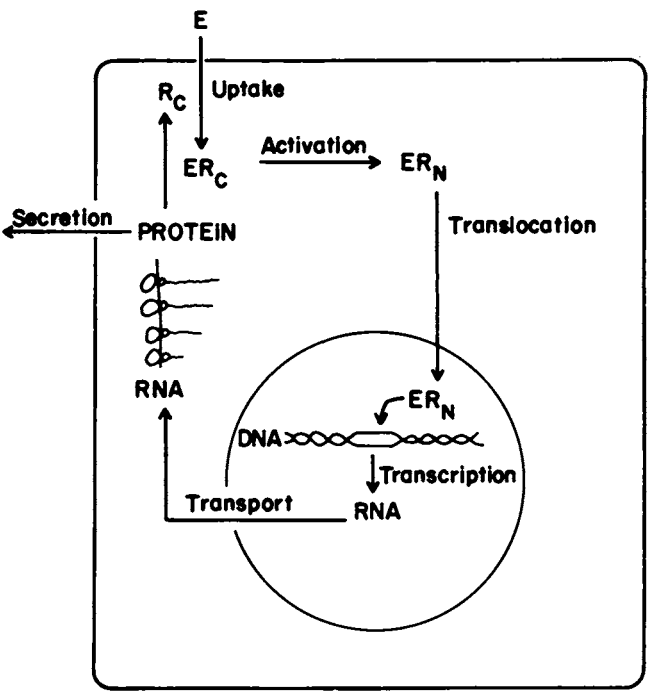

FIGURE 2 General representation of estrogen (E) interaction pathway and biochemical responses in target cells, R_c = cytosol receptor protein; ER_c = cytosol estrogen–receptor complex; ER_N = nuclear estrogen–receptor protein.

Detailed reference to individual literature reports can be found in the reviews and monographs cited.

HORMONE–RECEPTOR INTERACTION

The recognition that steroid hormones exert their biologic effects in combination with specific receptors and the subsequent elucidation of the pathway of their interaction in target cells has come chiefly from experiments in which tritiated steroids serve as radioactive markers for the receptor proteins to which they bind (Gorski and Gannon, 1976; Jensen, 1977; Jensen and DeSombre, 1972, 1973; King and Mainwaring, 1974; Liao, 1975; O'Malley and Schrader, 1976; Williams-Ashman and Reddi, 1971). Because the first steroids to be available in suitably labeled form were the estrogens, the main features of hormone–receptor interaction were established for estradiol in the immature rat uterus, with subsequent extension of the estrogen model to other classes of steroid hormones. More recently, however, much of our detailed knowledge of the molecular biology of the action of hormone–receptor complexes in the nucleus has come from other experimental systems, including the chick oviduct and frog liver.

The development of basic concepts of the interaction pathway followed a series of experimental observations over a 12-year period, beginning in 1958 when tritiated estrogens of high specific activity were first synthesized. The fact that the female reproductive tissues contain a characteristic estrogen-binding component, called estrogen receptor or estrophilin, was first indicated by their striking ability to take up and retain tritiated estrogens, either after the administration of physiologic doses *in vivo* or, later, on exposure of excised tissues to the hormone *in vitro* (Figure 3). It is now recognized that most, if not all, mammalian tissues contain small amounts of estrogen receptor and that the unique characteristic of the hormone-dependent tissues is the magnitude of their estrophilin content. Estradiol combines reversibly with the receptor and initiates growth of the immature rat uterus without itself undergoing chemical change, thereby suggesting that the action of the hormone involves its interaction with macromolecules rather than participation in reactions of steroid metabolism, as had once been assumed.

The specific uptake and retention of estradiol by target tissues, both *in vivo* and *in vitro,* can be inhibited by a class of compounds that includes nafoxidine, clomiphene, Parke Davis CI-628, and tamoxifen (Figure 3). These substances have provided a valuable means for distinguishing specific binding of hormone to receptor from the nonspecific binding that estradiol shows with all tissues or with other

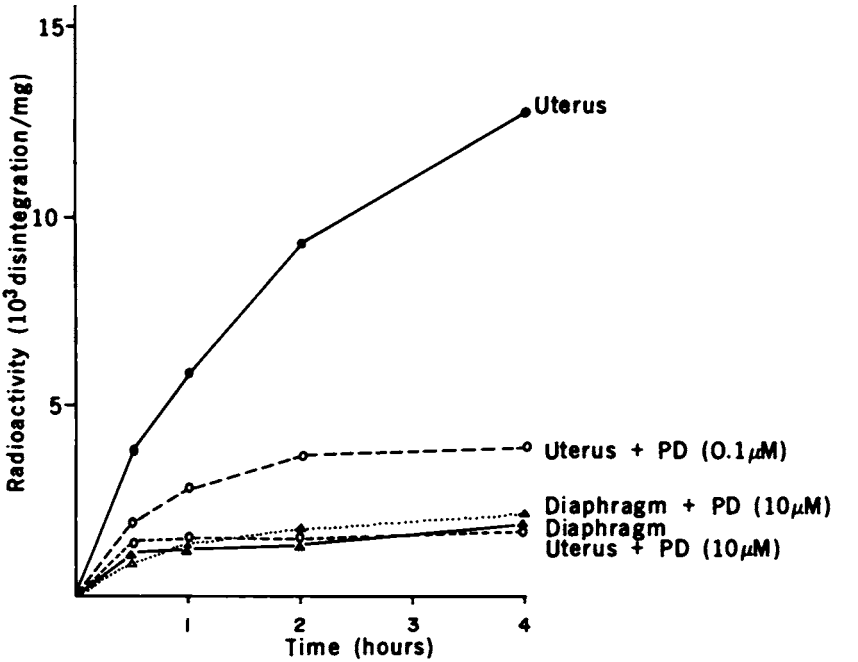

FIGURE 3 Concentration of radioactivity in uterine horns and hemidiaphragms of immature rats after exposure to 0.12 nM tritiated estradiol at 37°C in Krebs-Ringer-Henseleit glucose buffer, pH 7.3, in the presence and absence of the estrogen antagonist, Parke Davis CI-628 (PD). Five specimens per time point. From Jensen *et al.*, 1972.

macromolecules in broken cell systems. The correlation observed between the reduction in hormone incorporation and the inhibition of uterine growth when different amounts of nafoxidine are administered along with estradiol to the immature rat provided the first evidence that binding of hormone to receptor actually is involved in its biologic action. In contrast, actinomycin-D and puromycin, substances that prevent the uterotrophic action of estradiol, show no inhibition of the characteristic uptake and retention of hormone, suggesting that the binding of estradiol to receptor is an early step in the uterotrophic process, apparently initiating a sequence of biochemical events that can be blocked at later stages by these inhibitors of RNA and protein synthesis.

As shown both by centrifugal fractionation of homogenates and by autoradiography (Figure 4), most (70%–80%) of the radioactive estradiol taken up by the uterus *in vivo* or at physiologic temperature *in*

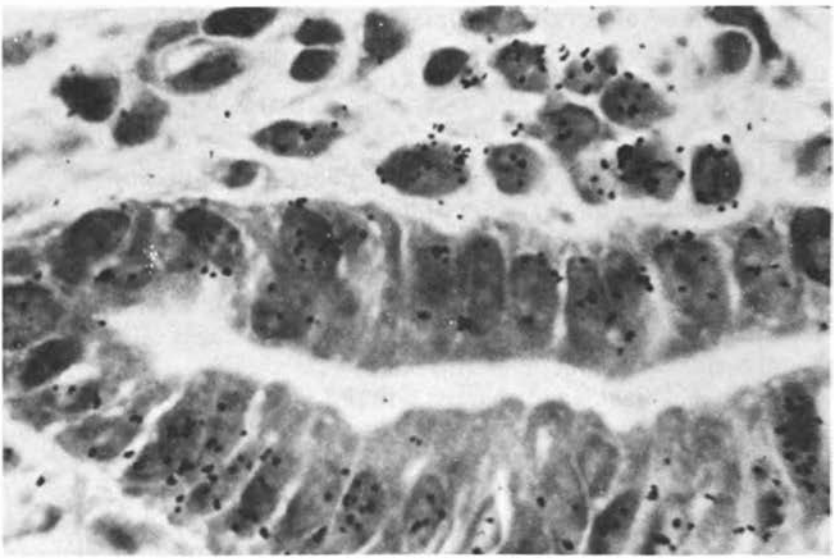

FIGURE 4 Autoradiograph of a frozen section of rat uterine endometrium excised 2 hours after subcutaneous injection of tritiated estradiol in saline. Courtesy of Dr. W. E. Stumpf.

vitro becomes localized in the nucleus with a smaller amount present in the cytosol. After exposure of uteri to estradiol at 2°C *in vitro*, the incorporated steroid is predominately extranuclear, shifting to the nucleus as the tissues are warmed to physiologic temperature. In both intracellular locations, the estradiol is present in combination with a receptor protein, and the technique of sucrose gradient ultracentrifugation has provided a valuable means for identifying and distinguishing these steroid–protein complexes (Figure 5). The extranuclear complex sediments as an 8-S entity, reversibly dissociated into a 4-S subunit in sucrose gradients of high ionic strength, while the estradiol in the nucleus is extracted by salt solutions as a 5-S steroid–protein complex. The 8-S extranuclear complex, or its 4-S subunit, is formed by direct addition of tritiated estradiol to uterine cytosol in the cold, but no 5-S nuclear complex is produced by hormonal treatment of the nuclei unless uterine cytosol is also present. Incubation of nuclei with an estradiol–cytosol mixture at temperatures of 25°C to 37°C gives rise to a 5-S nuclear complex, indistinguishable from that formed *in vivo*. Thus, it appears that estrophilin is not present in the nucleus before the uterine cell is exposed to estrogen and that the estrogen–receptor

complex found in target cell nuclei of hormone-treated animals is of cytoplasmic origin.

The foregoing observations, taken with the finding that the administration of estradiol to immature rats causes a temporary depletion of their extranuclear uterine receptor, which is then restored by resynthesis, led to the proposal of a two-step interaction mechanism in which the steroid hormone enters the target cell, binds to an extranuclear receptor protein, and induces its temperature-dependent translocation to the nucleus where it associates with chromatin (Figure 6). Later it was found that the temperature-dependent process in this translocation phenomenon is the estrogen-induced conversion of the native (4-S) form of the receptor protein to the nuclear (5-S) form, a transformation that can be effected simply by warming an estradiol–cytosol mixture. The 5-S estradiol–receptor complex thus produced, like that extracted

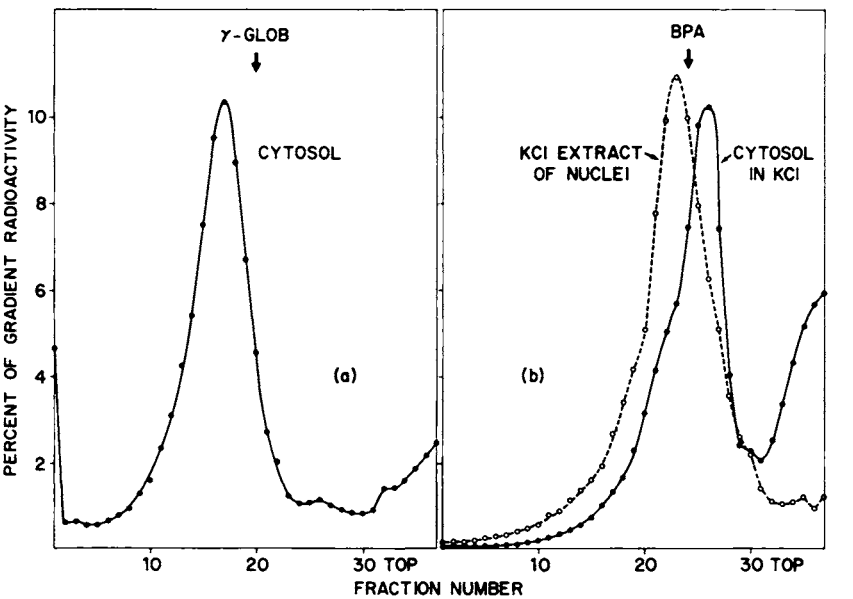

FIGURE 5 Sedimentation patterns of radioactive estradiol-receptor complexes of rat uterine cytosol and nuclear extract (400 mM potassium chloride) from uteri of immature rats excised 1 hour after the subcutaneous injection of 100 ng (20.8 μCi) tritiated estradiol in saline. To saturate its receptor capacity, the cytosol fraction was made 5 nM with additional tritiated estradiol. γ-GLOB and BPA indicate positions of bovine immunoglobulin (7.0 S) and bovine plasma albumin (4.6 S) markers. Gradients are: (a) 10% to 30% sucrose without added salt; (b) 5% to 20% sucrose containing 400 mM potassium chloride. From Jensen and DeSombre, 1973.

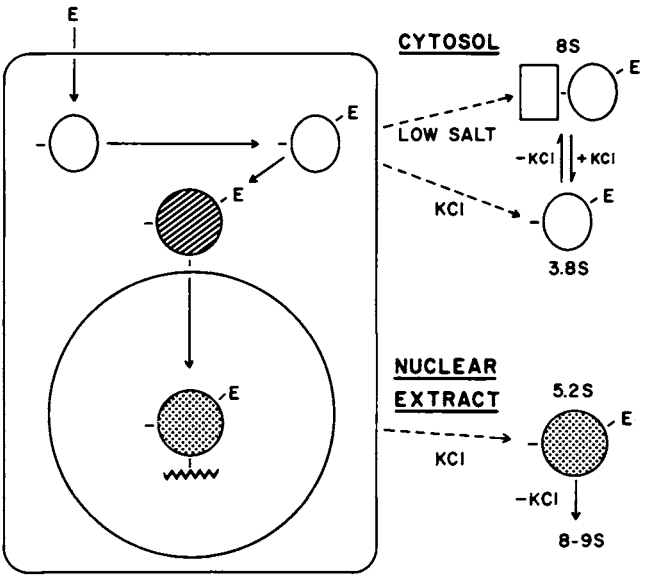

FIGURE 6 Schematic representation of interaction pathway of estradiol in target cell. Diagram at left indicates estradiol (E) combining with estrophilin to induce receptor activation followed by translocation of the transformed complex to bind to chromatin in the nucleus. Diagram at right indicates sedimentation properties of complexes extracted from cell after homogenization.

from uterine nuclei of estrogen-treated animals, has two properties not shown by the native form: it can bind to isolated nuclei or chromatin, and, as described below, it can enhance the RNA polymerase activity of isolated nuclei from hormone-dependent tissues and tumors. Because of these newly acquired properties, the hormone-induced, temperature-dependent transformation of the native receptor to the biochemically functional nuclear form is known as receptor activation.

Although the molecular details of hormone-induced activation of estrophilin are not completely understood, the reaction has been shown to follow second-order kinetics, which is suggestive of dimerization. How such a process endows the activated receptor with the ability to bind to chromatin as well as to DNA and other polyanions is not completely clear. Nor is it certain that activation, which can be effected simply by warming an estradiol–cytosol mixture, may not actually take place in the nucleus in the living cell. The exact nature of

the acceptor site to which the activated hormone–receptor complex binds in the chromatin is another question that requires elucidation.

Investigations in many laboratories have established that other classes of steroid hormones interact with their respective target tissues by similar translocation to the nucleus of an initial extranuclear hormone–receptor complex. Steroid-induced conversion of the receptor protein to an active form that can bind to chromatin is a common feature. However, only with the estrogens has an increase in sedimentation rate been found to accompany hormone-induced activation of the receptor. Still, in the case of the progesterone receptor of chick oviduct, the extranuclear receptor protein, called progestophilin, has been separated into two progesterone-binding subunits, both of which are incorporated equally into oviduct nuclei on hormone treatment *in vivo* or *in vitro*. Component A binds nonspecifically to DNA but not to chromatin, whereas component B, which does not bind to DNA, shows a specific affinity for chromatin from target tissues. This selective affinity appears to reside in the nonhistone proteins of the chromatin. On the basis of these and other observations, a modified version of the intracellular interaction mechanism has been proposed (Figure 7), in which a dimeric progesterone–receptor complex is translocated to the nucleus where concerted interaction with both DNA and nonhistone proteins leads to an activation of template sites for RNA synthesis. Extension of this dual interaction model to other classes of steroid hormones awaits experimental verification.

STEROID–RECEPTOR COMPLEXES AND RNA SYNTHESIS

For all classes of steroid hormones, an early response is the enhancement of RNA synthesis in target cells. In the case of the primary stimulation of a hormone-deprived tissue, such as the action of estrogen in the immature rat uterus, incorporation of labeled precursors into all types of RNA is rapidly accelerated, whereas in the secondary stimulation of a previously developed tissue, such as the action of either estrogen or progesterone in the estrogen-pretreated chick oviduct, the predominant effect of the steroid hormone is enhanced production of messenger RNA's for specific proteins. There have been many experiments concerning the molecular biology of the effect of steroid hormones on transcription (Jensen, 1977; Jensen *et al.*, 1974; King and Mainwaring, 1974; Mueller, 1971; O'Malley and Means, 1974; O'Malley and Schrader, 1976; Williams-Ashman and Reddi, 1971; Yamamoto and Alberts, 1976). Consequently, a detailed account of

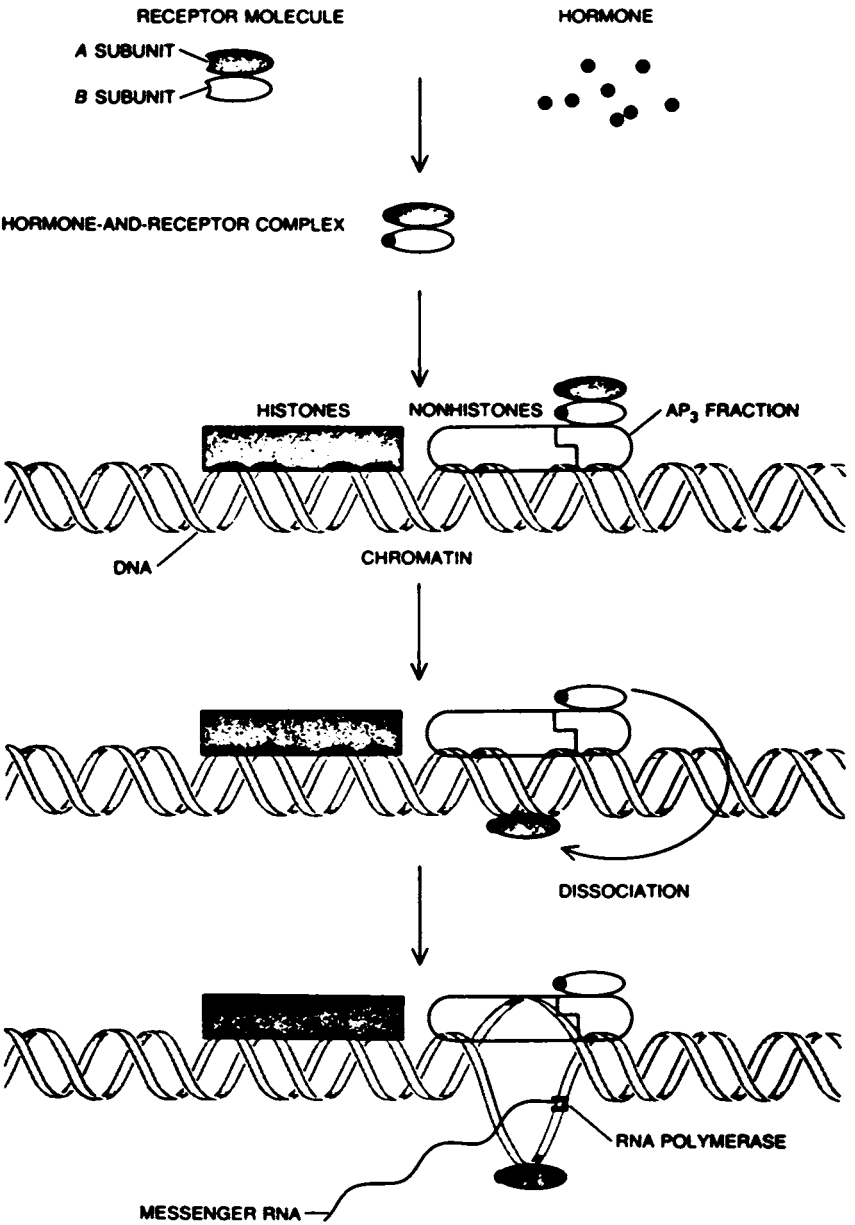

FIGURE 7 Schematic representation of the mechanism of gene activation by interaction of dimeric progesterone-receptor complex with target cell chromatin. From O'Malley and Schrader, 1976.

them is beyond the scope of this paper, which will be limited to a consideration of the evidence for the participation of steroid–receptor complexes in the tissue-specific stimulation of RNA synthesis and the importance of receptor activation in this phenomenon.

Related to the enhancement of RNA synthesis, which is believed to mediate the hormonal induction of growth in reproductive tissues, are effects on the RNA polymerase system. Administration of testosterone to castrated rats leads to an increase in the ability of their prostatic nuclei to incorporate labeled precursors into RNA, while a similar enhancement of RNA polymerase activity is observed in uterine nuclei isolated from rats injected with estradiol. The template function of uterine chromatin from estrogen-treated rats or rabbits or of oviduct chromatin from progesterone- or estrogen-treated chicks is increased over that of corresponding chromatins from untreated animals. After estrogen injection, both RNA polymerase I and polymerase II are stimulated in rat uterine nuclei but with different time patterns: polymerase II activity increases at 15 to 30 minutes, and then subsides to be followed by a second rise after 2 to 3 hours, whereas polymerase I activity, as well as template function of the uterine chromatin, shows a prolonged enhancement, which is first detectable at about 1 hour. The transient early increase in polymerase II activity is not in itself sufficient for hormonal response, because agents such as nafoxidine or estriol, which induce the transient stimulation of polymerase II but not the prolonged effect on both polymerase I and polymerase II, do not promote significant uterine growth.

The participation of hormone–receptor complexes in the enhancement of RNA synthesis in target cell nuclei can be substantiated by their direct effect on the RNA polymerase activity of isolated nuclei or on the template function of target cell chromatin. The RNA polymerase I activity of uterine nuclei, while not sensitive to estradiol itself, is doubled after the nuclei are incubated with estradiol in the presence of uterine cytosol containing the receptor. Only the activated or nuclear form of the estrogen–receptor complex is effective in stimulating RNA synthesis in isolated uterine nuclei, and the effect is specific for nuclei of hormone-dependant tissues (Figure 8). Nuclei of hormone-dependent mammary tumors in rats resemble uterine nuclei in the sensitivity of their RNA polymerase systems to enhancement by estrogen–receptor complex *in vitro,* whereas nuclei from autonomous tumors are not susceptible to such stimulation. Using either bacterial or endometrial RNA polymerase enzyme, the template function of chromatin that is isolated from target, but not from nontarget, cells is significantly increased after exposure to estradiol–receptor complex *in vitro.*

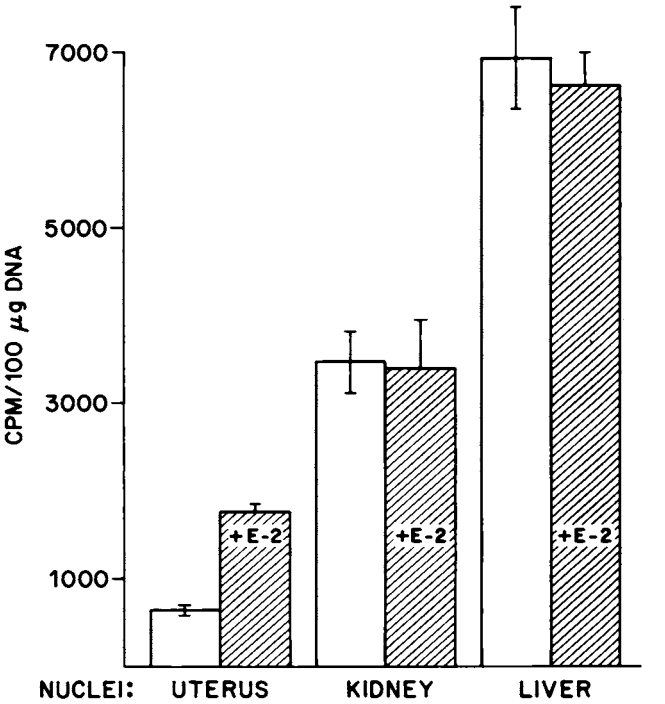

FIGURE 8 Tissue specificity of the influence of estrogen-receptor complex *in vitro* on RNA polymerase activity of uterine nuclei. Nuclei, isolated from 2.2-M sucrose homogenates of various immature rat tissues, were incubated at 25°C for 30 minutes without uterine cytosol (in 2.2 M sucrose, 1 mM magnesium chloride) in the presence and in the absence of 10 nM estradiol (E-2). The nuclei were then separated by centrifugation and resuspended in 0.32 M sucrose for assay of magnesium-dependent RNA polymerase by measuring the incorporation of tritiated uridine monophosphate (UMP) from uridine triphosphate (UTP). Results are the mean values of seven replicate determinations. From Jensen and DeSombre, 1973.

For androgenic hormones, incubation of prostatic nuclei with the dihydrotestosterone–receptor complex of prostatic cytosol leads to the enhancement of both polymerase I and polymerase II activities. The largest effect occurs on the polymerase I system, which is also stimulated in isolated nucleoli by exposure to the androgen–receptor complex. Highly purified progesterone–receptor complex from chick oviduct enhances the template function of chick oviduct chromatin but not of liver or erythrocyte chromatin or of chick DNA, when the

number of initiation sites is determined using a bacterial polymerase enzyme.

From the foregoing observations it appears that hormone-dependent tissues and tumors have a characteristic limitation in the activity of their RNA synthesizing or processing systems. This probably involves, at least in part, a restriction on chromatin template function, which can be alleviated by an activated hormone–receptor complex of extranuclear origin. For uterine growth, this action appears to require the continued presence of estrogen–receptor complex in the nucleus for several hours. It has been variously estimated that a single physiologic dose of estradiol results in the translocation of between 6,000 and 14,000 estrogen–receptor complexes to the uterine nucleus. Thus, it appears that the uterotrophic effect of estrogen involves a process requiring the ongoing participation of substantial numbers of estrogen–receptor complexes rather than the triggering of an initial event at a few specific gene sites.

IMMUNOCHEMICAL STUDIES WITH RECEPTORS

Despite our knowledge of the overall pattern of hormone–receptor interaction, a detailed understanding of the processes of receptor synthesis, activation, translocation, and nuclear binding is still far from complete. In the hope that the techniques of immunochemistry might permit new approaches to the study of hormone receptors by providing a means of detecting the receptor protein independent of its association with labeled hormone, specific antibodies to estrophilin have been prepared by immunizing rabbits (Greene *et al.*, 1977), as well as a goat (Greene *et al.*, 1979), with highly purified preparations of estradiol–receptor complex from calf uteri.

Five procedures have been used to show that the serum of rabbits that have been immunized with purified estradiol–receptor complex contains specific antibodies to estrophilin. In all of these procedures, interaction with the antibody does not destroy the ability of the receptor to bind estrogen. Therefore, the radioactive steroid can serve as a marker for the receptor, both before and after its reaction with antibody. Three of these criteria are standard techniques of immunochemistry: double antibody precipitation using goat antirabbit immunoglobulin, adsorption of the tritiated estradiol–estrophilin complex by immunoglobulin linked to Sepharose, and adsorption of the complex in the presence of IgG by *Staphylococcus aureus* protein A linked to Sepharose. Because the antibody reacts with estrophilin to form a nonprecipitating immune complex, two additional techniques

can be used to demonstrate the presence of antiestrophilin in the immunoglobulin from immunized animals: the ability of the antibody to increase the sedimentation rate of estrophilin in sucrose gradients and to accelerate its elution on gel filtration through Sephadex columns (Figure 9).

The effect of the antibody on the sedimentation behavior of the estrogen–receptor complex has been especially informative. In the presence of IgG from an immunized rabbit, the sedimentation rate of the purified nuclear estradiol–receptor complex, which is used as the antigen for immunization, is increased from 4.8 S to greater than 10 S (Figure 10). With the crude nuclear complex of calf uterus, which sediments at 5.2 S in salt-containing sucrose gradients, interaction with the antibody gives rise not only to this rapidly sedimenting product but also to a slower peak at approximately 8 S (Figure 11a). Reaction also takes place with the extranuclear complex, providing support for the concept that nuclear estrophilin is derived from translocation of the extranuclear receptor. However, the cytosol form of calf uterine receptor,

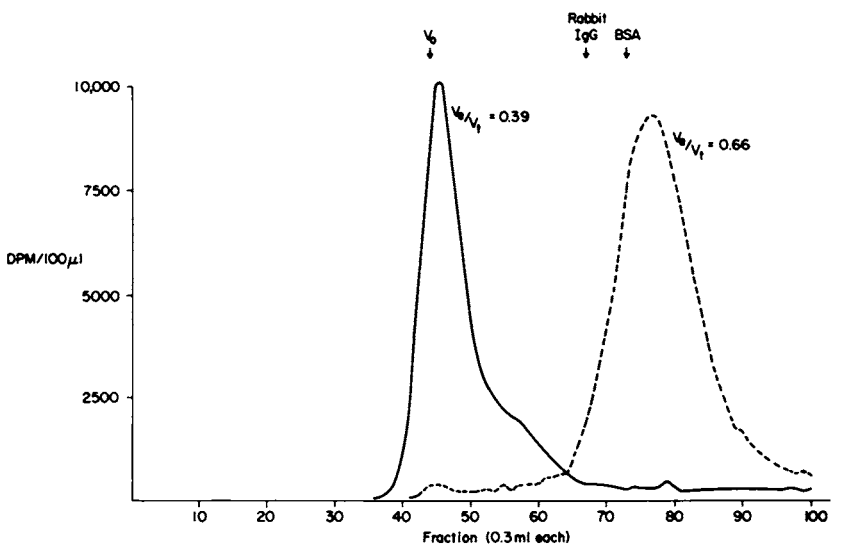

FIGURE 9 Elution pattern from Sephadex G-200 of calcium-stabilized [^{3}H]estradiol-receptor complex of calf uterine cytosol treated with IgG from immunized (—) or nonimmunized (---) rabbit. Gel filtration was carried out in 400 mM potassium chloride in 10 mM Tris, pH 7.4 V_e = volume of eluate at which the peak of radioactivity was eluted. V_t = the bed volume of the column (35 ml). V_0 = the void volume as determined with blue dextran. Bovine serum albumin (BSA) and rabbit IgG were chromatographed separately as markers in the same column. DPM = disintegrations per minute.

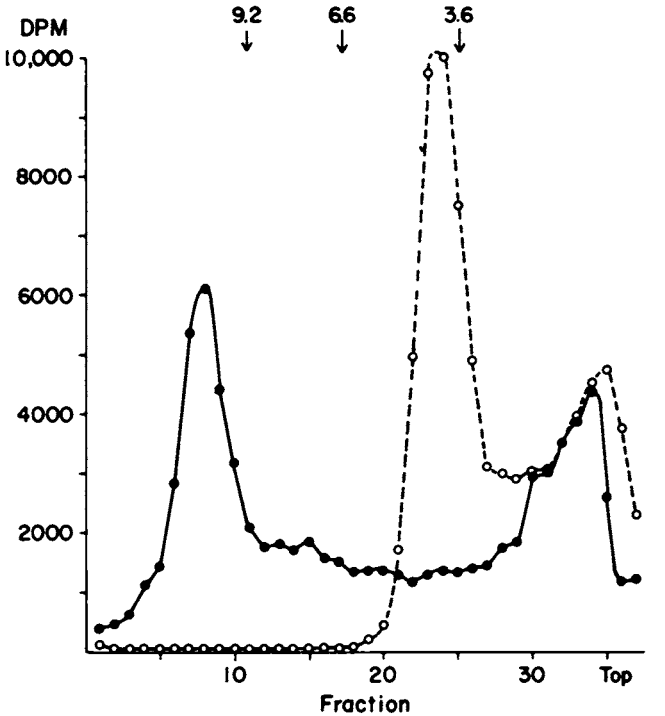

FIGURE 10 Sedimentation pattern of highly purified [^{3}H]estradiol-receptor complex from calf uterine nuclei in 10% to 30% sucrose gradient containing 10 mM potassium chloride in the presence of immunoglobulin from immunized (●) or nonimmunized (○) rabbit.

which sediments in salt-containing gradients at approximately 4 S, reacts with the rabbit antibody to form a single new entity, which sediments at approximately 7.5 S (Figure 12a). The same sedimentation peak occurs whether the antibody is added to the preformed estradiol–receptor complex or the hormone is added to the mixture of receptor and antibody. In media of low ionic strength, where the cytosol receptor sediments at 8 S, reaction with the rabbit antibody shifts the sedimentation peak to approximately 11 S. With antiestrophilin produced in the goat, similar reactions with nuclear and extranuclear estrogen–receptor complexes are observed, except that in this case the shift in sedimentation rate is somewhat greater, suggesting that the immune complexes with goat antibodies may contain more molecules of immunoglobulin per receptor.

As evident from the foregoing observations, antibodies produced

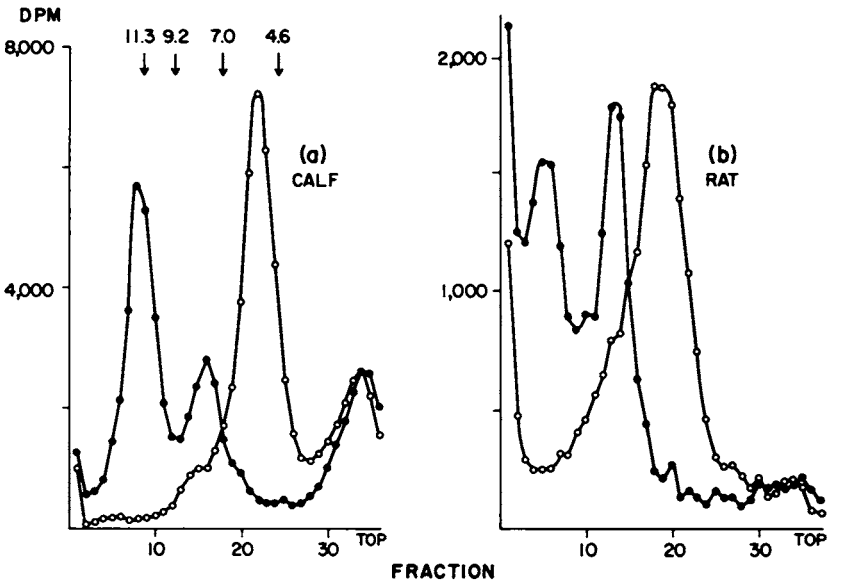

FIGURE 11 Sedimentation pattern in 10% to 30% sucrose gradients containing 400 mM potassium chloride of (a) 400 mM potassium chloride extract of calf uterine nuclei after incubation for 60 minutes at 25°C with 20 nM [^{3}H]estradiol in calf uterine cytosol and (b) similar extract of uterine nuclei from immature rats 4 hours after injection of 100 ng [^{3}H]estradiol *in vivo* in the presence of immunoglobulin from immunized (●) or nonimmunized (○) rabbit. Reproduced from Greene *et al.*, 1977.

against the highly purified (4.8-S) form of nuclear estrophilin from calf uterus react not only with this antigen but also with the aggregating (5.2-S) form of the nuclear receptor as well as with the cytosol receptor. Moreover, there is cross-reactivity with both cytosol and nuclear forms of estrophilin from other tissues and species. Reactions of the rabbit antibody with the nuclear uterine receptor from rats injected with tritiated estradiol *in vivo* and with the cytosol receptor of human breast cancer are illustrated in Figures 11b and 12b, respectively. Nuclear and/or extranuclear estrogen–receptor complexes from all target tissues thus far investigated react with antibody to the nuclear form of estrophilin from calf uterus, as indicated by an increase in the sedimentation rate. These tissues include uterine tissues in the rat, mouse, guinea pig, rabbit, sheep, and monkey; endometrial, mammary, and pituitary tumors in rats; and breast cancer and MCF-7 breast cancer cell line in humans. With crude nuclear complexes, two new sedimentation peaks are observed in all cases except that of MCF-7

tumor cells, where interaction with rabbit antibody shifts the sedimentation rate from 3.3 S to a single peak at approximately 7 S. The cytosol complexes examined all give rise to a single peak, which is similar to those illustrated in Figure 12.

In contrast to their cross-reactivity with estrogen–receptor complexes from various sources, antibodies to calf uterine estrophilin do not cross-react with either androgen–receptor complexes of rat prostate or progesterone–receptor complexes from the rabbit uterus, rat endometrial tumor, or chick oviduct. Nor is there any reaction with free estradiol. Although there is immunochemical similarity among estrophilins from different tissues of a wide variety of mammalian species, receptors for different classes of sex hormones appear to be immunologically distinct, at least in regard to the determinants recognized by the antibody to the estrogen–receptor protein.

Antibody to estrophilin provides a reagent that should prove useful in many aspects of receptor research. For the first time, one has a

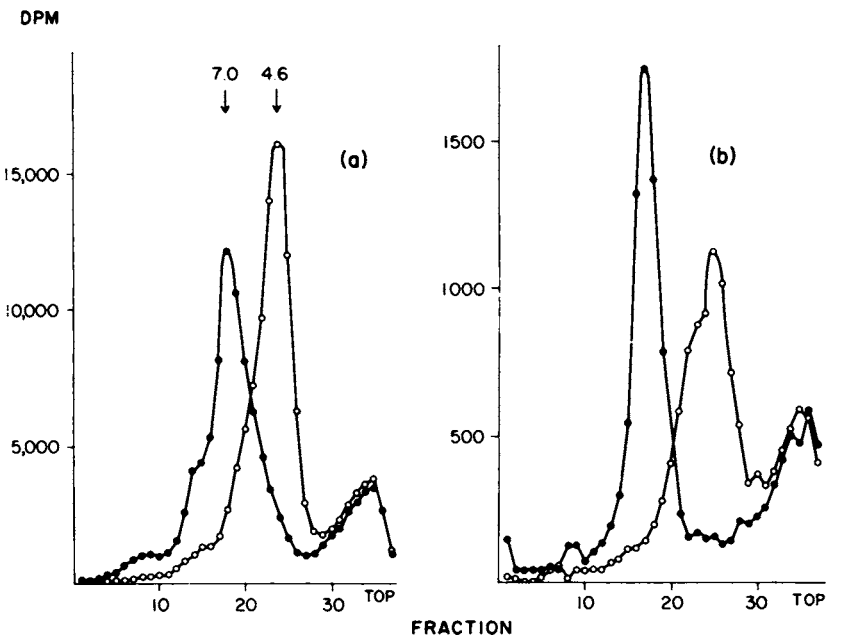

FIGURE 12 Sedimentation pattern in 10% to 30% sucrose gradients containing 400 mM potassium chloride of (a) calf uterine cytosol and (b) human breast cancer cytosol, each containing [^{3}H]estradiol, in the presence of immunoglobulin from immunized (●) or nonimmunized (○) rabbit. Reproduced from Greene *et al.*, 1977.

potential means for detecting the receptor protein that does not depend on its ability to bind radioactive steroid. The cross-reactivity of antibody to the calf receptor with estrophilin from human breast cancer, but its lack of reactivity with androgen or progesterone receptors, opens the possibility of a simple radioimmunoassay for the receptor content of breast cancers as a guide to therapy. Immunoglobulin linked to Sepharose or other support may prove to be an efficient tool for the purification of estrophilin, whereas insight into the molecular details of hormone action may come from the application of immunohistological techniques for the precise intracellular localization of nuclear and extranuclear receptor through electron microscopy. For many of these purposes, the availability of a monospecific antibody preparation should prove highly advantageous, if not obligatory. Following the procedure of Milstein (Köhler and Milstein, 1975), we have succeeded in fusing lymphoid cells from immunized animals with appropriate mouse myeloma cells. We are now attempting to isolate clones of hybridoma cells that are producing the desired antibody. Finally, the reaction of antiestrophilin, or of its Fab fragments, with receptor proteins in target tissues may offer the possibility of modifying cellular response to sex hormones. This suggests a new approach to fertility control.

SUMMARY

Steroid sex hormones react with target cells in reproductive tissues by a two-step mechanism in which an initial complex of the steroid with an extranuclear receptor protein is translocated to the nucleus where it interacts with chromatin, thereby enhancing the production of different types of RNA. This process is accompanied by a hormone-induced alteration of the receptor protein, known as receptor activation, to a form that can bind to chromatin and influence transcription. Exposure of isolated nuclei of hormone-dependent cells to the activated, but not the native, form of the hormone–receptor complex results in stimulation of their RNA polymerase activity resembling that observed after administration of the hormone *in vivo*.

Antibodies to a highly purified preparation of the nuclear estradiol–receptor complex of calf uterus cross-react not only with the extranuclear form of the receptor but also with nuclear and extranuclear estrogen–receptor complexes of reproductive tissues of all mammalian species tested. However, there is no cross-reaction with androgen or progesterone receptors. Such cross-reactive, estrophilin-specific antibodies offer promise as valuable reagents for receptor analysis and

purification as well as for the elucidation of many still unresolved questions concerning receptor structure, localization, and function.

ACKNOWLEDGMENT

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Human Chorionic Gonadotropin

ROBERT E. CANFIELD *and*
STEVEN BIRKEN

The theme of this symposium calls attention to the urgent need for major advances in contraceptive technology and to the question of how best to invest the available resources toward that goal. As in all other scientific disciplines, a logical source to turn to for new ideas concerning how to interfere with or interrupt human reproduction is an expanded base of knowledge of the biochemistry and physiology of the process. One focus of such an inquiry is the glycoprotein hormone, human chorionic gonadotropin (hCG), which has evolved as a unique and essential endocrine message for pregnancy in humans. This paper addresses that topic.

The chemistry and physiology of hCG have been the subject of several recent reviews (Birken and Canfield, 1979; Canfield *et al.*, 1976; Ross, 1977). Some pertinent aspects of the chemistry of this molecule are summarized briefly below, but the major emphasis is placed on the relationship of this information to applications in contraceptive technology.

CHEMICAL STUDIES OF hCG

Purification

The usual starting material for hCG purification is a commercial preparation that has been partially purified from pooled, first trimester pregnancy urine. Such preparations typically have 2,500–3,500 IU/mg;

the biological activity of purified hCG preparations is usually in the range of 10,000 to 18,000 IU/mg (Canfield and Ross, 1974; Van Hell *et al.*, 1966). Under the auspices of the National Institute of Child Health and Human Development, we have prepared, in collaboration with Dr. Griff T. Ross, several reference preparations of hCG and its subunits for distribution to the scientific community (Morgan *et al.*, 1974). During the past 5 years, nearly 10 g of these reference materials have been distributed for research in reproductive endocrinology, and identical preparations have been used for the determination of amino acid sequence. The details of methods of purification of the hormone and its subunits have been given elsewhere (Canfield and Morgan, 1973; Morgan *et al.*, 1973b).

Structure

In 1970 it became clear that hCG was composed of nonidentical subunits (Canfield *et al.*, 1970), which were subsequently designated as alpha and beta according to the nomenclature proposed by Pierce (1971). In retrospect, it had been known that luteinizing hormones (LH) also possessed a similar subunit structure (Papkoff and Samy, 1967), which hCG could have been expected to share because of the similar biological actions of these two hormones. Analogous structural arrangements for thyroid-stimulating hormones (TSH) and follicle-stimulating hormones (FSH) were proposed shortly thereafter, linking these four glycoprotein hormones together as a class that evolved from similar ancestral genes.

By 1973, proposals for the amino acid sequences of both subunits had emerged from two laboratories (ours and that of Dr. Bahl) (Bellisario *et al.*, 1973; Carlsen *et al.*, 1973; Morgan *et al.*, 1973a). Both proposals were in general agreement except for differences in the COOH-terminal region of the beta subunit. Subsequently, these were clarified by us and independently by Keutmann (Birken and Canfield, 1977; Keutmann and Williams, 1977). The complete amino acid sequence of the hCG alpha subunit is shown in Figure 1 and that of the beta subunit in Figure 2. Since comparison of the primary structures of the beta subunits of human luteinizing hormones (hLH) and of hCG forms the basis of much of the discussion in this chapter, both structures are shown in Figure 2.

The alpha and beta subunits of hCG are held together by noncovalent bonds. Studies with the fluorescent probe anilinonaphthalenesulfonate (ANS) indicate that these do not dissociate readily (Aloj *et al.*, 1973). It is possible to recombine the subunits to form the native hormone.

ALPHA SUBUNIT

```
                                                                10
ALA - PRO - ASP - VAL - GLN - ASP - CYS - PRO - GLU - CYS - THR - LEU -

                                                    20
GLN - GLU - ASP - PRO - PHE - PHE - SER - GLN - PRO - GLY - ALA - PRO -

                                        30
ILE - LEU - GLX - CYS - MET - GLY - CYS - CYS - PHE - SER - ARG - ALA -

                    40
TYR - PRO - THR - PRO - LEU - ARG - SER - LYS - LYS - THR - MET - LEU -

      50        CHO                                                 60
VAL - GLN - LYS - ASN - VAL - THR - SER - GLU - SER - THR - CYS - CYS -

                                                            70
VAL - ALA - LYS - SER - TYR - ASN - ARG - VAL - THR - VAL - MET - GLY -

                                    CHO             80
GLY - PHE - LYS - VAL - GLU - ASN - HIS - THR - ALA - CYS - HIS - CYS -

                                        90
SER - THR - CYS - TYR - TYR - HIS - LYS - SER
```

FIGURE 1 The amino acid sequence of the hCGα subunit. It consists of 92 amino acids and contains two large branched-chain carbohydrate groups which are attached to asparagines 52 and 78. There is heterogeneity at the NH_2-terminus (initial amino acids are underlined). Approximately 60% of the molecules begin with alanine, and the remainder of molecules begin with valine or aspartic acid.

Among the glycoprotein hormones, hCG possesses the largest amount of carbohydrate, averaging approximately 30% of the weight of the molecule. The sites of attachment are known to be asparagine and serine residues, but there is some disagreement about the precise structure of the carbohydrate side chains (Bahl, 1969; Kennedy and Chaplin, 1976). However, there is general agreement that the *in-vivo* biological action of the hormone is drastically reduced by loss of the terminal sialic acid residues on the carbohydrate side chains due to an accelerated rate of clearance of the desialylated hormone by the liver (Morell *et al.*, 1971).

Recent recognition that many secreted proteins are synthesized in a precursor form, with a hydrophobic, NH_2-terminal extension or precursor piece, has stimulated studies of the synthesis of hCG in both wheat germ and ascites extract systems in response to placental mRNA. The available data indicate that separate mRNA's code for the alpha and beta subunits respectively, and that the alpha subunit is synthesized in a precursor form (Birken *et al.*, 1978; Chatterjee and Munro, 1977).

The structures of beta subunits of the four human glycoprotein

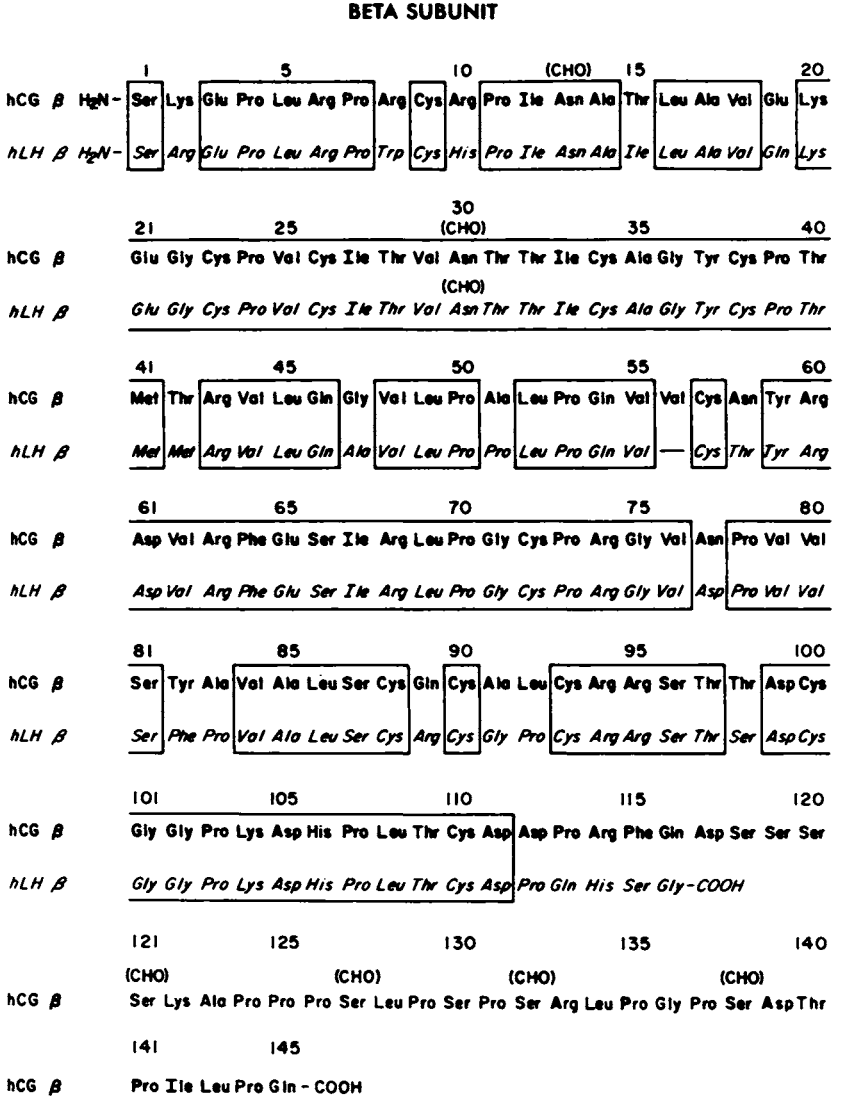

FIGURE 2 The amino acid sequence of the hCGβ subunit (upper, dark lettering) is compared with that of the hLHβ subunit (lower, slanted lettering). The regions of identity are shown in boxes. Alignment is by cysteines. The unique COOH-terminal addition to hCGβ begins at residue 115.

hormones have been analyzed for homology by Stewart and Stewart (1977), who found that there are "constant" regions in which structures are preserved (residues 16–39 and residues 56–100) and "variable" regions in which there is a great deal of dissimilarity (Stewart and Stewart, 1977). These investigators suggested that the constant regions may represent the part of the structure that interacts with the alpha subunits, which are essentially the same in each hormone, while the variable regions interact with the receptor conveying tissue specificity on the hormone. These suggestions are supported by the finding that the tyrosines in the beta subunit of LH, which appear to be masked by the alpha subunit in the native hormone, occur in the "constant" region at positions 37 and 59 (Burleigh *et al.*, 1976; Cheng and Pierce, 1972; Liu and Ward, 1976; Ward, 1979). The carboxy terminal extension of the beta subunit of hCG is unique to this hormone. Since hLH, which lacks the structure, and hCG bind to the same receptor, the additional 30 amino acids in hCG do not seem to convey any special hormone action. Rather, the high content of proline and carbohydrate side chains in this region may serve as a "piece of armor," which makes the surface of the molecule more resistant to proteolytic degradation. It may also account in part for the longer biological half-life of hCG as compared with hLH.

POTENTIAL APPLICATIONS TO CONTRACEPTIVE TECHNOLOGY

In view of the crucial role that hCG plays in the human reproductive process, it seemed inevitable that basic studies of the chemistry of the hormone would yield information of both theoretical and practical value. Indeed, the results have been rewarding. The application of this knowledge is popularly known as a technology transfer, which is an important product of basic science. However, while some organizations dedicated to contraceptive development hasten to make practical applications of this new knowledge, e.g., in the testing of pregnancy vaccines, proper attention should continue to be paid to the type of basic science endeavors on which such technology transfer is based. We are particularly concerned that too heavy an emphasis is being placed on early practical applications and too little emphasis on the extension of a sound scientific base of knowledge for the future.

In several areas, the application of information that has been derived from the studies of the hCG chemistry promises to be of value in contraceptive technology. All of these areas are related to the discipline of immunology. Three are discussed briefly below.

Immunosuppression During Pregnancy

There is a theoretical requirement for at least localized immunosuppression in pregnancy to prevent rejection of the fetus, and a variety of observations support the existence of such an immunosuppressed state. For example, atrophic lymph nodes, decreased thymus size, a decreased incidence of positive delayed hypersensitivity skin tests, and prolonged skill allograft survival have all been observed in pregnant women. There is also epidemiologic evidence of a weakened host defense against viral infections (Canfield *et al.*, 1976; Morse *et al.*, 1976). Kaye and Jones (1971), Adcock *et al.* (1973), and Contractor and Davies (1973) reported that hCG inhibited phytohemagglutinin (PHA) stimulation of incorporation of ^{3}H-thymidine into human lymphocytes and suggested that the hormone might play a major immunosuppressive role in pregnancy. These investigators worked with crude urinary hCG preparations. Taking advantage of the reagents that we had available from our program for the purification of hCG, we attempted to reproduce these results in collaboration with Dr. Jane Morse (Morse *et al.*, 1976), as did others using these same reagents (Caldwell *et al.*, 1975) or other purified preparations (Gundert *et al.*, 1975; Merz *et al.*, 1976). The general finding has been that the immunosuppression is not an effect of hCG but, rather, a property of an unknown component found in urine of pregnant females that has a molecular weight less than that of hCG. While many other factors, such as the level of steroid hormones, affect the immune system during pregnancy, it is still important to purify and characterize this unknown substance from the urine of pregnant subjects. Once this is done, it can be determined whether or not its synthesis is unique to pregnancy and whether or not it is also synthesized by other primates. If the latter occurs, it should be possible to assess the role in pregnancy in animal studies by such techniques as passive immunization to neutralize its effects. Also, if the factor in pregnancy urine has evolved as a unique adaptation to the problem of suppressing the immune challenge of fetal antigens, studies of its action on the immune system might provide other useful ideas about how to interrupt the acceptance of the fertilized ovum.

Detection of hCG

Prior to the demonstration of a subunit structure for the gonadotropins, it had not been possible to develop antisera that were capable of reacting with hCG without simultaneously exhibiting a significant degree of cross-reactivity with hLH. Early immunization efforts em-

ploying the hCG subunit demonstrated that it was possible to produce antisera with a high degree of discrimination for hCG. The SB_6 antibody of Vaitukaitis *et al.* (1972) is probably the best example. The reagent has been extensively employed in clinical assays, especially to study ectopic hCG production by neoplastic tissues (Braunstein *et al.*, 1973; Vaitukaitis, 1974). When the amino acid sequence for hCGβ and hLHβ became known, it was apparent that the COOH-terminal extension of the hCGβ subunit could serve as an immunogen that would give rise to antibodies unique for hCG. We employed the 123–145 region, isolated from the asialo beta subunit (Louvet *et al.*, 1974), and others have used synthetic peptides with equally good results (Stevens, 1976). Most recently Chen and Hodgen and their coworkers have made extensive studies of antisera that were raised against this COOH-terminal region. They have shown that the antisera consistently react with the same group of amino acids, i.e., the terminal 15 residues (Chen *et al.*, 1976; Matsuura *et al.*, 1978). In our laboratory we have been able to make preparations of hCGβ completely lacking the COOH-terminal region (i.e., missing residues 115–145). These appear to be fully reactive with the SB_6 type of antiserum (Birken and Canfield, 1979). Therefore, there are at least two recognizable antigenic sites on hCGβ that are not present in hLH. One is the COOH-terminal region, and the other is located in the main portion of the molecule.

With the development of sensitive and specific assays for hCG, these reagents were applied in a collaborative study that produced evidence that hCG is synthesized and excreted by nonpregnant, nontumor-bearing humans (Chen *et al.*, 1976; Matsuura *et al.*, 1978; Ross, 1977). Further improvements in assay technique have made it possible to measure hCG in the urine of most normal individuals with a range of 6–52 ng/24 hours (Ayala *et al.*, 1978). This finding lends credence to other observations that have suggested that hCG is normally synthesized in a variety of human tissues (Ayala *et al.*, 1978; Braunstein *et al.*, 1975; Yoshimoto *et al.*, 1977).

Considerably more work remains to be done in perfecting hCG radioimmunoassays (i.e., more highly specific and sensitive antisera are required as well as improved methods) so that they can be routinely available as diagnostic tests. Certainly the demand is significant. The main problem with the specific COOH-terminal radioimmunoassay is its low sensitivity relative to SB_6 type antisera (Ayala *et al.*, 1978). A radioreceptor assay for hCG is now commercially available and offers a sixfold greater sensitivity over conventional hemagglutinin or latex agglutination tests (Saxena and Landesman, 1978). However, the receptor cannot discriminate between hCG and hLH, and both are

measured simultaneously in the presence of serum from the luteal phase of a nonpregnant subject to compensate for basal LH levels. The value of specific immunoassays in diagnosing pregnancy before the first missed menstrual period may establish the opportunity to test new methods of intervention. It may become possible to settle the debate concerning whether or not women with IUD's actually have a transient rise in hCG reflecting fertilization (Hodgen *et al.*, 1978). Finally, knowledge of a normal secretion rate for hCG now makes it possible to assess whether elevations of hCG may be significant indicators of malignancy in a higher percentage of patients than previously suspected.

Another valuable application is illustrated by the work of Chen and Hodgen (1976), who used antibodies against the COOH-terminal region of hCHβ to test for antigenic similarity with other primate chorionic gonadotropins. They found the greatest similarity with the chimpanzee, indicating that this species was most ideal to test an antifertility vaccine that utilizes synthetic COOH-terminal antigens. The marmoset and the baboon, for which the whole beta subunit can be effectively used in a vaccine, displayed virtually no cross-reactivity with the COOH-terminal region antibodies and would be a poor choice to test this form of vaccine. Another contribution of the work of Chen and Hodgen is the indication that the COOH-terminal hCGβ radioimmunoassay would be a reliable method for testing for pregnancy in fertility experiments with chimpanzees.

Pregnancy Vaccine

Early experiments in animals indicated that immunization with gonadotropins could interfere with reproductive function (Laurence and Ichikawa, 1969; Madhwa *et al.*, 1968; Pineda *et al.*, 1968), but the challenge, similar to that discussed above, has been to identify immunogens that would not give rise to antibodies that cross-react with hLH. In an early study of the effects of immunization on the human menstrual cycle, Stevens and Crystle (1973) used a hapten-complex form of hCG to immunize women. They found that all subjects showed evidence of interference with hLH. In other experiments in primates conducted by Stevens (1976) and by Hearn *et al.* (1976), it has become clear that immunization with the beta subunit of hCG was an effective pregnancy vaccine at least for a short time following immunization. Talwar *et al.* (1976) conducted a limited field trial immunizing women with an hCGβ subunit preparation (Talwar *et al.*, 1976), which was coupled to tetanus toxoid (Hearn *et al.*, 1976). Other investigators are

attempting to use synthetic COOH-terminal beta subunit antigens (Stevens, 1976). In both situations, the major concern revolves around the evidence that humans normally synthesize hCG with the resulting possibility that immunization could lead to damage of the tissues that synthesize hCG, or after many years, to some type of immune-complex disease. Hence, a case can be made for focusing initial studies on immunization of humans bearing neoplastic tissue with evidence of ectopic hCG secretion. As a consequence of clinical trials, it is of vital importance to attempt to define precisely the antigenic sites on the beta subunit that give rise to antibodies from the human immune system, for such information could lead to a second generation of reagents that could be used in a vaccine, if such a vaccination proves to be safe and effective in humans.

CONCLUSION

This paper summarizes some of the elements of current knowledge of the chemistry of human chorionic gonadotropin that are applicable to contraceptive technology. It is presented to emphasize the importance of basic science research as a sound foundation on which to build such practical applications.

ACKNOWLEDGMENT

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Releasing Factors and Other Neuroendocrine Factors

ROGER C. L. GUILLEMIN

None of the important discussions that we have been hearing in this symposium would have been possible without considerable financial backing. At the Salk Institute, all of our research into the observation and characterization of LRF, the luteinizing hormone releasing factor, with which I shall be dealing here, through to the analogs of LRF, was actually sponsored by the Population Division of the U.S. Agency for International Development (USAID). Some support was also provided by both the Ford Foundation and the Population Council at crucial times. Since USAID support came to an end, most of this research has been sponsored by the National Institute of Child Health and Human Development (NICHD).

In this short lecture I shall be reviewing briefly some recent observations, mostly those pertaining to LRF analogs. While not altogether new, many of these observations are still relatively novel for many of us. I shall also mention some of the more current developments, particularly those pertaining to some of our present efforts in the field of contraception. Most of the data I shall be discussing were obtained in our laboratories at the Salk Institute, and the majority of the conclusions reached have been agreed upon by a number of other laboratories. I will not review the hypothalamic control of pituitary function in this brief "minireview."

The amino acid sequence of LRF was first proposed by Schally *et al.* (1971) using material of porcine origin. It was confirmed by our group at the Salk Institute with material of ovine origin and reproduced by total

synthesis. I really believe that this substance should be called the gonadotropin-releasing factor, although I may have to qualify this later on in view of the lecture by Dr. Channing and the discussion that followed her paper.

It soon became obvious that this synthetic material was highly active in all the species in which it was tested for gonadotropin release. As both Schally's group and ours found at about the same time, it was obvious that either the highly purified native material or the synthetic replicate would stimulate the secretion of both LH and FSH consistently in all *in-vivo* or *in-vitro* preparations that were used. We can now say that LRF has no major species-specificity in its gonadotropin-releasing function. However, there is evidence that the structure of the amino acid sequence of avian LRF is somewhat different from that of mammalian LRF.

A series of very early clinical studies were conducted by Yen and his clinical fellows at the Department of Obstetrics and Gynecology at the University of California in San Diego (Rebar *et al.*, 1973; Yen *et al.*, 1973), who used the peptide that was synthesized by Monahan at the Salk Institute (Monahan *et. al.*, 1971; Monahan and Rivier, 1972). They showed that 15 repeated injections of 10 μg of the peptide in the same individuals—in this case males—produced remarkably consistent results and that there would be a dose relationship even though there would be some absolute variation among subjects (Figures 1, 2, and 3).

In another early study on these same subjects by Sam Yen's group (Rebar *et al.*, 1973), injections of these relatively small amounts of LRF in normal males were accompanied by secretion of testosterone, and there was a peculiar relationship with the age of the normal individual receiving LRF.

When LRF was administered to healthy young women throughout their menstrual cycles, it became obvious that the same dose of LRF—in this case 50 μg—would give different absolute values in terms of the response to luteinizing hormone (LH) as a function of the menstrual cycle. The highest response in terms of LH and, to some degree, follicle-stimulating hormone (FSH), occurred on the ovulation date—on day 14 in the case of this particularly well-studied young woman.

Extensive studies have been made by several groups, not only of clinicians, but also of laboratory researchers. The results of these studies have borne out what we suspected from the menstrual cycle studies, namely that administration of estrogen in a normal individual would also lead to changes in the response to a given dose of LH. They also showed that the response of a normal individual to a given dose of LRF was remarkably constant, as long as the exact state of the steroid

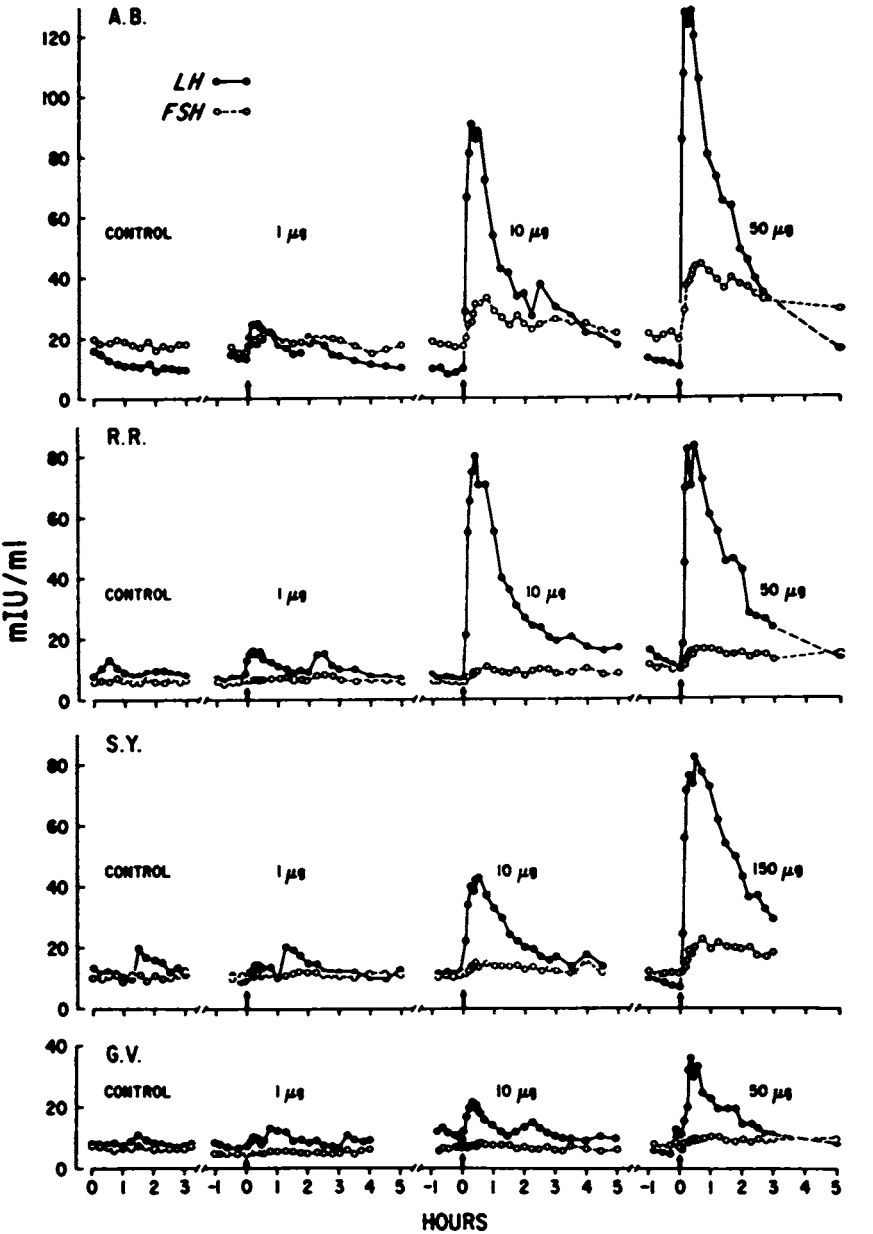

FIGURE 1 Serum gonadotropin levels during 3 representative hours of baseline (control) and in response to three doses of synthetic LRF in four subjects. All subjects received 1, 10, and 50 μg except for one in whom the largest dose administered was 150 μg. Arrows indicate time of LRF administration. (The initials are those of the researchers.)

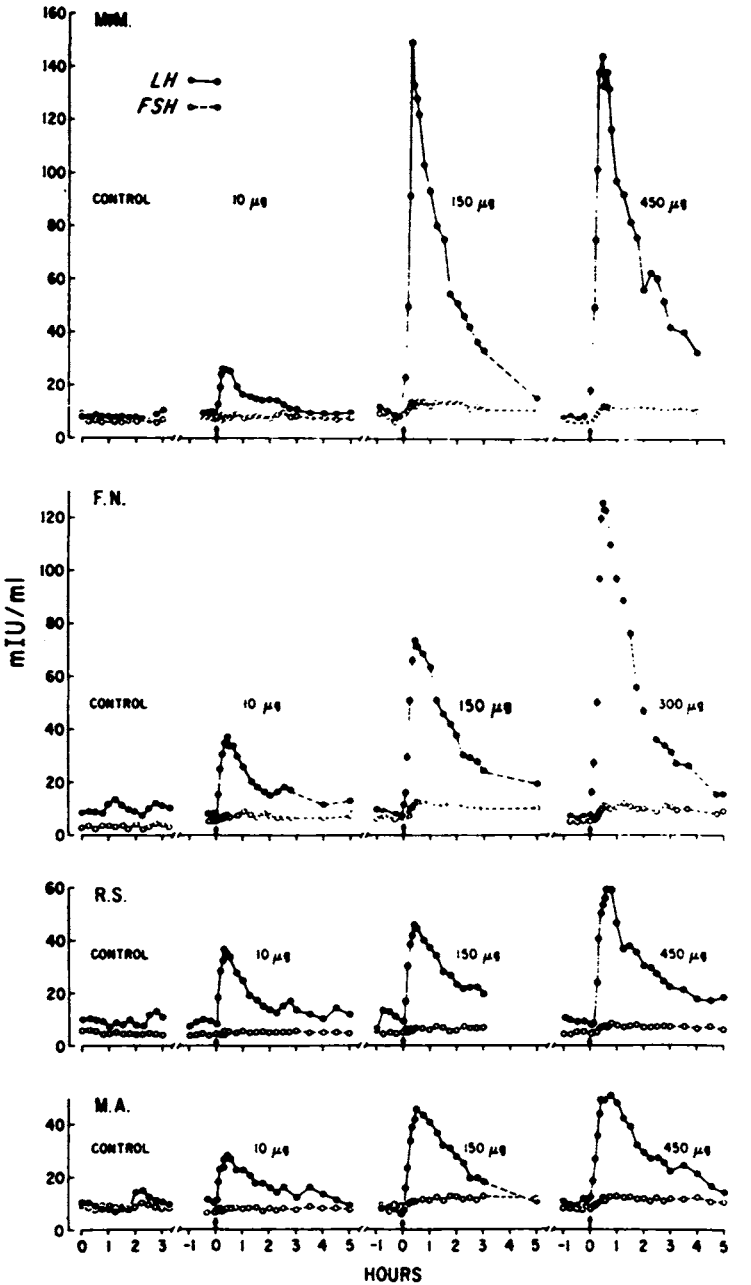

FIGURE 2 Responses to 10, 150, and 450 μg in four subjects. (The initials are those of the researchers. The largest dose given by F.N. was 300 μg.)

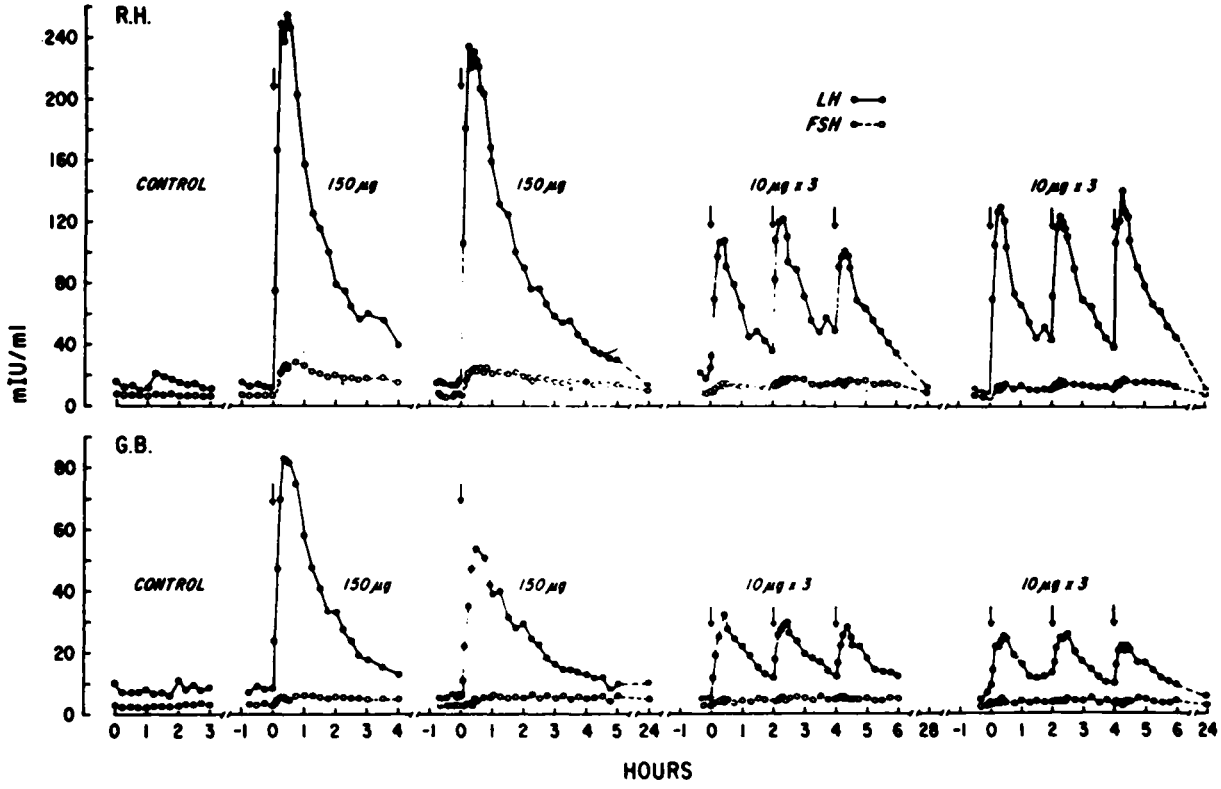

FIGURE 3 Serial responses to repeated maximal (150 μg) and threshold (10 μg) doses of synthetic LRF in the same subjects at weekly intervals. (The initials are those of the researchers.)

secretory pattern in a particular patient was known, i.e., early follicular phase, late follicular phase, modification by estrogen treatment in the early follicular phase, etc.

The exact mechanism by which estrogen affects response to LRF at pituitary levels is not completely understood. However, it is highly dose-dependent. Depending on the dose of estrogen that is administered, one can either potentiate or decrease the release of LH due to the same dose of LRF. Despite a number of studies on this question, to my knowledge no ultimate cellular mechanism has yet been proposed to explain it all.

With the knowledge that administration of a given dose of LRF produces a remarkably constant and consistent type of response in both males and females, a type of acute testing of pituitary function was devised by several groups. A typical test for pituitary secretory ability consists of infusing arginine (one of the few means we have at the moment) to stimulate the secretion of growth hormone and, following that, injecting a single dose of LRF and TRF to induce the secretion of gonadotropins and TSH (Figure 4).

A young woman on the second day of the ovarian cycle shows a typical normal pattern of normal pituitary response. During the last few years many published papers have described modifications—variations of one or more parameters in various types of either functional or organic pituitary diseases. This type of test is also now commonly used by neurosurgeons to ascertain and follow up completeness of hypophysectomy.

There is no doubt that administration of LRF with the proper steroid background can stimulate ovulation in women. In addition, several clinical groups have observed that LRF may actually stimulate the secretion of gonadotropins, both LH and FSH, not only in laboratory animals given large amounts of steroids or a regimen of contraceptive steroids but also in women who have been on contraceptive medication for a very long time (Yen *et al.*, 1973).

One puzzling question concerns some of the work of Moriarty *et al.* (1973). They have shown (and it has been confirmed by others) that if you prepare antisera to the synthetic decapeptide and antibodies to rat LH, you can, using the immunocytochemical technique, demonstrate the presence of LRF, the releasing factor, inside the cytoplasm on the same granules that can be shown to be immunoreactive to gonadotropin antisera.

It is also clear that there are LRF receptors on the plasma membranes of the gonadotrope-secreting cells. This has led various groups to propose that cyclic AMP (adenosine 3′:5′-cyclic phosphate) and the

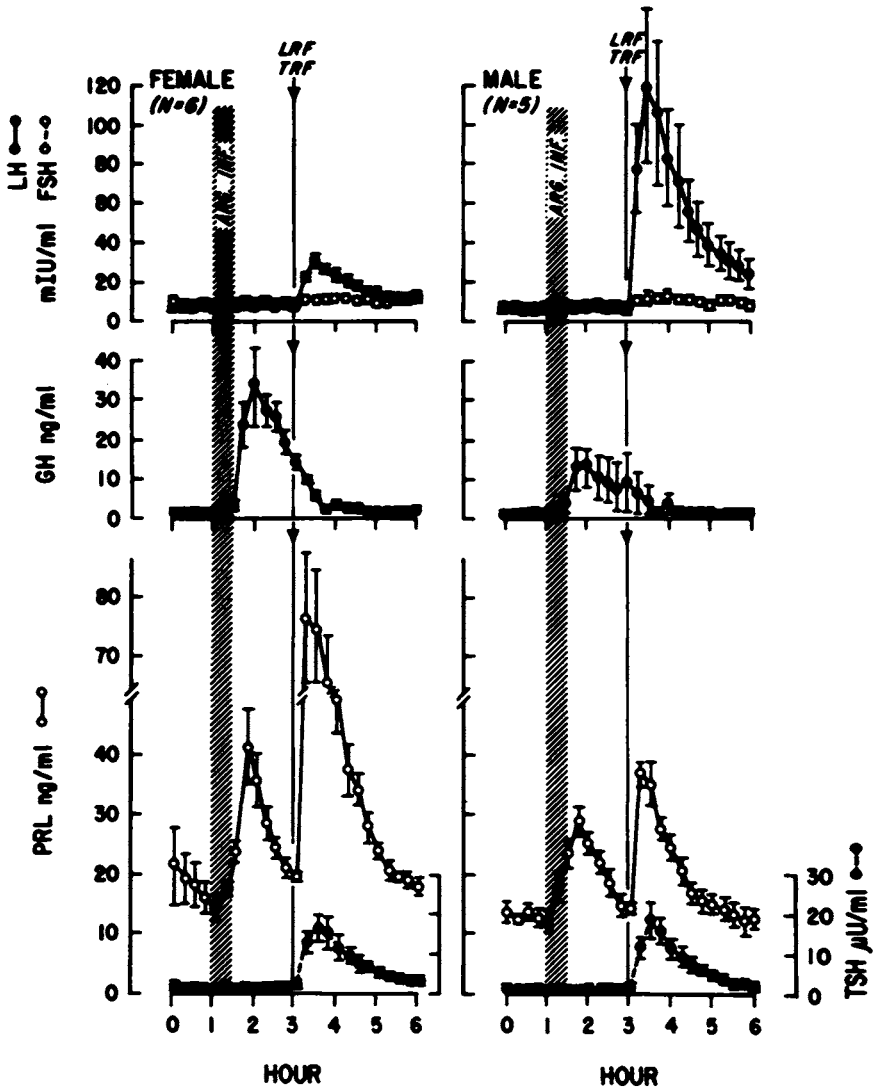

FIGURE 4 Testing of the ability of the anterior pituitary to secrete growth hormone (GH), thyroid-stimulating hormone (TSH), prolactin (PRL), LH, and FSH in normal human subjects. Stimulation of the secretion of GH is achieved by intravenous administration of arginine; stimulation of the secretion of TSH and PRL, LH and FSH is produced by intravenous injection of a solution in saline of synthetic thyrotropin-releasing factor (TRF) (250 μg) and synthetic LRF (150 μg). Note that arginine infusion stimulates secretion of GH and PRL. All pituitary hormone plasma concentrations measured by radioimmunoassays. From Yen *et al.*, 1973.

adenylcyclase system may be involved in the action mechanism of LRF. In our laboratory, going back to the early studies of Grant *et al.* (1972) on TSH secretion, we have never been convinced that this was an exclusively effective mechanism for TSH, LH, or FSH.

To get back to one of the questions raised after Dr. Channing's presentation, no one that I know of has yet found any natural substance extracted from the hypothalamus that would specifically stimulate the secretion of FSH over that of LH. Of all the probably more than 1,000 synthetic analogs of LRF that have been prepared, not one has been found that would stimulate the secretion of LH or FSH in a preferential manner. Until today, I would have said that this definitely eliminated the possibility of a specific, direct, exclusive mechanism controlling the secretion of FSH. The new observations by Dr. Channing may completely modify this concept.

In some of the studies by Moriarty *et al.* (1973) and several other groups, particularly that of Anna Steinberger, it was proposed that all gonadotropes contained both the gonadotropins, LH and FSH, in the same granules. The same investigators now say that perhaps no more than 5% of gonadotropes may contain FSH exclusively and maybe 1% or 2% contain LH exclusively, while the greatest number do contain both gonadotropins in the same granules. This question has since been reopened in view of the studies of Dr. Channing and her group at the University of Maryland (Channing *et al.*, 1977; Marder *et al.*, 1977; Schwartz and Channing, 1977; and Tsafriri *et al.*, 1976).

LRF is not only to be found as hypophysiotropic substance in the ventral hypothalamus. There is evidence that in the human brain, as in the rat brain, immunoreactive LRF can be found in the ventral hypothalamus as well as in the anterior nucleus of the amygdala (Knigge *et al.*, 1978).

We do not really know what LRF does in any of these locations. Several studies, particularly those of Moss and McCann (1975), have shown that LRF injected in the lateral ventricle or in the third ventricle of the brain of gonadectomized and/or hypophysectomized rats can stimulate copulatory behavior. When applied by microiontophoresis to parts of the brain where LRF has been seen, e.g., to some neurons in the hypothalamus, LRF can actually modify the firing pattern of the neurons next to which it is being applied. We and others (Dubois, 1975; Dubois *et al.*, 1975, 1976) have recognized that LRF is present not only in specific neurons both in the hypothalamus and in the anterior nucleus of the amygdala, but also in a very large number of fibers (Hökfelt *et al.*, 1978). The distribution of LRF in the ventral hypothalamus is different from that of TRF, which appears to be more

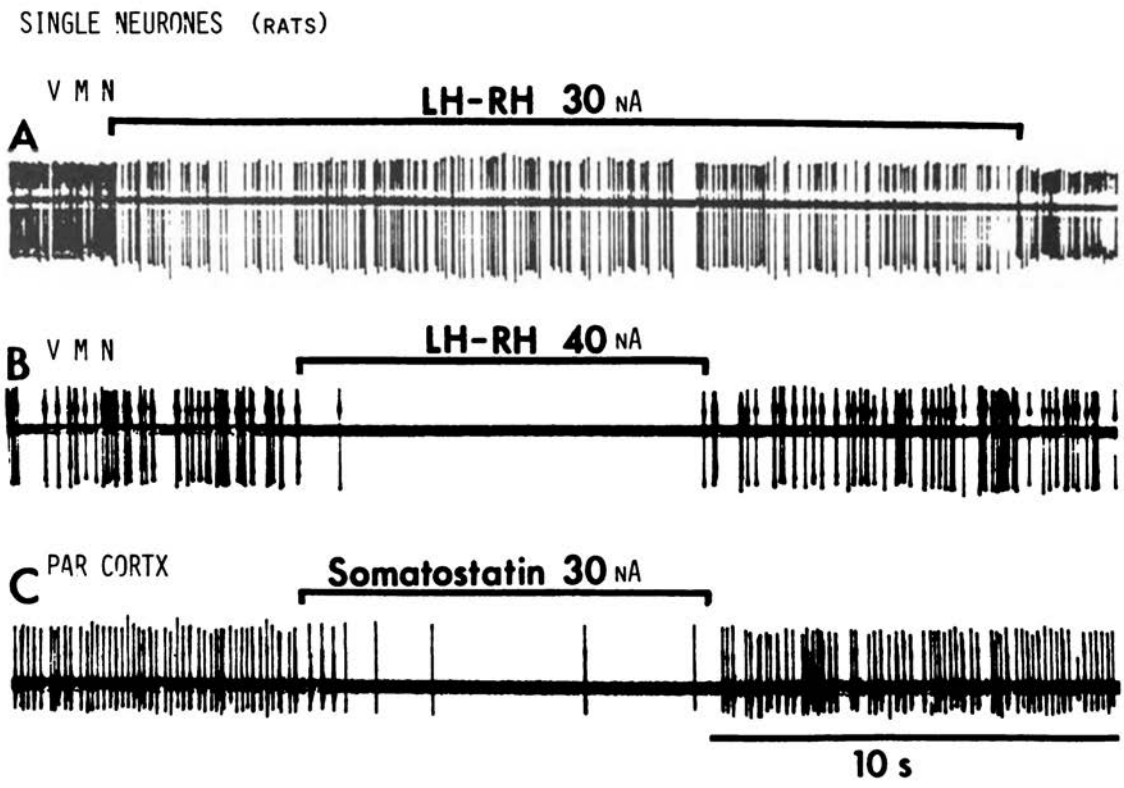

FIGURE 5 Inhibitory activity on spontaneous firing of somatostatin and LRF applied by microiontophoresis to single neurons. From Renaud *et al.*, 1975.

closely packed and mostly on the midline. It is also quite different from that of somatostatin.

There is definitely a pattern for these peptides within the central nervous system, as is also true for other peptides. Though they are ubiquitous, they are not randomly distributed. To the contrary, particularly in the case of LRF, there is no doubt that it is in very discrete locations in the brain, as observed in both laboratory animals and, in some studies, humans.

Figure 5, taken from some studies by Renaud's group at McGill (Renaud *et al.*, 1975), shows the effect of a synthetic LRF preparation when applied by microiontophoresis to single neurons in the ventromedial nucleus. In every case, all neurons to which LRF was applied in this manner either slowed down or totally inhibited the firing pattern. In no case that I know of has there been any activation of either the spontaneous or the glutamate-activated firing pattern of any of the neurons. This is also the case with somatostatin.

The location of LRF in the rat brain is very reminiscent of the study by Bloom *et al.* (1978) on the distribution of immunoreactive beta-endorphin in the rat brain.

In a proposal to study the characterization of the hypothalamic factor involved in the secretion of LH, I suggested to the granting agency that one of the practical goals that could be considered after the primary sequence of LRF had been established was not only the reproduction of the peptides by synthesis but also the synthesization of a series of analogs, some of which could be antagonists of LRF; hence, the possibility of affecting gonadotropin secretion by such analogs and of approaching this as an entirely new means of contraception.

Several thousands of these analogs were prepared in a few academic laboratories and in a number of industrial laboratories. Some have proven to be more potent than the native LRF. The very first report, claiming a substance to be about 10 times more active than LRF, came from Fujino's laboratory. This modification—DES-GLY-10, now PRO-9-ethyl-amide—is referred to below as the "Fujino modification." While this material was the first of the LRF analogs that was more active than the native structure by deletion of the C-terminal glycine, another series of analogs was prepared at the Salk Institute by Monahan and found by Amoss to be more active than LRF upon replacement by a D amino acid in this hinged glycine in the sixth position (Monahan *et al.*, 1973). One can actually combine a series of these modifications to obtain a super-LRF.

Very soon after the sequence of LRF had been established in a series of systematic studies by Burgus and Monahan, and later by Rivier, we

started deleting every residue of the decapeptide or replacing it with alanine. During the early studies on the *in-vitro* system with monolayer culture, Vale *et al.* (1972) recognized that in all cases in which there was a deletion of the histidine in the second position or a replacement of histidine by, in this case, alanine, we would get substances that would be partial agonists and partial antagonists. The antagonists were not potent antagonists: 3,000 ng of the substance inhibited the activity of 1 ng of LRF. For a while, there was a lot of discussion about this particular point, especially between our group and Schally's (1971). But there never has been any doubt in my mind that these early observations were to lead to present very potent LRF antagonists.

All of the potent LRF antagonists that are based on this concept have a modification, either a deletion of the histidine in the second position of the native molecule or replacement of this histidine by a D amino acid. The Fujino modification, when entered into an antagonist, does not increase the antagonistic activity of that analog. To my knowledge, nobody has given a complete explanation of this phenomenon.

On the other hand, with introduction of the D amino acid into the antagonist and deletion of the histidine in the second position, the biological activity of that analog as an antagonist is increased. There is good reason to believe that this particular modification is associated with the binding of the peptide to the receptor. In one of the early studies we were able to show *in vivo* that the first early analog of the deleted histidine of LRF, and then the later more potent analog as seen by the *in-vitro* test in Vale's monolayer system (Vale *et al.*, 1972), were indeed active *in vivo*. This illustrates the inhibition of the response, as a function of the dose of the antagonist, to a given constant dose of LRF.

As an agonist, the D-tryptophane-6-Fujino modification of LRF is still the most potent super-LRF analog that has been made. In some tests, like some of the ovulation tests, it can be as much as 1,000 times more potent than the native LRF. It is also very long-acting. There is evidence that this particular material can be active for as long as 36 to 40 hours in laboratory animals and humans.

In the laboratory, the most interesting observations are very often the most unexpected. For example, Rivier *et al.* (1977) observed that one of the super-LRF's, namely D-tryptophane-6-Fujino modification, when given to otherwise normal male or female animals in relatively large amounts (in this case ~ 1 μg/day) is, to everybody's surprise, a very potent inhibitor of gonadal functions. This observation was originally reported by the group of Abbott with Wilfred White and his collaborators at the endocrinology meeting in Hamburg (DeSombre *et al.*, 1976) and was subsequently confirmed by several other groups (Dutta *et*

al., 1978). They had been working with female animals. We noted that the observation was also correct for males and that administration of 10 μg/day for 15 days of D-Trp-6-Fujino LRF in otherwise normal rats led to a dramatic decrease in testicular and seminal vesicle weights. LH levels were 10 times normal. FSH levels were also statistically elevated, and testosterone levels were low.

In a series of ongoing studies, Rivier *et al.* (1978) observed that the same substance, super-LRF, the D-Trp-6-Fujino LRF, administered to female rats from the first to the tenth day following mating, becomes a powerful inhibitor of implantation when reaching doses of 1 to 2.5 μg. The same results are obtained if this super-LRF is administered from the first to the seventh day after mating, or later, from the seventh to the tenth day after implantation. The shortest time during which the peptide has been given is actually 5 to 7 days. So here is a super-LRF that acts as an abortifacient.

Similar observations have been made by other groups such as those of Labrie *et al.* (1976) in Quebec and Schally *et al.* (1971). Everybody seems to agree that some sort of down-regulation is involved, to use the common term, meaning that it certainly is not a depletion of the pituitary's stock of LH.

All of this is very much in keeping with what we had proposed originally regarding the possibility of designing LRF antagonists, of designing new methods to alter the normal ovarian cycle, and, hopefully, of developing new means of contraception. None of these substances is as yet optimal for contraception. We may well get some extremely interesting molecules out of all of this. The contraceptive effects of the super-LRF, however unexpected, may turn out to be some of the most interesting ones for practical use.

Yen *et al.* (1973) have started a few studies in which the antagonists are given to women, and it looks as if in relatively small amounts these will lower the levels of LH and FSH in postmenopausal women. Regarding the superagonists, we have done very little clinical study with these as yet. We are still clearing them for an IND with the U.S. Food and Drug Administration.

Dr. Shao Ying in our laboratory at the Salk Institute found that administration of μg amounts of beta-endorphin, which was isolated from the hypothalamus and pituitary a few years ago because of its opiatelike activity, results in powerful inhibition of both LH and FSH secretion.

How does it work? We do not know as yet. However, we do know that it does not work directly at the pituitary level. We had actually added the endorphins on the monolayer systems as soon as we had the synthetic

replicate of the substance. We also know that it does not inhibit the secretion of gonadotropins in response to LRF when added directly at the level of the pituitary tissue.

This effect of beta-endorphin is very interesting. We know very little about its peripheral effect. The opiatelike activity and the behavior of beta endorphin are well recognized. They can be replicated easily by injecting the peptide directly into the third ventricle or one of the lateral ventricles.

We know of very few effects of beta-endorphin injected into the periphery. Several of us are puzzled by the large amounts of beta endorphin that circulate along with ACTH, not only in response to stress but also in the diurnal rhythm. What are the possible roles of beta-endorphin and the mechanism of action through which it inhibits LH secretion? This is part of the puzzle that laboratory workers are trying to solve.

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PSYCHOSOCIAL ASPECTS OF CONTRACEPTION

PHILIP A. CORFMAN

Session Chairman

Psychosocial Aspects of Contraception

WARREN B. MILLER

Technology, as the application of scientific method and knowledge to a practical, everyday problem, is applied science. As such it is a manifestation of one of the most important characteristics of the human species, namely the ability to manipulate and change the environment in the service of individual and group interests. Of course, each environmental change that is introduced to solve one problem almost invariably creates a new problem. This follows from the nature of biobehavioral adaptation. Organisms are generally adapted through evolutionary processes to a particular environmental niche. Change that environment and the organism must deal with new challenges. Thus, humans, in changing the world around them and, to some extent, the world within them to suit their purposes are constantly creating unanticipated and often undesired "side effects." These, in turn, commonly stimulate efforts toward the development of alternative or modified technology. And so the process continues.

Contraceptive technology represents the human effort to apply scientific knowledge and method to the problem of preventing conception. Although traditional methods of contraception have been used throughout the world's cultures for centuries (Himes, 1963), it has only been during the last 50 years, beginning with Knauss and Ogino's studies of human ovulation in the 1930's (Dickenson and Bryant, 1938), that modern scientific techniques have been systematically applied to the solution of this problem. As a result of their very high level of effectiveness, the modern contraceptive methods that have been de-

veloped through these efforts, such as intrauterine devices and oral antiovulatory agents, have contributed greatly to improved conception control and fertility regulation. However, each of these modern methods appears to be associated with important medical complications and undesirable side effects (Hatcher *et al.*, 1976). For this reason, and because each method has significant rates of nonacceptance, discontinuation, and failure, the search goes on for new and improved contraceptive technology.

It is common for physical and, more recently, biological research to lead to the introduction of new technological devices well before their social and psychological impact has been fully considered, much less scientifically explored. Contraceptive technology is no exception. Although some social and behavioral research has been devoted to contraception during the last 50 years, especially by demographers (e.g., Whelpton and Kiser, 1959), it has only been in the last decade that psychologists, sociologists, and anthropologists have become deeply involved in the study of contraceptive behavior. Thus, our current psychosocial knowledge is limited and preliminary. Before attempting to describe and synthesize this knowledge, it will be useful to discuss three basic assumptions that will guide the discussion.

First, contraceptive behavior can be fully understood only in the context of the evolution of mammalian reproductive behavior and the historical development of human reproductive behavior. In any living organism, reproduction is regulated by a set of mechanisms that act in concert to promote survival of the local breeding population (Miller and Godwin, 1977, Chapter 2). In higher mammals these mechanisms are anatomical, physiological, behavioral, and social. In humans, the behavioral and social mechanisms have assumed a predominant role. In early gathering and hunting societies, the connection between heterosexual intercourse and conception was generally recognized, and reproduction appears to have been regulated largely by abstinence, lactation, abortion, and infanticide. The individual behaviors involved in these four regulatory methods were controlled to a large extent by social norms. It was not until the development of modern contraceptive methods that sexual intercourse could be separated reliably from reproduction. As a result, there have evolved two separate psychological and behavioral domains that are closely connected behaviorally and emotionally to the sexual domain but that have nonsexual goals (Miller, 1978a). One is the contraceptive domain, which includes the various cognitions, feelings, motivations, and behaviors that are involved with efforts to prevent or avoid the occurrence of conception. The other is the "proceptive"

domain, a term that includes the cognitions, feelings, motivations, and behaviors that are involved with efforts to achieve conception.

Although contraception and proception are on opposite poles of a continuum for some people, this is not the case for many others who participate in sexual intercourse without either contraceptive or proceptive intent. In fact, this is probably the modal pattern in most of the industrially less-developed nations. For example, in many nations no effort is made to time the birth of the first child within marriage through contraceptive or proceptive efforts (Miller and Newman, 1978, Chapters 19 and 26). The primary significances of this first basic assumption, then, are that contraceptive behavior has only recently emerged in human history, that it is not yet a part of the behavioral repertoire of many individuals in most cultures and most individuals in some cultures, and that cultural and subcultural norms affecting its expression have yet to be fully developed and consolidated.

The second basic assumption for this discussion, which is almost self-evident from the consideration of the first assumption, is that a complete understanding of contraceptive behavior can be attained only with awareness of multiple, nested systems operating at the biological, psychological, and social levels of organization. In other words, it is essential to conceptualize the individual—the actual or potential contraceptor—on the one hand as made up of component tissues, organs, and organ systems, some of which interact directly with the contraceptive method and, on the other hand, as a component in a nested series of social systems including the marital dyad, the family, the neighborhood, the community, and larger political–cultural units, all of which act to shape contraceptive behavior.

Consistent with these three levels of organization, the empirical findings that are summarized below are discussed under three main categories: characteristics of the contraceptive method, characteristics of the contraceptive user, and characteristics of the context of contraceptive use. This method–user–context framework not only embodies the nested systems assumption, but it also calls attention to three important and distinct sources of variation in contraceptive use.

The third basic assumption is that contraceptive behavior can be understood adequately only when it is conceptualized as a dynamic process that changes constantly. Different behavioral patterns and psychological characteristics occur within various time frames—the entire life course, several months or years within a particular developmental period, or several days or weeks. Interpretation of much of the research on the psychosocial aspects of contraception is affected by

these differences. The dependent variables that are used in this research are commonly categorical and static in character. Some investigators talk about family planning "adopters" or "resisters." Others compare "effective contraceptors" with "ineffective contraceptors" or contraceptive clinic "dropouts" with "nondropouts." However, within each of these categories there are numerous aspects of contraceptive behavior that deserve study. For example, consider just the three psychological/behavioral complexes of method selection, method utilization, and method discontinuation. Each of these complexes involves its own set of cognitions, feelings, motivations, distinct decisionmaking processes, and different behavioral sequences. Moreover, each is tied to the other in an extended psychosocial process. It is unlikely that contraceptive behavior will be well understood without separate consideration being given to each of these three complexes and to the relationships among them.

What is currently known about the psychosocial aspects of contraception? A useful way to approach this question is in terms of the three nested systems discussed above: the contraceptive method, the user of the method, and the context of use. As will be apparent, it is virtually impossible to discuss one of these three systems without including one or both of the other two. Nevertheless, the distinction is heuristic and pragmatic.

METHOD

All contraceptive methods have a variety of characteristics that affect their use. In recent years, several different approaches have been taken in describing and categorizing these characteristics (Freeman and Berelson, 1976; Polgar and Marshall, 1976; Rogers *et al.*, 1973). For the purpose of this section, the important characteristics are those that are intrinsic to the method, i.e., those that are a function of the inherent nature of the method. These intrinsic characteristics may affect the use of a method through either biological, psychological, or social mechanisms.

At the psychological level, some intrinsic characteristics are idiosyncratic to a particular method. For example, the condom, foam, and the tail of an IUD each has a unique effect upon penile sensation during sexual intercourse. Other characteristics may vary considerably within a particular method. This is the case of such physical properties as color, odor, taste, and shape. Finally, certain intrinsic characteristics are common to two or more methods. On the basis of a literature review and my own research in the United States, I identified a number of different

dimensions of behavior that were specifically affected by certain contraceptive methods (Miller, 1975c). For example, the abstinence methods—including complete abstinence, periodic abstinence or rhythm, and withdrawal—all involve the inhibition of sexual activities or responses; the coitus-dependent methods—including the condom, foam, and the diaphragm—generally involve the interruption of ongoing sexual behavior; the coitus-independent methods—including oral contraception and the IUD—involve behavior that is separate in time and place from particular sexual acts; the vaginal insertion methods—including the diaphragm and foam—both require genital manipulation on the part of the women; the medical methods—including oral contraception, the IUD, vasectomy, and tubal ligation—all invade the body and thereby directly impinge upon perceptions and conceptions of the body; the daily routine methods—including oral contraception and temperature rhythm—require the daily use of complex mental processes that involve habit, reasoning, and memory; and the male methods—including withdrawal, condom, and vasectomy—all require the man to assume responsibility for control of conception and the woman to rely on his doing so. In an analysis of acceptability ratings of contraceptive methods, Gough (1973) identified four primary groupings of contraceptive methods. These were identical with the first three that I described (Miller, 1975c), namely the coitus-inhibiting, the coitus-dependent, and the coitus-independent methods. A fourth grouping included vasectomy and tubal ligation. Two important characteristics of this latter grouping are the surgical requirement and their general irreversibility.

The importance of a behavioral or psychological classification of contraceptive methods can be illustrated by discussing the use of the condom, foam, and diaphragm. Traditionally, these have been referred to as "barrier" methods, a classification based on mechanism of action. Above, they are referred to as "coitus-dependent" methods, which has the advantage of suggesting what is required behaviorally and psychologically of the user of this type of method. Thus, someone contracepting with condom, foam, or diaphragm must be able and willing to stop sexual activity in order to apply the method. Users who are impulsive or who resent the interruption are candidates for inconsistent contraceptive use. Ultimately then, the behavioral classifications of contraceptive methods suggest certain complementary psychological characteristics of users that may interact favorably or unfavorably with the methods to affect contraceptive practice.

At the biological levels, the intrinsic characteristics of methods include their effectiveness, the number and quality of their side effects, their safety, the duration of their action, their route of administration,

and their reversibility. While all of these characteristics tend to have important effects upon contraceptive selection, use, or discontinuation, the first two appear to have special importance. Both of them interact significantly with psychological factors.

The recognition that use-effectiveness is well below theoretical effectiveness has been reconfirmed by the most recent studies of method failure rates (Vaughan *et al.*, 1977). A major cause of this reduction in use-effectiveness appears to be the motivational and behavioral requirements of particular methods. With respect to contraceptive side effects, experience with oral contraception provides ample illustration of the importance of both physiological effects and user attitudes for the experience of side effects. On the one hand, the physiological effects of oral contraception on mood and physical (especially menstrual) symptoms appear to affect a large proportion of women and are substantial for about 10% of users (Grounds *et al.*, 1970; Kane, 1976; Moos, 1968; Paige, 1971). On the other hand, several well-designed studies indicate that the expectation of side effects may add considerably to their quantity and quality (Goldzieher *et al.*, 1971; Honigfeld, 1964; Pincus, 1966). In addition, clinical observations indicate that an individual's tolerance of a physical sign or symptom is influenced by the interpretation and personal meaning of that sign or symptom (Miller, 1975a). Clinical and research findings suggest that this principle applies well to the practice of oral contraception (Bardwick, 1973).

Of course, by no means all of the psychological "side effects" of oral contraception are negative. Many women experience decreased menstrual pain or beneficial mood effects while using oral contraception (Moos, 1968). Physiological effects interacting with user attitudes to produce negative evaluations of methods are by no means limited to the use of chemical agents for oral contraceptive purposes. Much of what has been described above appears to apply to the IUD as well (Reading and Newton, 1977). Furthermore, there does not seem to be a substantial overlap between the two groups of women who negatively react to the two methods (Moos, 1968).

At the social level, the intrinsic characteristics of contraceptive methods affect their utilization by affecting the degree and manner of their distribution. Methods that deteriorate rapidly need either an active distribution pipeline or special storage conditions. Methods that require medical personnel for their administration are generally limited to distribution through medical outlets. Methods that are complicated to manufacture, distribute, or administer are likely to be more costly. In all three of these examples intrinsic characteristics of the methods affect user access to them and, thereby, their selection and subsequent use.

USER

Contraceptive users also have characteristics that tend to affect the processes of contraception. However, it is difficult to describe these characteristics and understand their dynamics without first focusing on a specific cultural or subcultural population. This is largely because contraceptive behavior is at very different points of development and elaboration cross-culturally. For example, in those cultures or subcultures that are early in the process of incorporating modern contraceptive practice as an important and legitimate form of behavior, a favorable attitude toward contraception in general (Sinquefield, 1974) or simply knowing about specific methods (Baldwin and Ford, 1976) may be crucial psychological variables. However, in much of the United States, where contraceptive practice in married couples is presently approaching universality (Westoff, 1976), the crucial psychological factors appear to be very different.

One of the most important of these is the motivation to prevent conception. A recent investigation explored the relationship between motivation for fertility control and strength of contraceptive practice (Card, 1978). The motivational variable was measured by an index with high internal consistency that was based upon questions about the perceived value of having another child in the future. The strength-of-contraceptive-practice variable was measured by an index of contraceptive behavior, which was based on both the efficacy of the method used and the frequency of its use. Motivation for fertility control explained one-quarter of the variance in strength of contraceptive practice for 100 Caucasian men and almost one-third of the variance for 100 Caucasian women.

Another important psychological factor is the individual's attitude toward sexuality. Although there is little systematic evidence on this point, several investigations have lent strong support to the notions that single women who do not accept themselves as sexual beings (Miller, 1976), married women who reject sexuality (Rainwater, 1960), and married men and women who are not mutual in their sexual activity and who are sexually unsatisfied (Rainwater, 1960), all tend to be relatively ineffective in their contraceptive practice.

Another important factor for which evidence is lacking is the individual's attitude toward specific contraceptive methods or characteristics of contraceptive methods. One recent investigation explored the relationships between antecedent scores on a group of contraceptive attitude scales and several subsequent variables that reflected contraceptive practice, including whether or not the subjects used oral

contraception or an IUD, frequency of contraceptive use, and conception during the use of oral contraception (Miller, 1977). Six of the 19 contraceptive attitude scales predicted the use or nonuse of oral contraception in all of the three independent samples of women that were studied (the number of subjects in each sample was about 320). One of these six scales indicated negative attitudes toward coitus-dependent methods, another indicated tolerance of methods with somatic effects, and a third reflected a cluster of attitudes that are likely to promote satisfaction with oral contraception. Four of the 19 scales predicted the use or nonuse of the IUD in all three samples. Three of these four scales were different than those predicting oral contraception use. The fourth—the pill satisfaction scale—showed an inverse relationship. Four of the 19 scales predicted frequency of contraceptive use in all three samples, including one based on attitudes that would tend to lend to contraceptive risk-taking. In one sample, 11 women became pregnant while using oral contraception during the 2-year follow-up interval. Four of the contraceptive attitude scales predicted this occurrence, using the contraceptive risk-taking scale.

A set of psychological factors that are important determinants of contraceptive behavior in the United States are those that integrate the various cognitive, affective, attitudinal, and motivational forces that affect contraceptive practice, thereby producing a more or less adaptive stream of behavior. One subset of these has been demonstrated repeatedly to be significantly related to effective contraceptive behavior. This includes the tendency to plan (Sinquefield, 1974), future orientation (Kar, 1971), future time perspective (Mindick *et al.*, 1977), and future striving (Harvey, 1976). Other general psychological traits, such as maturity, personal adequacy, impulse control, and optimism, have also been found to relate to effectiveness of contraceptive practice (Bakker and Dightman, 1964; Kar, 1971; Whelpton and Kiser, 1959), but their importance has not been as consistently shown as it has for the planning and future-oriented subset.

An important limitation for the factors that have been discussed to this point has been the common tendency to conceptualize them as relatively enduring characteristics of the person. Unfortunately, many of the determinants of contraceptive behavior tend to be specific to the situation. Several reports convincingly suggest that the predictability of contraceptive behavior increases substantially as the predictive attitude becomes more specific with respect to object and time period (Davidson and Jaccard, 1978; Werner, 1977). Davidson and Jaccard were able to predict correctly for 80% of their subjects whether or not a woman would adopt oral contraception over a 2-year period (Davidson and

Jaccard, 1978). This was accomplished by combining a specific set of attitudes toward oral contraceptive use with a set of normative influences for and against oral contraceptive use in a weighted formula according to the method of Fishbein (Ajzen and Fishbein, 1973).

An important component of the attitude measure utilized in this last investigation is the subject's perceived probability that her action—in this case the adoption of oral contraception—will produce specific consequences. This approach is one of several that seek to understand the way that multiple, situationally specific attitudes and other psychological factors affect contraceptive behavior in terms of decisionmaking under conditions of uncertainty (Miller and Godwin, 1977, Chapter 3). Another example is a recent, largely descriptive investigation by Luker (1975), which focused on the decision to use or not to use contraception on any particular occasion. She concluded that contraceptive use or nonuse is determined on each occasion by an implicit, not necessarily conscious, balancing of the pros and cons—the benefits and costs—of the possible consequences of different contraceptive behaviors, together with an assessment of the probability of these consequences (most particularly pregnancy) actually occurring.

These approaches tend to focus on the more intentional and deliberate aspects of contraceptive use. Some research has documented the many types of psychological factors affecting contraceptive use that do not readily fit with this rational model. For example, one study investigated the psychological antecedents to conception among 642 women seeking an abortion for an unwanted pregnancy. Each of the following psychological factors were identified by between 5% and 27% of the subjects as playing an important role in their getting pregnant: denial of the possibility of pregnancy; an inaccurate perception of their ability to conceive; previously made intentions not to have sexual intercourse; psychological inertia over seeking and obtaining a contraceptive method; embarrassment or fear over seeing a doctor about contraception; fear of discovery by others if contraception was sought and obtained; a mistaken assumption that their sexual partner would use a contraceptive method; and impairment of their judgment by alcohol (Miller, 1975b). Many other factors were identified by these women, but the ones listed here are most directly at odds with a strict cost–benefit analysis of contraceptive nonuse.

The many situation-specific psychological factors that affect contraceptive practice can be understood by recognizing the changing capabilities and needs of individuals as they move through their sexual and reproductive careers. In fact, several recent investigations suggest that, given a variety of contraceptive methods from which to choose,

individuals in the United States move through contraceptive careers during which their selection and use of contraceptive methods undergo developmental changes that reflect the stage-specific psychological and interpersonal tasks with which they are coping. Thus, many individuals move through a typical sequence at the start of their contraceptive careers (Lindemann, 1974; Miller, 1976). Beginning with the abstinence methods of contraception, they progress to the coitus-dependent methods, and then, commonly in the context of a lasting heterosexual relationship, to the coitus-independent methods. With the breakup of that relationship there often is a reversion to the more *ad-hoc* coitus-dependent methods, but with resumption of a stable relationship or with marriage, there is usually a return to the coitus-independent methods. Usually, but not necessarily, this general sequence occurs during adolescence and prior to marriage. The speed of the transition depends upon such factors as the ability of the individual to think about and deal with the world in an abstract way; the individual's knowledge of and affective responses to sexuality, contraception, and reproduction; and the opportunities for sexual and contraceptive experience that the social structure presents to the individual.

Within marriage, especially during the first 10 years, when most childbearing occurs, contraceptive careers tend to be characterized by use of one or both of the coitus-independent methods (Westoff, 1976). These methods are discontinued for 1 to 2 years in connection with each child that is born. In addition, there is often switching to the alternative coitus-independent method for a "rest" interval. The reasons cited for these switches most commonly involve side effects, although fear of effects on health and doctors' orders are often considerations (Miller, 1977). Although these switches frequently appear to be cued by external events such as negative publicity about the medical effects of oral contraception or the IUD, it seems that many of them are inspired by a desire to experience a different mixture of the costs and benefits that are associated with any one of these methods.

When couples reach the end of their childbearing, contraceptive careers commonly change to involve use of tubal ligation or vasectomy (Westoff, 1976; Westoff and Jones, 1977). Although there has been little systematic research, this decision appears to revolve around issues of confidence in marital stability, certainty about the termination of childbearing, satisfaction with sexual interaction, and feelings about the prospect of continued use of nonsurgical methods of contraception (Miller, 1978b). An additional issue concerns which member of the couple should have the sterilizing procedure.

This brief sketch of model patterns of contraceptive careers in the

United States highlights the diversity of developmental tasks with which contraceptive practice is associated. Considering the recent changes in American family life related to cohabitation, divorce, remarriage, and single parenthood (Westoff, 1978), this diversity is undoubtedly far greater than the above career outline suggests. Thus, at each stage there is much new behavior for the individual to learn and master and a number of new psychological issues with which he or she must deal. It appears that the greatest contraceptive competence can be achieved by acquiring the broadest possible repertoire of contraceptive response options and by being prepared to meet ever-changing contraceptive capabilities and needs. Before these principles are extended too quickly outside the United States, it should be reemphasized that the contraceptive career patterns that are discussed above appear in the American culture. Other cultures or certain subcultures within the United States may have very different patterns. Therefore, what contributes to individual contraceptive competence in other cultures may also be very different.

Up to this point the discussion has focused on the individual as the user. However, in many instances, most particularly where there is an enduring relationship, it is more appropriate to focus on the couple as the user. This may be illustrated by extending the concepts of the contraceptive career and of contraceptive competence to married couples. Thus, it may be said that in married couples there are likely to be trade-offs and agreements as to who contracepts at one time or in one situation and who contracepts in another. Indeed, the contraceptive competence of a couple depends upon the contraceptive response options of both members, the agreed upon pattern of contraceptive practice, and their ability to adapt that pattern to changing circumstances.

Although very little systematic research has been conducted, there is some evidence regarding what factors affect the contraceptive practice of couples (Back and Hass, 1973). A recent investigation found that women with multiple unplanned pregnancies were less frank and direct in their communication and provided less verbal disclosure (Campbell and Barnlund, 1977). Previous studies in other cultures have observed that effective marital communication was associated with the length, regularity, and success of contraceptive uses (Hill *et al.*, 1959; Stycos and Back, 1964). In his pioneer study of marital couples and childbearing, Rainwater (1965) found that lower class couples with highly segregated role relationships were far less effective than middle class couples in their contraceptive practice after the birth of the last wanted child. The same investigator found that middle class couples who expressed mutual enjoyment of the sexual relationship were far more effective contracep-

tors than those where one spouse expressed greater enjoyment. These and the findings of other investigators (Back and Hass, 1973) suggest that effective contraceptive practice by a couple depends upon their functioning as a cooperative, communicating, and mutually satisfying unit, particularly in the sexual and reproductive domains. Anything constraining this type of functioning, whether it be disparate goals between spouses or a cultural norm of male marital dominance or of female sexual modesty, would tend to disrupt effective contraceptive practice.

CONTEXT

The contextual characteristics that affect contraceptive behavior may be divided into three main groups: characteristics of the individual's social network, characteristics of the contraceptive delivery system, and general cultural and normative characteristics. These are not independent or mutually exclusive; many cultural and normative influences operate through social networks and determine the nature of the delivery system, and the delivery system commonly is made available through or actually includes the social networks of users or potential users. Nevertheless, the three categories will serve as a useful guide for the following discussion.

Two recent investigations provide some understanding of the relative impact of social networks and the delivery system on contraceptive behavior. Kar (1978) examined the relationship between personal attitudes toward the use of contraception, perceived social support for that use, and perceived accessibility to contraception in a sample of almost 2,500 urban Venezuelan women. He found that when all three factors were favorable, 90% of the women had used contraception, when all three were unfavorable less than 30% had used contraception, and when the three factors were mixed in various favorable/unfavorable combinations the percentage of users fell at appropriate intermediate values. Two multiple regression analyses, with "ever used" and "currently using" contraception as the dependent variables, revealed that all three factors were independent determinants. Perceived social support was somewhat stronger than perceived accessibility which, in turn, was somewhat stronger than personal attitudes.

Copp (1977) studied 174 women who had attended two family planning clinics in Chicago. He interviewed the subjects, most of whom were black, about their clinic attendance and their use of contraception. His preliminary findings indicate that continuation of clinic visits was most influenced by the client's perception of the clinic, the clinic staff,

and the service that was provided; that continuation of the adopted contraceptive method was related primarily to method satisfaction and social support; and that continuation of some form of contraception was related to risk of exposure to sexual activity, knowledge about use of the adopted method, and social support after adopting the method.

Both of these investigators indicated that social support, or at least the perception of it, has an important effect on contraceptive behavior. This conclusion is supported by the work of others. Rogers (1973) summarized some of the important earlier research on the role of interpersonal communication in transmitting family planning information and persuading potential contraceptive users to adopt family planning. He concluded that the influence of family members, friends, neighbors, and others in the personal network is of primary importance. Similarly, in a recent investigation of almost 2,000 women in South Korea, Chung and his colleagues (1972) found that the social–environmental pressure to use contraception was one of the strongest correlates of contraceptive use among a very large group of social and psychological variables (Chung *et al.*, 1972, Chapter 7). The environmental press variable was composed of the perceived attitudes of the husband, relatives, friends, and neighbors toward use of contraception and limitation of family size.

The findings of Kar and Copp also indicate the importance of the contraceptive delivery system. There are many different factors in that system that have been found to affect the selection and use of contraception. These include features of family planning clinics, their services, and their staff (Sung, 1977); administrative aspects of the contraceptive delivery system (Valsan, 1977); access to family planning clinics (Baldwin and Ford, 1976; Sirageldin *et al.*, 1976); characteristics of field workers (Repetto, 1977); characteristics of family planning opinion leaders (Palmore *et al.*, 1976); features of the incentive systems for potential contraceptive adopters (Rogers, 1973, Chapter 5) and for contraceptive delivery system staff (Phillips *et al.*, 1975); and cultural symbols that are associated with contraceptive methods (Rogers, 1973, Chapter 6). Not to be ignored are the effects that commercial efforts can have (Black and Harvey, 1972). These efforts range all the way from contraceptive package inserts (Fleckenstein *et al.*, 1976) to a systematic, national social marketing program (Davies and Louis, 1977). With the latter type of approach, marketing programs that focus on a specific contraceptive method such as the condom may also promote the general practice of all forms of contraception (Black and Harvey, 1976). Moreover, a delivery system operating totally outside the formal medical-care system can be especially effective (Black and Harvey, 1972, 1976).

The general cultural and normative influences upon contraceptive behavior are also numerous. Perhaps the most important current investigations concerned with this topic are being conducted by the World Health Organization's (WHO) Task Force on Acceptability Research in Family Planning (World Health Organization, 1977, 1978). The Task Force projects, which are being conducted in at least 24 different nations from all regions of the world, focus on the acceptability of various fertility-regulating methods. One of their primary objectives is to help in the design of new contraceptive technology that will fit the needs, capabilities, and preferences of people in specific cultural contexts. This effort is designed to complement the usual approach in which people are persuaded to adjust to given features of the technology (Marshall, 1977).

There is now considerable evidence that there are major cultural differences in the acceptability of different contraceptive methods and that information about these cultural preferences may be utilized to promote national family planning programs (Harding *et al.*, 1973, 1975; Hass, 1976; World Health Organization, 1977, 1978). As Marshall (1977) has indicated, contraceptive use is affected by the acceptability of contraceptive methods to at least three distinct groups of people: policymakers, contraceptive program personnel, and users and potential users. What the policymakers consider to be acceptable can affect use by determining the availability of specific methods. For example, the administrative decision to distribute oral contraception on a nonprescription basis has significantly affected contraceptive behavior (Davies and Rodríques, 1976). What program personnel consider acceptable can affect use in the ways that they organize and provide contraceptive services. For example, a wide range of contraceptive failure rates is reported in the family planning literature, and clinic personnel tend to quote the rates that are favorable to the methods that they prefer, thereby influencing client selection (Trussell *et al.*, 1976).

The potential effect of user acceptability on contraceptive practice may be illustrated by two types of methods, currently being studied by the WHO Task Force, that are especially relevant to ongoing efforts to develop new contraceptive technology: male methods and methods that affect menstrual bleeding (World Health Organization, 1977, 1978). The acceptability of male methods is being investigated in Fiji, India, Iran, Korea, and Mexico. In all of these countries a large proportion of men expressed willingness to assume responsibility for family planning—even in Mexico and Iran, where men tend to see contraceptive use as a woman's responsibility. In Mexico, Korea, Iran, and rural India two hypothetical male methods—a daily pill and a monthly injection—were

viewed as more acceptable than the existing male methods of condom and vasectomy. In Fiji and urban India the condom was viewed as the most acceptable male method. In all the countries there was general agreement about duration of action and route of administration. Other things being equal, a longer duration of action was more acceptable, reaching a peak at 6 months, and oral administration was more acceptable than injection. These findings were related to certain beliefs that were different among the different countries. For example, in Korea men believed it would be less convenient and more embarrassing to obtain monthly injections compared to daily pills, whereas in Mexico men believed that monthly injections would be "very painful" and would more likely lead to a decrease in sexual desire. On the other hand, Indian men believed that their wives, families, and friends would be more likely to approve use of a daily pill rather than a monthly injection.

The WHO investigation of perceptions of menstrual bleeding has been conducted in 10 countries. The preliminary findings suggest that a large proportion of women in the industrially less-developed countries would be reluctant to use a contraceptive method that resulted in amenorrhea. There appear to be three reasons for this: menstrual bleeding is perceived as a regular reassurance to the woman that she is able to bear children; for a woman who does not want children at the time, menstrual bleedings are perceived as a regular reassurance that she is not pregnant; menstrual bleedings are perceived as necessary in order to rid the body of impure blood. Other investigations in countries such as the United States and England suggest that the induction of amenorrhea may be acceptable to a sizeable proportion of women (Loudon *et al.*, 1977; Miller and Smith, 1975). Other tentative findings of the WHO cross-national investigation indicate that most women experience some form of bodily and/or psychological distress in relation to menstruation, most women feel that they should not have sexual intercourse while bleeding, and many women—especially the less educated—are misinformed about the temporal relationship between menstruation and ovulation.

CONCLUSION

In view of the many characteristics of the contraceptive method, the contraceptive user, and the context of contraceptive use that appear to affect contraceptive practice, there is no simple way to summarize the scientific observations that have been reported and discussed here. Indeed, perhaps the most important conclusion to be drawn is that simplicity in the field of contraception is an illusory concept. There is no perfect contraceptive method, no best way to contracept, no ideal

delivery system. What we have—and probably will continue to have for some time—is an increasing number of methods, each of which has positive and negative characteristics that interact in complex ways with the different (and changing) capabilities and needs of users and with the different (and changing) social and cultural context of use. Perhaps the most appropriate term to characterize this situation is pluralism. Thus, there is a plurality of methods for a plurality of user needs and capabilities provided through a plurality of delivery systems for use in a plurality of contexts.

Ongoing research concerning the development of new contraceptive technology should increase this pluralism. If so, there will be a greater array of contraceptive choice, users will be better able to expand their contraceptive repertoires, and administrative units will be able to offer a greater diversity of services. It is hoped that behavioral and social scientists will be deeply involved in these developments, working in close collaboration with biological and medical scientists, with consumers, and with policymakers in order to identify and understand the detailed psychosocial features of the very large terrain that has only been roughly mapped to date.

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Discussion of Paper Presented by Warren B. Miller

WENDY BALDWIN

Dr. Miller has presented a very comprehensive review of literature on psychosocial aspects of contraception and a useful paradigm of the intersection of biology, psychology, and sociology in regard to contraception. He has also related these domains to characteristics of methods, users, and the context in which contraceptives are used. Dr. Miller has noted that the typical user, at least in the United States, has a contraceptive career and that this career is increasingly tied to medical methods of contraception. I would like to elaborate on some aspects of this idea of a contraceptive career.

The contraceptive career becomes increasingly complex as individuals begin their sexual activity at younger and younger ages, have a longer period of sexual activity prior to marriage or prior to the desire to conceive, want and have fewer children, and consequently have a longer period after the last child is born when they are still at risk of an unwanted pregnancy. This final stage is often closed out by sterilization. But we know that a small percentage of individuals seek to undo this termination of their reproductive abilities with a reversal of the sterilizing operation, and some succeed. This contraceptive career is influenced by the high incidence of divorce and remarriage, which means that contraceptive decisions that are made by one couple may ultimately affect two new couples. Thus, the contraceptive career may diverge from its expected path if fertility desires differ with a new mate.

I would like to focus on the entry point into a contraceptive career, which for many people occurs during the teenage years. How does

contraceptive technology influence the initiation of contraception or the early path of that career?

We know from recent surveys of adolescent women in the United States that increasing proportions of unmarried teenage women are sexually active and that this activity occurs at younger ages than in the past. In 1976, 30% of sexually active women between the ages of 15 and 19 reported that they always used contraception, but 26% reported that they never used contraception. Inspection of the likelihood of use of contraception and of the type of method can tell us something about contraceptive careers. These data are cross-sectional, but we can compare different age-groups to infer such changes. Younger women (15 to 17 years of age) are less likely to use contraception. Young couples are more likely to use the condom or rely on withdrawal than are older teenagers (18 or 19 years of age). Use of these male methods declined for both age-groups from 1971 to 1976, and use of the pill increased (Zelnik and Kantner, 1977).

What does this tell us about contraceptive careers and the impact of technology? There is a trend for adolescents to improve their contraceptive behavior as they grow older and also a secular improvement in the practice of contraception. Increasing proportions of adolescents are beginning their contraceptive careers with contraceptive methods that must be obtained through a physician, but most are not. Frequently, young couples begin their sexual careers without using any contraceptives; move on to "drug store" methods, such as the condom; and then on to more effective methods, usually oral contraceptives. This transition may reflect a growth in the woman's or the couple's perception of the risk of a pregnancy, and it may reflect a growth or change in the couple's relationship.

We know that only 40% of adolescent women can accurately report the time of the month of greatest risk of pregnancy (Zelnik and Kantner, 1977). Other research indicates that this figure is likely to be an overestimate of accurate knowledge due to women guessing the correct answer (Presser, 1977). This awareness increases with age, but when teenagers who were not using contraception and not trying to become pregnant were asked why they were not contracepting, 40% gave "time of the month" as their reason, and an additional 31% believed that they were at low risk of conceiving. The perception of low risk was based on infrequent intercourse, their youth, or a general belief that they could not become pregnant (Shah *et al.*, 1975). (Multiple answers were possible, so the total exceeded 100%.) The work of Dr. Kristin Luker points out that adolescents, and women and men in general, have an internal calculus in assessing the risks and the benefits of behavior that

they will undertake regarding their fertility (Luker, 1975). For any act of unprotected intercourse an individual may weigh the risk of pregnancy as opposed to waiting until contraceptives are obtained. And if you assume that adolescents have a very poor knowledge of their real risk of pregnancy, then other concerns may take on more importance.

It appears, therefore, that the first "problem" in one's contraceptive career may be accepting the fact that a contraceptive is needed. This may have little relevance to general questions about the technological aspects of contraceptives, but perhaps not. We do not know whether adolescents would be more likely to use a method, even if they thought their risks of pregnancy were slight, if the method were viewed as safe, easy to obtain, and not interfering with sexual pleasure. When contraception is viewed as problematic, people may be more likely to put off its use. How does knowledge of risk, and therefore the need for contraception, increase? As adolescents mature, they may be more likely to encounter information about the risk of pregnancy, experience a pregnancy themselves (or in a friend), or reassess their likelihood of pregnancy because of increased sexual activity.

A second aspect in a contraceptive career may be related to the development of the relationship with the partner. Such development may increase the likelihood that the need for contraception will be discussed and may also reduce the interpersonal barriers to using contraception. Adolescent girls report that they do not want to seem prepared for sex or appear experienced. In an ongoing sexual relationship this should cease to become so much of a problem. Many adolescents appear to begin their contraceptive career with a male method. Of course, withdrawal is free and available, but the use of condoms may reflect that the male is older and has less concern about the reaction of a druggist regarding the purchase of contraceptives. It may also reflect a reluctance on the part of the young girl to seek a medical method through the medical care system.

Methods vary in their requirements for medical supervision. This control of methods influences their accessibility to those for whom contraception is a sensitive subject, who cannot afford medical services, or who are afraid to use such services. The medical monitoring that is required of the most effective methods now available—and those likely to become available—means that their use will be somewhat restricted for adolescents.

Many of the "issues" relating to the contraceptive behavior of adolescents are intra- or interpersonal in that they relate to the individual's acceptance of sexuality, the couple's ability to discuss contraception, the psychological barriers to acquiring methods, and so forth.

These may not seem to be "technological" issues, but I believe that they must be addressed by those involved in the technological aspects of contraception. First, the availability of very effective, coitus-independent medical methods has, I believe, reduced our tolerance for the inconvenience or questionable effectiveness of other methods. This high valuation on the best methods could result in some people just not using anything rather than going through the inconvenience, interruption of pleasure, cost, and so forth, for a method that is not so effective anyway.

The challenge, it would then seem, is to move contraceptive technology in such a direction as to recapture the positive features of nonmedical methods and to improve nonmedical methods for those special audiences for whom they may be most appropriate. The corollary to technological development is, of course, improvement in the area of human services to assist people in their dealing with their own sexuality and reproductive capability. Education in these areas should not focus solely on the individual who is to use the contraceptive, but should include physicians, nurses, and others who are the contact points between the user and the method.

While I have noted the difficulties that are encountered by adolescents, I do not believe that they are restricted to adolescents. Adults also miscalculate their risk of conceiving or sometimes elect to risk pregnancy if a contraceptive is not available. While I have highlighted the problems of adolescents, the development of new methods should focus on human needs, not just the needs of one age-group.

In conclusion, my concern with regard to contraceptive development is only that our past success in contraceptive technology and hopes for future development may cause us to forget that people must implement these methods and that the inability of the patient or the provider to deal with the human aspect could forever limit the application of technology.

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Status of Funding and Costs of Reproductive Science Research and Contraceptive Development

LINDA E. ATKINSON

In 1974 the Ford Foundation, in collaboration with the International Development Research Centre of Canada and the Rockefeller Foundation, undertook an intensive review of the reproductive sciences and contraceptive development (Greep *et al.*, 1976). It assessed the progress of knowledge of the reproductive processes and examined the sources of funding for reproductive science and contraceptive development research from 1965 to 1974.

As a continuation and update of that review, the first part of this paper indicates the amount of money that was available to this field during 1975 and 1976 and develops an estimate of 1977 expenditures. The second part concerns the estimated costs of developing contraceptive products. The original Ford Foundation review estimated the cost of product development of the advanced contraceptive leads that were under consideration in 1974 and projected the necessary financial requirements for developing those leads from 1976 to 1980. Subsequently, the Foundation has attempted a more precise cost analysis of product development with advanced leads that are currently in clinical trial or are expected to enter Phase I clinical trials shortly.

SOURCES AND AMOUNTS OF FUNDS FOR REPRODUCTIVE SCIENCES AND CONTRACEPTIVE DEVELOPMENT

In collecting data for 1975 and 1976, the Ford Foundation obtained information from government agencies and from U.S. foundations contribut-

ing $1 million or more to reproductive science and contraceptive development. For countries where funding data are not computerized, it solicited the aid of consultants who were familiar with ongoing research in their country. These consultants requested information on reproductive research support from individual laboratories.

Specific 1975–1976 data for 3 of the 16 industrialized countries and for 6 of the 9 developing countries originally surveyed could not be obtained. In these instances, 1974 data were brought forward to the current total. In most cases, consultants indicated that the funding situation in these countries had not changed substantially. New information came from 8 Latin American countries. Since the continuation data were assembled under the same criteria and from essentially the same sources, the Ford Foundation believes that they are compatible with the original report.

The total worldwide expenditures for research in reproductive sciences and contraceptive development are shown in Table 1. Trends in this decade are indicated by the 1970, 1973, and 1974 figures, as well as those for 1975 and 1976. The original review showed that 1973 and 1974 were peak funding years and estimated that a downward trend was occurring in 1975. This proved to be a transient decline for current dollars but a true decline in constant dollar amounts. The current dollar total of all countries giving support in 1975 was slightly more than $115 million. In 1976 this increased to over $125 million.[1]

Since the mid-1960's the United States, combining contributions from private and Federal agencies, has been the major contributor to a worldwide research effort. Its contribution was $82 million in 1973, $79 million in 1974, $74 million in 1975, and $82 million in 1976. In comparison, other industrialized countries—Australia, Belgium, Britain, Canada, the Scandinavian countries, France, Germany, Israel, Italy, Japan, The Netherlands, and New Zealand—did not increase the proportion that they contributed to worldwide funding from 1974 through 1976. However, the amounts provided by the governments of developing countries have increased from $1.6 million in 1974 to more than double that amount, $3.3 million, in 1976.

Contributions from traditional participants in the contraceptive development research effort, such as industry and foundations, have shown a downward trend. A survey prepared by the Battelle Memorial Institute for the Ford Foundation reported the contribution of phar-

[1]Because of a change in the starting date of the U.S. Government's fiscal year, FY 1976 was extended from July 31 to September 30, and an additional $8 million was budgeted to cover the so-called "transitional quarter." This amount is not included in the 1976 total.

TABLE 1 Total Expenditures for Research in the Reproductive Sciences and Contraceptive Development by Country for 1970, 1973, 1974, 1975, and 1976

Country[a]	U.S. Dollars (thousands)				
	1970	1973	1974	1975	1976
Total, all countries					
Current dollars	71,462	117,430	118,723	115,553	125,836
Constant dollars[b]	71,462	100,957	91,146	79,721	82,104
United States					
Current dollars	55,009	82,070	79,104	73,992	82,787
Constant dollars	55,009	71,991	62,287	53,232	61,769
Other industrialized countries					
Current dollars	15,267	33,039	38,029	39,176	39,720
Constant dollars	15,267	27,093	27,771	25,046	23,874
Developing countries					
Current dollars	1,186	2,321	1,590	2,385	3,329
Constant dollars	1,186	1,873	1,088	1,443	1,912
Percent distribution, based on constant U.S. dollars					
All countries	100.0	100.0	100.0	100.0	100.0
United States	77.0	69.9	68.3	66.8	68.6
Other industrialized countries	21.3	28.1	30.5	31.4	29.1
Developing countries	1.7	2.0	1.2	1.8	2.3

[a]Countries reporting for 1970, 1973, and 1974: United States; other industrialized countries: Australia, Belgium, Britain, Canada, Denmark, Finland, France, Germany, Israel, Italy, The Netherlands, New Zealand, Norway, and Sweden; developing countries: Africa, Egypt, Hong Kong, India, Iran, the Philippines, South Korea, Thailand, and Turkey. Countries reporting for 1975 and 1976: United States; other industrialized countries: Australia, Belgium, Britain, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, The Netherlands, New Zealand, Norway, and Sweden; developing countries: Africa, Egypt, Hong Kong, India, Iran, Latin America, the Philippines, South Korea, Thailand, and Turkey.

[b]Constant dollars based on value of 1970 dollar.

maceutical firms to be approximately $13 million in 1975 and $14 million in 1976, down from their peak effort in 1972 of $17 million (Duncan, 1977). Philanthropies donated $13 million in 1974, $8.9 million in 1975, and $8.3 million in 1976.

The funding data that were obtained from agencies and representatives of various countries were coded according to purpose: "fundamental studies in the reproductive sciences"; "contraceptive development," which includes only research on leads in clinical trials; "safety studies of current contraceptive methods"; and "strengthening of professional capacity," which includes relevant doctoral and postdoctoral training, seminars, and workshops. The percentages spent on each of these categories for 1970 and 1973, as reported by the U.S. Government and major private agencies, are shown in Table 2. In 1975 and 1976 category expenditures were extended to all countries reporting in those years. Fundamental studies in the reproductive sciences continue to absorb the major portion of funding for this field, increasing from 62% in 1973 to 66% in 1976. This increase in 1975 and

TABLE 2 Percent Distribution of Expenditures in All Reporting Countries for the Reproductive Sciences and Contraceptive Development by Purpose for 1970, 1973, 1974, 1975, and 1976, Based on Constant U.S. Dollars (1970 Dollar = 100%)

	Percent Distribution				
Purpose	1970[a]	1973[a]	1974[a]	1975[b]	1976[b]
Fundamental studies in the reproductive sciences	61.6	61.7	56.6	65.6	66 4
Contraceptive development	24.7	26.2	29.5	20.5	19.4
Studies on safety of current fertility control methods	7.3	7.2	8.7	7.7	6.8
Strengthening professional capacity	6.4	4.9	5.2	2.6	4.4
Unclassified	0	0	0	3.6	3.0
TOTALS	100.0	100.0	100.0	100.0	100.0

[a]Country reporting 1970–1974: United States. Agencies reporting: World Health Organization, International Planned Parenthood Federation, the Ford Foundation, the Rockefeller Foundation, the Population Council.

[b]Countries reporting 1975, 1976: Australia, Britain, Canada, Denmark, France, Germany, Israel, Italy, Japan, Latin America, The Netherlands, Norway, South Korea, Sweden, Thailand, and the United States. Agencies reporting: World Health Organization, International Planned Parenthood Federation, the Ford Foundation, the Rockefeller Foundation, and the Population Council.

1976 is due to the inclusion of additional countries whose expenditures were nearly all in fundamental studies. The proportion of the total that has been devoted to contraceptive development expenditures has decreased from a peak of 30% in 1974 to 19% in 1976. The decline partially reflects the inclusion in the data base of more countries that do not allocate funds in this area but also represents a decrease in absolute amounts, from $32.5 million to $23 million (current dollars). Training of a new cadre of professionals has also received a slightly smaller portion of the total funding in recent years while the proportion devoted to studies on safety of contraceptive methods has remained constant.

The contribution of the U.S. Government to the reproductive sciences and contraceptive development is primarily through the Center for Population Research (CPR) of the National Institute of Child Health and Human Development (NICHD), with smaller amounts through other National Institutes of Health and the Agency for International Development. In 1973, U.S. Government expenditures amounted to $44.6 million but decreased to $38 million in 1974. Expenditures rose to $51 million in 1975 and to $60 million in 1976. The proportion of the total world funding provided by U.S. Government agencies has gradually increased from 35% in 1970 to 48% of the total in 1976. Clearly, the U.S. Government is the major donor of funds to reproductive sciences and contraceptive development.

Table 3 presents an estimated total of worldwide funding in 1977. The U.S. Government spent $71 million on reproductive sciences and contraceptive development, and U.S. philanthropies approximately $10.7 million. As noted above, the contribution by philanthropies decreased between 1974 and 1976. The increase from $8.4 million in 1976 to $10.7 million in 1977 reflects a one-time contribution by the Mellon Foundation to research and training. With contributions from nonprofit research organizations, pharmaceutical firms, and governments of industrial countries, the total for 1977 is approximately $140 million in current dollars.

The trend of worldwide expenditures in current and constant dollars for reproductive research and contraceptive development during the past 12 years is illustrated in Figure 1. There had been a steady increase from about $30 million to $118 million in 1974. In 1975 there was a decrease in funding to $114.6 million and then a rise to $125 million in 1976. The Ford Foundation analysis suggests a slight increase in 1977. The current dollar figures do not reflect the erosion in purchasing power that has been caused by inflation. Constant 1970 dollars, which were calculated from the consumer price indices of all reporting countries during the relevant years, are shown by the lower line. In 1976, for

TABLE 3 Estimated Worldwide Funding for Reproductive Biology and Contraceptive Development in 1977

Source of Funding	U.S. Dollars (millions)
U.S. Government	71.3
Philanthropies	
Ford Foundation	5.7
Rockefeller Foundation	1.8
Mellon Foundation	3.2
SUBTOTAL	10.7
Nonprofit research organizations	
Population Council	1.5
Other	4.4
SUBTOTAL	5.9
Industry	14.0
Other governments[a]	38.0
TOTAL (rounded)	140.0

[a]Based on 1976 information.

example, 35% of the expenditures were consumed by inflation. The "real" dollars that were available for the field have dropped from $100 million in 1973 to $80 million in 1975 and $91 million in 1977. This drop appeared to affect contraceptive development expenditures exclusively. These funds decreased from a constant dollar value of $25.9 million in 1973 to $15.7 million in 1976.

Recent funding for contraception and reproduction continues to increase. The prime indicator of this trend is the allocation of the U.S. Government to the Center for Population Research. In FY 1978 the CPR budget (including social science research) was raised by $17 million over FY 1977. Fiscal year budgets for 1979 and 1980 show increments of $10.6 million and $6.1 million, respectively. At least 50% of these allocations will go to reproduction research. At this time we know of no other major increases in worldwide funding by other donor agencies or governments, so the CPR expenditures over the next 2 years may be the only advancement that occurs.

The original review (Greep *et al.*, 1976) examined the cash required simply to maintain a 1974 level of activity in 1980. The worldwide

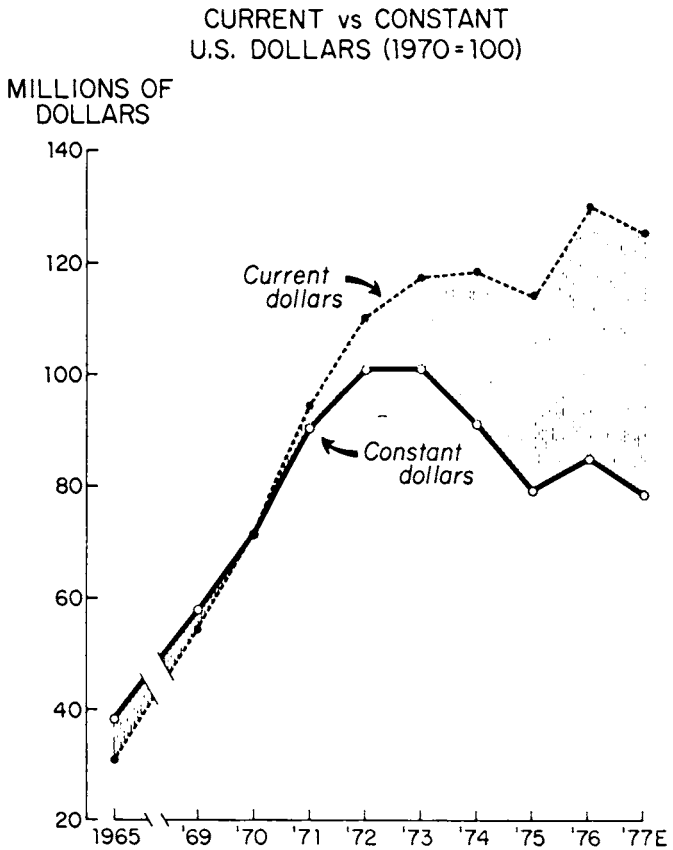

FIGURE 1 Worldwide expenditures for reproductive research. Current versus constant U.S. dollars. Constant dollar based on value of 1970 dollar.

expenditure would have to increase from the 1974 level of $119 million to $197 million in 1980. In 1977 worldwide expenditures of $140 million indicated that this projection is not being met. If, in 1974, the field was thought to be underfinanced, it will surely continue to be so in 1980.

THE COST OF CONTRACEPTIVE PRODUCT DEVELOPMENT

A major societal goal of investment in reproductive science research is the development of improved methods of fertility control. This paper now directs attention to the costs of a contraceptive development program.

The Ford Foundation's original review (Greep *et al.*, 1976) contained estimates of the total cost of an optimum contraceptive development effort. Building on specific activity costs, it also provided allowances for repetitive toxicological and clinical experiments, recurrent development of dosage forms for a single product, and multiple variations of a single advanced lead concept. These became realistic multipliers of the basic cost of toxicology, clinical trials, and process development. The original costing exercise also telescoped the progress of activities over time to include all phases of clinical trials, field trials, and production scale-up in a 5-year period. Thus, while the development of a pregnancy vaccine might actually require 10 years before entering Phase III clinical trials, the earlier estimate assumed that the more advanced field trials would be completed during the 5-year period. The resulting projection of $280 million for contraceptive product development from 1976 to 1980 ($56 million annually) appeared to some experts as overoptimistic in terms of available funds and progress in the drug development process.

To develop more realistic estimates of actual costs of contraceptive development by the public sector in the next 5 years, the Ford Foundation recently asked the principal scientists of the major participants in this effort—the Contraceptive Development Branch of the National Institutes of Health, the International Committee for Contraception Research of the Population Council, and the Special Programme in Human Reproduction of the World Health Organization—to examine their product development activities and project their costs from 1978 to 1982.

The contraceptive technology in advanced stages of development (advanced leads) that are included in the current estimates are restricted to those now in clinical testing and those that will enter Phase I in a year or so. This assumes that a specific product and dosage formulation (not necessarily the final one) have been identified and that animal toxicology and mechanism-of-action studies are being undertaken. Expected project activities under optimal progress are tracked on a yearly basis for each advanced lead. Since some products are further along than others, the yearly estimates reflect different combinations of activity subsets. The large cost of field trials was excluded on the assumption that other agencies would absorb those expenses. Costs for independent experiments in toxicology and pharmacodynamics and parallel development by groups outside the agency sponsorship were not included in the recent estimates but were assumed in the 1976 projection.

The categories that were included in the costing estimates are: "administration," which includes general managerial costs, support of

testing facilities, and overhead costs; "product development," which includes development of single dosage forms, pilot manufacturing and support, process development, quality control, and stability studies; "biological research," which includes the pharmacodynamics and toxicology costs; "clinical testing," whose costs would begin with Phase I, when the product is first tested in humans, and which includes extended Phase III studies for efficacy and safety evaluation but not field trials; and "regulatory affairs," which includes the costs of filing an IND (Investigational New Drug application), meetings, updating data, and cost of submission of an NDA (New Drug Application). Regulatory agency requirements have escalated recently. The cost of satisfying current requirements was incorporated without considering future increases.

The estimated cost requirements for the projects listed in Table 4 indicate that $14.6 million will be needed during 1978 by these three agencies. The cost of development of these contraceptive products over the 5-year period totals $91.6 million. Work on new and improved contraceptive methods by other public sector agencies, the International Fertility Research Program and Program for Applied Research on Fertility Regulation, would add approximately $3 million annually to the total (based on 1977 expenditures).

In 1976, approximately $23.7 million was available worldwide for advanced lead development of contraceptive products (defined as activities related to projects in clinical testing). Fourteen million dollars of this was spent exclusively in the industrial sector, leaving less than $10 million available for *all* public sector endeavors. In 1978, the requirement for contraceptive product development and evaluation has been computed to be $17.6 million for all agencies. The 1978 figure reflects a compromise between optimal progress and money that is available in agency budgets. Advanced product development projected through 1982 anticipates $5 million of increased expenditures per year to be required by these three agencies to continue immediate tasks of developing new contraceptive methods. The yearly total of $19 million shown in Table 4 does not include any allowance for inflation, for cost of increased regulatory requirements, or for repeating any phase of development. Approximately $22 million worldwide would be a minimum requirement to move this list of advanced leads through the process developing phases and to cover the work of the other agencies. This amount of money is not clearly on the horizon. Less than subsistence funding will result in slower progress and perhaps the reallocation of funds that are used for less advanced leads.

The cost of supporting development of less advanced leads was not

considered in the above tabulation. This is a most important aspect of contraceptive development, lying at the interface of fundamental research and product development. It is the source of potential new products to replace advanced leads that have not proved feasible in clinical testing. This work absorbs a smaller portion of an agency's budget than contraceptive product development, but this area is critical to future progress and should not be neglected as product development demands increasing amounts of an agency's budget.

Estimates of the year in which advanced leads now under development will be distributed to the public sector and the total costs of these leads are presented in Table 5. It can be seen that no products currently under development are expected to reach the public sector before 1981. The costs from 1978 to the completion year range from a low of $2.8 million to $31.4 million. The differences in these estimates reflect the fact that substantial amounts have already been invested in certain products, but not in others. The total cost to completion also includes ongoing toxicology commitments beyond the year of distribution to the public sector. Therefore, the estimated year of project completion extends beyond the year of distribution to the public sector.

The past 7 years of contraceptive development have led to the identification of products for potential distribution to the public during the 1980's and 1990's. The major needs are evident. One is sufficient funding for the efficient pursuit of leads that have a realistic chance of becoming a product, so that the less promising can be eliminated early and replaced by more appropriate leads as they evolve from fundamental studies. A second need is to strengthen the process of product development within public sector agencies. The talented staffs of development organizations in the public sector are overburdened because they deal with many more products than would normally be the responsibility of their counterparts in industry. We need a way to help these agencies add necessary personnel or contract mechanisms and, perhaps, to encourage interaction with industry to pursue product development activities more rapidly and effectively. The cost of contraceptive development in the public sector seems to be less than that for industry, but progress may be slower. It will be 1981 before a new contraceptive method that has been developed in the public sector is likely to be available—10 years after the work was initiated. Thus, there is a need for increased funding, organizational strengthening, and creative collaboration between the public and private sectors if the contraceptive development process is to be materially accelerated. All of these strengthening activities, if pursued, would add to the $107 million cost of contraceptive product development over the next 5 years.

TABLE 4 Five-Year Summary of Estimated Cost Requirements for Products Currently under Development and Evaluation[a]

Product	U.S. Dollars (thousands)					
	1978	1979	1980	1981	1982	TOTALS
Implant/injectables						
Nondegradable—5 year	1,590	3,020	1,505	540	170	6,825
Biodegradable—pellet or improved rod	620	1,530	1,850	1,670	870	6,540
Bioerodible—Chronomer®	1,538	1,070	1,223	1,749	1,837	7,417
Biodegradable—caprolactone	230	515	660	1,200	1,235	3,840
Injectable—long-acting progestin	430	615	635	550	155	2,385
Injectable—long-acting progestin	515	491	725	462	405	2,598
Uterine methods						
Intrauterine devices						
Steroid-releasing	465	990	1,265	1,290	900	4,910
Steroid-releasing	398	479	498	1,164	1,188	3,727
Intracervical device						
Steroid-releasing	216	386	626	684	872	2,784

Vaginal methods						
Contraceptive ring	1,070	1,425	1,910	1,150	460	6,015
Steroid-releasing ring	532	907	1,147	1,170	1,264	5,020
Improved suppository	230	690	930	645	770	3,265
Prostaglandin suppository	556	878	924	1,018	936	4,312
Nonsurgical tubal occlusion						
Methylcyanoacrylate injection	638	497	649	1,094	987	3,865
Male methods						
Androgen—progestin combination	883	883	556	521	1,486	4,329
Chlorinated sugar	550	500	556	755	486	2,847
Immunological						
βhCG vaccine	1,955	2,540	1,930	1,495	1,185	9,105
βhCG fragment vaccine	1,463	1,463	1,457	2,159	2,393	8,935
Chemical abortifacient						
Plant derivative	725	497	515	456	690	2,883
TOTALS	14,604	19,376	19,561	19,772	18,289	91,602

[a]Categories included in the cost estimates are listed above.

TABLE 5 Estimated Total Cost and Time Requirement to Achieve Public Sector Distribution of Products Currently Under Development

Product Under Evaluation	Target Year for Public Sector Distribution	Total Cost from 1978 to Completion, U.S. Dollars (thousands)	Estimated Year of Project Completion
Implant/injectables			
Nondegradable—5 year	1981	7,505	1987
Biodegradable—pellet or improved rod	1982	7,535	1987
Bioerodible—Chronomer®	1986	18,697	1992
Biodegradable—caprolactone	1990	11,635	1992
Injectable—long-acting progestin	1984	2,770	1985
Injectable—long-acting progestin	1990	13,994	1994
Uterine methods			
Intrauterine devices			
Steroid-releasing	1982	5,160	1983
Steroid-releasing	1987	10,027	1988
Intracervical device			
Steroid-releasing	1988	12,349	1992
Vaginal methods			
Contraceptive ring	1981	6,480	1987
Steroid-releasing ring	1985	9,372	1989
Improved suppository	1982	3,265	1982
Prostaglandin suppository	1984	6,675	1984
Nonsurgical tubal occlusion			
Methylcyanoacrylate injection	1988	10,296	1993
Male methods			
Androgen—progestin combination	1987	17,538	1992
Chlorinated sugar	1991	12,987	1994
Immunological			
βhCG vaccine	1987	16,405	1988
βhCG fragment vaccine	1993	31,432	1997
Chemical abortifacient			
Plant derivative	1988	9,717	1993

The $22 million yearly estimate for product development is an absolute minimum which optimistically assumes that any development stage progresses "as planned" with no return to the drawing board. As previously mentioned, dollar inflation and escalated regulatory requirements have not been taken into account, nor has work done by other groups. We can therefore consider this amount to be a "lower bound" of expenditures to keep a conservative program going. An "upper bound" of twice this amount would not be unreasonable when the need to accelerate the current efforts is considered.

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SUMMARY

Symposium on Contraceptive Technology[1]

LUIGI MASTROIANNI, JR.

A symposium on contraceptive technology, which was sponsored by the Division of Medical Sciences, Assembly of Life Sciences, National Research Council, was held on May 16–17, 1978, at the National Academy of Sciences in Washington, D.C. Its purposes were to review the efficacy of contraceptive methods and practices, to look at new and developing technologies, and to evaluate these in the light of social and psychological factors that influence their acceptance.

Initially, the current status of contraception was reviewed with emphasis on experiences in both developed and developing countries. The opening paper, presented by Mr. George Zeidenstein of the Population Council, made an eloquent case for supporting the development of new contraceptive methods. This theme was reinforced by the demographic data in subsequent papers which assessed the impact that the lack of availability of methods has on the individual, the family, and society. In both developed countries (discussed by Dr. Jane A. Menken of Princeton University) and developing countries (considered by Mr. W. Parker Mauldin of the Population Council), each of the currently used methods is associated with problems. Occurrence of side effects and public awareness of potential risks have led to a high discontinuance rate or substitution of less effective methods. The net result has been an increasing incidence of unplanned conceptions, often followed either by abortion or by birth of an unwanted child. Dr. Menken's data, although

[1]Reprinted from *Federation Proceedings* 37:2664–2665, 1978, with permission.

indicating that contraceptive use in developed countries is increasing among all socioeconomic strata, revealed that as many as one-third of marital births in the United States are unplanned. Recent data indicate that black couples who are using contraceptives for child spacing are the most effective contraceptive users, and Catholics, not unlike others, now tend to use the most effective methods. In less developed countries, illegal, unsafe abortion is still the alternative method most often used. Sterilization is an increasingly important method, and religious barriers appear to be less significant than expected. Additional new contraceptive acceptors and a high continuation rate are both essential if there is to be a significant reduction in the crude birth rate. The importance of developing new methods was highlighted further by Dr. Howard Ory of the Center for Disease Control in Atlanta, who presented data on the safety of existing methods.

Some of the problems associated with the development of new contraceptive modalities were considered by Dr. Sheldon Segal of the Rockefeller Foundation. He emphasized the importance of involvement of all sectors in contraceptive research, including the pharmaceutical industry, government, and private foundations. Presently on trial are subdermal implants; vaginal rings, which deliver constant low doses of steroids; and an immunologic method using the beta subunit of human chorionic gonadotropin (hCG) combined with tetanus toxoid as an antigen. Male contraceptive technology has not come as far, largely because the basic information that could lead to the new methods for the male is still being collected.

Attention was given to the research horizons in contraception development. In his detailed discussion of the male reproductive tract, Dr. Don Fawcett of the Harvard Medical School projected that the testis may some day be a target organ for contraception. He described the newly revealed functions of Sertoli cells which insulate spermatogenesis from potentially noxious influences.

Dr. Cornelia P. Channing of the University of Maryland focused attention on inhibitors that are present in and about the ovarian follicle. An oocyte maturation inhibitor inhibits meiosis. Its influence is modified only in those follicles that are destined to ovulate in a given cycle and whose oocytes proceed through maturation in preparation for fertilization. The production and possible functions of a luteinization inhibitor, which keeps granulosa cells from producing progesterone, and an ovarian inhibitor of follicle-stimulating hormone (FSH) were also considered.

The mechanism of steroid hormone action was reviewed by Dr.

Elwood Jensen of the University of Chicago. He described the steps involved from the release of steroids into the circulation to their stimulating effect on ribonucleic acid (RNA) and protein synthesis by target cells. It is now known that the formation of the steroid receptor complex in the cytoplasm and its transfer to the nucleus is a two-step process that carries the regulatory signal to the chromatin acceptors, the location and nature of which remain enigmatic. The recent preparation of specific antibodies to estrogen receptor protein provides a new approach to unresolved questions of hormone action mechanism through the techniques of immunochemistry.

Recent advances in the chemistry and physiology of hCG were reviewed by Dr. Robert E. Canfield of Columbia University. His data reemphasized the importance of looking carefully at the chemistry of any agent proposed as an antigen for immunologically induced fertility control. Proteins that cross-react to the hCG beta subunit appear in various tissues, including those of the male.

Dr. Charles Metz of the University of Florida outlined recent work with a zona-pellucida-specific antigen, which has opened the way to the development of an immunologic system directed at fertilization itself.

The role of the gonadotropin-releasing factor and other neuroendocrine factors was addressed by Dr. Roger C. Guillemin of the Salk Institute. A recently developed analog of luteinizing hormone-releasing factor (LRF) "down-regulates" pituitary and gonadal receptors. The latter are not replenished; hence, the target cells can no longer respond to specific stimuli. He then examined beta endomorphine, the morphine receptor in the brain, which has also been shown to inhibit gonadotropin release. Its potential interference with normal reproductive processes at these various levels merits additional concentrated attention.

The psychological aspects of contraception were then discussed by Dr. Warren B. Miller of the American Institutes for Research in the Behavioral Sciences. He stressed that there is no perfect contraceptive method, no best way to contracept, and no ideal delivery system, but that methods must be evaluated within the framework of the emotional capacity of people to use them. In our efforts to understand and consider the efficacy of contraceptive modalities, the importance of behavioral and social research should not be overlooked.

Dr. Linda Atkinson of the Ford Foundation reviewed the status of funding of reproductive science research and the cost of contraceptive development. Recently gathered data indicate clearly that, in terms of 1970 dollars, support of contraceptive research has declined in recent years. The peak funding years were 1973 and 1974. If contraceptive

development is to be materially accelerated, there is a need for increased funding, organizational strengthening, and creative collaboration between the public and private sectors.

The conference encompassed an objective review of the present status of contraceptive methodology and a projection of future needs. A convincing case was made for greater emphasis on research on the reproductive systems of both males and females. This area of research has not received sufficient attention, especially in consideration of its worldwide importance and its impact on health and welfare.

Participants and Coauthors

LINDA E. ATKINSON, Program Officer, Population, International Division, The Ford Foundation, New York, New York

WENDY BALDWIN, Chief, Social and Behavioral Sciences Branch, Center for Population Research, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland

STEVEN BIRKEN, Research Associate, Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York

ROBERT E. CANFIELD, Professor of Medicine and Director, Division of Hormonal and Metabolic Disorders, Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York

CORNELIA P. CHANNING, Professor of Physiology, University of Maryland School of Medicine, Baltimore, Maryland

PHILIP A. CORFMAN, Director, Center for Population Research, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland

LESLIE CORSA, Professor of Population Planning, School of Public Health, University of Michigan, Ann Arbor, Michigan

DON W. FAWCETT, Hersey Professor, Department of Anatomy, Harvard Medical School, Boston, Massachusetts

KATHLEEN FORD, Assistant Professor, Department of Population Dynamics, Johns Hopkins University, School of Hygiene and Public Health, Baltimore, Maryland

LISE FORTIER, Professor of Obstetrics and Gynecology, University of Montreal, Canada

ROGER C. L. GUILLEMIN, Professor and Chairman, Laboratories for Neuroendocrinology, Salk Institute for Biological Studies, San Diego, California.

FREDERICK S. JAFFE (deceased), former President, the Alan Guttmacher Institute, New York, New York

ELWOOD V. JENSEN, Charles B. Huggins Professor of Biological Sciences and Director, Ben May Laboratory for Cancer Research, University of Chicago, Chicago, Illinois

LUIGI MASTROIANNI, JR., William Goodell Professor and Chairman, Department of Obstetrics and Gynecology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

W. PARKER MAULDIN, Senior Fellow, The Population Council, New York, New York

JANE A. MENKEN, Senior Research Demographer, Office of Population Research, Princeton University, Princeton, New Jersey

CHARLES B. METZ, Professor of Biology, Institute of Molecular and Cellular Evolution, University of Miami, Coral Gables, Florida

WARREN B. MILLER, Principal Research Scientist, American Institutes for Research in the Behavioral Sciences, Palo Alto, California

HOWARD W. ORY, Chief, Epidemiologic Studies Branch, Family Planning Evaluation Division, Bureau of Epidemiology, Center for Disease Control, Atlanta, Georgia

WILLIAM F. PRATT, Chief, Family Growth Survey Branch, National Center for Health Statistics, Hyattsville, Maryland

FRANK W. PUTNAM, Professor of Molecular Biology and Biochemistry, Department of Biology, Indiana University, Bloomington, Indiana

SHELDON J. SEGAL, Director, Population Division, The Rockefeller Foundation, New York, New York

JAMES TRUSSELL, Faculty Associate of Office of Population Research and Assistant Professor of Economics and Public Affairs, Princeton University, Princeton, New Jersey

GEORGE ZEIDENSTEIN, President, The Population Council, New York, New York