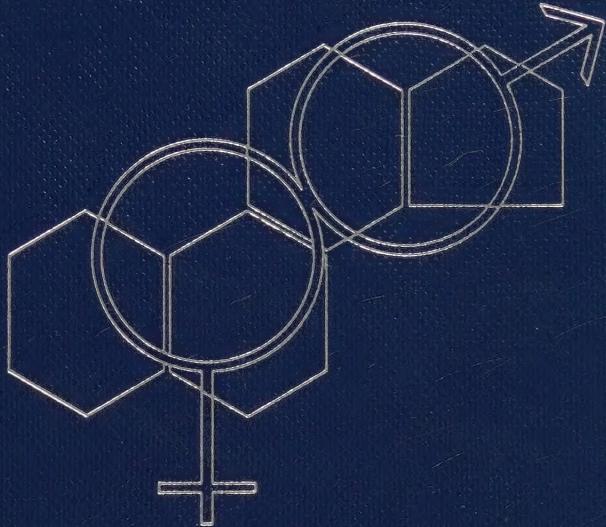


Hormonal Contraceptives, Estrogens, and Human Welfare



edited by
Marian Cleeves Diamond
and
Carol Cleaves Korenbrot

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**HORMONAL CONTRACEPTIVES,
ESTROGENS,
AND HUMAN WELFARE**

Proceedings of a conference on
Contraceptive Hormones and Human Welfare
Sponsored by the CCEW—Women's Center
of the University of California at Berkeley
April, 1977

Hormonal Contraceptives, Estrogens, and Human Welfare

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PREFACE

With over 50 million women in the world altering their reproductive hormones by taking contraceptive pills or menopausal estrogens, it is understandable that accurate and up-to-date information is sought in order to make intelligent decisions about the use of these hormones. Biomedical journals and news media sporadically report side effects of these sex steroid hormone pills, and as a consequence many people have expressed the need for a synthesis of these findings, accompanied with precise information explored at some greater depth. For this reason twelve outstanding medical and scientific researchers were invited by the CCEW—Women's Center of the University of California at Berkeley to a conference on Contraceptive Hormones and Human Welfare in April, 1977. The primary purpose of this book is to offer the information provided at that symposium so that medical professionals and concerned lay men and women throughout the world can make informed decisions about the use of sex steroid hormones, whether in their own bodies or in those of others. Not only will this book serve as a reference for those who need reliable information about the risks and benefits of the sex steroid hormones used for contraception, but also for those concerned with these hormones in the treatment of menopausal symptoms and disorders of the reproductive system not related to contraception. This book also reports on the aims of current research in the development of new contraceptives and offers a number of challenges to future biomedical researchers in contraceptives and menopausal therapy.

The first section of the book deals with the use of oral contraceptives and the current ideas on development of future alternatives. The risk—benefit ratio for the use of oral contraceptives must be determined for every individual woman, because no two persons are identical. Every woman, and those advising and prescribing contraceptives, should know all its potential risks. Dr. Elizabeth Connell presents a concise evaluation of the risks and benefits compiled to date for "the Pill." People must reexamine today's available "cafeteria" of contraceptives in light of the risks of the pill. Even though the pill is reportedly the most effective method of contraception, it is not surprising that there have already been reports of new found popularity in the use of the condom and diaphragm in light of the side effects of the pill.

The chapter by Dr. Greep gives an idea of potential alternatives being developed for contraception. Dr. Greep is the editor of the Ford Foundation report "Reproduction & Human Welfare: A Challenge to Research," which surveyed a tremendous amount of current biomedical research and was published as the conference was being organized. Dr. Greep's chapter includes the global population problem as he sees it, a view that is indeed controversial. One lesson well learned by population planners in the 1960s is that the population problem cannot be approached globally, and instead requires sensitivity and understanding of local mores, values, and cultural level. The role of new contraceptives in providing appropriate safe and effective alternatives to the oral contraceptives is of prime importance so that people may have a measure of choice in their destiny. The funding of biomedical research in reproduction can inspire new approaches to contraception.

The chapter by Dr. Leon Speroff is included to show how the risk-benefit ratio of the use of sex steroid hormones is drastically changed when oral contraceptives are to be taken not by healthy women seeking to avoid pregnancy, but by women with disorders that hinder childbearing, disorders associated with anovulation, dysmenorrhea, and premenstrual tension, and other gynecological disorders. From time to time it has been suggested that the oral contraceptives should be banned altogether, but Dr. Speroff's presentation reminds us of those individuals for whom there are no ready alternatives.

A biological understanding of oral contraceptives for women and proposals for contraceptives for men are presented in the second section of this book. Dr. Richard Blandau discusses how ovulation and fertilization occur. The actual expulsion of the egg from the ovarian follicle, the undulating movements of the fimbria directing the ovulated egg to the opening of the oviduct (Fallopian tubes), the rows of cilia beating and the contractile muscular movements simultaneously moving the egg down, and the sperm up, the oviduct, all become a most dramatic background to show how little we know about human ovulation. On the other hand, much is known about circulating ovulatory hormones, luteinizing hormone (LH), follicle stimulating hormone (FSH), estrogens, and progesterone (see chapter by Speroff). But how do these cycling hormones actually orchestrate a single egg to ovulate? How do they prevent other follicles from developing to ovulate at the same time? How do sperm travel from the uterus to the oviduct? Dr. Blandau's chapter is a unique view of the anatomy and physiology of the primary events in conception.

Understanding how the sex steroid hormones of the oral contraceptives act on specific cells has only been established in the last few years. The unraveling of the biochemical mechanisms by which they act has led to ideas of how these hormones can be prevented from acting and how they affect so many different tissues not directly associated with reproduction. In addition, because these hor-

mones directly act on the genome, the mechanism by which they act on cells may explain how sex steroid hormones can play a role both in the development and the treatment of cancer. These intricate interactions are discussed in the chapter by Dr. Katzenellenbogen.

For whatever reasons, traditionally conception as well as contraception has been primarily a woman's role. However, it is clear that contraception is indeed a man's responsibility, too. The vast number of voluntary vasectomies being performed indicates the desire on the part of many men to contracept, but the apparent sterility in many cases following the reversibility of the vasectomy prevents many more men from having the procedure done. The failure rates associated with the condom and spermicides indicate that these are not ideal alternatives. Need for an assortment of male contraceptives is widely felt. Dr. Donald Fawcett's chapter discusses several contraceptives being considered for men based on current research in male reproductive biology.

The association of estrogens and oral contraceptives with the development of cancer is one of the most vital and timely areas discussed in the book. The development of cancer is generally slow, with symptoms appearing years after repeated exposure to carcinogens. Now that estrogens and oral contraceptives have been in general use for over 15 years, the most complete studies on their association with cancer have only recently been published. Although estrogens have not been shown to be carcinogenic, they do appear to increase the risk of developing cancer. Dr. Howard Jones presents data from a study at the Mayo Clinic showing that patients who took any form of estrogen therapy for 6 months or longer had a two- to threefold increase in the risk of endometrial cancer. Dr. Elfriede Fasal presents data from her own study showing an 80% relative rise of breast cancer in women using oral contraceptives for 2–4 years. The risk of breast cancer was three times higher if the individual had used oral contraceptives before the birth of her first child. Such findings are cause for special consideration before recommending oral contraceptives or menopausal estrogen therapy.

The impact of the oral contraceptive hormones on particular areas of human behavior is examined in the final section of the book. The chapter by Dr. Valerie Jorgensen examines the impact on adolescent contraception; that of Mr. Frederick Jaffe, the impact on fertility control programs; and that of Dr. Julian Davidson, the impact of sex steroid hormones on individual human behavior itself. The chapter by Dr. Jorgensen does show in one particular group of people, American adolescents, just how intimately human sexuality becomes involved in the use of oral contraceptives and how the particular immediate needs of teenage women must be balanced against the risk–benefit ratio of oral contraceptives to those who will use it. What is indeed potentially tragic is that such adolescents become, often unwittingly, volunteers in a new test of safety on the risks of oral contraceptives, for they are using oral contraceptives at a younger age, and po-

tentially for a longer time, than have others previously. What problems and solutions will come of this test is a serious consideration.

The chapter by Mr. Jaffe points out that consideration of medical risks alone in examining risk–benefit ratios does not take into account at least two considerations that most people seem to weigh heavily: effectiveness in prevention of unwanted pregnancies and independence of use from the time of intercourse itself. With the introduction of oral contraceptives in the first half of the 1960s, the caseload of Planned Parenthood tripled. In spite of media reports of medical risks associated with oral contraceptives appearing around 1970, the number of women using oral contraceptives has continued to increase. But how many of these women read about or personally understood the medical risks involved? How many people prescribing oral contraceptives tried to put safety into perspective for the women for whom they prescribed them?

One major unknown is the effect of sex steroid hormones on the human central nervous system. The results reported by Dr. Katzenellenbogen do indeed show that certain brain areas bind sex steroid hormones in a way associated with cell action of these hormones in other tissues. Certainly, in the hypothalamus, actions of sex steroid hormones are well documented. But what might other effects of sex steroid hormones be on the higher regions of the brain? Dr. Julian Davidson emphasizes how little we know about this problem because research into the effects of sex steroid hormones on behavior has generally been so poor and scanty. In this area there is indeed a challenge to researchers to determine if the use of therapeutic circulating sex steroid hormones affect brain structure and chemistry. Dr. Fawcett points out in his chapter that development of male contraceptives involving the sex steroid hormones testosterone and estrogen are considered “no-nos” because they are purported to reduce male libido. However, women using oral contraceptives report a variety of effects on libido and often a general mental depression, and yet oral contraceptives are widely prescribed. The documentation that allows use of the one contraceptive, but not development of the other, is not clear. The need to know more about the effects of oral contraceptives on human sexuality and behavior is critical.

The information in this book is of importance to people in several professions, as well as to a wide variety of lay people. The authors and editors have tried to minimize the use of jargon peculiar to anatomists, physiologists, biochemists, epidemiologists, and obstetrical and gynecological clinicians. The language of the text is meant to be a more widely acceptable language, yet always scientifically and medically accurate.

To the editors of this book, a most important concern right now is that women everywhere better understand their bodies, their health, and their diseases. That so many healthy women use sex steroid hormones such as “The Pill” or menopausal estrogens and have little or no idea of what they are, and what they

can do, was the chief motivation for compiling this book. We also found many concerned men and medical health professionals in numerous roles who wanted to share in the responsibility for governing the widespread use of sex steroid hormones. The final determination of the risk-benefit ratio in the use of any of these hormones is left to the woman herself and to those who advise and prescribe their use. Yet no one can begin intelligently if the basic facts are not brought together. To this purpose this book is dedicated.

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Finally, we would like to acknowledge the persistent patience of our families throughout the preparation of this book.

THE PILL: RISKS AND BENEFITS

Elizabeth B. Connell

*Rockefeller Foundation
New York*

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We know from medical history that for centuries women have attempted to control their fertility. Many interesting, esoteric, and sometimes fatal methods have been tried. Actually, each of the methods we use today had an antecedent in the dim and distant past. The diaphragm was preceded by all sorts of vaginal pessaries, made of elephant and crocodile dung signifying strength, held together by bees wax and honey. The prototype of the intrauterine device (IUD) was a stone placed in the uterus of a camel to keep her from getting pregnant on her long trips across the Sahara Desert. The early condoms were made from animal intestines, and Cassanova reportedly used these and also balls made out of gold, which he placed in the vaginas of his lady friends in order to prevent pregnancy. Abortion and male and female sterilization were widely practiced, often in a rather brutal and mutilating fashion. A wide variety of agents was swallowed by women to prevent or abort unwanted pregnancies, many of them dying during the Middle Ages of lead and mercury poisoning. In general, all of these techniques varied in their usefulness. Some were highly effective, some were totally useless, and some ended in death.

Today for the first time, with the advent of the oral contraceptive, women now have a technique for preventing unwanted pregnancy that is virtually 100%

effective, if used properly, other than abstinence, which has never been very popular. At the present time, there are more than 50 million women taking the pill, 10 million of them living in the United States. When the pill was first developed there was great rejoicing all over the world because it was believed that the ideal contraceptive had finally been found, a method that was totally safe, totally effective, easy to administer, inexpensive, reversible, and not related to the time of sexual intercourse. However, as the result of the intense study that has been made of the oral contraceptive over the past 20 years, we now know that, unfortunately, this is not totally true. We have amassed large amounts of data on oral contraceptives because they have been studied more thoroughly than any other type of medication in the history of mankind. Thus we have learned that they have adverse but also beneficial side effects (Connell, 1975).

I. TYPES OF ORAL CONTRACEPTIVES

Many changes have been made in oral contraceptives since their development began in the mid-1950s. The earlier pills contained relatively large doses of an estrogen and a progestin; with continued experience it was found that it was unnecessary to use such large doses. Therefore, with time the dosage of both hormonal components has gradually been decreased. At the lower end of the dosage scale, however, it has been found that dosages that are too low will increase the pregnancy rate and will also produce irregular bleeding.

During the time of the development of the oral contraceptives, three types of preparations have been used. The first and still the most widely used today is the combination pill, both hormones being present throughout the cycle. These are given for roughly three weeks, followed by one week off or with a placebo being given in order for withdrawal bleeding to occur. The second type of pill that has recently been removed from the market is the sequential. As its name suggests, the estrogen was given for two weeks, the progestin was then added for one week, and again withdrawal bleeding was allowed to occur, either by stopping the pill or by using a placebo. Most recently the minipill, which contains only the progestin, has been studied and has become available for use. This medication was developed following the discovery that the majority of the adverse side effects were estrogen- and not progestin-related, and attempts were made to see if the progestin alone would be effective. However, the pregnancy rates with the minipill have been found to be somewhat higher than those with the combined pill. In addition, the cycle control with this type of medication is less complete, irregular bleeding often presenting a problem.

Much has also been learned about the best way to administer the pill. When the pill was originally studied, it was started on the fifth day of every cycle and then given for 20 days. Starting and stopping the pill correctly depended on the keeping of an accurate menstrual calendar, which proved to be difficult for

many women, leading to discontinuation or unplanned pregnancy. The next method was the 21-day pill regime, with one week off allowed for withdrawal bleeding before starting a new cycle; this improved pill-taking somewhat. The technique now most frequently used and the one that has been found to be the easiest for women to follow is the use of the pill for roughly three weeks followed by five to seven days of a placebo, either an inert preparation or iron. In this way a pill is taken every day, and pills are less likely to be forgotten.

II. SIDE EFFECTS OF ORAL CONTRACEPTIVES

As the use of oral contraceptives continued and expanded, it became clear that certain side effects were associated with their administration. These side effects may be divided into those which are annoying and those which are a risk to health. The former includes nausea, vomiting, breast swelling and tenderness, the development of pigmentation of the face, and the periodic retention of fluid. The latter type of side effects is discussed below.

A. Vascular Problems

The earliest serious side effect to be recognized and the one that is still the major source of concern is the development of vascular problems. The formation of clots in leg veins and the possible breaking off of these clots with subsequent embolization to the lungs has long been recognized as the major risk of oral contraceptive usage (Royal College of General Practitioners, 1976; Sartwell *et al.*, 1969; Vessey and Doll, 1968). Although the degree of this risk has decreased as the dosage has been decreased, there is still the possibility that such a complication may occur. Studies have also shown an increased risk of stroke in women taking the pill (Bickerstaff and Holmes, 1967; Collaborative Group for the Study of Stroke in Young Women, 1975; Royal College of General Practitioners, 1974). Most recently it has been determined that women starting at about the age of 35 have a slightly increased risk of both fatal and nonfatal myocardial infarction when using the oral contraceptives. This risk goes up only slightly in a normal healthy woman over the age of 35, but if she is a heavy smoker, the risk goes up considerably (Jain, 1976; Royal College, 1977). The risk has also been found to increase, although not as much, if she is obese, has high blood pressure, has an abnormally high level of cholesterol in her blood, or is a diabetic.

Many studies have been carried out attempting to determine whether or not use of the pill induces hypertension. In general, it appears that a small increase occurs in many women (Royal College of General Practitioners, 1974). However, their blood pressure is usually still within normal limits. Rarely, severe hypertension occurs shortly after starting the pill, but this disappears promptly after discontinuing its use.

B. Gall Stones and Liver Tumors

Women taking the pills for several years have been found to have an increased incidence of gall stones (Boston Collaborative Drug Surveillance Program, 1973). It is not known whether these individuals already have a predisposition to this condition. In addition, a small number of women have been observed to develop benign liver tumors (Christopherson *et al.*, 1975; Mays *et al.*, 1976; Nissen and Kent, 1975). These are potentially dangerous since they are quite vascular and if rupture occurs, there may be severe intra-abdominal hemorrhage. Both of these, however, are very rare complications.

C. Carbohydrate and Lipid Metabolism

The taking of the oral contraceptives induces many changes in carbohydrate and lipid metabolism (Spellacy, 1969). Concern has been expressed that these might result in premature aging and the development of diabetes. To date, there is no evidence to suggest that this may occur in healthy women. In fact, these changes go back to normal very quickly after stopping the pill. However, some women who are prediabetic have been observed to become insulin-dependent, active diabetics while on the pill, and so this condition is now classified as a relative contraindication to its use.

D. Fertility

A recent study, widely reported in the media, suggested that women who never had children had a lower pregnancy rate after stopping the pill (Vessey, 1976). The author of this paper has just recalculated his data after further studies were carried out and found that this is not actually the case (Vessey, 1977). It has been noted by several investigators that pregnancies occurring immediately after stopping the pill show a slight increase in certain types of congenital abnormalities (Janerich *et al.*, 1974; Nora, 1973; Nora and Nora, 1975). Therefore, it is currently recommended that another form of contraception be used until regular menses have returned.

E. Cancer

One of the major concerns in relation to the use of the pill has always been the possible stimulation of a pre-existing malignancy or the development of a new one, particularly in the female reproductive tract, the breast, the cervix, the uterus, or the ovaries. These concerns were heightened by the finding of a rare type of vaginal malignancy in a number of girls whose mothers had taken DES (diethylstilbestrol), an estrogen, during pregnancy (Herbst *et al.*, 1974). Multiple studies have been carried out attempting to assess this particular situation with oral contraceptive usage (U.S. Food & Drug Administration, 1968). There are no data at the present time that would suggest that the pill produces malignancy (for conflicting views see chapters by Fasal and Jones). However, since it is well known that it takes a long time for cancer to develop, careful monitoring of women taking oral contraceptives is being continued.

III. BENEFICIAL SIDE EFFECTS

Side effects are usually and unfortunately only discussed in terms of those which are adverse. However, the use of the oral contraceptives has been shown to have some very positive side effects, which also need to be discussed if the proper risk to benefit balance is to be maintained. For example, in addition to being the most effective contraceptive ever developed, the pill has been shown to make irregular menstrual cycles regular and to decrease the amount of blood lost with each menstrual period. In addition, it has been noted that women taking oral contraceptives has fewer benign breast and ovarian tumors (Fasal and Paffenbarger, 1975; Ory *et al.*, 1976; Royal College of General Practitioners, 1974; Vessey *et al.*, 1972). It is well known that the frequency of malignancy is greatest where there have been pre-existing benign tumors. However, whether this decrease will influence the ultimate rate of the development of malignancy of these organs is not well known at the present time. (In addition, a fascinating fact has emerged—the pill produces a 25% decrease in ear wax, certainly a matter of considerable significance; Royal College of General Practitioners, 1974).

IV. CONTRAINDICATIONS

There are a number of contraindications to the use of the pill, both absolute and relative. The current list of absolutes, as outlined by the Food and Drug Administration, includes thromboembolic disorders, estrogen-dependent neoplasia, malignancy of the breast or other reproductive organs, abnormal genital bleeding, and pregnancy. The relative contraindications now include migraine, high blood pressure, gall bladder disease, varicose veins, lactation, obesity, endocrine disorders, and a history of depression.

V. CONCLUSION

In general it may be stated that, up to the age of 35, the use of the pill, as well as the use of every other current form of contraception, is for almost all women except heavy smokers, safer than pregnancy and delivery (Tietze *et al.*, 1976; Royal College, 1977). This is true in this country; it is infinitely more true in those areas of the world where medical care is minimal or virtually nonexistent. When compared to many of the risks of everyday living, the complications have been found to be comparatively quite low. In fact it has been suggested, only partly facetiously, that given their relative risks of producing disease and death, pills should be sold over the counter and cigarettes placed on prescription. Thus, despite its known side effects, there is every reason to believe that the pill will continue to play a major role in contraceptive practice throughout the world.

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THE CHALLENGE TO CONTRACEPTIVE RESEARCH

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The challenges to contraceptive research are manifold and of overarching strategic concern to the future welfare of humankind. From our vantage point the challenges are both national and global in scope. The revolution in contraceptive practices sparked by the introduction of the pill and the IUD in the early 1960s has provided little more than a beginning in the control of human fertility. That the array of existing contraceptive measures both conventional and modern is not meeting the needs of individuals, families, or society will be evident from the following situations. Our planet earth is now supersaturated with over 4 billion people who are defiling the landscape with cities that lead to scab formation with surrounding encrustations of urban sprawl. They are also depleting the earth's nonrenewable resources, polluting the atmosphere, contaminating the rivers, lakes, and oceans, exterminating wildlife, and laying waste to the woodlands and recreational areas. Of these 4000 million inhabitants, more than 2000 million live in poverty, 450 million live in perpetual hunger, and 800 million are illiterate. Worse still is the fact that untold millions live without hope in a world where the potential for human fulfillment is virtually boundless.

What makes the need for control of human fertility now and in the future so urgent is that with each passing year the total population swells by another 70

million or more persons (Echols, 1976). In order to grasp the impact of such a rate of gain, think of it in terms of adding a city of 200,000 people every single day of the year, year in and year out.

I. THE NATIONAL POPULATION PROBLEM

In the United States we take justifiable pride in having reduced our birth rate below the replacement level but we have not yet attained a contraceptive utopia. Unfortunately a decreasing birth rate does not necessarily mean a decrease in number of births. Simply stated, for any given birth rate, the more fertile women there are, the more babies there will be. Since the number of women of prime reproductive age has increased as a result of the baby boom of the 1950s our population is growing despite our low birth rate. If we accept the principle that child bearing should accord with responsible parenthood then we have quite some way to go. Of our slightly over 3 million births per year, over 40% are by chance and not by choice (Center for Population Research, 1977). Among these 1,300,000 unplanned births, 235,000 are unwanted and subject to all the adversities inherent in that unhappy circumstance. Since *Homo sapiens* is the only rational being ever created and the only species with the power to control its reproductive behavior, it is an unflattering commentary that so many of its offspring are the unintended by-product of sexual intercourse for sensual purposes.

We are also experiencing an epidemic of teenage pregnancies. In 1975, 20% of all live births, or 608,000, were to women under 20 years of age. In percentage terms that may be a world record. The contrasting figure for Japan, where pre-marital sex is frowned upon, is 1%. Most distressing of all is that the number of births occurring among the youngest of the teenage group is expanding. In 1974 there were 122,000 births to girls 14-16 years of age, of whom 60% were unmarried. That teenage pregnancies involve added risk to the offspring and to the social and economic welfare of the mother is well documented (Greep *et al.*, 1976).

II. GLOBAL POPULATION PROBLEMS

As to the practice of contraception it is estimated that of the 500 odd million women at risk of pregnancy only 30%, or 150 million, use any form of contraception, and of these a large percentage live in the developed world where the birth rates are already much reduced. In the developing nations of the world, ignorance, superstition, economic conditions, religious beliefs, and cultural traditions dictate heavily against any form of interference with procreation. Small wonder then that 80-85% of the expected addition of another 2 billion to the human population over the remainder of this century will come from the developing nations.

As to the extent of contraceptive practice, it is estimated that 50 million women are currently using the pill and another 10 million the intrauterine

device (IUD). Both of these agents are handicapped by side effects and by being tied to health services that are extremely scarce in many parts of the world. The number of women using the pill is leveling off and perhaps declining (Rinehart and Ravenholt, 1977). A recent study shows that the termination rates for users of the copper-bearing IUD over a two-year period rose from 40.5 to 100 insertions in 1972 to 44.6 in 1975 (Jain and Sivin, 1977). Obviously the need for new contraceptives having a high degree of safety, acceptability, and continuity in use is urgent. In terms of effectiveness it will be difficult to improve upon the modern versions of the pill and the IUD. With strict adherence to treatment schedule the pill is virtually 100% effective and the new copper-bearing IUDs have a failure rate of only two or three pregnancies per 100 women years of use.

III. URGENT NEED FOR NEW CONTRACEPTIVES

A. Financing Current Research

Contraceptive research of both fundamental and applied nature is proceeding at a modest pace. What prevents this research from expanding into an activity commensurate with the magnitude of the problem is inadequate funding and severe regulatory requirements that have caused the pharmaceutical industry to lose much of its earlier interest in contraceptive development. Industry estimates that it would require 10-15 years and some 20 million dollars to put a new contraceptive on the market. Since the price would then have to be within the purchasing power of the poor, the chances of obtaining a fair return on the investment are slim. Some of the slack left by the withdrawal of industry has been taken up by the Biomedical Division of the Population Council and the Contraceptive Development Branch of the National Institute for Child Health and Human Development, but they have neither the capabilities nor the resources of industry for the synthesis and screening of new chemical substances of possible contraceptive significance.

Much emphasis is now being placed on the improvement of existing contraceptive methods for the female and the development of new ones for the male (see chapter by Fawcett). In addition some totally new approaches to fertility control are in the early stages of clinical testing and others are under experimental evaluation in laboratory animals.

B. Improvements in Existing Methods for Women

1. Subcutaneous Capsules

Most advanced among the improvements in existing methods is the development of new means of delivering contraceptive drugs so as to obtain long-term protection from a single treatment. One promising method involves incorporation of the drug into a plastic cylinder or rod (e.g., silastic capsules), which on implantation under the skin releases the contraceptive at a constant rate over a long period of time (Segal and Diczfalusy, 1976). Six such implants have been

shown to provide protection for over one year and there is reason to expect that this could be extended to perhaps as much as six or eight years. The subdermal implantations are usually made on some fatfree area such as the forearm. They are inserted under local anesthesia by means of a small incision or trocar. Such implants have the advantage of continuous protection without daily attention to pill taking and complete reversibility. Their disadvantages are the slight trauma of insertion, constant long-term exposure to the contraceptive steroid, and irregular bleeding.

Another step forward involves the medication of IUDs with a contraceptive progestin (Segal and Diczfalusy, 1976). The steroid is placed in a hollow plastic segment of the IUD and allows the agent to act locally on the internal lining of the uterus, rendering it nonreceptive to attachment by an early developing embryo. Such IUDs are highly effective, do not interfere with normal course of menstruation, and are suitable for use by nulliparous women. In similar fashion, progestin-medicated rings have been developed for insertion into the vagina (Mishell *et al.*, 1975). The released steroid is absorbed into the blood stream through the vaginal wall and inhibits ovulation. These intravaginal rings are generally worn between menses and can be removed during intercourse if so desired. They may also be worn continuously with renewal every three months. A drawback of the latter regimen is that the rings tend to develop an offensive odor due to absorption of blood during menstruation. Vaginal rings designed to deliver low levels of a progestin and mimic the action of the minipill have also been tested with encouraging results. Since medicated vaginal rings can be self-inserted and provide a reasonable degree of protection with minimal hazard to health, they have the potential of becoming a valuable means of limiting conception in underdeveloped regions.

2. Chinese Paper Pills

The Chinese have developed a variation of the pill that comes in the form of thin wafers packaged in small booklets much resembling our booklets of postage stamps (Djerassi, 1974). Each day the user tears off one of the squares and places it under the tongue. The contents are rapidly absorbed into the general circulation and inhibit ovulation. These are cheap to manufacture and are distributed free. There are no reliable data on the results of this government sponsored program but estimates by on-the-scene observers suggest that the impact on the birth rate may be the greatest ever achieved.

3. Armbands

Contraceptive steroids can also be absorbed through the skin and some initial effort is being given to the development of armbands that could be worn with little discomfort and provide protection (Segal and Diczfalusy, 1976).

4. "Injectables"

The development of another mode of steroid contraception known as "injectables" is being vigorously pursued. This involves the simple intramuscular injection of a long acting progestin that confers sterility for three to nine months (Ortiz *et al.*, 1977). The steroid is in crystalline form and suspended in a vehicle that delays absorption. The duration of sterility depends upon dosage, size of crystal, and the suspending medium (Segal and Diczfalusy, 1976). The most commonly used progestin is Depo-medroxyprogesterone acetate. This form of contraception is preferred by women in isolated areas and is especially favored by those who have completed their families. They associate an injection with protection against some health hazard, and protection from the hazards of repeated pregnancies is what they desire. Injectables are not approved in the United States and are beset by two troublesome features, abnormal bleeding and reversibility. The bleeding occurs at highly irregular intervals and is of variable duration. The delay in return of fertility following cessation of treatment may be brief or of worrisome duration. Better injectables are being sought through combination of progestin with an estrogen. There are at least four long-lasting progestins and as many longlasting estrogens to work with in developing a successful formulation for use as an injectable (Bennett, 1974).

5. Intracervical Devices

Worthy of mention but still in the initial stages of development are steroid medicated intracervical devices. The presumption is that they alter the cervical mucus so as to inhibit the passage of sperm through the cervical canal. A further possibility that is under test in animals is the intracervical injection of long-acting progestin crystals coated with a biodegradable substance that would slow absorption and provide extended protection.

6. Opposing Cellular Actions of Progesterone

At the level of fundamental research there is an immense effort underway to understand the mechanism of action of progesterone. It is known that progesterone is bound by receptors in the target organs (see chapter by Katzenellenbogen). Such receptors have been isolated from laboratory animals. The immediate thrust of this work is to gain understanding, but the long-term goal is to point the way to some means of blocking the binding of progesterone and thereby protect against the establishment of pregnancy.

Other lines of investigation include the search for an antiprogestrone, one that might bind to the progesterone receptors or otherwise block the action of progesterone. Antiestrogens and antiandrogens are available but no promising antiprogestrone has been uncovered. A search is also being conducted for other agents that would interfere with the biosynthesis of progesterone by the corpus luteum. This, however, must await the acquisition of greater understanding of that biosynthetic process. The search is also underway for substances

that would destroy the corpus luteum and thus abolish the secretion of progesterone. Such luteolysis has been observed in experimental animals as a result of the action of estrogens, prostaglandins, and prolactin, but the results thus far have not been transferrable to *Homo sapiens*. As yet, we have no clue as to what causes the human corpus luteum to cease functioning near the end of the menstrual cycle.

7. Vaccines

Certainly one of the more exciting prospective additions to the contraceptive armamentarium is a vaccine against pregnancy (Talwar *et al.*, 1976; Hearn, 1976). Actually it is an antibody against chorionic gonadotropin (hCG), a placental hormone that rescues the corpus luteum of the cycle and stimulates it to continue secreting progesterone for the maintenance of pregnancy. In order to avoid the neutralization of a similarly acting maternal hormone, LH, the antibodies are developed against only a fragment of hCG. This method has been tested in baboons and marmosets and in each instance the animals have remained sterile for approximately one year following the immunization. Although much is yet to be learned about this method, it does appear to be reversible once the antibody titer has fallen to a low level. Immune responses have also been induced in sterilized women with no ill effects and without disturbance of the normal menstrual cycles. From present evidence, it appears that a booster injection of the hCG fragment would be necessary at yearly intervals in order to keep the antibody titer at an effective level.

8. Menstrual Regulation

In the realm of birth control as opposed to conception control, the self-administration of a vaginal suppository containing 15-methyl prostaglandin F₂ α -methyl ester for induction of menstruation in cases of delayed menstruation may find wide usage as an outpatient procedure (Filshie, 1976). Considering that between 35 and 50 million women obtain abortions each year, the availability of a simple method of inducing menstruation when pregnancy is suspected would go a long way toward meeting an overwhelming need.

9. Opposing Actions of GnRH in the Pituitary

Lastly, mention must be made of an intensive effort now underway to find a means of preventing the midcycle pituitary discharge of ovulation-inducing hormone (LH). That discharge is under the control of a gonadotropin-releasing hormone (GnRH) of brain origin. The strategy is to synthesize an analog of GnRH that will block the release of LH and prevent ovulation. This method has already been used successfully in laboratory animals (Guillemin, 1977). While the problems that can be anticipated in utilizing this means of controlling ovulation in women are onerous, they do not at this point seem insurmountable.

IV. CONCLUSION

The challenges to contraceptive research are manifold and of compelling urgency. Current contraceptive technology, though highly effective, has limitations in regard to safety, acceptability, and continuity of use. That the needs of individuals, families, and society are not being met is attested by the existing high rates of abortion, teenage pregnancies, and unplanned, unwanted, and out-of-wedlock births. Improvements in existing methods of contraception are likely to be forthcoming over the next few years but new methods can only come from better understanding of the reproductive process in males and females. The only way this can be expedited is by a vastly enlarged program of both fundamental and clinical research. This cannot be achieved without the prior availability of financial support commensurate with the magnitude of the problem of controlling human fertility in today's three worlds—the advanced, the developing, and the nondeveloping. The desire on the part of most women and couples to regulate their childbearing proclaim loudly and clearly that the availability of safe, effective, inexpensive, and convenient means of controlling fertility in both sexes is the surest and fastest means of reducing the multiplication of the human species.

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ESTROGEN AND PROGESTIN THERAPY FOR REASONS OTHER THAN CONTRACEPTION

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There are benefits other than contraception to be gained with the judicious use of the various steroid agents. There are a few indications for such therapy in women who ovulate, and these will be briefly mentioned. However, a more common use for steroid therapy is to treat the various manifestations of anovulation. Therefore, most of this chapter will be devoted to the problem of anovulation, focusing on the clinical problems of irregular menses, hirsutism, and dysfunctional uterine bleeding.

I. PROBLEMS ASSOCIATED WITH OVULATION

Behavioral changes may be associated with the menstrual cycle, and occasionally the gynecologist is consulted by a psychiatrist for advice regarding a patient with cyclic emotional disturbances. Presumably, these behavioral problems are due to cyclic changes in hormone levels, and an empiric approach to eliminating hormonal changes is worth considering. While depression and mood liability may

be associated with oral contraceptive use, an opposite stabilizing effect may also be achieved. In extreme circumstances complete elimination of sex steroid variability may be achieved with the daily use of an oral contraceptive, as in the treatment of endometriosis, or with administration of Depo-Provera, 150 mg intramuscularly every three months. On occasion, one may see beneficial and gratifying results in patients with incapacitating emotional swings.

The irritability and depression that many women experience just prior to the menstrual period have been attributed to fluid retention and to changes in the levels of estrogen and progesterone. This premenstrual tension is frequently accompanied by a slight increase in weight and varying degrees of edema. Diuretic therapy, however, is not uniformly effective. Although the judicious use of a mild tranquilizer may be helpful, inhibition of ovulation with an oral contraceptive may be still more beneficial.

It now appears very likely that primary dysmenorrhea is due to myometrial contractions induced by prostaglandins originating in the endometrium (Halbert *et al.*, 1976). Endometrial production of prostaglandins is higher in the luteal phase of the cycle, and with the onset of menstruation, prostaglandin levels rise even higher (Halbert *et al.*, 1976). Thus the correlation of dysmenorrhea with ovulation is probably due to the higher prostaglandin production in the secretory endometrium. The beneficial effect of oral contraceptives can be explained, therefore, by the presence of decidualized, atrophic endometrium with lower prostaglandin levels. Relief of dysmenorrhea has been achieved with the administration of potent inhibitors of prostaglandin biosynthesis. However, because these inhibitors affect prostaglandin synthesis throughout the body, their use requires extensive evaluation for safety and toxicity. Currently birth control pills taken in the usual fashion provide the most efficacious treatment for severe dysmenorrhea.

II. PROBLEMS ASSOCIATED WITH ANOVULATION

Anovulation is a very common problem, which presents itself in a variety of clinical manifestations, ranging from amenorrhea to irregular menses and hirsutism. Serious consequences of chronic anovulation include infertility, heavy menstrual bleeding, and a greater risk for developing carcinoma of the endometrium. The physician must appreciate the clinical impact of anovulation and undertake therapeutic management of all anovulatory patients to avoid these unwanted consequences.

III. PATHOGENESIS OF ANOVULATION

During menses, the hypothalamus responds to the low levels of estradiol with the production of a releasing hormone (GnRH) to stimulate gonadotropin secretion from the anterior pituitary. This initial increase in gonadotropins (LH

and FSH) is essential for follicular growth and steroidogenesis. With continued growth of the follicle, estradiol production within the follicle maintains follicular sensitivity to FSH by inducing FSH receptors (Kammerman and Ross, 1975). The combined action of FSH and estradiol increases the number of LH receptors, allowing the responses of luteinization and ovulation (Richards and Midgley, 1976). Ovulation is triggered by the rapid rise in circulating levels of estradiol, a positive feedback response within the hypothalamus that results in the midcycle surge of gonadotropins necessary for expulsion of the egg and formation of the corpus luteum. A rise in progesterone follows ovulation along with a second rise in estradiol, forming the well-known 14-day luteal phase characterized by low FSH and LH levels. The demise of the corpus luteum, with a fall in hormone levels, allows the gonadotropins to increase again, initiating a new cycle (see Fig. 1).

This recycling mechanism is regulated largely by estradiol. The negative feedback relationship of estradiol with FSH results in the critical initial rise in that gonadotropin during menses, and the positive feedback relationship with LH is the ovulatory stimulus. Within the ovary, estradiol induces follicular receptor responses necessary for growth and function. Estradiol may therefore be viewed as the critical agent for appropriate hypothalamic-pituitary-ovarian responses in this system. Dysfunction in the cycle may be due to an abnormality in one of the various roles for estradiol. Problems in normal function may be conveniently organized into central defects, abnormalities in the feedback signals, and abnormal function within the ovary itself.

A. Central Defects

Given adequate and appropriately timed feedback signals, the hypothalamic-pituitary axis may be unable to respond. Although difficult to demonstrate definitively, malfunction within the hypothalamus is both a likely as well as a favorite explanation for ovulatory failure. A variety of problems, such as stress and anxiety, borderline anorexia nervosa, acute weight loss after a crash diet, and perhaps increased levels of circulating androgens, can inhibit function of the anterior hypothalamic "cyclic" area, such that only the "tonic" medial area of the hypothalamus operates. With this disability, the gonadotropin surge is not possible, and only homeostatic pituitary-ovarian function is maintained. In addition to inadequate GnRH synthesis and release, central dysfunction may take the form of a failure to sustain GnRH stimulation over a sufficient time period, or it can involve functional pituitary refractoriness to GnRH.

B. Abnormal Feedback Signals

Abnormal feedback can be due to failures within the system or due to the introduction of confounding factors. It is instructive to focus on the blood estradiol concentration as the critical signal for the machinery of the ovulatory

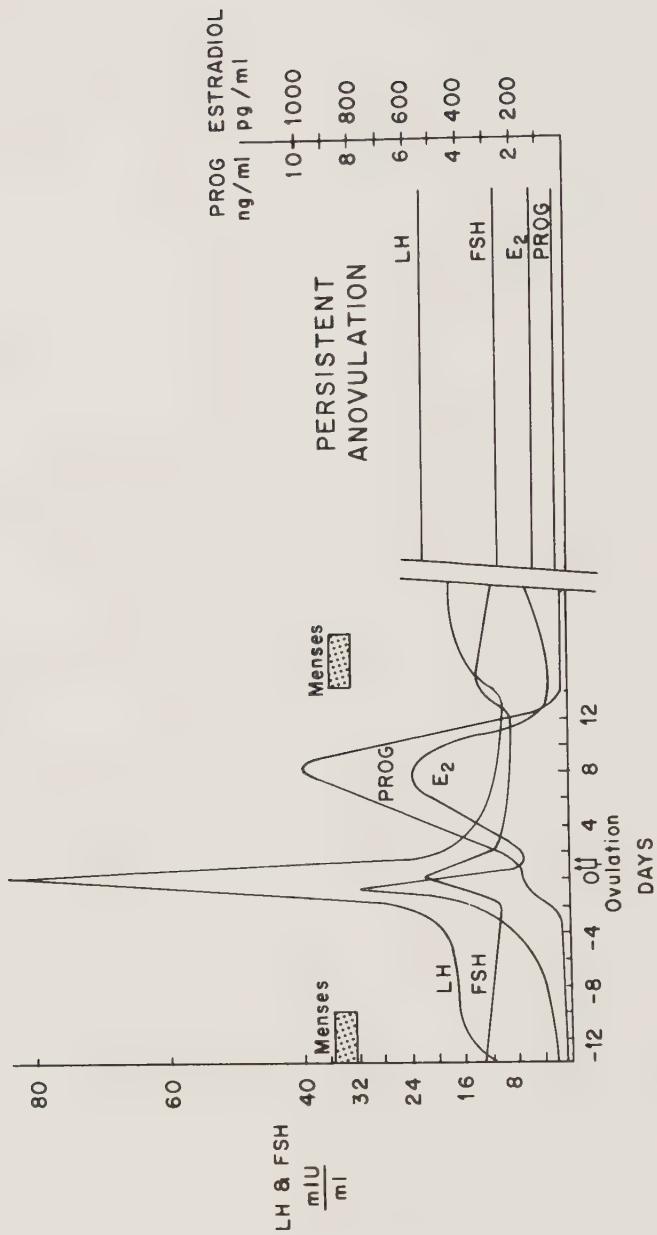


Fig. 1. Hormonal levels during persistent anovulation lose their characteristic cyclic pattern, and achieve what is exaggerated here as "steady state."

cycle. In order to achieve the appropriate changes within the cycle, estradiol levels must rise and fall in synchrony with morphologic events. Therefore two possible signal failures may occur: (1) estradiol levels may not fall low enough to allow sufficient FSH response for the initial growth stimulus, and (2) levels of estradiol may be inadequate to produce the positive stimulatory effects necessary to induce the ovulatory surge of LH.

1. Loss of FSH Stimulation

In order to achieve recycling, a nadir in blood sex steroid levels must occur so that the initial event in the cycle may take place, the rise in FSH. Sustained estradiol levels at such a key moment would not permit FSH stimulation of follicular growth and maturation, and recycling would be thwarted. The necessary decline in blood estradiol requires cessation of secretion, appropriate clearance and metabolism, and the absence of a significant contribution of estrogen to the circulation by extragonadal sources.

The clearance and metabolism of estradiol can be impaired by other pathologic conditions, such as hypothyroidism or hepatic disease. For this reason a careful history and physical examination are important elements in the differential diagnosis of anovulation.

Extragonadal contributions to the blood estrogen level can reach significant proportions. While the adrenal gland does not secrete appreciable amounts of estrogen into the circulation, it directly contributes to the total estrogen level. This is accomplished by the extragonadal peripheral conversion of C₁₉ androgenic precursors, mainly androstenedione, to estrogen (Siiteri and MacDonald, 1973). In this manner, psychologic or physical stress may increase the adrenal contribution of estrogenic precursor, and subsequent conversion to estrogen may sustain the blood level of estrogen at a time when a decline is necessary for successful recycling of the menstrual system. In addition, adipose tissue is capable of converting androstenedione to estrogen; hence the percentage conversion increases with increasing body weight (Siiteri and MacDonald, 1973). This could be the mechanism for the well-known association between obesity and anovulation.

2. Loss of LH Stimulation

A failure in gonadal production of estrogen need not be absolute. Obviously the patient with gonadal dysgenesis and ovarian failure will present with amenorrhea and infertility because of a total lack of estrogen secretion. More commonly, the clinician is concerned with the patient who has gonadotropin and estrogen production, but does not ovulate. The failure to achieve a critical midcycle level of estradiol necessary to trigger the gonadotropin surge may be due to a relative deficiency in steroid production, perhaps associated with asynchrony in follicular growth and maturation.

The teenager between menarche and the onset of ovulation cannot generate an adequate estradiol signal and response until a certain degree of coordination

of the hypothalamic-pituitary-ovarian axis is accomplished. The perimenopausal woman undergoes a terminal period of anovulation, which may represent a steroidogenic refractoriness within the remaining elderly follicles. These inadequacies may be due to intrinsic follicular-gonadotropin interaction, due to immaturity, aging, or local steroid effects. In any case, the end result is the same—a failure to achieve critical signal levels of estradiol at appropriate times in the cycle.

C. Local Ovarian Effects

An understanding of the critical role for estradiol within the follicle indicates possible points of failure that may lead to anovulation. Estradiol prevents atresia despite declining FSH levels by increasing the number of FSH receptors within the follicle, thus increasing follicular sensitivity to FSH. In addition, estradiol enhances the induction of LH receptors by FSH, making it possible for the follicle to respond to the LH surge at midcycle. A follicle can fail to grow and ovulate either because of inadequate estradiol production within the follicle, or because of interference with the action of estradiol.

The factors that control follicular production of estradiol are poorly understood. Surely a very precise coordination is necessary between morphologic development and hormonal stimulation. Perturbations may arise in an infectious process, from the presence of endometriosis, or the necessary biologic effects may be blocked by an improper molecular constitution of the gonadotropins or by abnormal qualitative or quantitative changes in tropic hormone receptors.

Local androgens may induce follicular atresia (Febres *et al.*, 1976). While this action in the normal cycle may be important in ensuring that the proper number of follicles reaches the point of ovulation, an excessive concentration of androgens may prevent normal cycling. This effect of androgens may be mediated by interference with estradiol action, perhaps by reducing the concentration of cytoplasmic estradiol receptors. Thus the important effects of estradiol on gonadotropin receptors will be impeded, and premature atresia may result, leading to chronic anovulation.

D. Precise Etiology

In considering abnormal menstrual function, except in severe disease states such as pituitary tumors, anorexia nervosa, gonadal dysgenesis, and perhaps obesity, it is usually impossible to reduce the issue of etiology to a single factor. The normal ovulatory function of the menstrual system relies on a dynamic coordination of complex actions. Abnormal function may represent discordance at all of the levels reviewed in the above paragraphs. Thus a minor deficiency in the estradiol signal will be associated with a subnormal hypothalamic response, and inappropriate pituitary production of gonadotropins, and an impaired or inappropriate degree of follicular growth and function. Dysfunction is sustained therefore by the internal feedback mechanisms within the system, and anovulation may become a chronic problem. The major morphologic characteristic of anovulation is the polycystic ovary.

E. The Polycystic Ovary

In contrast to the characteristic picture of fluctuating estradiol levels in the normal cycle, a "steady state" of tonic gonadotropin and estrogen function, associated with persistent anovulation, can be depicted (Fig. 1). This steady state is only relative, and is being exaggerated here to present a concept of this clinical syndrome.

In patients with chronic anovulation, the average daily production of estrogen and androgens is increased (see Fig. 2). This is reflected in higher circulating levels of testosterone and androstenedione, and higher levels of estrogen, largely estrone derived from the peripheral conversion of androstenedione. When compared to levels found in normal women, patients with this syndrome have higher mean concentrations of LH, but low or low-normal levels of FSH (DeVane *et al.*, 1975; Kletzky *et al.*, 1975; Rebar *et al.*, 1976). The elevated levels of LH may be in the range of the midcycle surge or equivalent to postmenopausal values. Evidence (an augmented response to gonadotropin-releasing hormone) suggests that the elevated LH levels are due to an increased sensitivity of the pituitary to releasing hormone stimulation (Rebar *et al.*, 1976). This increased sensitivity is probably the effect of the increased estrone levels since a correlation exists between the estrogen and the LH levels. It is possible that the elevated androgens contribute to the increased LH in another fashion. The hypothalamus aromatizes androgens to estrogens (Naftolin and Ryan, 1975), and this local change may sufficiently raise estrogen levels in the anterior hypothalamus to stimulate the positive feedback mechanism. The lower FSH levels probably represent the sensitivity of the FSH negative feedback system to the elevated levels of estrogen.

Because the FSH levels are not totally depressed, new follicular growth is continuously stimulated, but not to the point of full maturation and ovulation. Despite the fact that full growth potential is not realized, follicular lifespan may extend several months in the form of multiple follicular cysts, 2-6 mm in diameter. These follicles are surrounded by hyperplastic theca cells, often luteinized in response to the high LH levels. The accumulation of follicular tissue in various stages of development allows an increased and relatively constant production of

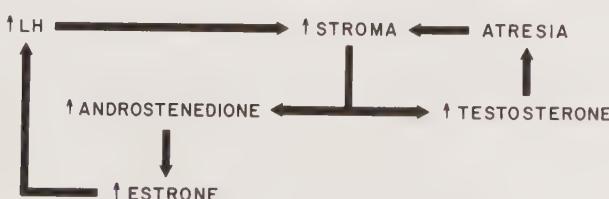


Fig. 2. Relationships associated with the polycystic ovary.

steroids in response to the gonadotropin stimulation. This condition is self-sustaining. As various follicles undergo atresia, they are immediately replaced by new follicles of similar limited growth potential.

The tissue derived from follicular atresia is also sustained by the steady state and now contributes to the stromal compartment of the ovary. This functioning stromal tissue secretes significant amounts of androstenedione and testosterone. In response to the elevated LH levels, the androgen production rate is increased. In turn, the elevated androgen levels, through the process of extraglandular conversion, result in elevated estrogen levels (principally estrone). This steady elevated estrogen level is a major factor in sustaining this condition by depressing FSH levels and elevating LH secretion by augmenting the pituitary response to GnRH. The elevated androgens may also contribute to the morphologic effect within the ovary by blocking the actions of estradiol on the granulosa cells and inducing premature atresia. Indeed, the ovulatory response to wedge resection appears to follow a sustained reduction in testosterone levels, suggesting that the intraovarian androgen effects are the major obstacles to complete follicular maturation and normal cycling (Judd *et al.*, 1976).

In this manner the classic picture of the polycystic ovary is attained, displaying numerous follicles in all stages of development and atresia, and dense stromal tissue. The loss of recycling has resulted in a hormonal steady state causing persistent anovulation that may be associated with the increased production of androgens. This condition has been referred to by many eponyms, most commonly the Stein-Leventhal syndrome, polycystic ovary disease, or sclerocystic ovaries.

The polycystic ovary is palpably enlarged (up to two times) and is characterized by a smooth pearly white capsule. For years, it was erroneously believed that the thick sclerotic capsule acted as a mechanical barrier to ovulation. A more accurate concept is that the polycystic ovary is a consequence of the loss of ovulation and the achievement of a steady state of persistent anovulation. The histologic characteristics reflect this dysfunctional state. An accumulation of atretic tissue along with the constant and elevated LH stimulation results in stromal hyperplasia.

One group of investigators has indicated that high LH levels in anovulatory patients are associated with big ovaries, while low LH levels are found in association with small ovaries (Berger *et al.*, 1975). Another group has failed to find a relationship between the size of polycystic ovaries and the levels of LH (Rebar *et al.*, 1976). There is a spectrum of time involved in the development of this clinical syndrome, and it is useful to view the attainment of high LH levels and large ovaries as a stage of maximal effect of persistent anovulation. However, the key to understanding this clinical problem is an appreciation for the disruption in ovulatory recycling function. The size of the ovaries is not a critical feature, nor is it necessary to assign a specific etiology. The polycystic ovary may be associated with a variety of disorders in the hypothalamic-pituitary-ovarian axis, as well as extragonadal sources of androgens, or with ovarian androgen-producing tumors.

F. Clinical Presentation and Treatment

Anovulation presents as amenorrhea in approximately 55% of cases, and with irregular, heavy bleeding in 28% (Prunty, 1967). True virilization is rare, but 70% of anovulatory patients complain of cosmetically disturbing hirsutism (Prunty, 1967). Obesity has been classically regarded as a common feature, but its presence is extremely variable and has no diagnostic value.

There are potentially severe clinical consequences of the steady state of hormone secretion. Besides the problems of infertility, hirsutism, amenorrhea, and bleeding, the effect of the unopposed and uninterrupted estrogen is to place the patient in considerable risk for cancer of the endometrium. If left unattended, patients with persistent anovulation develop clinical problems, and therefore appropriate therapeutic management is essential for all anovulatory patients.

The typical patient presents with anovulation and irregular menses. If there is no hirsutism or virilism, evaluation of androgen production is not necessary. There is no need for urinary 17-ketosteroids, plasma testosterone, or any other laboratory procedures. In the patient whose only problem is long-standing anovulation, and especially if the patient is over 35, an endometrial biopsy (with extensive sampling) is a wise precaution. The well-known association between this syndrome and abnormal endometrial changes must be kept in mind. Documentation of anovulation is usually unnecessary, especially in view of menstrual irregularity with periods of amenorrhea.

Therapy of most anovulatory patients can be planned at the first visit. If the patient desires pregnancy, she is a candidate for the medical induction of ovulation. If the patient presents with amenorrhea, an investigation must be pursued. The management of significant hirsutism and dysfunctional uterine bleeding is discussed below.

For the patient who does not wish to become pregnant and does not complain of hirsutism, but is anovulatory, therapy is directed toward interruption of the steady-state effect on the endometrium. The use of Provera (10 mg daily for five days, every two months) is favored to ensure complete withdrawal bleeding and to prevent endometrial hyperplasia and atypia. Spacing of the progestational medication in this fashion (every two months) will allow the patient to be aware of spontaneous bleeding due to the onset of ovulatory cycles. The use of oral contraception medication for therapy in these patients requires individual patient judgment. When reliable contraception is essential, the use of low dose combination oral contraception in the usual cyclic fashion is appropriate.

IV. TREATMENT OF HIRSUTISM

Almost all patients presenting to a gynecologist with hirsutism represent excess androgen production in association with the steady state of persistent anovulation. Treatment is directed toward interruption of the steady state. Two

treatment regimens are available. In those patients who wish to become pregnant, ovulation can be induced with Clomiphene. In patients in whom pregnancy is not desired, the steady state can be interrupted by suppression of ovarian steroidogenesis with a combination oral contraceptive.

Androgen production in hirsute women is usually an LH-dependent process and suppression of ovarian steroidogenesis depends upon adequate LH suppression. The use of estrogen to suppress LH is not recommended since estrogen has both a positive and a negative feedback effect on LH, and in pharmacologic doses, the positive effect prevails. LH suppression with estrogen has been demonstrated to be unreliable despite long-term treatment (Kirschner *et al.*, 1970). The combination pill, on the other hand, has a potent negative feedback effect. Plasma testosterone levels are effectively suppressed with any combination type pill, even including the new low estrogen-dose pills (containing 30 µg ethinyl-estradiol). The testosterone value in hirsute patients shows a decrease within one to three months of treatment. This reduction is associated with a gratifying clinical improvement in the progression of hirsutism.

In the patient in whom oral contraceptive pills are contraindicated, good results can be achieved with the use of Depo-Provera, 150 mg intramuscularly every three months. The mechanism of action of Depo-Provera is slightly different from that of the oral contraceptives. Suppression of gonadotropins is less intense, and hence ovarian follicular activity continues. Even though LH suppression is not as great, some reduction in LH results in a decreased testosterone production rate. In addition, testosterone clearance from the circulation is increased (Gordon *et al.*, 1970). This latter effect may be due to an induction of liver enzyme activity. The overall effect (decreased production and increased clearance) yields a clinical result comparable to that achieved with the oral contraceptives (where the mechanism is principally decreased androgen production with a minor contribution from an elevation in binding globulin capacity).

A noteworthy feature of this clinical problem is the slow response to treatment. The average patient should be cautioned that treatment with a combination oral contraceptive will be necessary for six months to one year before an observable diminution in hair growth occurs. Combined treatment with electrolysis is not recommended, therefore, until hormone suppression has been used for at least six months (except with extreme hirsutism).

New hair follicles will no longer be stimulated to grow but hair growth that has been previously established will not disappear with hormone treatment alone. This may be affected temporarily by shaving, tweezing, waxing, or the use of depilatories. None of these tactics alters the inherent growth of the hair; therefore, they must be reapplied at frequent intervals. Permanent removal of hair can be accomplished only by electrocoagulation of dermal papillae. The combination of ovarian suppression preventing new hair growth and electrolysis removing the old hair yields the most complete and effective treatment of hirsutism.

V. DYSFUNCTIONAL UTERINE BLEEDING

Of all the types of hormonal-endometrial relationships, the most stable endometrium and the most reproducible menstrual function in terms of quantity and duration is the postovulatory estrogen-progesterone withdrawal bleeding response. It is so controlling that many women over the years come to expect a certain characteristic flow pattern. Any slight deviations, such as plus or minus one day in duration or minor deviation from expected napkin or tampon utilization, are causes for major concern in the patient. So ingrained is the expected flow that considerable physician reassurance may be required in some instances. The usual duration of flow is four to six days, but many women flow as little as two days, and some as much as eight days. While the postovulatory phase averages 14 days, greater variability in the proliferative phase produces a distribution in the duration of a menstrual cycle.

There are three reasons for the self-limited character of estrogen-progesterone withdrawal bleeding:

1. It is a universal endometrial event. Because the onset and conclusion of menses are related to a precise sequence of hormonal events, the initiation of menstrual changes occurs almost simultaneously in all segments of the uterine endometrium.

2. The endometrial tissue that has responded to an appropriate sequence of estrogen and progesterone is structurally stable. Furthermore, the events leading to ischemic disintegration of the endometrium are orderly and progressive, being related to rhythmic waves of vasoconstriction of increasing duration.

3. Inherent in the events that start menstrual function following estrogen-progesterone are the factors involved in stopping menstrual flow. Just as waves of vasoconstriction initiate the ischemic events provoking menses, so will prolonged vasoconstriction abetted by the stasis associated with the endometrial collapse enable clotting factors to seal off the exposed bleeding sites. Additional and significant effects are obtained by resumed estrogen activity.

Most instances of anovulatory bleeding are examples of estrogen withdrawal or estrogen breakthrough bleeding. The most virulent type of bleeding is secondary to high sustained levels of estrogen associated with the polycystic ovary syndrome, obesity, immaturity of the hypothalamic-pituitary-ovarian axis as in postpubertal teenagers, and late anovulation, usually involving women in their late 30s and early 40s. Unopposed estrogen induces a progression of endometrial responses in the following pattern: proliferative hyperplasia, adenomatous hyperplasia, and in some, over the course of many years, atypia and carcinoma. In the absence of growth-limiting progesterone and periodic desquamation, the endometrium attains an abnormal height without concomitant structural support. The tissue increasingly displays intense vascularity, back to back glandularity, but without an intervening stromal support matrix. This tissue is fragile, and will

suffer spontaneous superficial breakage and bleeding. As one site heals, another, and yet another new site of breakdown will appear.

In these instances the usual endometrial control mechanisms are missing. This bleeding is *not a universal event* but rather it involves random portions of the endometrium at variable times and in asynchronous sequences. The fragility of the vascular adenomatous hyperplastic tissue is responsible for this experience, in part because of excessive growth, but mostly because of irregular stimulation in which the *structural rigidity of a well-developed stroma or stratum compactum does not occur*. The flow is prolonged and excessive not only because there is a large quantity of tissue available for bleeding, but more importantly, because there is a disorderly, abrupt, random, accidental breakdown of tissue with consequent opening of multiple vascular channels. There is *no vasoconstrictive rhythmicity*, no tight coiling of spiral vessels, no orderly collapse to induce stasis. The anovulatory tissue can only rely on the "healing" effects of endogenous estrogen to stop local bleeds. However, this is a vicious cycle in that this healing is only temporary, and leads to certain repeat breakdown in the near future.

VI. TREATMENT OF DYSFUNCTIONAL UTERINE BLEEDING

The immediate objective of medical therapy in anovulatory bleeding is to retrieve the natural controlling influences missing in this tissue: universal, synchronous endometrial events, structural stability, and vasomotor rhythmicity. This is accomplished rapidly and easily (but sometimes with considerable symptomatology) with oral high dose progestin-estrogen combination oral contraceptives. Any of the oral combination tablets are useful. Whatever dose is available or chosen, therapy is administered as one pill four times a day for five to seven days. This four pills a day therapy is prolonged over this duration despite the anticipated cessation of flow within 12-24 hours. If flow does not clearly abate, other diagnostic possibilities (pathologic causes such as polyps, incomplete abortion, and neoplasia) should be reevaluated by examination under anesthesia and dilation and curettage (D & C). If flow does diminish rapidly, the remainder of the week of treatment can be given over to the evaluation of causes of anovulation, hemorrhagic tendencies, and iron or blood replacement. In addition, the week provides time to prepare the patient for the progestin-estrogen withdrawal flow that will soon be induced. For the moment, this therapy has induced the structural rigidity intrinsic to the compact pseudodecidual reaction. As a result, continued random breakdown of formerly fragile tissue is avoided and blood loss stopped. However, a relatively huge amount of tissue remains to react to progestin-estrogen withdrawal. Consequently the patient must be warned to anticipate a heavy and severely cramping flow two to four days after stopping therapy. If not prepared in this way, it is certain that the patient will view the problem as a recurrent disease or failure of hormonal therapy, and will surely wind up on the operative D & C treadmill.

Even more reassuring than the anticipation of difficulty is the confident prophecy that this withdrawal bleeding, despite the pain and volume, will be self-limited (as a result of the induced vasomotor rhythmicity). However, to ensure success in this regard, on the fifth day of flow, a low-dose cyclic combination oral contraceptive is initiated with three three-week treatments, punctuated by one-week withdrawal flow intervals. Not only does the decreasing volume and pain with each successive cycle reaffirm confidence in control mechanisms, but it also serves to prevent any unopposed estrogen regrowth that might occur. Early application of the progestin-estrogen combination limits growth and allows orderly regression of excessive endometrial height to normal controllable levels. If the progestin-estrogen combination is not applied, abnormal endometrial height and persistent excessive flow would recur.

In the patient not exposed to potential pregnancy, in whom cyclic progestin-estrogen for three months has reduced endometrial tissue reservoirs to normal height, the pill may be discontinued and unopposed endogenous estrogen permitted to reactivate the endometrium. At two-month intervals in the absence of spontaneous (possibly postovulatory) menses, the recurrence of the anovulatory status is suspected, sustained estrogen stimulation of the endometrium is assumed, and before overstimulation of the endometrium is permitted to occur, a brief course of an orally active progestin derivative is administered, e.g., Provera, 10 mg orally daily for five days. Restrained reasonable flow (progesterone withdrawal flow) will occur two to seven days after the last pill. With this therapy, excessive endometrial buildup is avoided.

Certain exceptions apply in the medical control of dysfunctional uterine bleeding with progestin therapy. Obviously in the age group over 35 years, an initial endometrial biopsy (with multiple sampling) is required to seek worrisome pathology that requires specific therapy. This is especially true in the older woman in the fourth or fifth decade, where adenocarcinoma of the endometrium is a significant problem.

Bleeding manifestations are frequently associated with *minimal (low) estrogen stimulation*, yielding intermittent vaginal spotting. In this circumstance, where minimal endometrium exists, the beneficial effect of progestin treatment may not exert its organizational, strengthening action. A similar circumstance also exists in the younger anovulatory patient in whom *prolonged hemorrhagic desquamation* leaves little residual tissue. In these instances the appropriate therapeutic reaction is *not* the traditional operative D & C, which, although it frequently manages the acute problem, does not improve but, in fact, compounds the long-range difficulty by denuding the endometrial reserve even further. High-dose estrogen therapy is recommended, using Premarin, 25 mg intravenously every four hours until bleeding abates (up to six doses can be given). This is the sign that the "healing" events are initiated to a sufficient degree. Progestin treatment can be started at the same time.

Progestin therapy is not always a positive controlling factor. Two examples in

clinical medicine are evidence of the problems associated with progestin breakthrough bleeding. These are the breakthrough bleeding episodes occurring with prolonged use of oral contraceptives or with depot forms of progesterone derivatives (such as Depo-Provera; see the chapter by Greep). In the absence of sufficient endogenous and exogenous estrogen, the endometrium shrinks to a shallow height. Furthermore, it is composed almost exclusively of pseudo-decidual stroma and blood vessels with minimal glands. Peculiarly, experience has shown that this type of endometrium also yields to the fragility bleeding more typical of pure estrogen stimulation. The clinical story is often that of oral contraception of long standing, with marked diminution of withdrawal flow. Frequently no bleeding occurs in the nontreatment interval. This is associated with intermittent, variable vaginal spotting during the month. The clinical reflex is to double therapy, but this only rarely succeeds because the effect is to intensify the progestin atrophic effect. The more appropriate reaction in view of the endometrial condition is estrogen therapy (ethinyl estradiol 20 µg or conjugated estrogen 2.5 mg daily for ten days) during and in addition to the oral contraceptive administration. This rejuvenates the endometrium, intermenstrual flow stops, and appropriate withdrawal resumes.

One problem frequently encountered is the progestin breakthrough bleeding experienced in chronic depot administration of progestin. This therapy is used not only for contraception, but also in certain situations for chemotherapy. In 75% of cases, continuous therapy provides control without menstrual bleeding. In the remainder, breakthrough progestin bleeding occurs. Judicious use of estrogen is appropriate and effective therapy.

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THE MECHANISM OF OVULATION AND HOW EGGS AND SPERM REACH THE SITE OF FERTILIZATION¹

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Reijnier de Graaf discovered the ovarian follicle in 1672. He described and illustrated ovarian follicles in several species and recognized that the ova were shed from the "vesicles." De Graaf's greatest contribution was to assign to the egg its central importance for reproduction in the female. He surmised correctly that the ovulated eggs were transported from the ovaries to the uterus through the oviducts. It is remarkable that the first live meaningful documentation of human ovulation on motion picture film should have been achieved in 1973 by Professor Hans Frangenheim of Germany, precisely 300 years after de Graaf's correct interpretation of the ovarian follicle.

It is now clearly established that the primordial egg cells (perhaps 50-60 of them) first arise in the yolk sac endoderm of the 23-day-old human embryo. They migrate in a manner similar to amebae and enter the gonadal ridges at approximately 30 days after fertilization. These cells are the sole progenitors of all of the eggs in the human female. These are remarkable cells since they embody all of the genetic memory of all past generations. By five months of development their number has increased by mitotic divisions to several million, in some human females reaching as high as seven million. An arresting phenomenon is the decline in the number of eggs in the fetal ovaries in the latter third

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of pregnancy and during the early postnatal period owing to atresia, a phenomenon in which certain of the egg cells die and disappear. Thus, at the time of birth the two ovaries contain about 500,000 eggs of which 420-480 may ovulate during the reproductive life of the human female.

Gonadotropins from the pituitary are clearly necessary for the development of the ovarian follicle. The complex interrelationships of the hypothalamus, the pituitary, and gonads in effecting cyclic follicular growth and ovulation have formed one of the fascinating sagas in endocrinological investigation during the past few decades. These investigations have involved the localization of the neurons in the hypothalamus, which synthesize the various pituitary hormone-releasing factors, and their indirect control through complex auditory, olfactory, visual, and psychic stimuli (Edwards and Porter, 1975). The demonstration of a separate portal vascular system from the hypothalamus to the pituitary, as well as a potential cellular conducting system via the third ventricle, has helped clarify the hypothalamic, pituitary, gonadal interrelationships. The complexity of the hormonal interrelationships is described in the chapter by Speroff.

In any particular menstrual cycle primordial follicles are stimulated to begin their growth and maturation by the action of the follicle-stimulating hormone (FSH). It remains a biological mystery why certain follicles and their contained eggs should be chosen to complete their cycle of growth and development at any particular time in the reproductive life of the female.

I. GROWTH OF THE EGG AND FOLLICLE LEADING TO OVULATION

A. Follicular Development

A primordial follicle consists of a rapidly enlarging oocyte surrounded by a single layer of flattened granulosa cells resting upon a definitive basement membrane (Fig. 1). The growth of the follicle has two distinct phases. The first is the rapid growth of the egg itself and the deposition of a highly polymerized membrane, the zona pellucida, that surrounds it. The second phase is characterized by a transformation of the flattened layer of follicular cells into rapidly dividing cuboidal cells, the hallmark of the growing and expanding follicle. The multi-layered granulosa of follicular cells develops rapidly until approximately 20 layers of cells are present (Fig. 2). Isolated fluid-filled spaces appear that ultimately unite to form the antral cavity filled with a viscous fluid rich in hyaluronic acid (Fig. 3). An enlarging vesicular follicle is formed, still separated from a well-differentiated and highly vascularized theca interna by a delimiting basement membrane. No blood vessels invade this epithelium during its initial growth. The mature preovulatory follicle, a spherical structure that bulges above the ovarian surface, is visible as a translucent vesicle (Fig. 4). Its wall is composed of at least five layers of cells and tissues, the thickness of which varies in different animals. In all animals, there is a superficial germinal epithelial layer of cuboidal cells that

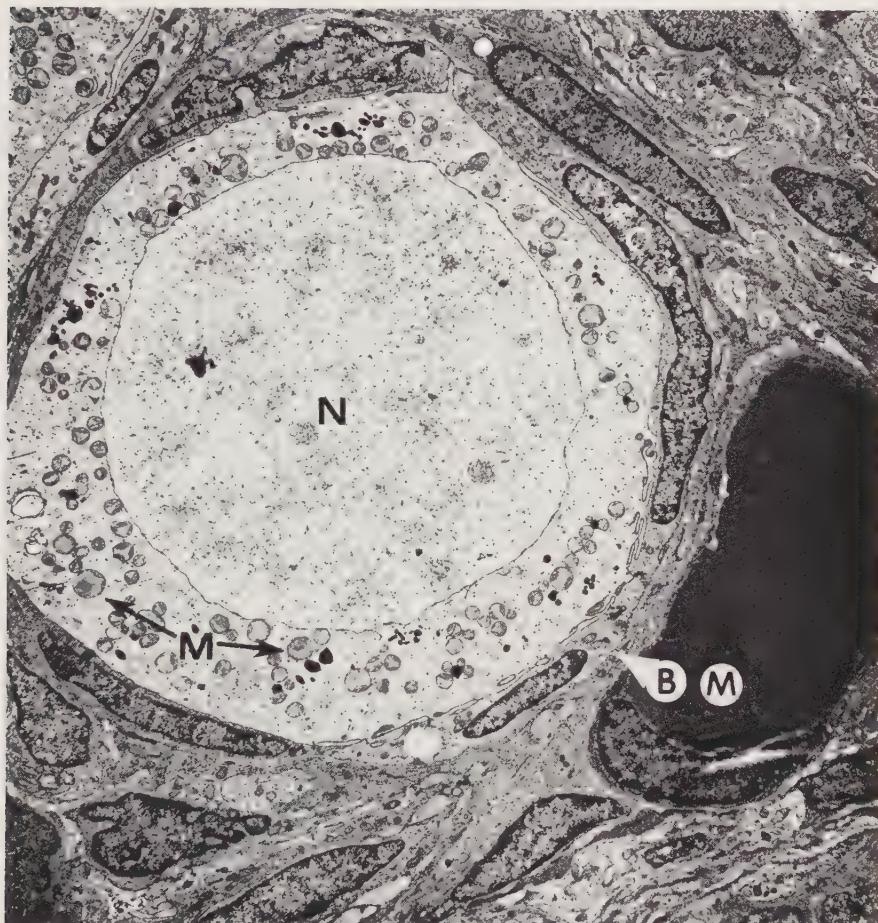


Fig. 1. A low-power electron micrograph of a primordial follicle. Note the large size of the egg in relationship to the encompassing follicular cells. N, nucleus; FC, follicular cell; M, mitochondria; BM, basement membrane.

appears to peel away just before ovulation. The epithelial layer rests upon a relatively thick collagen connective tissue layer, the tunica vaginalis. Beneath the tunica vaginalis is a highly vascularized layer, the theca interna; it in turn rests upon a homogenous basement membrane that separates it from the multiple-layered granulosa.

B. Ovulation

A number of investigators have shown that intrafollicular pressure does not increase prior to follicular rupture (Rondell, 1970). This finding has focused

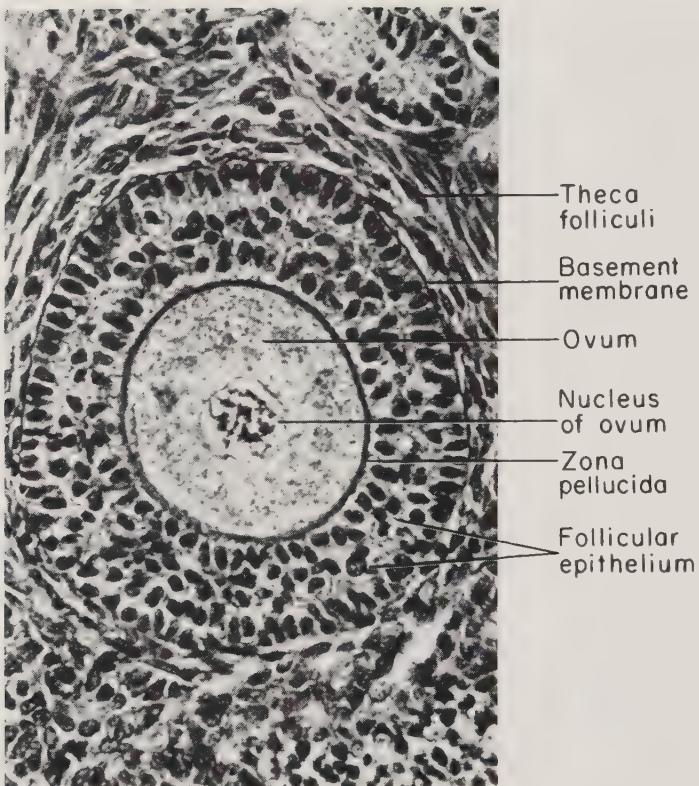


Fig. 2. The first and second phases in the development of a growing follicle after it has been stimulated by FSH. A definite basement membrane separates the follicular cells from the theca cells. Note that a zona pellucida has formed.

attention on the progressive deterioration and weakening of the follicular wall at a specific site on its surface, which is called the stigma (Fig. 5D, arrow). The progressive thinning and depolymerization of the connective tissues in the region of the stigma are fundamental to the final maturation of the follicle and are a prerequisite to ovulation. Sequential stages in the thinning out and depolymerization of the stigmal area are shown in Fig. 5A-E. The stigma occupies a relatively restricted area of the bulging follicle (Fig. 5). The formation of the stigma begins with a decreased blood flow; therefore, it often appears blanched. There follows a rapid reorganization of the vasculature in the form of a ring of vessels around the edge of the stigma. Small hemorrhages (Fig. 5B), due to an increase in vascular permeability, are commonly observed in the tissues just beyond the stigma.

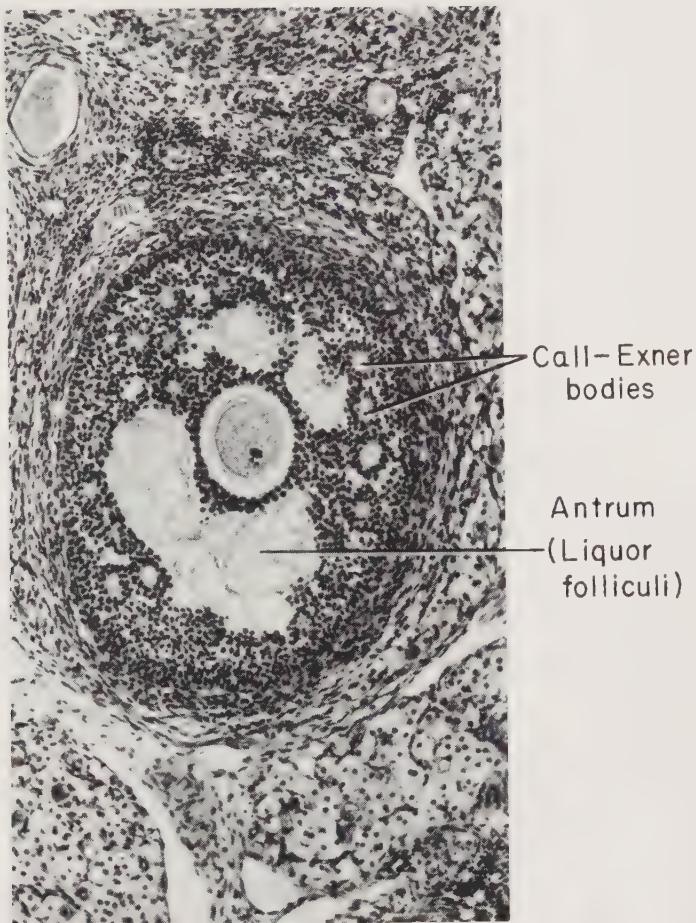


Fig. 3. An enlarging vesicular follicle in which a fluid-filled antrum is forming and filling with liquor folliculi. The Call-Exner bodies are the precursors of the follicular fluid.

Histological and ultrastructural studies of tissues of the stigma just prior to rupture reveal a dissociation and loss of the granulosa cell layer, a depolymerization of the connective tissue comprising the tunica albuginea, and an increase in vascular permeability. Biophysical studies of the preovulatory follicles have revealed also that the tensile strength of the follicle wall gradually deteriorates as ovulation approaches. All of these observations as well as others have led naturally to the suggestion that some kind of enzymatic digestion may be involved in the weakening of the follicular stigma. Studies on the possible roles of collagenases, proteinases and plasmins have received the most attention, with some investigators

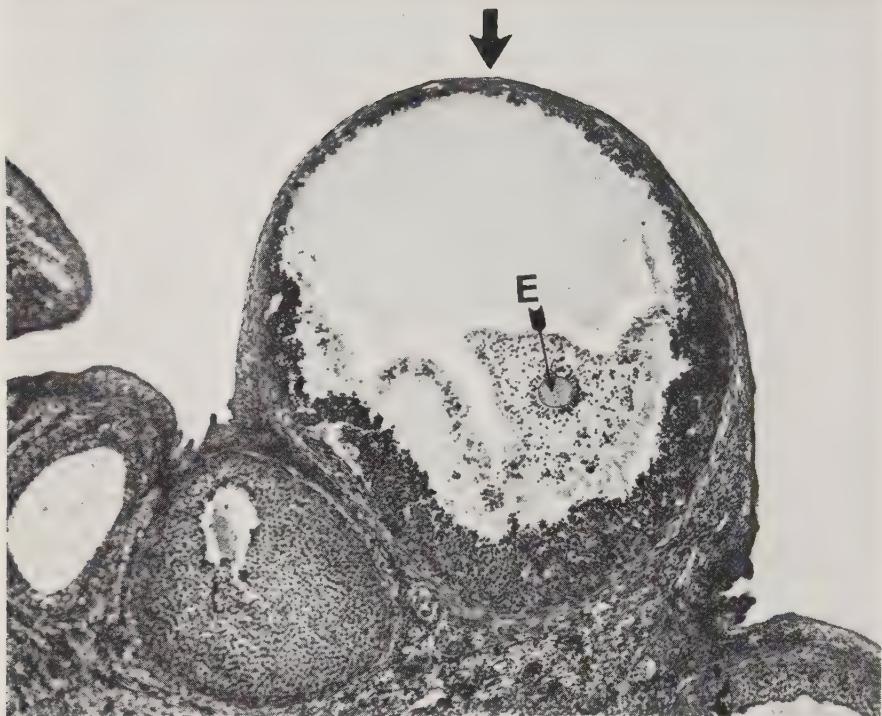


Fig. 4. A mature preovulatory follicle that will ovulate in approximately one hour. The arrow indicates the approximate site of rupture. E, egg surrounded by the loosened follicular cells forming the cumulus oophorus.

enthusiastically supporting one or several of these enzymes as the principal mediators for effecting the degradative changes within the connective tissue in the stigmal area. However, based on present knowledge, no specific enzyme activity can as yet be associated with follicular rupture. We reemphasize that the qualitative and experimental observations leave no doubt that degradation of follicular tissue, especially in the region of the stigma, is a fundamental aspect of maturation of the ovulatory follicle and a prerequisite to its rupture (Nalbandov and Biggers, 1974).

II. EGG TRANSPORT

At the time of ovulation the fimbria of the oviduct almost completely surrounds the ovary, forming a kind of sac or bursa (Fig. 6). The fimbria is a complex tissue with numerous folds in which at least 50% of the lining cells are ciliated (Fig. 7). The cilia all beat in the direction of the ostium of the

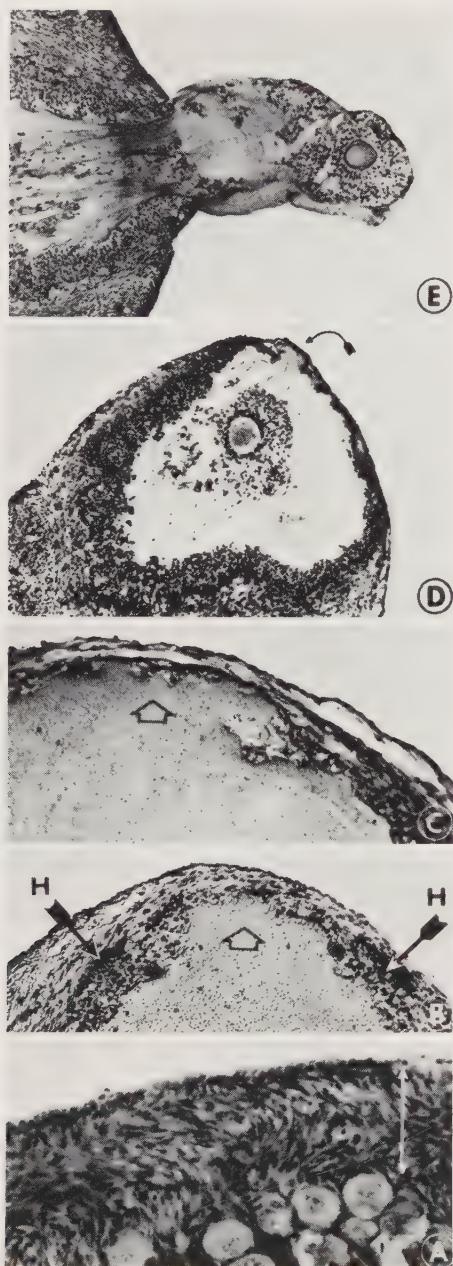


Fig. 5. The sequence of changes in the tissues at the localized site where follicular rupture will occur. Note the thickness of the connective tissue layer at A and its gradual thinning out in B, C, and D. Hemorrhages, H, invariably appear in the region of the stigma shortly before ovulation. At E, ovulation has just been completed.

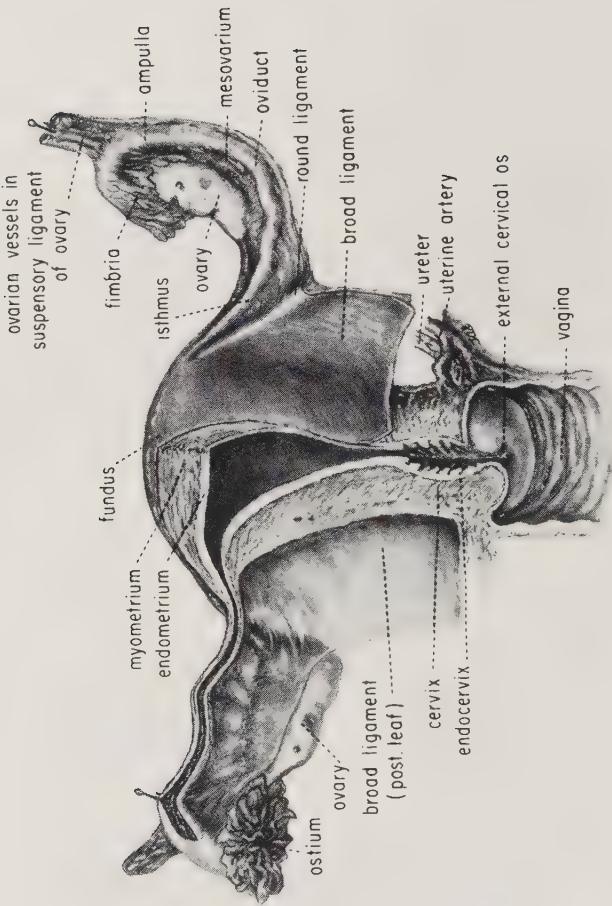


Fig. 6. The reproductive tract of the human female showing the relationship of the fimbria of the oviduct to the ovary.

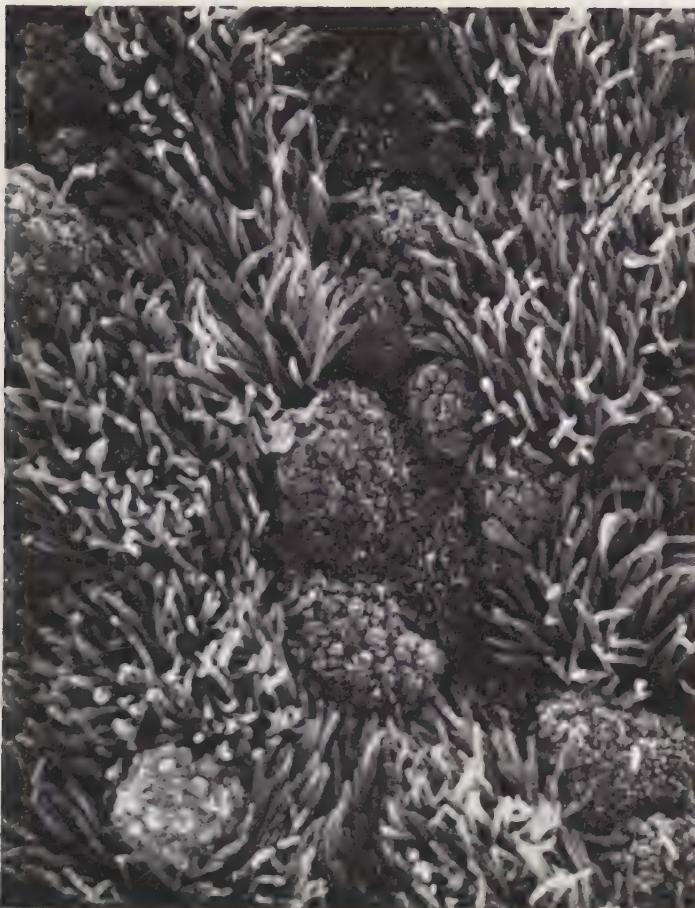


Fig. 7. A scanning electron micrograph illustrating the appearance and arrangement of the ciliated cells on the fimbria.

oviduct and sweep the ovulated egg from the surface of the ovary into the ampulla. Although it has never been observed in the human female, we believe that the ovulated egg is transported through the ampulla to the ampullo-isthmic junction, the site of normal fertilization, primarily by the sweep of the cilia. The remarkable complexity of the mucosal fold of the ampulla in the human at about the time of ovulation is seldom appreciated. Figure 8 is a frozen section of a human ampulla, removed at midcycle. This technique preserves the natural condition and illustrates that the lumen of the ampulla is crowded with interdigitating folds, the surfaces of which are covered by at least 50% ciliated cells all of which beat in the direction of the ampullo-isthmic junction (Blandau, 1973).

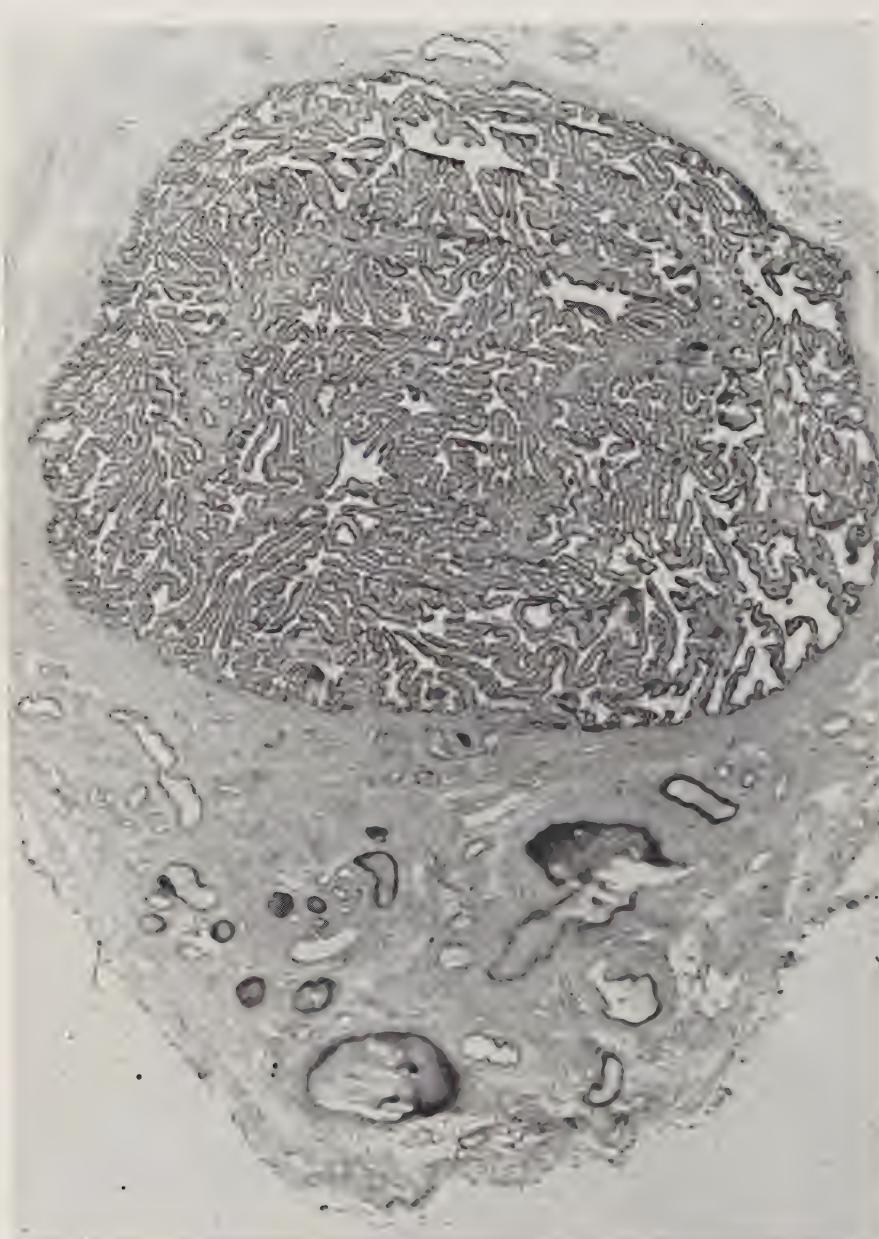


Fig. 8. A frozen section of the ampulla of a human oviduct removed at about midcycle. Note the complexity of the interdigitating mucosal lappets. At least 50% of all surface cells are ciliated. They all beat toward the ampullo-isthmic junction.

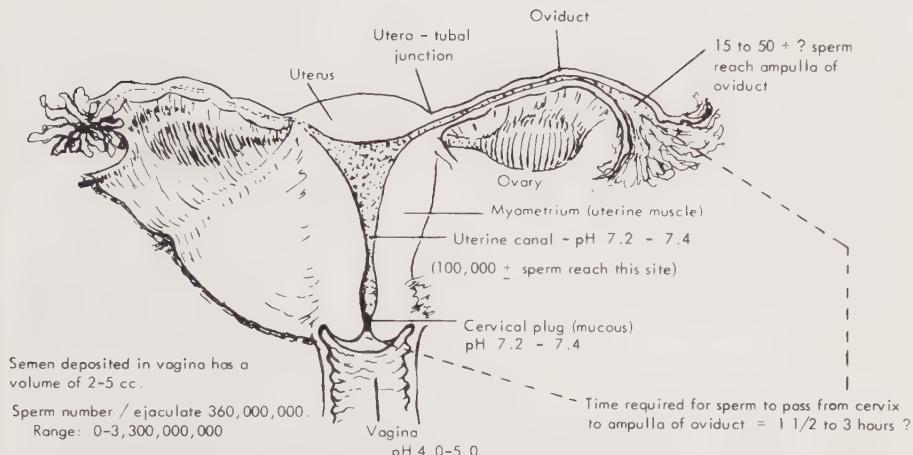


Fig. 9. A diagrammatic speculation of the number of spermatozoa reaching various subdivisions of the human female reproductive tract.

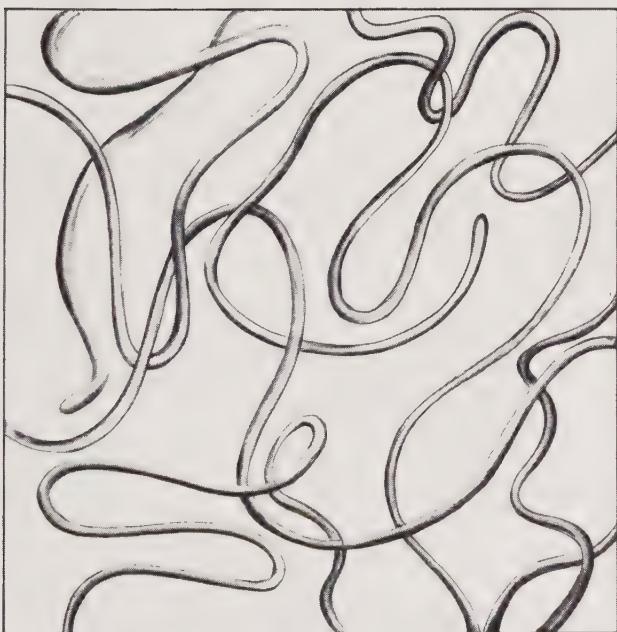


Fig. 10. A model of the ensemble of entangled macromolecules representative of human midcycle cervical mucus.

III. SPERM TRANSPORT TO THE SITE OF FERTILIZATION IN THE HUMAN FEMALE

Millions of spermatozoa are deposited in the vagina at the moment of ejaculation in the human female. Of these, perhaps less than 100 spermatozoa reach the site of fertilization in the ampulla of the oviduct (Fig. 9). The manner by which the fertilizing sperm reaches the ampulla is still surrounded by considerable mystery. The first "bottleneck" the sperm encounter is the cervical mucus.

At midcycle or about the time of ovulation the mucus is most hospitable to sperm. At this time of the menstrual cycle it is most abundant, is almost crystal

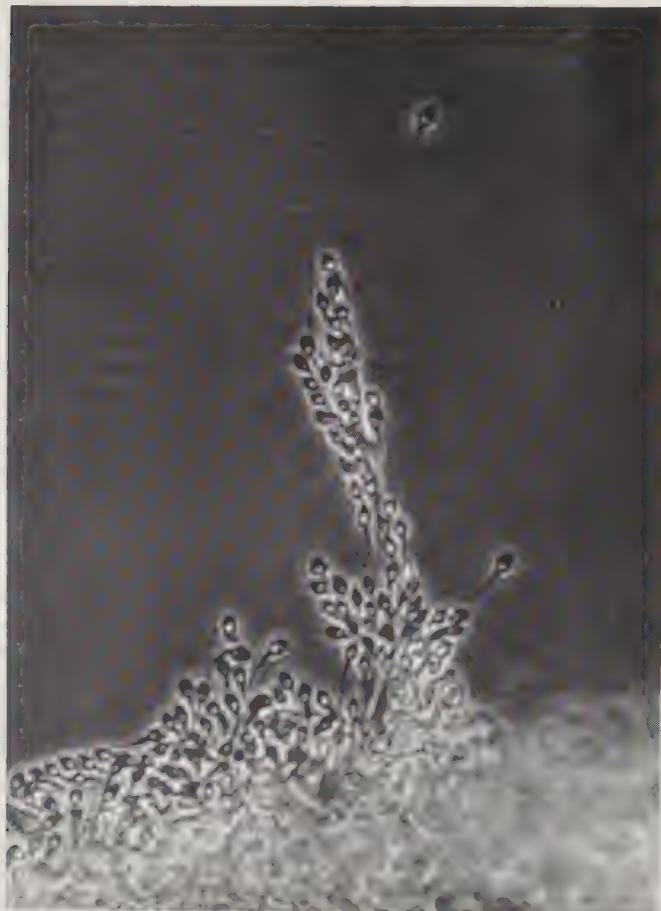


Fig. 11. Human spermatozoa entering stretched human cervical mucus. Note that all sperm are moving in a unidirectional fashion.

clear, and has a greater *spinnbarkeit* than at any other time in the cycle. The "spinability" of cervical mucus is often used as a diagnostic sign of an impending ovulation. The viscoelastic properties of cervical mucus are due to the mucins it contains. These are complex glycoproteins rich in carbohydrates. The study of cervical mucus by laser light-scattering spectroscopy has revealed that the molecular arrangement of the mucins may be more accurately described as an ensemble of entangled, random-coiled macromolecules (Fig. 10; Lee *et al.*, 1977).

When spermatozoa enter the cervical mucus they invariably do so in a linearly directed fashion (Fig. 11). They are orienting the entangled random-coiled macromolecules, which facilitates penetration of spermatozoa in an axis parallel to the oriented macromolecules (Fig. 12).

On the basis of all available evidence, spermatozoa in women move through the cervical mucus by their own innate motility. At one time we thought that proteolytic enzymes in the seminal plasma or perhaps enzymes released from the

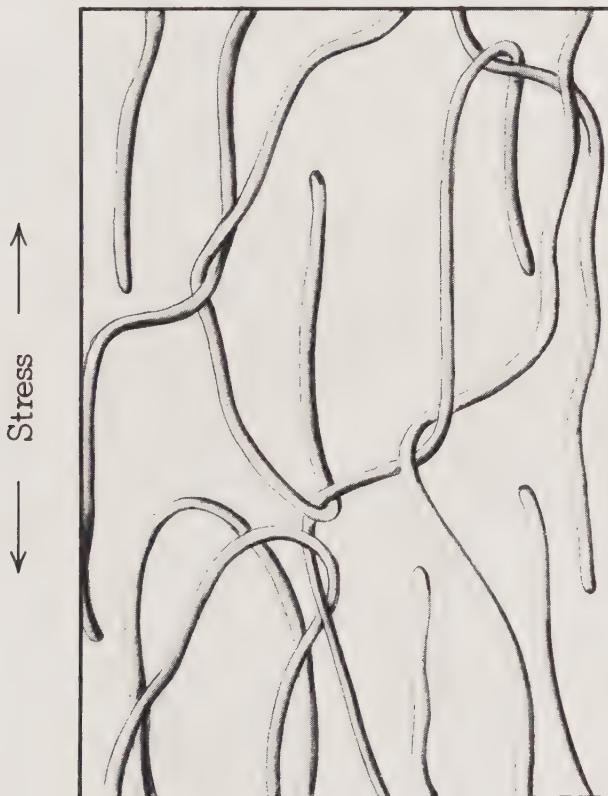


Fig. 12. A model of entangled macromolecules after "stress" has been induced. The randomly coiled and entangled macromolecules align themselves along the direction of stress.

sperm acrosomes played a role in depolymerizing the mucus, enhancing sperm transport through this hydrogel. Several recent studies have emphasized that enzymatic lysis of cross links is not an initial requirement for sperm penetration of cervical mucus (Blandau and Moghissi, 1973).

Of the millions of spermatozoa deposited in the vagina a remarkably small number reach the uterine lumen (Fig. 9). How those entering the uterine lumen reach the utero-tubal junction to enter the oviducts is still a mystery.

Uterine contractions, perhaps enhanced by prostaglandins present in the seminal plasma, may hasten the transport of the uterine contents toward the oviduct. In the human sperm, flagellation is also an important consideration. The utero-tubal junction may act as a selective valve through which only a few sperm enter the isthmus of the oviduct. Transport of sperm through the isthmus and into the ampulla is affected primarily by remarkable, sequential contractile waves toward the ovary that carry the luminal contents of this segment to the site of fertilization within a few seconds. The rate and amplitude of these waves varies in different mammals but in general the principle of movement is the same.

It is of great interest that the oviducts have the paradoxical facility of transporting eggs from the ovary toward the ampullo-isthmic junction in one direction and spermatozoa through the isthmus in the opposite direction simultaneously. There is no other tubular system in the body that can accomplish such a complex feat. The oviduct is indeed a most remarkable organ.

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CELLULAR ACTIONS OF ESTROGENS AND ORAL CONTRACEPTIVE SEX STEROID HORMONES

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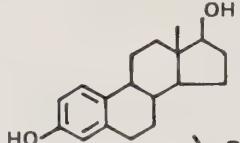
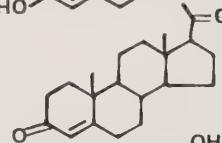
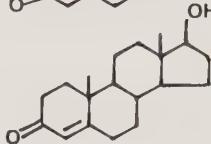
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Oral contraceptives, which contain steroidal estrogens and progestins, exert profound effects on a variety of tissues. This chapter will focus on the mechanisms by which these sex steroid hormones exert their effects and will describe some of their actions.

I. SITE OF SYNTHESIS

The sex steroid hormones include the estrogens, progestins and androgens (Table I). Estrogens are synthesized primarily in the ovary (but also in the adrenal and testis, and in the placenta during pregnancy), and the principal estrogen in the cycling female is estradiol-17 β . The progestins are synthesized primarily in the ovary and placenta and to a lesser extent in the adrenal. The principal progestin in males and females is progesterone. The androgens are

TABLE I. Sex Steroid Hormones

Hormone	Principal source	Example	Chemical formula
Estrogen	Ovary	Estradiol-17 β	
Progestin	Ovary, placenta	Progesterone	
Androgen	Testis	Testosterone	

synthesized principally in the testis, although at low levels in the ovary, and testosterone is the major androgen in the male. All steroids consist of a simple four-ring structure, which is derived from cholesterol, and have molecular weights of about 300.

II. SITE OF ACTION

A. In Reproductive Tissues

The specificity of hormone action has been known for a long time. For example, estrogens act primarily only on certain tissues, termed target tissues. As seen in Table II, the principal target tissues for estradiol include the uterus, vagina, breast, and hypothalamus. Target tissues acted upon by progesterone include the uterus and oviduct. Progesterone prepares these tissues for implantation and the maintenance of pregnancy. Testosterone acts primarily on the seminal vesicles, prostate, and testes of the male, and plays a principal role in the development of male reproductive function and sexual characteristics.

Although hormones exhibit specificity and act principally on only certain tissues, when hormones are given either at high levels or under conditions of chronic hormone stimulation, other tissues may also show changes due to the hormone (Table III). Estrogen influences the growth and differentiation of cells in the uterus, vagina, and breast, and it also acts on the hypothalamus to regulate gonadotropin output, and hence subsequent ovulation. In addition, estrogen may exert behavioral effects.

TABLE II.^a

Steroid	Target tissues	Principal functions
Estradiol	Uterus, vagina, breast, hypothalamus	Development of female reproductive function and sexual characteristics
Progesterone	Uterus, oviduct	Maintenance of pregnancy
Testosterone	Seminal vesicles, prostate, testis	Development of male reproductive function and sexual characteristics

^aOral contraceptives = estrogen + progestin.

TABLE III. Estrogen

Target tissues	Effects
<i>Major</i>	
Uterus, vagina	Growth and differentiation
Breast	Mammary gland growth; duct development
Hypothalamus	Regulation of gonadotropin output (ovulation); behavioral effects
<i>Other</i>	
Liver	Liver metabolism; blood clotting factors; blood pressure
Connective tissue	Elasticity
Bone	Antiosteoporosis, improved calcification?

B. In Nonreproductive Tissues

Aside from the major target tissues influenced by estrogens, other tissues are also affected in a less dramatic fashion. For example, estrogen influences liver metabolism and thereby affects the production of blood clotting factors and influences blood pressure. Estrogens affect the elasticity of connective tissue such as that beneath the skin and may oppose osteoporosis of bone.

It is these secondary effects of hormones that frequently make hormones unusable for certain persons or enhance the risk of undesirable side effects. What researchers would like to find are estrogen derivatives that possess enhanced specificity only for the reproductive system or for specific tissues within the reproductive system with little, if any, activity on tissues outside the reproductive system.

III. MECHANISM OF ACTION

A. Steroid Hormones

The observation that estrogens elicited major effects on only certain tissues led to the concept that these tissues possessed a specific mechanism for recognizing the hormone. Studies by Glascock and Hoekstra (1959) and Jensen and

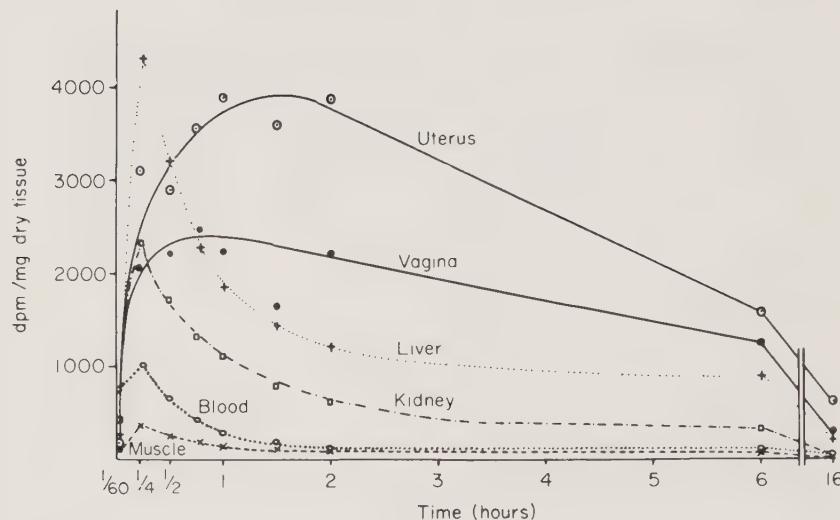


Fig. 1. Tissue tritium levels after single subcutaneous injection of 98 ng (11.5 μ Ci) [$6,7-^3\text{H}$] estradiol in 0.5 ml saline to immature rats. Each point based on six animals (from Jensen and Jacobson, 1960).

Jacobson (1960, 1962) in the late 1950s demonstrated that estrogen was retained longer in cells known to respond to the hormone. In Fig. 1, immature rats were injected with radioactive estradiol and the amount of radioactivity remaining in different tissues was measured as a function of time after injection. The major tissues known to respond to estradiol, namely, the uterus and vagina, take up and retain estradiol for a prolonged period of time, whereas tissues showing little response to hormone (muscle, kidney), show a more rapid loss of radioactivity. Further work in several laboratories documented that these hormone-responsive tissues contained protein molecules capable of tightly binding and interacting with the hormone (Gorski *et al.*, 1968; Jensen *et al.*, 1966; King *et al.*, 1965; Talwar *et al.*, 1964). This binding protein is generally termed a *receptor* for the hormone.

Studies over the last 10-15 years have documented in considerable detail the interaction of the steroid hormone with the receptor and its role in the initiation of physiological effects characteristic of the hormone (Fig. 2). In estrogen target tissues in the absence of hormone, estrogen receptors are found in the cytoplasm of the target cell. Upon binding steroid hormone, the hormone-receptor complex moves into the nucleus, where it interacts with chromatin in the target cell and initiates, among other processes, the synthesis of RNA and subsequent proteins involved in the physiological response to the hormone. (The reader is directed to recent reviews on the mechanism of action of the sex steroids for further details: Gorski and Gannon, 1976; Jensen and DeSombre, 1972, 1973; Jensen *et al.*,

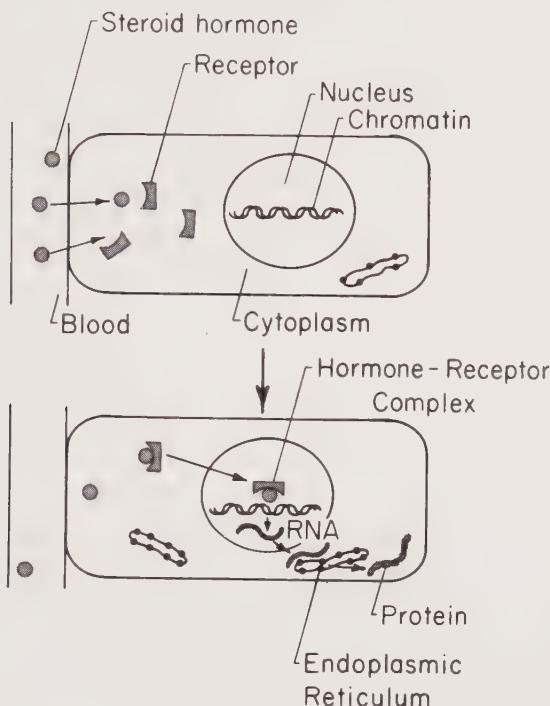


Fig. 2. Schematic depiction of cellular response to steroid hormones in target cells containing specific receptor proteins that bind the hormones.

1974; Katzenellenbogen and Gorski, 1975; Liao, 1975; O'Malley and Means, 1974; Rosen and O'Malley, 1975; Williams-Ashman and Reddi, 1972; Yamamoto and Alberts, 1976). In the lower panel of Fig. 2, new RNA is shown migrating to the endoplasmic reticulum and being translated into protein.

It is important to note that the characteristic response to the hormone only occurs after the hormone receptor complex has moved into the nucleus. In this sense, one may think of the steroid hormone as being a regulatory agent that triggers a cell response that is genetically programmed. This mechanism of action is summarized in Fig. 3.

B. Comparison with Protein Hormones

Steroid hormones as well as the thyroid hormones readily pass through the membrane of cells, and the receptor proteins for these hormones are present in the cytoplasm (Fig. 3). The binding of these hormones to their receptors evokes the movement of the hormone-receptor complex into the nucleus and its effect is at the level of the gene. In contrast, protein hormones such as insulin and

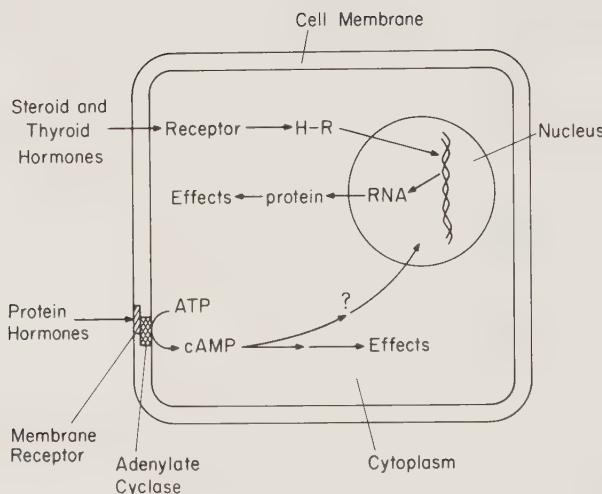


Fig. 3. Model depicting the different mechanisms by which steroid and thyroid hormones and protein hormones interact with their respective target cells to elicit the physiological effects of the hormone. H-R, hormone-receptor complex.

prolactin, which are large and highly charged, have difficulty getting through the cell membrane and instead interact with protein receptors located in the cell membrane [see reviews by Butcher *et al.*, (1972) and Hollenberg and Cuatrecasas (1975) for a more detailed discussion]. Formation of this hormone-receptor complex activates the membrane-bound enzyme, adenylate cyclase, resulting in increased intracellular levels of cyclic adenosine monophosphate (AMP). Cyclic AMP, which is frequently termed the second messenger for protein hormones, then acts through a variety of pathways, influencing the activity of various enzymes, and thereby elicits the physiological effects of these protein hormones. There is no direct evidence at present that protein hormones exert their initial action via the genome.

IV. DURATION OF STEROID HORMONE ACTION

There is good evidence to indicate that the estrogenic potency of a given estrogen depends on both its affinity for the estrogen receptor and its persistence in the blood (Fig. 4). Both of these factors determine the length of time that the hormone-receptor complex spends in the nucleus, and the more potent the compound, the longer its time of residence in the nuclear compartment of the target cell (Anderson *et al.*, 1973, 1975; Lan and Katzenellenbogen, 1976). Mestranol, which is a common estrogenic component of oral contraceptives, is a long-acting estrogen. Its ethynodiol group ($-C\equiv CH$) is essential for maintaining oral

1. Affinity for receptor (high)
2. Persistence in blood (slow clearance rate)

Determine:

Length of time in nucleus (long)

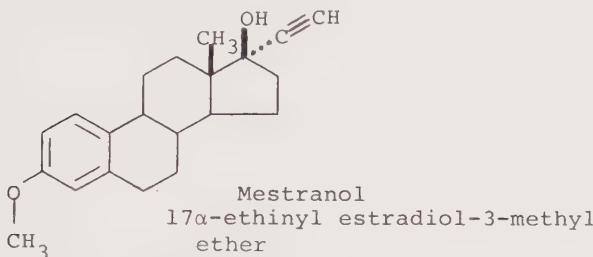


Fig. 4. (A) Factors determining the estrogenic potency of different estrogens, (B) the chemical structure of a long-acting estrogen, mestranol.

activity of this estrogen, and its methyl ester ($-\text{OCH}_3$) function increases its duration of action (Fig. 4).

V. HORMONAL THERAPY IN TREATMENT OF BREAST CANCER

The knowledge that hormone-responsive cells contain receptors for the hormone has led to a greater understanding of the endocrine regulation of growth of hormone-responsive tumors, such as those of the breast, and the use of estrogens in treatment of reproductive cancers. Hence, the remaining portion of this chapter will focus on the use of hormonal therapy in treatment of breast cancer.

Normal mammary gland development is dependent on several hormones. In addition to estrogen and progesterone, the hormones insulin, cortisol, prolactin, and growth hormone also play important roles in mammary gland development. It appears that many cancers that develop in the breast are responsive to endocrine or hormonal manipulation. In other words, cancers of the breast often retain the hormone dependence characteristics of the original tissue.

A. Determination of Estrogen Receptors

Based on the knowledge that estrogen-responsive cells contain the estrogen receptor, it was suggested by Elwood Jensen in the early 1970s that the presence of the estrogen-binding receptor protein in breast tumors might be useful in predicting the responsiveness of a patient to endocrine therapy. Studies over the past five years have documented that assessment of the presence or absence of estrogen receptors in breast cancers enables more accurate predictions of patient benefit from hormonal therapy (see McGuire *et al.*, 1975, 1977, for more detailed discussions).

TABLE IV. Estrogen Receptors in Breast Cancer^a

	ER ⁺ (%)
1° Biopsy	77 (326/421)
Metastatic	66 (66/100)
Total	75 (392/521)

^a Response to endocrine therapy, ~35%. Many contain receptor yet do not respond.
(Adapted from McGuire *et al.*, 1977.)

TABLE V. Estrogen Receptor and Clinical Response^a

Endocrine therapy	ER ⁻ (%)	ER ⁺ (%)
Ablative	8	55
Additive	8	60
Total	8	57

^a Adapted from McGuire *et al.* (1975).

Evaluation of the presence of estrogen receptors in breast cancers (Table IV) indicates that approximately 75% of breast cancers contain the estrogen receptor (i.e., are "ER positive"). However, the response to endocrine therapy is only about 35%; hence, many tumors contain the estrogen receptor, yet do not respond to hormonal therapy.

In breast tumor samples that lack the estrogen receptor, only 8% show a positive clinical response to endocrine therapy (Table V). However, if the estrogen receptor is present in tumor samples, approximately 57% of patients will benefit from endocrine therapy. Hence, with the estrogen receptor assay, the chances of selecting an appropriate therapy are increased considerably.

It is of note that endocrine therapy may take two forms. It may be ablative, in which case the source of hormones, such as the ovary, adrenal, or pituitary gland, is removed; or it may be additive, in which case hormones such as estrogens are given to patients in very high concentrations. In both cases, the normal hormone level is disrupted, interfering with the growth of hormone dependent tumors.

The level of estrogen receptor in the tumor also indicates the likelihood of clinical response; the higher the estrogen receptor content, the higher the likelihood of response (Table VI).

TABLE VI. ER Level and Clinical Response (Metastatic)^a

fmol/mg cytosol protein	Response (%)
<3	6 (2/31)
3-10	45 (10/22)
11-100	46 (14/30)
101-1000	81 (21/26)

^a Adapted from McGuire *et al.* (1977).

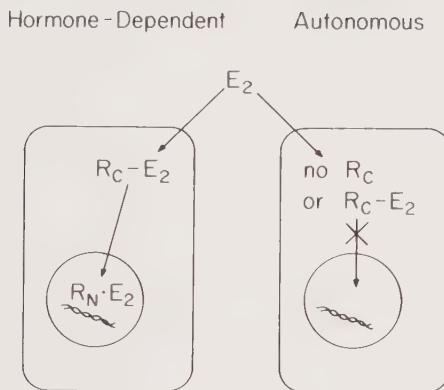


Fig. 5. Schematic representation of the interaction of estradiol (E₂) with the cytoplasmic (R_C) and nuclear (R_N) receptors in hormone-dependent mammary carcinomas, and the possible defects in the receptor mechanism of autonomous carcinomas.

From the available data, it is clear that for a tumor to be hormone dependent, it must contain the estrogen receptor; if it lacks receptors, it will be hormone independent or autonomous (Fig. 5). However, what is particularly perplexing is the fact that about 40% of the tumors that do contain receptors fail to have their growth controllable by hormones. It is possible, in these cases, that the cytoplasmic estrogen receptor may be unable to enter the nucleus or interact appropriately with chromatin such that the estrogen, although receptor-bound, is ineffective.

B. Determination of Progesterone Receptors

Hence scientists have sought better predictors of hormone-responsive breast cancers. Laboratories are now attempting to measure both the cytoplasmic estrogen receptor and nuclear localized estrogen receptor, in an attempt to demonstrate whether the receptor mechanism is intact in these cells. Attempts have also been made to monitor other biochemical markers of an intact estrogen response system. One such marker is the progesterone receptor, whose synthesis is dependent on normal estrogen receptor interaction in the nucleus.

Recent studies have indicated that the ability to predict clinical response to endocrine therapy is improved by measurement of both estrogen receptor and progesterone receptor content in tumor samples (Table VII). Tumors containing the estrogen receptor but not the progesterone receptor show only a 39% rate of response. However, tumors containing the estrogen receptor *and* the progesterone receptor show a 64% response.

It is apparent that an understanding of the mechanism of hormone action has led to more accurate predictions of response to endocrine therapy in treatment

TABLE VII. Estrogen and Progesterone Receptors and Clinical Response^a

ER	PgR	Response (%)
—	—	0 (0/11)
—	+	(no cases)
+	—	39 (7/18)
+	+	64 (16/25)

^a Adapted from McGuire *et al.* (1977).

of breast cancer patients. Our understanding of the hormonal involvement in this disease is still, however, quite imperfect. Future studies will hopefully lead to a more complete understanding of how hormones influence the growth of tumors of the reproductive system and regulate the complex functioning, as well, of normal reproductive tissues.

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PROSPECTS FOR FERTILITY CONTROL IN THE MALE

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The development of oral contraceptives for women was the culmination of many years of intensive basic research on the endocrine mechanisms involved in ovulation and regulation of the menstrual cycle. But what about men? The investment of research support and investigative effort on mechanisms involved in spermatogenesis, sperm release, and sperm maturation has been far less and our basic understanding of the reproductive biology of the male is still many years behind our knowledge of the female. It would be easy to conclude that this disproportionate effort and expenditure on contraception for women has been due to chauvinism in a scientific community dominated by men, and I will not deny that this may have been a contributing factor. It is only fair to point out, however, that there is a fundamental difference in the nature of the problem in the two sexes that made oral contraceptives for the female seem to be a more easily attainable goal. In women, by manipulating the endocrine control mechanisms, we are able to prevent the midcycle surge in the gonadotrophic hormone LH that triggers ovulation—a single event that occurs only once each month and releases a single ovum. In the male, on the other hand, we seek to interfere with a continuous process of development and maturation that yields tens of millions of spermatozoa each day throughout adult life.

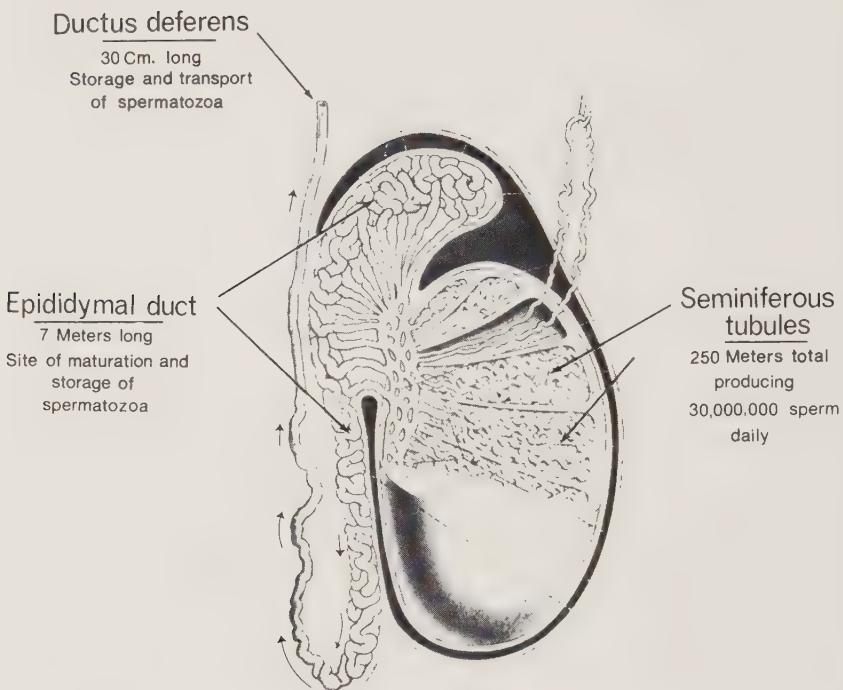


Fig. 1. Drawing of the structure of the human testis and its excurrent ducts. One of the seminiferous tubules has been uncoiled to illustrate its relationship to the rete testis. The seminiferous tubules are the site of production of spermatozoa, the epididymal duct is the site of their maturation and storage, and the ductus or vas deferens is their outflow path. (Drawing modified after W. J. Hamilton, Textbook of Human Anatomy, London, Macmillan and Company, 1957).

I. ANATOMY OF SPERMATOGENESIS

A consideration of the anatomy of the male reproductive tract may contribute to an understanding of the possible approaches to fertility control (Fig. 1). Each testis is composed of minute, highly convoluted seminiferous tubules, lined by the seminiferous epithelium, the site of sperm production. The high degree of convolution of the tubules some 280 meters in total length results in an enormous area of sperm producing tissue, producing some 30 million sperm per day. The seminiferous tubules converge upon a branching system of thin-walled channels called the rete testis. From there the spermatozoa are transported through a dozen or so ductules to an adjacent organ, the epididymis, which consists of a single 7-m long duct coiled and convoluted into a compact elongated organ less than 5 cm overall, adherent to the posterior surface of the testis. The spermatozoa

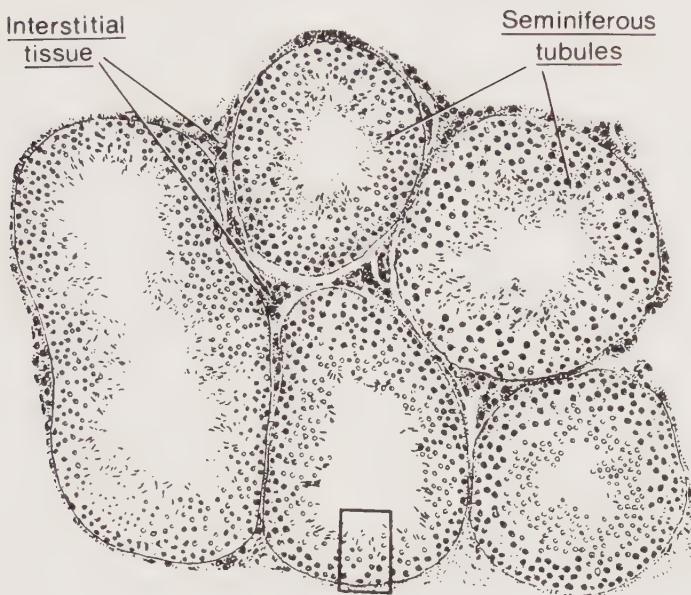


Fig. 2. Drawing of a small area of testis as seen under a microscope, showing a few seminiferous tubules in transverse section and interstitial tissue composed mainly of Leydig cells in the angular intertubular spaces. The Leydig cells secrete the male hormone testosterone, which must be present in high local concentration to maintain spermatogenesis. (From Moore and Quick, *Am. J. Anat.* 34, 317, 1924).

are not finished when they leave the testis, but as they slowly pass through the epididymis and accumulate in its lower pole, they undergo further maturation and acquire fertilizing capacity and the potential for independent motility. The duct turns upward at the lower pole of the epididymis, straightens out, acquires a thicker wall and continues upward out of the scrotum as the vas or ductus deferens which conducts the sperm to the urethra.

Thus we have in the male tract a site of sperm production (seminiferous tubules), a site of maturation and storage (epididymis), and an organ of transport (vas deferens). The normal function of all of these structures is dependent upon gonadotropic hormones of the pituitary gland (LH) and in turn upon male sex hormone (testosterone) produced by cells in the spaces between the seminiferous tubules of the testis. Accordingly in developing contraceptive strategies for the male, we might attempt to (1) stop sperm production by interfering with the hormonal control of testicular or epididymal function, (2) stop sperm production by drugs acting selectively upon the spermatogenic cells in the seminiferous tubules, (3) prevent sperm maturation during their passage through the epididymis, or (4) prevent sperm transport through the vas deferens.

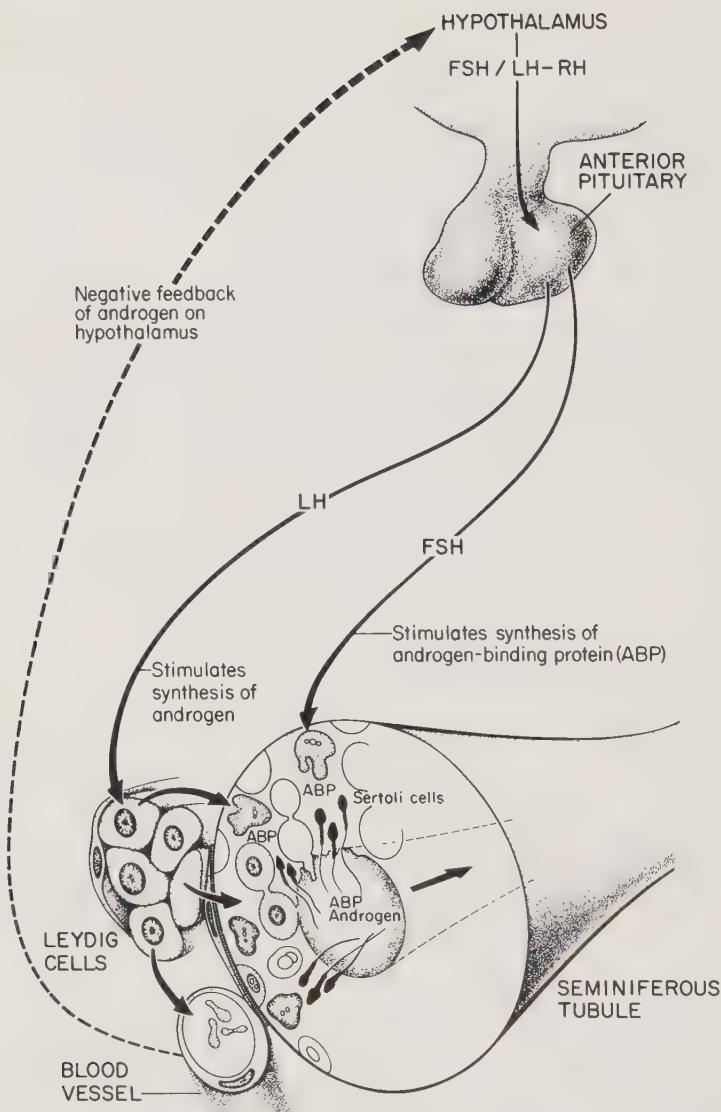


Fig. 3. Schematic representation of the hormonal control of spermatogenesis. Luteinizing hormone from the pituitary gland stimulates the Leydig cells to produce testosterone, which diffuses into the tubules to maintain spermatogenesis. Testosterone entering the bloodstream is carried back to the brain to maintain libido and acts on the pituitary in a negative feedback mechanism controlling the secretion of LH. The gonadotrophic hormone FSH acts upon the Sertoli cells in the tubules, stimulating their synthesis of androgen binding protein. (From Fawcett, 1975a.)

II. STRATEGY I: ENDOCRINE CONTROL MECHANISMS

Microscopic examination of thin slices of testis discloses two basic tissue components—the seminiferous tubules responsible for sperm production, and between the tubules, clusters of interstitial cells (Leydig cells) that synthesize and secrete the male sex hormone testosterone (Fig. 2). This hormone must be present around the tubules in high local concentration to maintain sperm production. Carried from the testis in the bloodstream in lower concentration, testosterone is essential for the function of the prostate, growth of beard, and other manifestations of maleness including maintenance of normal libido. The production of testosterone by the Leydig cells is in turn dependent upon continuous stimulation by the pituitary gonadotropin, luteinizing hormone (LH), the same hormone that is required for ovulation and secretion of progesterone in women. The amount of LH secreted is modulated by a negative feedback mechanism wherein an excess of circulating testosterone suppresses release of LH (Fig. 3).

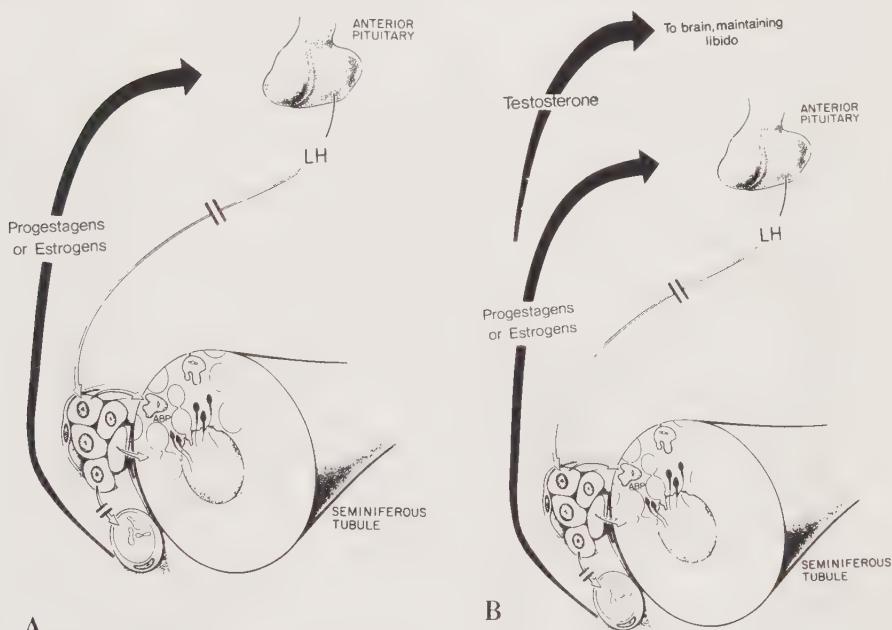


Fig. 4. (A) Diagram of the effects in the male of estrogen or progestagens such as those used in oral contraceptives for women. These hormones act on the pituitary to suppress release of LH. This results in diminished testosterone production and spermatogenesis ceases. Unfortunately, low testosterone production also causes loss of libido. (B) Suppression of libido by the female hormones can be overcome by giving small amounts of testosterone. The amount required to preserve libido is much less than that necessary to sustain spermatogenesis.

The successful oral contraceptives for women take advantage of a comparable feedback mechanism and employ estrogen or progestin to suppress release of LH, which normally triggers ovulation. One might expect that these same hormones of "the pill" given to men would lower LH release, and that the consequent withdrawal of Leydig cell stimulation would result in a low intratesticular concentration of testosterone, causing spermatogenesis to cease. This is in fact true; administration of estrogens or progestins or combinations of the two to men will inhibit spermatogenesis (Briggs and Briggs, 1974; Coutinho and Melo, 1973) (Fig. 4A). Unfortunately it may also produce some gynecomastia, a mild, but nonetheless uncomfortable, breast enlargement. But most importantly, the lowered level of testosterone in the circulation also results in a loss of libido, and this is proscribed in male contraception—one must not interfere with sexual desire. This complication can be circumvented by giving, in addition to a progestin, an amount of testosterone or another androgen sufficient to maintain libido, but not sufficient to sustain spermatogenesis (Fig. 4B). This is a rational approach and still a viable possibility for male contraception, but it carries the same risks as the pill for women plus some additional problems.

A closely related approach now being actively pursued in clinical trials involves administration of a synthetic steroid called Danazol (Sherins *et al.*, 1971; Skoglund and Paulsen, 1973). This appears to lower gonadotropin release without the undesirable endocrinological and metabolic side effects of estrogens and progestins. Testosterone enanthate is given with it in an amount sufficient to maintain normal libido. This approach shows some promise, and although Danazol is now prohibitively expensive, other synthetic compounds may be found that are less costly and equally effective.

Since in the male it is the testosterone level that normally modulates the release of LH, it is to be expected that giving exogenous testosterone alone would lower endogenous testosterone levels in the testis below the concentration required to sustain spermatogenesis. This has been explored in men and it is possible to lower sperm production to infertile levels by giving testosterone alone (Pantelli and Nelson, 1964; Reddy and Rao, 1972). When treatment is discontinued, normal fertility is gradually restored. There is, however, serious concern that long-term maintenance of elevated levels of circulating testosterone might accelerate the onset of prostatic hypertrophy and might also have serious metabolic and cardiovascular complications.

The physiological role of the other pituitary gonadotropin, follicle-stimulating hormone (FSH), in the mature male has long been a subject of controversy. There has been evidence that it acts upon the seminiferous tubules rather than the interstitial tissue and that it is essential for the initiation of spermatogenesis in puberal males, but its target cell and precise function were not known. A major advance in recent years has been the discovery that it stimulates the supporting or Sertoli cells of the tubules to synthesize an androgen-binding protein that may have an important function in sustaining a high intratubular concentration of testosterone.

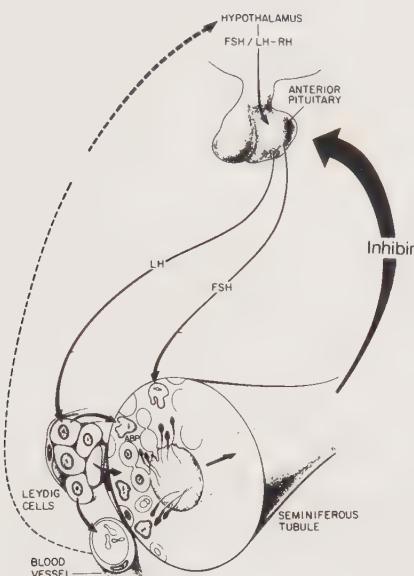


Fig. 5. There is now good evidence for production by the seminiferous tubules of a substance called inhibin that is involved in feedback regulation of FSH release. It is hoped that inhibin may be able to inhibit spermatogenesis by suppressing FSH release without an effect upon libido.

It was suggested over 40 years ago that the release of FSH in the male is under feedback control from the seminiferous tubules. Evidence for this rests upon the observation that damage to the tubules results in elevated levels of FSH. The hypothetical agent responsible for this control was not identified but was given the name "inhibin." Its cellular source and chemical nature remained controversial until quite recently. Now several laboratories have extracted from bull testis (de Kretser, 1975), from rete testis fluid (Setchell and Jacks, 1975), and from semen (Franchimont *et al.*, 1975) a protein with the defining property of inhibin—the ability to lower circulating levels of FSH. The isolation and partial characterization of this protein has kindled the hope that by the feedback suppression of FSH release, one might be able to inhibit spermatogenesis without impairment of libido (Fig. 5).

It has still not been conclusively demonstrated that FSH is necessary for spermatogenesis in adult men. But even if inhibin proves to be effective only in inhibiting the initiation of spermatogenesis, it might prove useful. Pregnancy among teenagers has reached epidemic proportions in this country. It has been suggested that when inhibin becomes available, it might be used in young boys to suppress the onset of sperm production without interfering in any other aspect of their development. Boys and young men might take inhibin regularly until ready for parenthood and then upon its discontinuation normal sperm

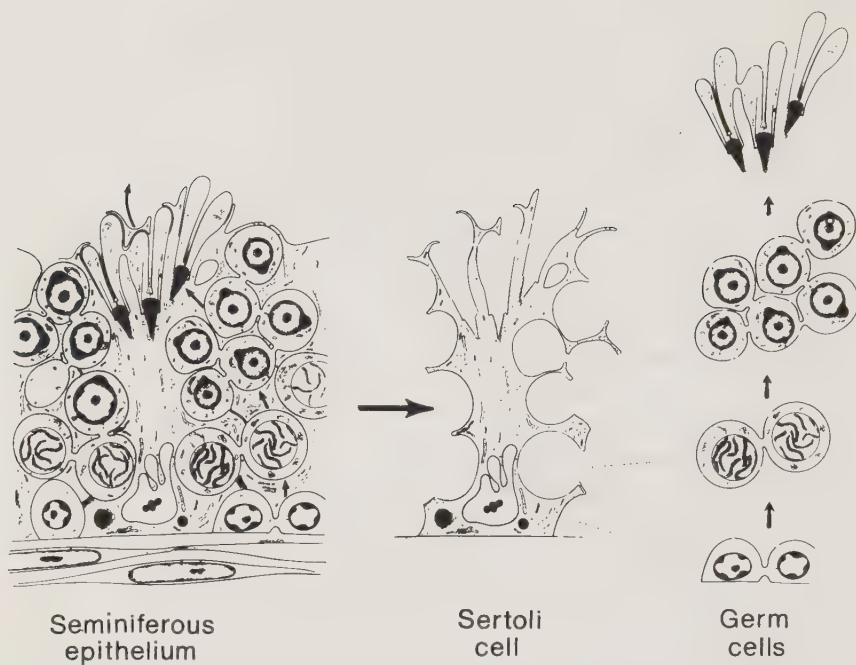


Fig. 6. Drawing of an area of the lining of a seminiferous tubule like that in the box in Fig. 2 showing the germ cells associated with the sides of the supporting or Sertoli cells. At the right, the two populations of cells have been dissociated to show the complex form of the Sertoli cell and the several stages of differentiation of the germ cells found at successively higher levels in the epithelium.

production would presumably begin. This interesting hypothetic approach is still in the realm of speculation.

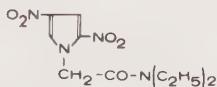
III. STRATEGY II: DIRECT PHARMACOLOGICAL SUPPRESSION OF SPERMATOGENESIS

The complex epithelium lining the seminiferous tubules consists of two categories of cells—a stable population of supporting cells (Sertoli cells) and a proliferating population of germ cells in the various stages of their development into spermatozoa. The proliferative early stages are located at the basal layer of this multilayered lining of the tubules and as the spermatozoa progress in their development, they are moved upward along the sides of the Sertoli cells toward the free surface. The completed spermatozoa are then released into the central cavity of the tubules (Fig. 6).

Over the past 30 years, a number of drugs being developed as antibiotics, amebicides, or for other therapeutic purposes have been found to arrest spermatogenesis and have then been investigated for their potential as anti-infertility agents (Drobeck and Coulston, 1962; Jackson, 1959). Several of these cause degeneration of spermatids and spermatocytes, ultimately reducing the cell

Antispermatogenic drugs

1. Drugs believed to act upon the germ cells



DINITROPYROLS

- Considered too toxic for human trials
- Highly effective in animal tests

BIS (DICHLORO-ACETYL)
DIAMINES

- Effective and reversible in human trials
- Abandoned because of incompatibility with alcohol

2. Drugs that may stop spermatogenesis by affecting the Sertoli cells

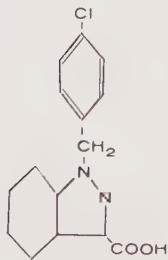
1-P-CHLOROBENZYL-1H-
INDAZOL-3-CARBOXYLIC ACID

Fig. 7. Some examples of drugs that appear to produce infertility either by acting directly upon the germ cells or by affecting them indirectly by a primary action upon the Sertoli cells.

population in the seminiferous epithelium to spermatogonia and Sertoli cells only. The fact that Sertoli cells invariably survived led to the assumption that these drugs acted directly and perhaps exclusively upon the germ cells.

Two of these classes of compounds that produced reversible infertility in male animals with relatively little systemic toxicity were the dinitropyroles and the bis(dichloroacetyl)diamines (Flores and Fawcett, 1972; Pantelli and Nelson, 1964) (Fig. 7). The latter advanced to human trials in prisoner volunteers and was found to be effective and reversible (Heller *et al.*, 1961). Despite its initial

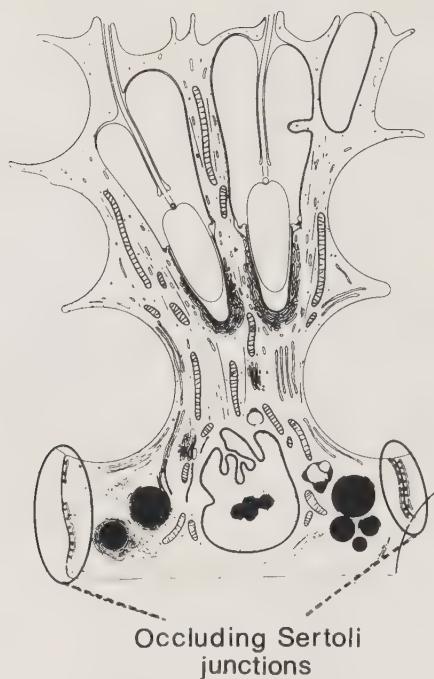


Fig. 8. Drawing of a Sertoli cell showing the location of its occluding attachments to adjacent Sertoli cells. These junctions seal the interspaces between cells, forming a permeability barrier that excludes many substances from the epithelium.

promise, it was abandoned for human use because it proved to have an incompatibility with alcohol, producing distressing symptoms comparable to those of Antabuse, which is used in the treatment of alcoholism.

Other antispermatic compounds were alkylating agents similar to those used in cancer chemotherapy because of their inhibition of cell division. There has been an understandable reluctance to pursue these compounds as possible contraceptive agents because of the likelihood that they would not only affect germ cells but would also interfere with the cell proliferation essential for cell replacement and tissue repair elsewhere in the body. Another basis for concern over the use of such drugs is the fact that in the course of germ cell development, the spermatocytes spend a long time in the process of meiosis. These stages are believed to be especially vulnerable to genetically damaging or mutagenic drugs. Therefore, there has been no enthusiasm in funding agencies for support of research on drugs acting directly upon the seminiferous epithelium because of the fear that such drugs might prove to be mutagenic and that if not completely effective in suppressing sperm production they might result in abnormal offspring. Recent advances in our understanding of the organization of the seminiferous

epithelium and the function of Sertoli cells now suggest that this judgment may have been based in part upon erroneous assumptions.

It seems that nature has provided special protection for two populations of cells—those in the brain and those of the male germ cell line. We have known since the turn of the century that a *blood-brain permeability barrier* prevents many blood-borne substances including numerous water-soluble drugs from leaving the capillaries to enter the substance of the brain. Recently we have become aware of a *blood-testis* or more accurately a *blood-seminiferous tubule barrier*. If we inject into the bloodstream of an experimental animal a dye or tracer substance that can be easily identified in electron micrographs, we find upon examination of the testis that it rapidly escapes from the blood vessels but is largely excluded from the seminiferous tubules (Dym and Fawcett, 1970; Fawcett, 1975a, b). It can be demonstrated that there are circumferential bands of membrane-to-membrane fusion between the neighboring Sertoli cells near the base of the seminiferous epithelium (Fig. 8). These seal off the intercellular spaces and form a permeability barrier interposed between the interstitial tissue of the testis and the developing germ cells.

This finding has important implications for the development of antispermato-genic drugs because it means that many compounds are probably denied access to the more advanced germ cells and may affect them only indirectly as a consequence of alterations in the physiology of the supporting cells.

The location of the occluding junctions between lateral processes of the Sertoli cells that arch over the spermatogonia divides the seminiferous epithelium into two compartments—a basal compartment containing the stem cells of spermatogenesis, and an adluminal compartment containing the more advanced stages of germ cell development (Fig. 9). The physiological consequences of this compartmentation are several. It isolates the developing germ cells from the general extracellular space of the testis and enables the Sertoli cells that form the walls of the adluminal compartment to create in it a special micro-environment favorable for germ cell development (Dyn and Fawcett, 1970; Fawcett, 1975b). It prevents antigenic products of post-meiotic germ cells in this compartment from reaching the bloodstream, where they would induce an autoimmune response. It protects the germ cell line from blood-borne antibodies, noxious drugs, and other substances that might be damaging. Although access to the more advanced germ cells is barred, peptide hormones and most water-soluble drugs are not prevented from reaching the Sertoli cells or the stem cells of spermatogenesis in the basal layers. It is now considered quite likely that some of the antispermato-genic drugs that were studied and abandoned in the past may not, in fact, have been reaching the more advanced germ cells. Their effects may have been secondary to interference with Sertoli cell function. There is an urgent need for renewed study of some of these compounds to determine where they do in fact localize in the epithelium. If it can be shown that they are largely excluded from the adluminal compartment by the permeability barrier, this should remove some of the current animus against research on drugs acting

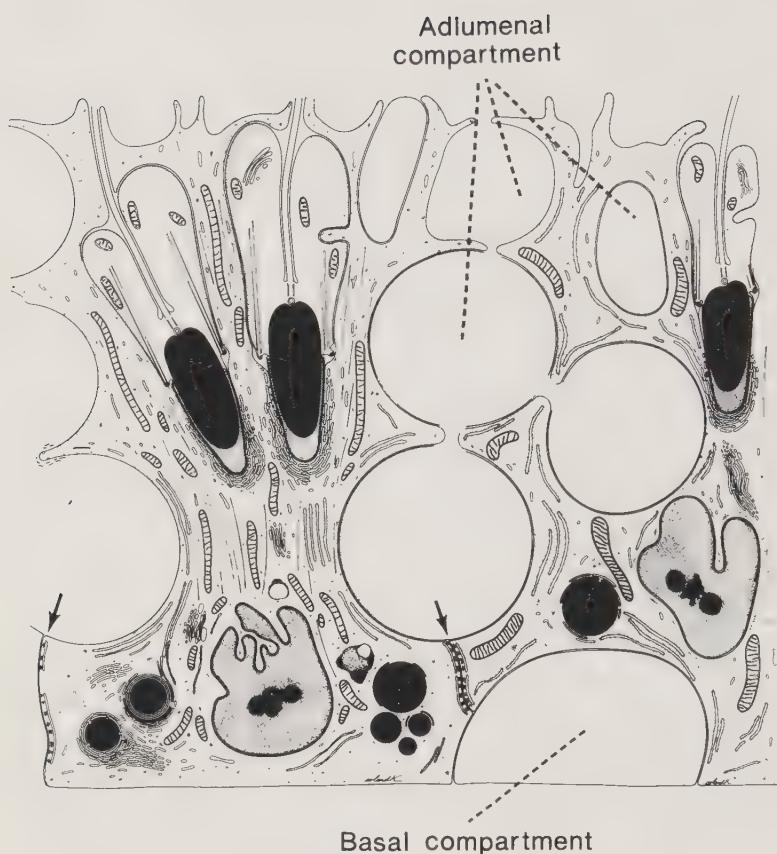


Fig. 9. Schematic drawing showing how the occluding junctions between Sertoli cells (at arrows) divide the seminiferous epithelium into a basal compartment containing the earliest stages of spermatogenesis and an adluminal compartment containing the more advanced stages. (From Fawcett, 1975b.)

Some of the most significant recent advances in male reproductive biology have been those clarifying the functions of the Sertoli cells. A decade ago they were considered to be a highly resistant, relatively inert population of cells doing little but providing mechanical support for the germinal elements of the epithelium. We now know that they possess specific receptors for FSH (Steinberger *et al.*, 1974) and respond to stimulation by this hormone with increased synthesis of androgen-binding protein (Fritz *et al.*, 1974). They are able to convert testosterone to estradiol in response to FSH stimulation *in vitro* (Dorrington and Armstrong, 1975) and they may also be able to convert C₂₁ steroids to androgens (Harris and Bartke, 1975). The Sertoli cells maintain the blood-testis permeability

barrier and create in the adluminal compartment the environmental conditions necessary for continued development of the germ cells. They are responsible for moving the clones of differentiating germ cells toward the lumen of the tubules and they play an active role in the release of the spermatozoa from their attachment to the epithelium (Fawcett, 1975b).

Our new appreciation of these important synthetic, metabolic, and motor activities of the Sertoli cells and of their vital role in spermatogenesis should change prevailing attitudes about the feasibility of suppressing sperm production by pharmacological agents acting directly upon the seminiferous tubules. There is increasing evidence that Sertoli cells are quite sensitive to a variety of physical and chemical agents. This encourages us to believe that spermatogenesis, or sperm release, or both might be inhibited by drugs acting selectively upon the Sertoli cells. Since these cells do not undergo cell division in the adult, this approach should not arouse anxiety over the possibility of drug-induced mutation or other genetic damage.

A new class of antispermatic compounds, the indazolecarboxylic acids, has recently been introduced by a group of Italian investigators (Coulston *et al.*, 1975; Sylvestrini *et al.*, 1975). These drugs do not inhibit the enzyme alcohol dehydrogenase and therefore they have no incompatibility with alcohol. They are active when taken by mouth and have been well tolerated by monkeys in daily doses over periods of six months and longer. There is reason to believe that they may act upon the Sertoli cells. Moreover, once spermatogenesis has been arrested, the infertile state can be maintained by a single weekly dose. This class of compounds has not yet advanced to clinical trials, but the favorable results on monkeys suggest the possibility that spermatogenesis in humans may some day be controlled reversibly by a single oral dose of a drug taken once a week.

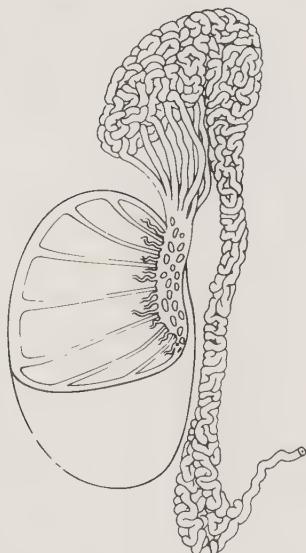
IV. STRATEGY III: SUPPRESSION OF POSTTESTICULAR MATURATION OF THE SPERMATOZOA

This approach is intended to take advantage of the fact that spermatozoa are not capable of progressive locomotion or fertilization when they leave the testis but must undergo further physiological maturation as they slowly progress through the epididymal duct. The biochemical functions of the cells lining this duct are still poorly understood but there is evidence they they create in the lumen the environment necessary for this continuing maturation of the spermatozoa. Drugs acting in this portion of the reproductive tract might achieve the desired result either by acting directly upon the sperm to inhibit their further development or by interfering with some essential function of the cells lining the duct and thus producing an environment unfavorable for the completion of sperm maturation (Fig. 10).

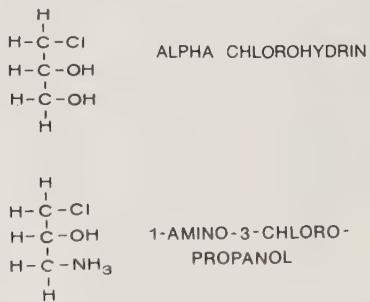
A posttesticular site of action for antifertility drugs is especially appealing because there is probably very little chance of genetic damage that might result

Posttesticular antifertility agents

Epididymis



1. Drugs acting directly upon sperm during epididymal transport



- Effective and reversible in animal tests
- Considered too toxic for human trials

2. Drugs acting indirectly on sperm by interfering with epididymal function

- None available now
- Await better understanding of epididymal function and its control

Fig. 10. Antifertility agents acting on the spermatozoa after they leave the testis should be quite safe because after condensation of the sperm head, the genetic material is relatively insensitive to mutagenic chemicals. Two examples of drugs acting upon epididymal sperm are shown here. As yet we have no prototype of a drug selectively interfering with epididymal function.

in abnormal offspring. By the time the spermatozoa leave the testis, the genetic material of their nuclei has undergone a remarkable concentration and chemical inactivation that makes the sperm nucleus metabolically inert and highly resistant to damage by anything short of ionizing radiation. This is apparently a strategy of nature to protect the genome of the father against damage in the long and potentially perilous journey into the upper reaches of the female reproductive

tract. Pharmacological agents acting upon epididymal sperm are thus expected to be relatively safe from the point of view of genetic damage.

As yet we have no drugs that specifically affect essential biochemical functions of the epididymis. The rational development of such drugs must await a more complete understanding of the functions of this organ. We do, however, have prototypes of drugs that appear to act upon spermatozoa in the epididymis to render them infertile. The compound α -chlorohydrin was found several years ago to induce reversible infertility in common laboratory animals without any interference with spermatogenesis (Ericsson and Baker, 1970). Its exact mechanism of action remains controversial but there is evidence that it inhibits a key enzyme in the sequence of reactions that yield the chemical energy for motility. This compound was considered to have too great a potential for toxicity to be used in humans. An analog, 1-amino-3-chloro-2-propanol hydrochloride, showed little toxicity in rodents (Coppola and Saldarini, 1974) and it was hoped that it would progress to human trials. Unfortunately, when tested in monkeys, effects on the brain were detected and the hope for human use was abandoned. Nevertheless, the experience with these drugs has demonstrated the feasibility of inducing infertility by an action on spermatozoa after they leave the testis and when they are relatively immune to genetic damage. The search for less toxic related compounds acting on epididymal sperm and on the epididymal epithelium goes on.

V. STRATEGY IV: INTERRUPTION OF THE OUTFLOW PATH

Millions of men have had vasectomies for many years and no significant long-term side effects have been demonstrated. There has been an increase in the number of men requesting this operation (Fig. 11). Its principal drawback is that the physician cannot assure the man that the procedure will be reversible. The frequent occurrence of divorce and remarriage often results in a desire to father a child of the new partner. Improvements in microsurgical techniques have made it possible to rejoin ends of the vas in a high percentage of such cases, so that sperm reappear in the ejaculate. From a surgical point of view, the vasectomy has been successfully reversed, but if one measures success in terms of pregnancies achieved, the results are very disappointing—probably less than 30%. The reasons for this low rate of success are multiple, but the principal one is probably immunological. The great majority of vasectomized men develop antibodies to sperm and these result in an immunological inhibition of sperm activity that contributes to infertility despite the presence of adequate numbers of sperm in the ejaculate (Ans�acher, 1973; Shulman *et al.*, 1972). There is no clear evidence that links the presence of these antibodies to auto-immune disease. Except for the negative effect on fertility in the event that reanastomosis of the vas is attempted, sperm antibodies pose no apparent threat to health. Thus vasectomy is a very safe procedure and a valuable method for preventing unwanted pregnancies.

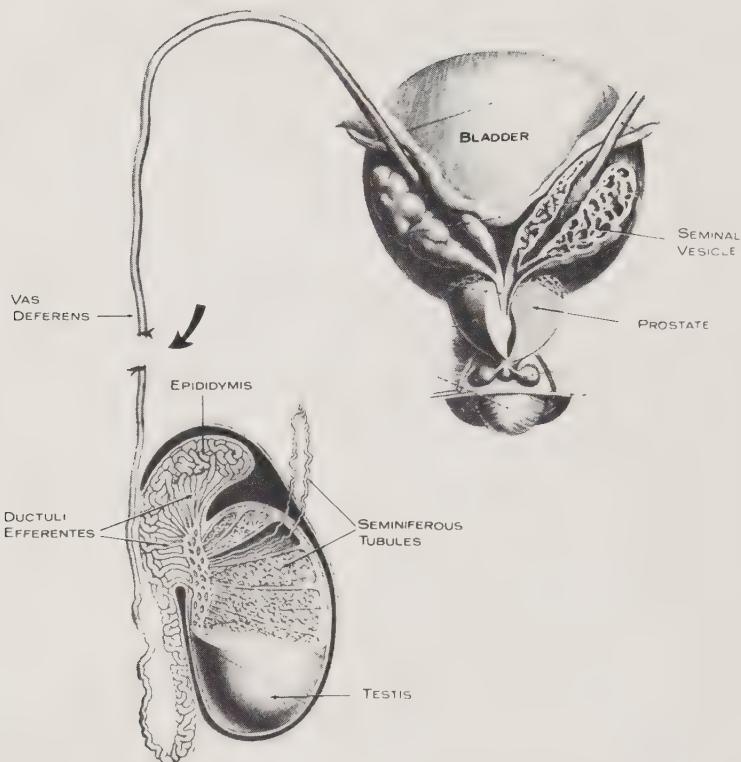


Fig. 11. Drawing of the male reproductive tract illustrating vasectomy, the surgical interruption of the vas deferens in the scrotum, thus preventing the sperm from reaching the ejaculatory ducts that enter the prostatic urethra. This is a safe procedure but has the disadvantage that it is usually irreversible.

A number of efforts have been made to devise valves that could be inserted into the vas with the expectation that fertility could be turned off and on at will by simply changing the position of the valve by manipulation through the scrotal skin (Brueschke *et al.*, 1974). None of these has been successful—tissue response to the foreign body invariably results in permanent occlusion of the vas. This is no longer an active area of investigation.

VI. CONCLUDING COMMENT

The ideal contraceptive would be self-administered, safe, inexpensive, and completely reversible. No existing method adequately fulfills all of these criteria. It is obviously unrealistic to expect that any oral contraceptive taken by either sex for months or years will be entirely free of undesirable side effects in all

users. But it is probably not unreasonable to expect that if an effective pill were available for men, as well as for women, a couple could alternate responsibility for contraception at intervals of several months and in this way, the risk of cumulative effects of long-term medication might be reduced for both. Those who do not accept this conclusion would probably agree that a higher degree of contraceptive effectiveness can be achieved when two independent methods of less than ideal effectiveness are used simultaneously. Thus, if one agent were taken by the woman and another by the man, the overall effectiveness of the joint medication should be greater than that of either taken alone (Biggers, 1973).

Reproductive biologists whose interest has been mainly in research on the female generally hold out little hope of success in the development of oral contraceptives for the male. There seems to me to be no real basis for this pessimism. It is true that research on the male has been less actively pursued and less generously funded, but there has recently been rapid progress. It is regrettable that the worldwide decline in support of research on reproductive biology comes at a time when we are beginning to approach for the male a level of understanding comparable to that which prevailed for the female before the development of "the pill." We still have a long way to go, but with continued support, there is every reason to believe that a relatively safe, reversible, oral contraceptive for men is an attainable goal.

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ESTROGEN REPLACEMENT THERAPY FOR THE MENOPAUSE

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I. A CLINICAL DEFINITION OF THE FEMALE CLIMACTERIC

The clinical implications of the female climacteric are the result of the impact of three factors: amount and rate of estrogen depletion, tendency to age, and the change of life.

A. Amount and Rate of Estrogen Depletion

Although attention focuses on the menopause, ovarian function begins to wane years before the last menstrual period. Women in their late 30s experience decreasing frequency of ovulation that is accompanied by relative infertility and variable menstrual cycles. Serum follicle-stimulating hormone (FSH) levels begin to rise, and some women may even display vasomotor flushes during this premenopausal decline in estrogen. At some point in her early 50s a woman's estrogen

production is not adequate for endometrial proliferation sufficient to cause menstrual flow. Despite amenorrhea, estrogen continues to be produced in lesser amounts, which are sufficient, nevertheless, to sustain secondary sexual characteristics for many years. Vaginal and vulvar atrophy may not occur until the seventh or eighth decade.

The ovary is not the source of the estrogen produced menopaually. The adrenal cortex is the origin of the prehormone Δ^4 -androstenedione, which is converted to estrone at peripheral nonendocrine metabolic sites, the most important of which is fat. This estrone production is not under the control of the usual factors modifying pituitary-ovarian interactions that ordinarily maintain physiologically appropriate quantities of estradiol during the reproductive years.

In the absence of this feedback mechanism, aging, stress, and obesity become important elements that lead to production of variable, sometimes clinically important, levels of estrone in the latter third of a woman's life. Not only does estrogen production decline, but there are variations in the rate of decline because of variations in either prehormone production or efficiency of conversion of prehormone to estrone.

B. Tendency to Age

Although the collective inherited and acquired mechanisms are obscure, there is a clinically observable propensity for some individuals to resist the impositions and manifestations of the overall aging process, while others succumb all too obviously to physical deterioration.

C. "Change of Life"

Just as the physical reaction to the aging process is variable, so is the psychological impact of the implications of the change of life. In some women, accommodation to the psychosocial and physical implications of aging is simple and nontraumatic. Others mistakenly assume their last menstrual period to be a signal of their entry into a period of life characterized by ever increasing physical disability, conflicts with and estrangement from family members, and dwindling sexual adequacy and interest—in short, inevitable loneliness, despair, and disability.

As a result, the clinical implications of the female climacteric can be viewed from a symptomatic point of view. In the perimenopausal period of life there may be (1) disturbances of the menstrual pattern with accompanying concerns about neoplasia, (2) sometimes troublesome but rarely disabling vasomotor disability seen early, (3) psychological symptoms of anxiety, tension, depression, and irritability and presumptive changes in libido, (4) atrophy of specific organ systems, leading to dyspareunia, pruritus, urinary urgency and frequency, as well as osteoporosis and vascular incompetence. Finally, and not surprising to clinicians, there is tremendous variability in the patient's presentation and personal perception of her situation.

II. DISADVANTAGES OF ESTROGEN REPLACEMENT THERAPY

The disadvantages of estrogen replacement therapy can be considered in three general categories: metabolic effects, side effects, and impact on the development of cancer in estrogen-dependent tissues, such as the endometrium and the breast.

A. Metabolic Effects

Evidence that oral contraceptives combining progestin and estrogen have detrimental effects on both venous and arterial portions of the vascular tree has cast serious doubt on the previously prevailing view that estrogen replacement therapy is of some benefit in prevention of atherogenesis.

Statistics supporting the beneficial effects of estrogen replacement therapy in coronary artery disease are now considered to have been derived from poorly controlled studies and the conclusions are uncertain. In fact, there is statistical evidence against benefits (Furman, 1973). The ratio of male to female deaths from coronary artery disease is high until the fifth decade but reaches unity by the ninth decade. There is no alteration in the steady increase in mortality from coronary artery disease in females during the perimenopause. Furthermore, coronary artery disease has a curious economic, national, and racial variability. The ratio of male to female deaths due to coronary disease at age 45 in the United States is 5:1, whereas in Italy it is 2:1, and in Japan 1:1. Finally, although in North America considerably fewer healthy white women than men at age 45 die from coronary artery occlusion, the apparent sex benefit does not extend to black women in the same age group. The changing sex ratios lead to the conclusion that there are probably two populations of males in North America: a population that is very susceptible to fatal occlusion or arrhythmia early in life, and a second population that experiences coronary artery disease roughly similar to that in female counterparts.

The negative impact of estrogen therapy was also shown in certain prospective studies. (1) In the Coronary Drug Project (1973) high doses of conjugated estrogens (5-10 mg) were given daily to prevent recurrent heart attacks in men; in comparison to controls, males receiving this therapy had an excess of nonfatal myocardial infarcts that was not evident with lower doses. Indeed, there was a high incidence of early vascular accidents of all types at high-dose levels, leading to withdrawal of a significant portion of the study group. (2) Similarly, in a stroke study undertaken at VA hospitals, estrogen therapy was associated with an increased recurrence of cerebral accidents and myocardial infarctions (Report of the Veterans Administration Cooperative Study of Atherosclerosis Neurology Section, 1966). (3) In a study of males with prostatic disease who were administered diethylstilbestrol 5-10 mg/day there was an increased incidence of myocardial infarction, thromboembolic disease, and strokes when compared to controls or lower-dose recipients (Bailar and Byar, 1970).

These studies and the findings in British and American studies were compatible with respect to the influence of oral contraceptives on vascular complications.

Finally, review of the lipoprotein patterns subsequent to estrogen administration revealed that such therapy does not convert lipoprotein levels to those of younger women (Bierman, 1969; Doar and Wyn, 1969). All lipid fractions in females increase with age. With estrogen therapy there is further increase in triglycerides. There is no (or, at best, a modest) decrease in cholesterol, and there is an increase in phospholipids.

In conclusion, the evidence is strong that *high-dose* continuous estrogen replacement therapy can contribute to the risk of thromboembolic disease, cerebrovascular accident, and coronary artery disease. The effects are dose related, and the risks increase with age.

Other metabolic effects of estrogen can also be considered detrimental to the aging woman. The increased incidence of hypertension as a result of progestin-estrogen therapy, the peripheral decrease in insulin activity with the subsequent stress on insulin reserves, and the alteration in bilirubin transport and the increase in gallbladder disease are seen as distinct disadvantages to administration of estrogens to aging females.

B. Side Effects

Depending on the psychological disposition of the postmenopausal woman and her concerns over body image and function, the side effects of estrogen such as bloating and edema can obviously be additional burdens of considerable significance.

C. Cancer Risk

The risk of cancer must be considered the major disadvantage of estrogen replacement therapy if it can be proven that there is a causal rather than casual relationship between it and the incidence of breast and endometrial carcinoma.

1. Breast Carcinoma

There is an increase in frequency of breast carcinoma in men given estrogen therapy for prostatic carcinoma, in men given treatment and support undergoing transsexual conversion, and in Bantu men with gynecomastia (Ryan, 1973). Although there is a continual rise in the incidence of breast carcinoma in women after the menopause, the increase is known to begin before the menopause (Third National Cancer Survey, 1975). At the moment there is no evidence to support a cause-and-effect relationship. Indeed, prospective studies of the effect of oral contraceptives on the incidence of benign and malignant breast disease showed that thus far a relationship is proven not to exist (Royal College of General Practitioners, 1974). (For a conflicting view, see chapter by Fasal).

2. Endometrial Carcinoma

Although there is no proven causal relationship between estrogen and breast carcinoma, there is a relationship between elevated levels of endogenous estrogen

and estrogen therapy and the incidence of endometrial hyperplasia and carcinoma. In general, certain constitutional abnormalities are present in patients with a high incidence of atypical adenomatous hyperplasia and endometrial carcinoma. Adenomatous hyperplasia and endometrial cancer appear with progressive aging, obesity, and with an inappropriately early incidence in polycystic ovary disease and functioning ovarian tumors. They are rarely seen, however, in individuals with senile vaginitis or those complaining of vasomotor symptoms. The relationship between the presence of endogenous estrogen and endometrial hyperplasia and atypia has been observed clinically.

There are two mechanisms by which increased production of endogenous estrogen could be manifested in the postmenopausal individual: Factors that increase the production of the pre-hormone androstenedione or the conversion of androstenedione to estrone would lead to increases of estrone and that would affect the endometrium. Both have been noted in individuals who developed postmenopausal bleeding, adenomatous hyperplasia, and endometrial carcinoma. In the cases of excess androstenedione production, stress, various tumors, and, less frequently, obesity are seen (Edman *et al.*, 1975). Among the factors increasing the conversion of androstenedione to estrone, obesity has appeared to be dominant, simple aging has been less important, and liver disease has played a role in specific cases. The contention then is that the constitutional abnormalities lead to increased production of endogenous estrone, which results in endometrial hyperplasia and carcinoma. Furthermore, those individuals who oppose the use of replacement therapy with estrone sulfate argue that it results in endometrial stimulation and that it therefore may result in endometrial neoplasia. Statistical support for this view has recently been presented in studies noting an increased incidence of endometrial carcinoma in association with estrogen replacement therapy (Herman *et al.*, 1975; Finkle and Ziel, 1975; Arthur *et al.*, 1976).

In conclusion, if estrogen is given continually or in injudicious doses to improper recipients (those who have increased endogenous estrogen), the estrogen replacement therapy, by creating excess quantities of estrone, can exaggerate or possibly uncover a constitutional predisposition to endometrial neoplasia. The exact increase in incidence (suggested as four to seven times that of controls) and dose-response data are not yet available (see chapter by Jones for further information).

III. ADVANTAGES OF ESTROGEN REPLACEMENT THERAPY

Advocates of estrogen replacement therapy claim that estrogen loss, even if it does not accelerate aging, when superimposed on aging places an unnecessary additional burden on the woman. Accordingly, the following advantages are claimed for estrogen replacement therapy: control of vasomotor reactions, reduction of emotional reactions to the climacteric, opportunities for preventive medicine, prevention and control of osteoporosis, prevention of atherosclerosis.

A. Control of Vasomotor Reactions

From clinical experience, there is no question that one clear gain of estrogen replacement therapy is control of the hot flash of the early postmenopausal period. The extent to which vasomotor symptoms appear and become troublesome depends upon the rapidity with which estrogen depletion occurs. Perhaps 20% of women experience sufficient difficulty as a result of this symptom that they seek therapeutic relief. This can be achieved easily with intermittent, low-dose, short-term estrogen replacement therapy.

B. Reduction of Emotional Reactions to the Climacteric

Although there is little biological evidence to support the contention that depletion of estrogen alters brain function and thus causes psychological disturbance, empiric observations abound that suggest that estrogen replacement therapy may be associated with alleviation of these difficulties. Whether the benefits of this therapy are direct, i.e., by a biologic replacement phenomenon, or indirect, i.e., the patient gains by "having something done" for her symptoms, they should be acknowledged but not overemphasized.

C. Opportunities for Preventive Medicine

All too frequently the postmenopausal patient assigns a variety of symptoms to a mystical "change of life" mechanism. As a result, major disease entities can be ignored until serious consequences or irreversible changes have occurred. Advocates of estrogen replacement contend that the surveillance required with this therapy enables her primary physician periodically to examine the patient, evaluate symptoms, and take preventive measures. Semiannual examinations are helpful in disclosing atherosclerosis, colonic disease, and pulmonary problems, common in this age group.

D. Prevention and Control of Osteoporosis

Age-related bone loss is seen more frequently in females than in males. In humans, bone mass reaches its peak at age 35, plateaus for several years, and, some time within the sixth or seventh decade, finally decreases. The reduction in mass and density occurs in both cortical and cancellous bone. Reduction in overall density results in bone fragility and subsequent disabilities, manifested by the frequency of spinal compression and fractures of the hip and distal part of the forearm in females as opposed to males.

Unquestionably various exercise programs and dietary plans have a beneficial effect on osteoporosis, but the fact that osteoporosis is age related and pronounced in females raises the questions, Is it related to estrogen depletion? Can estrogen replenishment be beneficial? The loss of density in long bones is at least temporally related to estrogen loss. There is preliminary evidence that estrogen

replacement therapy can retard the loss of density in specific bones, such as the phalanges, as well as the symptomatic manifestation and x-ray appearance of postmenopausal osteoporosis (Aitken *et al.*, 1976). There is an elevation of the plasma calcium and phosphate levels in the menopause, and this can be reversed by estrogen. There is a decrease in tubal reabsorption of phosphate when estrogen replacement therapy is given to postmenopausal women, and as a result, a positive calcium balance can usually be noted. Finally, estrogens appear to suppress bone resorption, as measured by calcium-tracer techniques, to an extent sufficient to explain the positive calcium balance. This can be noted even in such osteoporosis of disuse states as poliomyelitis. Although evidence in the literature is not extensive, it appears that estrogen administration is beneficial in osteoporosis, via its effect on calcium balance and bone resorption.

Even though estrogen therapy has a retarding effect on the reduction in bone density in these women, unfortunately there is also an associated decrease in bone formation within 3-9 months of initiation of estrogen replacement therapy that results in a stabilized, lower rate of bone turnover (Heaney, 1976). The clinical implication of this fact is that if estrogen therapy is to be beneficial in preventing osteoporosis, it must be instituted early, before serious loss of bone density has occurred. Estrogen replacement therapy does not result in new bone formation.

E. Prevention of Atherosclerosis

Traditionally, three types of evidence were cited to support estrogen replacement therapy in retardation of atherogenesis in the aging woman (Furman, 1973): (1) Retrospective autopsy data indicated that women receiving estrogen replacement therapy had less atherosclerotic change in large vessels than control groups. (2) There was early evidence that serum lipoprotein constituents were beneficially converted by estrogen replacement therapy to those of younger women. (3) Evidence that the risk of death from coronary vascular disease was significantly higher in men than in women was attributed to the fact that women were protected in some way by estrogen.

Current information and controlled studies no longer substantiate the contention that estrogen replacement therapy has a beneficial influence on atherosclerosis (Ryan, 1976).

IV. CONCLUSION

Only hot flashes and genital atrophy are unique features of the menopause and are proven to be responsive to low-dose estrogen replacement.

Estrone can be produced after the menopause and can alter the clinical course of the climacteric and have an influence on dosage and effectiveness of therapy.

While estrogen deprivation does not appear to be the sole factor in osteoporosis, unfavorable ratios between females and males and its increase postmenopause

are noted. Estrogen replacement therapy probably retards the rate of osteoporotic change but cannot reverse it.

There is an increased ratio of myocardial infarction in males to females that is not understood. In prophylactic and therapeutic trials the results with higher doses of conjugated estrogens included increases in the incidence of a variety of thromboembolic disorders, cerebrovascular accidents, and myocardial infarction. Furthermore, there is evidence that the larger the dose of estrogen the more likely the risk of thromboembolic disease, cerebrovascular accident, and possibly coronary disease.

Although there is a suggestion that breast disease may be related either to continuous production of endogenous estrogen or to administration of estrogen, the data, in my view, are inconclusive. On the other hand, estrogen replacement therapy has been shown to be associated with progression of endometrial stimulation to hyperplasia and even carcinoma. This possibility must be considered in the risk-benefit analysis of estrogen replacement therapy in a particular patient.

In my opinion, at the present time neither is it reasonable to deny relief of menopausal symptoms to patients by withholding moderate- to low-dose cyclic estrogen therapy nor is it acceptable to extol estrogen as a solution for aging, degenerative diseases, or psychic disturbances after the menopause. Estrogen obviously cannot be used indiscriminately in the hope of correcting nonspecific ailments or complaints. Therefore, certain decisions must be made regarding therapy in the female climacteric:

1. In the early menopause, in obese women over the age of 50 who have amenorrhea but display significant cervical mucus or vaginal cornification, progestin alone should be administered. If progestin-induced withdrawal bleeding does not occur, then the decline of endogenous estrogen can be determined by simple observation of symptomatology, vaginal cornification, and cervical mucus.

2. In nonobese individuals in the early menopause with little or no biologic evidence of estrogen, estrogen therapy can be utilized—conjugated equine urinary estrogens 0.3-0.6 mg per day for three weeks, or ethinylestradiol 0.01-0.02 mg per day for three weeks with a one-week rest period.

Because of the increased concern over endometrial hyperplasia as a result of this therapy, it is advisable to add a progestin daily during the last week of estrogen administration as an antimitogenic agent and to determine if withdrawal bleeding occurs. If endometrial bleeding should occur under these circumstances, then office aspiration or equivalent biopsy must be performed.

3. In the late menopause, when atrophy is clearly evident, then 0.625 mg estrogen, but not more than 1.25 mg, can be administered cyclically. Again, inclusion of progestin is advised.

4. When there are medical complications or restrictions, intermittent vaginal placement of estrogen may be useful.

5. The usefulness of androgen is often considered. In some patients the addition of methyltestosterone 5-10 mg provides a sense of well-being that some physicians have found effective in patient management.

6. There must be full physician-patient dialogue to achieve understanding of the therapeutic limits of estrogen replacement therapy and its advantages and disadvantages.

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ESTROGEN AND BREAST CANCER

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This chapter will be devoted mainly to a review of the epidemiologic studies that have been conducted to investigate the role of estrogens and oral contraceptives in the causation of cancer of the human breast and to a discussion of the findings to date.

I. BASIC FACTS ABOUT BREAST CANCER

A. Incidence

Breast cancer is the most frequently observed cancer of women in this country, but it is rare in men. It is estimated that one out of every 13 women in the United States will develop cancer of the breast in her lifetime. It is expected that 90,000 new cases of breast cancer will have been diagnosed in this country in 1977 and that 34,000 persons will have died from the disease. For California, the respective numbers are 8000 new cases and 3300 deaths (American Cancer Society, 1976). Of these, 99% will be women. While mortality rates for breast cancer among women in the United States have remained virtually unchanged over the past 40 years (Fig. 1), incidence rates, that is, numbers of newly diagnosed cases per

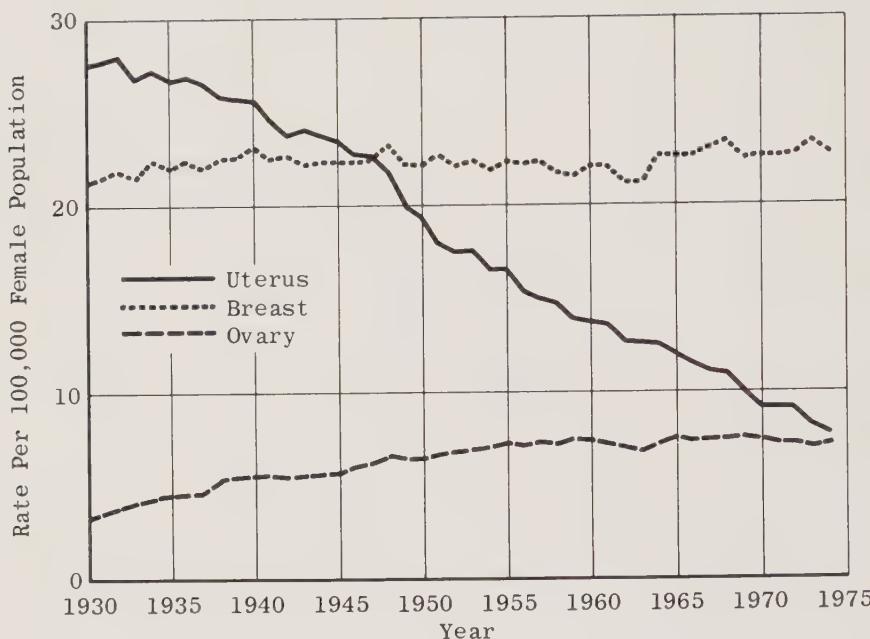


Fig. 1. Age-adjusted cancer death rates (standardized on the age distribution of the 1940 U.S. census population) for selected sites, females, United States, 1930-1974. Sources: U.S. National Center for Health Statistics and U.S. Bureau of the Census.

100,000 women per year, have been rising (Fig. 2). This applies to both white and black women, although rates are generally higher for white women. Breast cancer incidence rates vary among countries. North American and Western European women have high rates; Asian women, particularly the Japanese, have low rates (Doll, 1967). Interestingly, for Japanese women living in the San Francisco Bay Area a gradual rise in breast cancer incidence has recently been described (Buell, 1973). This observation lends support to the currently popular view that differences in cancer risk between countries may be determined to a large extent by environmental rather than by genetic factors.

B. Risk Factors

There is conclusive evidence, however, that genetic factors do play a role in the etiology of breast cancer, since women whose mothers or sisters had breast cancer are at greatly increased risk of developing this type of cancer themselves. Other factors that have been shown to be associated with differences in breast cancer risk are age, parity, age at first childbirth, age at start of menstruation,

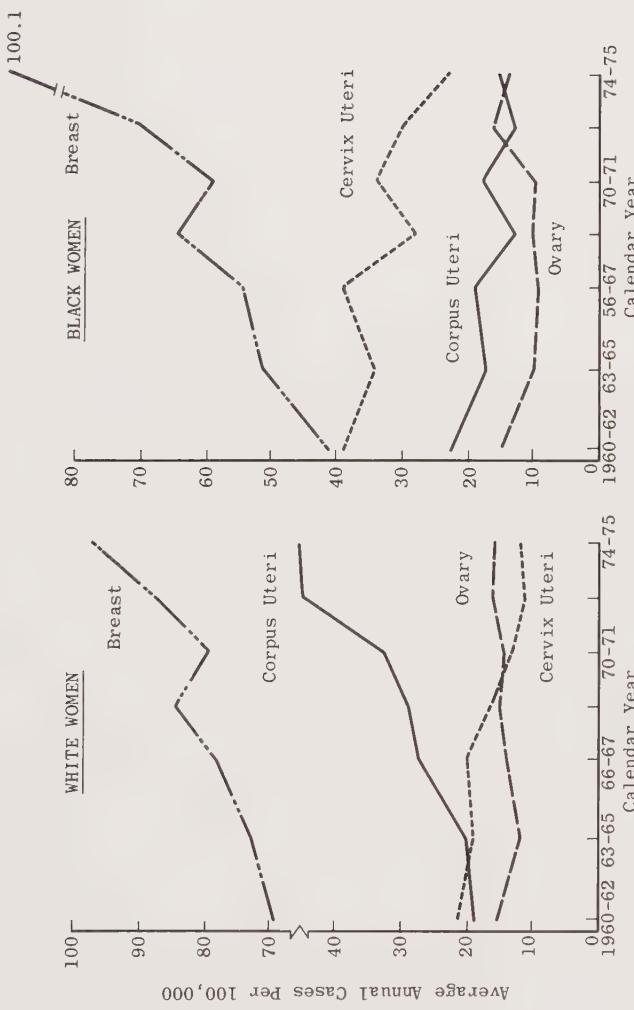


Fig. 2. Trends of age-adjusted incidence rates for cancer of female reproductive organs, Alameda County, California 1960-1975. Age-adjusted rates were computed by the direct method, using the 1950 population of the continental U.S. as the standard.

age at menopause, history of benign breast disease, obesity, and socioeconomic status. Cancer in one breast carries a high risk of cancer developing in the other breast. Exposure to X radiation increases breast cancer risk (MacMahon *et al.*, 1973).

Breast cancer is rare in women under the age of 35 years. Thereafter, incidence rates rise steeply up to age 50, and then continue rising but at a slower rate of increase throughout life (Table I). This age pattern is characteristic for countries with a high breast cancer incidence. In Japan and other low-incidence countries, incidence rates decline after age 50 (Buell, 1973).

Epidemiologic studies have shown that age at first birth is an important determinant of breast cancer risk (MacMahon *et al.*, 1973). The younger a woman is at first childbirth, the smaller is her risk of breast cancer. In general, parous women, that is, women who have delivered at least once, have a smaller breast cancer risk than nulliparous women, that is, women who have never given birth. But women whose first birth occurred after age 30 are at greater risk than nulliparous women.

The hypothesis that has been put forward to explain this phenomenon postulates that induction of most breast cancers occurs early in the reproductive period and that the woman's estrogen status during this period determines her risk of breast cancer. It further postulates that, of the estrogenic fractions excreted in a woman's urine, estriol is not carcinogenic in experimental animals while two other fractions, estrone and estradiol, are. The more estriol in relation to estrone and estradiol a woman produces, that is, the greater her so-called estriol ratio, the smaller is her breast cancer risk. Japanese women living in Asia have been found to have estriol ratios that are more than twice as high as those of Caucasian women (MacMahon *et al.*, 1974). Since estriol is selectively increased in pregnancy, a pregnancy during the early reproductive period critical for cancer induction is said to have a sparing effect. The exact mechanism by which this is accomplished is presently not known and is subject to continuing investigation.

Of the other risk factors mentioned, early menarche, that is, start of menstruation, and late menopause are consistently found associated with a higher breast cancer risk, while surgical menopause before age 40 reduces it. It has been known for over 80 years that removal of the ovaries in women with metastatic breast cancer may be followed by long-lasting remission of their disease (Beatson, 1896). This principle is still used today in the treatment of advanced breast cancer. Unfortunately, only about 30% of women respond to this hormone deprivation therapy (Jensen, 1974).

A history of benign breast disease is generally believed to increase breast cancer risk, although one of two recent studies failed to find an association (Devitt, 1976; Monson *et al.*, 1976). Obesity and socioeconomic status are associated with an increased breast cancer risk. As far as obesity is concerned, this holds true only for postmenopausal women. A link with nutritional factors

TABLE I. Trends of Age-Specific and Age-Adjusted^a Incidence Rates for Cancer of the Breast in Women of All Races, Alameda County, California, 1960-1975

Age group	Average annual cases per 100,000						
	1960-62	1963-65	1966-67	1968-69	1970-71	1972-73	1974-75
Total	66.4	68.5	74.6	81.1	75.4	83.1	104.2
20-24	3.1 ^b	0.8 ^b	2.1 ^b	1.0 ^b	0.9 ^b	2.6 ^b	2.7 ^b
25-29	4.4 ^b	8.5	5.2 ^b	4.9 ^b	8.2	10.4	7.0
30-34	18.6	32.1	24.2	15.3	18.5	39.4	36.7
35-39	63.6	53.7	67.7	75.0	75.6	54.1	83.5
40-44	117.8	108.7	112.7	137.3	115.9	95.7	128.7
45-49	157.6	150.7	150.1	157.9	171.4	174.3	190.2
50-54	161.8	152.2	187.7	181.9	186.6	222.6	242.5
55-59	143.2	186.0	189.7	212.9	199.7	231.7	265.4
60-64	191.2	172.5	200.5	256.3	267.0	303.1	289.8
65-69	210.0	210.7	237.4	258.3	208.4	269.8	315.5
70-74	200.0	236.6	288.5	306.4	239.7	223.3	377.3
75-79	298.2	306.3	331.9	375.1	235.6	313.1	319.8
80-84	263.4	311.7	357.9	297.5	229.5	326.7	461.1
85+	253.3	413.0	308.7	380.7	367.7	426.0	413.3

^a Age-adjusted rates were computed by the direct method, using the 1950 population of the continental United States as the standard. Note: Zero rates in age groups under 20 not shown.

^b Rate is based on five or fewer cases.

and their effect on estrogen metabolism is suggested and this subject is currently under intensive study (de Waard, 1975).

II. ESTROGEN AND BREAST CANCER

A. Rodents

Because mammary cancer of the mouse is of proven viral etiology, much research has gone into investigating the role viruses might play in the causation of human cancer. The causative agent of mouse breast cancer is a B-type RNA virus (Lyons and Moore, 1965). RNA viruses that appear closely related to the mouse breast cancer virus have also been found in human milk, but so far proof of their etiologic role in the production of human breast cancer is lacking (Axel *et al.*, 1972).

It has long been known that administration of estrogens to certain inbred

strains of castrated mice can produce breast cancer, but it has only recently been shown that estrogen stimulation of genetically susceptible mice without the mammary tumor virus is not effective unless it is stimulated by estrogen (Gass *et al.*, 1974).

Both naturally occurring and synthetic estrogenic substances have been shown to be capable of producing cancers of other organs as well, not only in mice but also in a variety of other experimental animals (Gardner *et al.*, 1959). It may be of interest to mention here that estradiol as well as diethylstilbestrol given to Syrian hamsters produced clear cell cancers of the kidneys (Kirkman, 1959). Using this model system, researchers were able to demonstrate that this estrogen-induced tumor could be inhibited by concurrent administration of progesterone, testosterone, or deoxycorticosterone.

B. Humans

For a long time, however, primates appeared resistant to this cancer-producing action of estrogens. Eventually, the first primate in which cancer of the breast appeared to have developed as a direct result of estrogen administration was man himself (Symmers, 1968). In 1968 it was reported in the medical literature that rapidly progressive fatal breast cancers had developed in two male transsexuals who had been castrated and treated continuously with high doses of estrogens. Subsequently, an epidemiologic study definitely linked the occurrence of clear cell cancer of the vagina in young women whose mothers had been treated with diethylstilbestrol during pregnancy to the administration of this synthetic estrogen (Herbst *et al.*, 1971). To round out this series of what one could call "estrogen experiments in humans," I should like to mention also that incidence of endometrial cancer, that is, cancer of the lining of the womb, was greatly increased in women with congenital anomalies of the ovaries following treatment with high doses of estrogens (Cutler *et al.*, 1972).

C. Menopause

Administration of exogenous estrogens to women for the treatment of the symptoms associated with the menopause has been practiced for many years. Estrogen preparations were considered to carry no increased cancer risk if given in a cyclical fashion. Originally diethylstilbestrol was the drug of choice. It was later replaced by Premarin, a conjugated estrogen preparation. In 1975 two studies were published that linked such estrogen replacement treatment to an increased risk of endometrial cancer in postmenopausal women (Smith *et al.*, 1975; Ziel and Finkle, 1975). In the fall of 1976, a study by Hoover *et al.* reported an increased risk of cancer of the breast in postmenopausal women treated with conjugated estrogens (Hoover *et al.*, 1976). In this latter study, the increase in breast cancer risk did not show up until the women had been followed for over ten years. For women followed for 15 years, breast cancer

risk was double that of the general population. Duration of estrogen treatment appeared to be of less importance than dosage, women taking higher dose pills being at higher risk. The study also showed a greater risk of breast cancer for women with a history of histologically confirmed benign breast disease. This risk was increased even further for those whose benign disease was diagnosed after institution of estrogen treatment. In this latter group, breast cancer risk was seven times greater than in the general population. The study was based on case histories of 1891 postmenopausal women seen in one private medical practice in Louisville, Kentucky, between 1939 and 1973. According to general population rates, 39 cases of breast cancer would have been expected in the study group, but 49 were observed.

The results of this study differed from those of a number of previous investigations carried out intermittently over a 30 year period (Wynder and Schneiderman, 1973). None of these had found an increased risk and several had suggested that estrogens given to postmenopausal women decreased or possibly delayed the occurrence of breast cancer. However, a critical review of the latter shows that numbers of patients studied were generally not large, ages fluctuated widely, and differences in duration of follow-up periods were not taken into account. Moreover, none of these earlier studies made allowance for patient characteristics that are known to be related to breast cancer risk and could have affected the outcome.

A recent study from Southern California describes the effect such an omission can have (Casagrande *et al.*, 1976). In an earlier publication these workers had reported finding a decreased breast cancer risk associated with estrogen use among women with natural menopause. When they recalculated their data to allow for differences in oral contraceptive use by age and age at menopause, this decrease all but disappeared. Also, no association between breast cancer risk and estrogen replacement therapy was found in studies conducted by Arthes and co-workers (1971) and Byrd *et al.* (1973).

D. Oral Contraceptives

Oral contraceptives were licensed in this country in 1960 and were readily accepted by women of reproductive age. By 1965 over a quarter of all married women less than 45 years of age in this country either were taking or had taken oral contraceptives and their popularity was increasing (Westoff and Ryder, 1968). Never in the history of mankind had so many young women been exposed to prolonged administration of such potent hormones, which had been shown to stimulate breast cancer growth in chemically induced cancers of animals and whose potential to induce cancer or enhance the growth rate of existing cancer in humans was unknown and untested. Therefore, in the latter part of the 1960s a number of epidemiologic studies were started in England as well as in the United States to determine whether women taking these drugs might be at increased risk of cancer.

TABLE II. Relative Risk of Breast Cancer from Ever-Use of Oral Contraceptives

Age (years)	Breast cancer patients			Control patients			Relative risk of breast cancer ^a	<i>P</i>		
	Ever-users		Percentage	Ever-users		Percentage				
	Number	Number		Number	Number					
Total	452	226	50.0	872	398	45.6	1.1	.42		
15-29	15	15	100.0	29	24	82.8	—	—		
30-39	89	61	68.5	167	112	67.1	1.2	.66		
40-49	348	150	43.1	676	262	38.8	1.1	.66		

^a Based on summary chi-square analyses adjusted for differences, in age, race, religion, and age at first childbirth.

Results of breast cancer studies have been reported by several investigators. Vessey and co-workers in England conducted a case-control study. They now have follow-up data on 322 cancer patients and 502 matched controls (Vessey *et al.*, 1975). These authors have consistently failed to find an association between oral contraceptives and breast cancer. Interim reports from three prospective studies investigating the effects of oral contraceptive use on the health of women have also been published. Two of these studies are being conducted in England (Royal College of General Practitioners, 1974; Vessey *et al.*, 1976), and one in the Greater Boston Area (Ory *et al.*, 1976). The British studies were started in 1968. One is conducted by the Royal College of General Practitioners and follows 46,000 women; the other studies women served by the British Family Planning Association under the direction of Vessey. In a 1976 report, Vessey *et al.* summarized findings from 17,000 women. In neither of these studies was there evidence of an increased breast cancer risk, but numbers of breast cancers found at the time of reporting were very small in both. Ory and co-workers recently published an analysis of hospitalization rates for benign and malignant breast disease among the 67,500 women participating in the Boston study. There were only 22 oral contraceptive users among the 137 women with breast cancer identified and their hospitalization rates did not differ from those of the nonusers.

Paffenbarger and I started a case-control study in the Greater San Francisco Bay Area in 1970 (Fasal and Paffenbarger, 1975, 1977; Paffenbarger *et al.*, 1977). We identified 452 patients with newly diagnosed breast cancer and 872 patients free of breast cancer who had been hospitalized for medical or surgical conditions to serve as controls. All were less than 50 years of age and were interviewed at home. We compared the frequency, duration, and other conditions of oral contraceptive use in the women with breast cancer with those of the control women free of breast cancer, and expressed the results as relative risks. A relative risk of 1.0 means that there is no difference in risk of breast cancer between

TABLE III. Relative Risk of Breast Cancer by Various Conditions of Oral Contraceptive (OC) Use

Condition of OC use	Breast cancer patients (N = 452)		Control patients (N = 872)		Relative risk of breast cancer	P
	Number	Percentage	Number	Percentage		
1. Duration (months)						
1-24	104	23.2	195	22.7	1.0 ^a	.93
25-48	49	10.9	53	6.2	1.8 ^a	.03
49-96	52	11.6	110	12.8	1.0 ^a	1.00
97+	17	3.8	26	3.0	1.7 ^a	.17
2. Interval since first use (months)						
1-36	41	9.1	64	7.4	1.1 ^b	.56
37-72	77	17.1	122	14.1	1.3 ^b	.17
73+	106	23.6	205	23.7	1.1 ^b	.65
3. Interval since last use (months)						
2-12	27	6.0	49	5.7	1.0 ^b	1.00
13-36	45	10.0	87	10.1	1.1 ^b	.70
37+	79	17.6	139	16.1	1.1 ^b	.52
4. Duration among current users (months)						
Total	72	15.9	113	13.0	1.5 ^a	.04
1-24	14	3.1	21	2.4	2.0 ^a	.13
25-48	16	3.5	19	2.2	2.2 ^a	.08
49+	42	9.3	73	8.4	1.3 ^a	.38
5. Duration among patients with prior benign breast disease (months)						
Total	27	45.0	26	34.2	1.5 ^c	.40
1-24	11	18.3	13	17.1	1.2 ^c	.99
25-48	4	6.7	6	7.9	1.3 ^c	.99
49-72	4	6.7	6	7.9	1.2 ^c	.85
73+	8	13.3	1	1.3	11.2 ^c	.04
6. Earliest use (year)						
Before 1965	92	20.5	183	21.2	1.0 ^a	1.00
1965-1969	119	26.5	195	22.6	1.1 ^a	.72
1970 & since	12	2.7	12	1.4	1.8 ^a	.34

^a Based on summary chi-square analyses adjusted for differences in age, race, religion, and age at first childbirth.

^b Based on summary chi-square analyses adjusted for differences in age, race, and religion.

^c Based on summary chi-square analyses adjusted for differences in age, race, religion, education, and menopause.

women taking oral contraceptives and those not taking oral contraceptives, while a relative risk of 1.5 would indicate that pill users are at 50% risk compared with nonusers.

There was no significant difference between cases and controls with respect

TABLE IV. Relative Risk of Breast Cancer among Nonmenopausal Women without Previously Diagnosed Benign Breast Disease Who Used Oral Contraceptives before First Childbirth

Age (years) at first childbirth	Breast cancer patients			Control patients			Relative risk of breast cancer	<i>P</i>		
	Use before first childbirth			Use before first childbirth						
	Number	Number	Percentage	Number	Number	Percentage				
Total	373	17	4.6	732	10	1.4	2.7 ^a	.03		
<20	54	0	0.0	167	0	0.0	— ^b	—		
20-24	145	2	1.4	317	5	1.6	0.8 ^b	.99		
25-29	109	9	8.3	184	4	2.2	13.9 ^b	.02		
30+	65	6	9.2	64	1	1.6	—	—		

^a Based on summary chi-square analyses adjusted for differences in race, religion, and age at first childbirth (ten age groups).

^b Based on summary chi-square analyses adjusted for differences in age, race, and religion.

to the proportions who had at some time used oral contraceptives (50.0% in cases, 45.6% in the controls) and the overall relative risk was 1.1 (Table II). Relative risks for ever users did not differ by age, interval since first or last use of oral contraceptives, or earliest year of use. However, we did find an 80% increase in the relative risk of breast cancer in women who had used oral contraceptives for from two to four years and a 50% increase for women who were current users. Among women who had had a biopsy for benign breast disease and had used the pill for six years or more, breast cancer risk was increased 11-fold (Table III). Finally, we also found that the risk of breast cancer was about three times higher for women who had used oral contraceptives before their first childbirth (Table IV). This last finding was based on small numbers, since only 17 cancer patients and 10 control patients met the necessary criteria. Women who had never given birth showed no increase in risk.

One of the four positive findings in our study, the excess risk of breast cancer in oral contraceptive users with a history of prior benign breast disease, was also reported by Hoover *et al.* (1976) for postmenopausal women treated with conjugated estrogens. Unfortunately, the Boston group had excluded women with benign breast disease from their study population. We recently learned that some physicians now treat benign breast disease with oral contraceptives (Fasal and Paffenbarger, 1977). The reason for this could well have been reports of the sparing effect oral contraceptives were found to have on the development of benign breast disease in several prospective and retrospective studies including ours (Royal College of General Practitioners, 1974; Vessey *et al.*, 1972; Kelsey *et al.*, 1974). However, Hoover *et al.*'s and our finding of an increased cancer risk in women with a history of benign breast disease who were on oral contraceptives provides strong evidence that such drugs are contraindicated in women with benign breast disease.

The twofold increase in risk for women taking oral contraceptives for from two to four years could be due to chance. On the other hand, if oral contraceptives were to increase the growth rate of preexisting cancers so that they become clinically apparent after two years of use and all have been diagnosed by the end of four years, such a pattern would result.

The most serious of the positive findings in our study is the increased risk of breast cancer associated with oral contraceptive use before first childbirth (Paffenbarger *et al.*, 1977). I have mentioned previously that age at first childbirth is an important risk factor and that breast cancer risk increases with increasing age at first childbirth. Our data show that postponement through use of oral contraceptives increases this risk still further.

Of the other positive findings reported by Hoover *et al.* (1976) the observation that there was an increase in breast cancer risk in women treated with conjugated estrogens that became apparent only after ten or more years of follow-up is sobering. If such a latent interval were also to be present for oral contraceptive use, one could expect soon to observe a rise in breast cancer incidence of women of reproductive age, as those who started oral contraceptives in the early 1960s reach the critical 10-15 year period of follow-up. We were unable to demonstrate such an effect in our data, perhaps because in all but a few of our patients the available follow-up period was under ten years.

III. CONCLUSION

The sum total of findings showing a positive association between estrogen use and breast cancer risk is not large. Only two of the reviewed studies contributed such findings. All others failed to show any association. The existence of these findings warns us, however, that continued vigilance and further study of the relationship between sex hormone use and breast cancer risk are definitely indicated.

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ESTROGENS AND GENITAL CANCER

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Several reports have appeared recently suggesting an association between exogenous estrogen therapy and endometrial carcinoma. Although this is not a new controversy, these recent studies were the first to show a significant association between estrogens and uterine cancer in women and have thus reopened heated discussion and interest in this area.

I. ESTROGENS AND ENDOMETRIAL CARCINOMA

A. In Animals

In 1923, Allen and Doisy reported an ovarian extract that was able to induce vaginal cornification in ovariectomized rats. This substance—now known as the hormone estrogen—was soon shown to cause hyperplasia of the genital tissues of experimental animals. In 1941 Greene described endometrial hyperplasia and adenocarcinoma of the endometrium in a group of estrogen-treated rabbits. Other investigators have reported estrogen-induced tumors of at least eight different sites including the uterus, ovary, and breast in no less than five different species of laboratory test animals. However, the repeated failure to produce cancers similar to those found in humans by prolonged, high-dose estrogen

TABLE I. Incidence of Endometrial Carcinoma in Patients with Granulosa Cell Tumors

All patients	(%)	Postmenopausal patients	(%)
(Greene, 1957)	3.5	(Ingram and Novak, 1951)	12
(Kottmeier, 1959)	5.6	(Larson, 1954)	15
(Diddle, 1952)	6.1	(Greene, 1957)	23
(Mansell and Hertig, 1955)	15	(Hertig, 1957)	24
(Smith <i>et al.</i> , 1942)	16	(Dockerty and Mussey, 1951)	27
(Speert and Hertig, 1949)	18		

administration to subhuman primates has led some investigators to question the applicability of the animal data to humans.

B. In Humans

1. Pathological Conditions

There are several naturally occurring pathologic conditions in women that shed some light on the estrogen-cancer relationship. Granulosa-theca cell tumors are uncommon tumors of the ovary, but they are of special interest because many of them produce estrogen. Thus, women with these tumors might serve as models of the effect of high levels of estrogen for a prolonged period on the uterus and endometrium. Several reviewers have examined the incidence of endometrial hyperplasia and carcinoma in patients with granulosa-theca cell tumors of the ovary (Table I). Although the incidence varies considerably between different series, the overall incidence of endometrial cancer is greatly increased among women with these estrogen-producing ovarian tumors. (The incidence of endometrial cancer in the general population is approximately 34 per 100,000 women or 0.034%.) This increased risk is even more striking when only postmenopausal patients are considered.

Endometrial carcinoma is primarily a disease of postmenopausal women because during a woman's reproductive life, the cyclic influence of estrogen and progesterone results in monthly shedding of the endometrium, which usually prevents a hyperplastic or malignant response. Patients with Stein-Leventhal syndrome or polycystic ovarian disease are frequently infertile as a result of a failure to ovulate. Because of this anovulation, the ovaries produce estrogen without the cyclic, monthly modification of progesterone. The normal monthly shedding of the endometrial lining of the uterus does not occur and instead, the endometrium may become hyperplastic or even malignant under the stimulus of "unopposed estrogen." This certainly does not occur in all, or even most, patients, but among the 10-15% of endometrial carcinomas that occur in young women, approximately one-fifth have associated polycystic ovarian disease—a very large proportion for this uncommon condition (Table II).

TABLE II. Incidence of Polycystic Ovarian Disease with Endometrial Carcinoma under Age 40

	(%)
(Speert and Hertig, 1949)	21
(Sommers <i>et al.</i> , 1949)	25
(Dockerty and Mussey, 1951)	19
(Silverberg <i>et al.</i> , 1977)	20

2. Estrogen Therapy

Gynecologists have been aware of these data for some time, and the possibility that estrogen medications might cause cancer in women has been studied by a number of investigators over the years. Jensen *et al.*, (1954) reported that 33% of 48 patients with endometrial carcinoma gave a history of estrogen use, while only 21% of control patients had a history of hormone exposure. Later reports by Wynder *et al.*, (1966), Dunn and Bradbury (1967), and Pacheco and Kempers (1968) described small numbers of patients with endometrial carcinoma with roughly the same incidence of estrogen exposure as compared with control patients. Although such reports were far from "proof" that no relationship existed between estrogens and endometrial carcinoma, the lack of a clear-cut association suggested that any association, if it existed at all, was probably quite small.

With the question of carcinogenicity somewhat quieted by these reports, there was an ever-increasing tendency in the late 1960s and early 1970s to use oral estrogen replacement in postmenopausal women. The slogan was "feminine forever" and the idea was to use oral estrogens to replace the ovarian estrogens that were no longer produced in women who had "outlived their ovaries." In 1963 American women purchased 18.4 million dollars worth of noncontraceptive estrogens, but by 1973 this figure had jumped to almost 70 million dollars per year (Weiss *et al.*, 1976). A study from the Seattle area estimated that 51% of postmenopausal women had taken estrogens for at least three months and the median duration of use was ten years (Stadel and Weiss, 1975). This great increase in the number of patients taking estrogens together with more precise statistical evaluation of the data probably accounts for the results that have been recently published.

At the present time there have been five case control studies reported concerning the association of exogenous estrogen therapy and endometrial cancer (Table III). These studies all found an increased risk of developing endometrial cancer among those women who had been or were on estrogen therapy. Although numerous objections have been raised concerning the earlier studies, the report by McDonald and his associates (1977) is excellent and answers the previous objections. Olmstead County, Minnesota, residents given a diagnosis of uterine cancer during a 30-year period were reviewed. A total of 145 patients with endometrial carcinoma were identified and each was matched with 4 control

patients of a similar age and degree of medical care. They found that the patients who took any form of estrogen therapy for six months or longer had a 2.3-fold increased risk of developing endometrial cancer. This is somewhat less than the 7-8 times increased risk reported in the studies of Smith *et al.* (1975), Ziel and Finkel (1975), and Mack *et al.* (1976). However, patients who use conjugated estrogens, the most commonly prescribed kind, for more than six months have an increased risk of developing endometrial carcinoma 4.9 times greater than nonusers of estrogen. The risk was greater for longer duration or exposure, higher dose levels, and continuous as opposed to cyclic administration of medication. Estrogen-treated patients had an increased tendency to develop early, highly curable types of endometrial cancer. The control group was well selected in this study and there was good pathologic evaluation of the material presented, which were the two major weaknesses of the previous studies. It is interesting to note that the overall incidence of estrogen use in Olmstead County, Minnesota, was only 10%, whereas 58% of the study subjects from Southern California were taking estrogen.

Thus, it appears that several independent studies from different parts of the country in both high- and low-use estrogen areas have found an increased incidence of endometrial carcinoma associated with estrogen therapy for the menopause. The magnitude of this increased risk is variable, depending on the dose of medication, the length of exposure, and the dosage schedule. Several of these studies have also shown that obese patients have a three- to fourfold increased risk of developing endometrial carcinoma and that people who smoke one pack of cigarettes per day have a 17-fold increased risk of developing lung cancer. Therefore, the risk from prolonged use of exogenous estrogens seems to be somewhat more than from overeating and considerably less than that from smoking cigarettes—a nonprescription item that, unlike estrogens, has no therapeutic benefit. It should also be noted that the demonstration of an association between exogenous estrogens and cancer does *not* mean that estrogens *cause* cancer. In all likelihood they are not carcinogens but act in a permissive way to provide favorable conditions for other carcinogenic agents to produce malignant transformation.

II. INTRAUTERINE ESTROGEN EXPOSURE AND VAGINAL CANCER—THE DES STORY

A. Background

Although the association of estrogen and endometrial carcinoma was difficult to demonstrate, the possibility that such an association existed had long been postulated on the basis of the obvious immediate hyperplastic response of the endometrium to estrogens. Not so easy to conceptualize, however, is the relationship now known to exist between synthetic nonsteroidal estrogenic compounds given to a pregnant woman and the development, years later, of cancer of the vagina in her daughter.

TABLE III. Association of Exogenous Estrogens with Endometrial Carcinoma

	Ca (Pts)	Patients on estrogen (%)	Controls on estrogen (%)	Relative risk
Smith <i>et al.</i> (1975)	317	48%	17%	7.5
Ziel and Kinkle (1975)	94	57	15	7.6
Mack <i>et al.</i> (1976)	63	89	50	8.0
McDonald <i>et al.</i> (1977)	145	17	8	2.3
Gray <i>et al.</i> (1977)	205	22	15	2.1

Although diethylstilbestrol (DES) was first synthesized by Dodds in 1938, our story does not really start until 1970, when Herbst and Scully published an article that described seven young women with adenocarcinoma of the vagina. These tumors were rather unique, because they were all adenocarcinomas and, classically, vaginal cancers are squamous cell carcinomas. In addition, the patients were aged 15-22 and vaginal cancer occurs almost exclusively in women over the age of 50. It was also of interest that these patients were seen at the Massachusetts General Hospital within a period of two years, and the authors were unable to find *any* similar cases in a review of all the earlier pathologic material at this very busy hospital. For these reasons, the authors suspected some specific etiologic agent that might account for the cluster of vaginal adenocarcinomas, and a detailed search for some unique aspect of these patients was undertaken. However, they did not uniformly use any specific douche, vaginal tampon, or vaginal irritant of any sort. Only one patient had had previous sexual exposure and none had taken birth control pills or other hormones. Many additional factors, such as other illnesses, cigarette smoking, cosmetic use, diet, and household pets, were examined but were not found to be different for this group of patients when compared with a group of control patients of the same age, born at the same hospitals to parents of the same socioeconomic group. However, when the mothers' pregnancies were evaluated, several significant differences became clear. The mothers of the patients with cancer had a significantly increased incidence of prior pregnancy loss and of bleeding during the pregnancy in question and, most significantly of all, six of eight mothers had been given DES during pregnancy, while none of the 32 control mothers were so treated (Herbst *et al.*, 1971). And so the DES story started.

B. Detection and Treatment

A registry was established to compile information on young women with adenocarcinoma of the cervix and vagina in an effort to determine the magnitude of the problem and to identify methods of detection and treatment. Almost 300 patients have now been registered and, interestingly enough, about 15% of these patients have no history of intrauterine exposure to exogenous hormones. Estimates of the number of women in the United States treated with DES during

pregnancy range as high as 2 million. Most patients were treated with DES in an attempt to prevent prematurity and toxemia of pregnancy on the basis of numerous scientific papers describing what was felt to be the very positive benefits of this therapy. Because of the large number of women treated with DES during pregnancy and the relatively few patients with carcinoma, it appears as if this is a rather infrequent complication, occurring probably no more than 1/1000 women exposed. Other changes in the cervix and vagina of these patients have been described, however, and approximately 30% of young women exposed to DES *in utero* have clinically apparent changes such as vaginal ridges, cervical collars, and cervical protuberances. An even larger number of patients have ectopic columnar epithelium on the exocervix or in the vagina—commonly called “ectopy” or “adenosis.” Although such changes have been described in patients not known to be exposed to hormones, they are very rare. Thus, there is good evidence to suggest the relationship of intrauterine exposure to synthetic estrogens and vaginal adenosis and adenocarcinoma.

The fact that all patients with adenocarcinoma had exposure prior to the eighteenth week of pregnancy and our knowledge that the vagina and cervix undergo embryologic development at approximately the eighth through twelfth week of gestation also serves to strengthen the case for the etiologic role of estrogenic hormones in these changes (Herbst *et al.*, 1974). Forsberg (1972) has also reported producing ectopic columnar epithelium in the vagina in mice treated neonatally with estradiol and DES. In this case the nonsteroidal estrogens seem to act as a teratogen rather than a carcinogen, that is, they produce developmental changes (columnar epithelium on the exocervix and vagina, etc.) rather than actually causing the cancer.

III. CONCLUSION

Thus we have seen that estrogen and estrogenic compounds are associated in several ways with different tumors of the female reproductive tract, and continued investigation of the role of these hormones is necessary in order to define more fully the nature of the role played by these hormones in the development of cancer.

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ADOLESCENT CONTRACEPTION

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I. INTRODUCTION

Many adolescent females are sexually active and are seeking contraception. These young women are now faced with the decisions of how to plan and utilize contraception for more than 30 years of their lives. The traditional moral, social, and medical arguments against providing contraception are not always relevant to the adolescent population. Adolescents need medically safe and socially relevant contraception.

II. SCOPE OF ADOLESCENT SEXUAL ACTIVITY

Recent U.S. population statistics estimate that there are 21 million young people between the ages of 15 and 19 years old. Eleven million U.S. teenagers are sexually active (Alan Guttmacher Institute, 1976). Intercourse is occurring in younger and younger age groups, and it is now estimated that one-fifth of the

TABLE I. "Sexually Active" Teenage Females^a

Age (years)	Sexually active (%)
13	10
14	17
15	24
16	31
17	35
18	43
19	51

^a From Alan Guttmacher Institute (1976).

8 million 13-14 year olds are having intercourse (Alan Guttmacher Institute, 1976). Premarital intercourse is common. The percent of 13-19 year old females sexually active in the U.S. is shown in Table I (Alan Guttmacher Institute, 1976).

This year one million 15-19 year olds will become pregnant; 30,000 females under 15 years of age conceive annually. In 1974, there were 608,000 recorded adolescent conceptions resulting in 290,000 live births (Vadies and Pomeroy, 1975): 27% of the conceptions ended in induced abortions and 14% of the conceptions ended in spontaneous abortions (Alan Guttmacher Institute, 1976). Approximately two-thirds of all adolescent pregnancies were "unintended," that is, not wanted at the time that they occurred. Among those who did not want to become pregnant, only 13-16% used contraception. The Johns Hopkins study of adolescent sexuality reported that about one-half of the sexually active unwed teenagers used no contraception with the last intercourse (Zelnick and Kantner, 1972). These statistics are probably only revealing the tip of the iceberg. The medical, social, emotional, and economic impact of adolescent sexual activity can no longer be ignored. We can always argue statistics; we can always hide behind our own moral and religious views; but at what price to our teenage population?

III. REASONS FOR ADOLESCENT SEXUAL ACTIVITY

Teenagers have intercourse for a variety of reasons. We cannot make medical care relevant until we begin to understand these reasons. Contrary to common belief, one of the least common reasons for intercourse is to conceive and have a baby. Although they know intellectually that this is a possibility, they routinely deny that this could happen to them. It is a common subcultural belief that one must have intercourse very frequently before one can become pregnant; and frequency is not at all related to timing. Generally, adolescents have intercourse for the following reasons:

- (1) To prove their desirability as females: To resolve the oedipal conflict and prove that they are as good or better than their mothers.

- (2) To act out fear, anger, and frustration from other areas of their lives.
- (3) To protect against homosexual fears and feelings.
- (4) To belong: It is often a peer group norm to have intercourse. The peer group commonly believes that if you love someone, it is permissible to have intercourse. Love is equated with strong physical attraction and need. Libido or desire is generally not separated from the concept of love.
- (5) To grow up: Adolescents use sexual activity as a way of developing who they are emotionally, physically, and morally. "You must try yourself out before you know who you are!"

There are many myths surrounding adolescent sexual activity. An adolescent female often feels that if she denies what she is feeling during the sexual act, then she is still a "good girl" and not a "tramp." She equates control of her feelings during intercourse with control over the sexual situation (i.e., *not* becoming pregnant). Adolescent males and females are preoccupied with finishing what they have started. It is widely believed that if you do not consummate the start of your feelings in vaginal intercourse, then you will physically damage one another. Stopping before intercourse creates anxiety and tension, and is therefore thought to be bad for the body and bad for future sexual activity. Boys are preoccupied with "keeping their rod in shape" and girls are preoccupied with "preserving their future fertility." In addition, acting out heterosexually successfully sublimates any homosexual feelings or fears.

Adolescent contraception has not worked because we have not made it relevant to their *modus operandi*.

IV. ADOLESCENT CONTRACEPTION

A. Sexual Education

Between 3 and 6 million adolescent females are in need of contraceptive services, but at this time approximately 80% of sexually active 15-19 year olds are not receiving contraceptive services. Early child-bearing subjects the adolescent to increased medical risks, increased fetal mortality and morbidity, increased drop-out rate from school and subsequent unemployment, and early marriages and repeated marital failures (Presser, 1977). By the adolescents' own accounting, it is a rapid downhill spiral.

The best form of adolescent contraception is factual, relevant, available sexual education. There is no more time left to argue over who should be giving family life education: everyone should be. Adolescents need and want control over their own bodies and their sexual lives, but control must be based on facts and not fiction. The basic information that any program should convey is that the male and female bodies are designed perfectly to conceive, that conception will occur with intercourse unless contraception is used, that contraception has nothing to do with sexuality, loving, needing, or belonging—contraception only

TABLE II. Failure Rates of Various Contraceptive Methods ^a

Method	Failure rate (%)
Pill	4
IUD	7
Condom	16
Diaphragm	18
Withdrawal	21
Rhythm	28
Foam	29

^a From Westoff and Westoff (1971).

prevents untimely conceptions—and that the available contraceptive methods can be used safely under medical care.

Ideally, the teenage patient needs a medically safe, highly reliable contraceptive method. Practically, she must be comfortable with the method or she will not use it. Her medical concerns center around changing her body image (i.e., getting fat), making sexual activity unnatural, and harming her future fertility. If the adolescent patient is realistically educated about the variety of available methods, she will choose one with which she can live. Our medical responsibility is to teach her how to live with her chosen method.

The traditional contraceptive methods have inherent failure rates. These failure rates can be minimized with careful usage. The most quoted failure rates are shown in Table II (Westoff and Westoff, 1971).

Prior to prescribing any contraceptive method, each female should have a thorough physical examination. Care should be taken to preserve her dignity and modesty and to educate her about her sexual organs. Each method should be discussed, describing how it works, how it fails, and what it does to the body. When she has chosen a method, she should be taught how to use it.

B. The Pill

It is my medical opinion that both the low-dose combined oral contraceptive and the pure progesterone, or minipill, can be used safely in the adolescent patient (see, however, chapter by Fasal). Plan with her a schedule of frequent visits every three to four months and also plan to rotate her off the oral contraceptives for several spontaneous cycles each year to allow her to ovulate. Preserving and reaffirming her ability to ovulate are very important to her. Side effects such as nausea, bloating, weight gain, and acne can be minimized if the pill is not taken on an empty stomach, for instance at night before going to bed. Do not minimize her concerns; deal with them openly. Teach her the medical danger signals.

C. Intrauterine Device (IUD)

This method is generally chosen by the adolescent who does not need daily control over her body and thus is less compulsive. The IUD can be safely placed

and kept in place. Generally, it is placed during a menstrual period and devices such as CU7, Nullip Saf-T coil, and the small Lippes Loop are very effective. Adequate cervical dilation can be obtained with the use of a Laminaria tent when the patient is not menstruating. Tell her exactly what to expect: do not negate her fears about pain, cramping, and bleeding. Do not abandon her after the procedure: provide adequate pain medicine until she is comfortable with the IUD. Teach her how to check for her IUD string: and see her frequently to reaffirm her health.

D. The Diaphragm

The diaphragm is an effective, medically safe method that the adolescent can use well. Adolescents will not use the diaphragm if it becomes a nuisance or decreases the "naturalness" of the sexual act. Fit her for the diaphragm; teach her to get it in and out; have her practice wearing it until she is comfortable with it. Teach her how to place it in the vagina before leaving home and then to quickly check its position with her finger before sexual activity begins. Minimize the use of creams and jellies. The diaphragm works because it is in place covering the cervix and has no holes. Adolescents become preoccupied with the use of the cream or jelly, and then abandon the use of the diaphragm because it is too messy and too inconvenient. Teach her how to wear it for six hours after the last intercourse and how to leave it in for an entire twenty-four hour period. The diaphragm is effective and inexpensive and does not alter the body. This appeals to an adolescent.

E. The Condom

The condom is one of the safest methods of contraception for the female. The condom combined with foam has a high protection rate. Teach the couple how to place the condom, how to check it for holes, and how to withdraw, holding the condom to the penis. Lubricated condoms generally cause less friction and break less easily. Adolescent males commonly believe that the condom causes the back-up of the semen and sperm and may impair their fertility. Express firmly that this is not so! If they insist on proving this to themselves, encourage them to plan trials without the condom during the menses.

F. Foams and Creams

Foams and creams alone have a high failure rate because the foam is generally not placed back far enough in the vagina against the cervix and squirts out of the vagina during penile penetration. Teach the adolescent how properly to insert the foam into the vagina and to reapply it before each intercourse. Have an extra supply available; strongly encourage the combination of condom and foam during her midcycle.

G. Withdrawal

Withdrawal is one of the most common forms of contraception used by the adolescent couple. Ejaculation outside the vagina on the external organs such as the clitoris, labia and thigh is thought to be safe, but sperm may spill into the vagina and migrate to the cervix. Withdrawal generally leads to male frustration, prolongation of the time the penis is inserted into the vagina, and then total ejaculation in the vagina.

H. Rhythm

Rhythm is only effective if the female is taking accurate basal body temperature. This is generally impossible for the active adolescent. If temperature charts are not being used, then unprotected intercourse is only safe during the menses.

I. Alternative Sexual Practices

Complete contraceptive information should include alternative sexual practices. Foreplay for the sheer pleasure of lovemaking without vaginal penetration is not dangerous to the body. No one has gotten pregnant from masturbation, mutual masturbation, fellatio, cunnilingus, or abstinence.

J. Abortion

Therapeutic abortion is not a form of contraception. It is a means of terminating an unwanted pregnancy.

V. CONCLUSION

There is no cure for the problems associated with adolescence but the passage of time. Our common response to adolescents with problems is to implore them to "grow up." Teenagers mature into adults by working their way through their physical, sexual, emotional, and intellectual changes. Ideally, they should be able to make sexual decisions by choice and not by chance. Our medical responsibility is to provide them with medically safe, socially relevant choices, and the information with which to make these choices.

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HORMONAL CONTRACEPTIVES IN FERTILITY CONTROL PROGRAMS

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I. INTRODUCTION

Two of the most profound social changes of the last 20 years have been the increasingly more effective regulation of fertility and the widespread movements for altering the roles and status of women. To judge by the evidence presented at recent United Nations conferences in Bucharest and Mexico City, both trends know no national or class boundaries, though there remain important national differences in the extent to which these trends have been developed. Both trends, moreover, interact with each other, both as cause and as effect, as more women recognize the centrality of fertility and its control in their lives, and as the importance of women's aspirations for different roles on their desire to control fertility is increasingly understood. Both of these processes have been facilitated in the last 15 years by the emergence of a new contraceptive technology, based primarily on the oral contraceptive. The principal characteristics of this new technology are that the new methods are highly efficient in preventing conception and can be applied at a time unrelated to sexual intercourse. In the U.S. and other industrialized nations, this technology has led to what has been characterized as the "contraceptive revolution," while in developing countries, it has made possible a rate of adoption of contraception that is historically unprecedented.

II. IMPACT OF THE PILL

A. Fertility Control Programs in the U.S.

The role of oral contraceptives in fertility control programs is a subset of the larger question of the impact of technological change on policy change and behavioral change. Based on my experience in Planned Parenthood from 1954 to the present, I can conclude that the advent of the oral contraceptive in 1960 (followed three years later by modern intrauterine devices) was an essential precondition for the emergence of a national family planning program in the U.S. and for the development of a conscious national effort to eliminate class differentials in fertility control practice. A national program for the U.S. could not have been seriously proposed, much less implemented, based on traditional contraceptive methods.

B. Fertility Control Programs in Other Countries

The 1950s was perhaps most aptly characterized by Dr. Abraham Stone's futile mission to India to teach the rhythm method by using a string of beads with which to count off the days of the menstrual cycle; the story had such enormous charm that even now it occasionally is resurrected by the media for human interest purposes. However charming, the story also demonstrated unequivocally the ineffectuality of the armamentarium available at that time with which to attempt to reduce fertility levels. It is no accident that of 66 nations that have adopted official policies to reduce population growth or to provide support for family planning programs, all but one adopted the policy or initiated the program *after* the new technology began to become available in 1960. The limitations of conventional contraceptive methods had previously been so extreme as to discourage many health and government leaders from undertaking programs, no matter how concerned they were to reduce fertility levels. The new technology for the first time made it possible to give serious consideration to large scale programs. Finkle (1971) documented this factor in his study of the development of national programs in India and Pakistan. Berelson (1969), reviewing the efforts in developing countries as a whole, found that the new technology, "by giving national programs some hope of success . . . stimulated a wholly new level of effort, improved the morale of family planning workers from the top down and most importantly, brought about the development of family planning organizations in a form and magnitude not previously known." By the early 1970s, the pill and the IUD had become the predominant methods used by new acceptors in all but 7 of 44 national programs in Asia, Africa, and Latin America for which data were available (Nortman, 1974), and apparently are major methods employed in the successful program in the People's Republic of China.

These are basic trends. Their interpretation is subject to dispute, depending

on one's ideology and purpose. Some vocal critics of the pill see in these trends only a massive conspiracy by the "population controllers," in league with the doctors and the pharmaceutical companies, to foist noxious agents on millions of unsuspecting women. Since these trends have involved tens of millions of women in many countries, it is more reasonable, I believe, to view them as reflecting the fact that the oral contraceptives met—and continue to meet—more of the needs of women and their partners than any other available form of fertility control. It will be useful, in this context, to sketch briefly some of the principal patterns of fertility control practice in the U.S. in the 1950s, so that the changes brought about by the pill can be seen more clearly.

C. Socioeconomic Patterns of Contraceptive Practice in the U.S.

In the 1950s, birth control was regarded as a settled issue in the U.S. for most of the middle and upper classes. Many could and did utilize the diaphragm and the condom, then the most effective methods, with some degree of success to limit family size; there were accidents, to be sure, and there was believed to be a large number of illegal abortions. But on the surface, it appeared that fertility control was no longer a serious problem for these classes. It must be pointed out here that the criterion used in these assessments was a very narrow one, namely, success in having more or less the number of children desired. Omitted entirely were more elusive criteria, such as the effect of the contraceptive employed on the quality of and satisfaction with sexual relations. To this day, we have no adequate measures of this dimension of the contraceptive experience.

In the 1950s, birth control was not seen as a settled issue for low-income persons, who continued to have higher rates of fertility—and of unwanted childbearing—than higher-income persons. The fertility studies of that period showed that twice as many low-income couples used no form of contraception as higher-income couples, and those low-income persons who did use contraception relied more heavily on such methods as douching. The proportion of couples using the diaphragm was twice as great among higher-income wives than among low-income wives. These findings confirmed the daily experience in Planned Parenthood clinics, which showed that the method of choice at that time, the diaphragm, was unsuitable for many of the low-income women who constituted the clinics' clientele. Many of the professional elites associated with the family planning movement concluded from these patterns that poor couples were not "motivated" to limit family size. These questions led Planned Parenthood to finance exploratory social research by Rainwater (1960) to study fertility values and practices of low-income persons. To the surprise of some, the studies showed that low-income couples had considerable motivation to limit family size. As Rainwater summed it up, "on the whole it is clear that working class people have a real interest in family planning and limitation." The studies also showed that low-income couples had a good deal of experience, most of it

unsuccessful, in trying different contraceptive methods, as well as a great deal of misinformation about contraception. As one of the respondents put it, "I've heard about lots of ways [to prevent conception] but I don't know if they are any good." (Rainwater, 1965). Perhaps the most important finding was that the life circumstances and sexual patterns of low-income couples made it difficult for them to adapt to the requirements of existing coitally related methods, particularly the diaphragm.

Rainwater's first study was done several years before oral contraceptives were marketed in 1960. It is of some interest to recall his conclusion at that time regarding the potential impact of the pill on low-income contraceptive practices:

From the responses of men and women in our sample, we doubt that the oral contraceptive now being publicized will prove widely successful among this group... There will be a number of women who will fear its possibly "poisonous" effects, just as many working class people are reluctant to take potent drugs and will do so voluntarily only when they feel desperately ill. More basic than this is the difficulty raised by having to take a pill every day. These people find it difficult to plan consistently or to follow routines that do not seem "natural." It is unlikely that many women in the working class... will follow a strict daily pill-taking regimen. (Rainwater, 1960, p. 171).

In fairness to Rainwater, it should be noted that in his second study, based on interviews in 1961, he revised this assessment substantially (Rainwater, 1965). His earlier conclusions fit almost exactly the prevailing class biases among physicians and other family planning professionals, and these attitudes led Planned Parenthood to make almost no preparations for changes in clinic programs following introduction of the pill. Despite the fact that the pill in its first formulations was expensive and the clinics could not subsidize its distribution, clinic caseloads, composed primarily of low-income women, tripled between 1960 and 1965. The unprepared organization found it difficult to keep up with very rapid growth. The principal change underlying this growth was the introduction of the pill, since the clinics did not in those days receive public funds to open up new sites, add clinic sessions, or undertake extensive outreach or educational efforts. It seemed clear to many of us who observed this process that the pill, as a coitally independent contraceptive method, met many basic needs of low-income persons that had not been met by conventional methods. In contrast to the conventional methods, the pill did not require manipulation of the genitals and it could be taken at a time unrelated to intercourse. These factors also made it easier to talk about the pill than it had been to talk about genitalily related methods. Information about the pill's effectiveness and its ease of use began to be spread by satisfied users in low-income communities, replacing the misinformation and stories about failure with conventional methods that Rainwater's studies had tapped in the late 1950s. These informal channels of communication became the principal means of recruitment of new patients. In the face of these evident advantages, the difficulties middle class professionals expected low-income women to have in taking a pill daily for 20 days a month seemed to vanish.

In a basic sense, this clinical experience provided the final evidence needed for a serious effort to change U.S. public policy and develop a national program. The fertility studies had shown conclusively that couples in all class and ethnic groups wanted small-to-moderate sized families, approved of fertility regulation, and had tried to control fertility with one or another traditional method. But low-income couples, who relied disproportionately on less effective nonmedical methods of contraception, had a greater incidence of unwanted and mistimed fertility. These studies demonstrated that the motivational base existed for a national effort to assist low-income persons to improve their fertility control practices. The experience in Planned Parenthood clinics between 1960 and 1965 demonstrated that a fertility control technology to sustain such an effort, based primarily on the pill and the IUD, also existed and would elicit a significant response from low-income persons if it were made available. Thus, when an affirmative federal policy on family planning emerged in 1965 and 1966, the new policy was not only sociologically valid and politically acceptable, but technologically feasible as well.

The results of that policy change are found in the growth of publicly supported family planning clinics and in changes in the contraceptive practices and fertility rates of low-income persons. By 1975, nearly 4 million low- and marginal-income women were enrolled as clinic patients, with 72% choosing oral contraceptives (Alan Guttmacher Institute, 1976). By 1973, the proportion of women in lower socioeconomic groups using pills was approximately equal to the proportion in higher socioeconomic groups, as were the proportions using pills, IUDs, and male and female sterilization, the most effective methods currently known (Ford, 1976). (This is perhaps the first time that the poor have shared the services of the U.S. medical system equally with higher-income persons.) Within the overall decline in U.S. fertility in the last decade, the decline has been greatest among the poor, the least educated, and minority groups that had previously experienced the highest rates of unwanted child-bearing. And as the results of the 1976 Johns Hopkins teenage study show, the proportion of sexually active unmarried teenagers using the pill more than doubled between 1971 and 1976 (Zelnik and Kantner, 1977). In most communities it was very difficult for unmarried teenagers to obtain medical contraception before 1969 and in some communities it is still difficult. Nevertheless, the rate of adoption of the pill by teenagers in the first half of the 1970s was more rapid than among married women a decade earlier. This is a remarkable change attesting to the motivation of teenagers to avoid early pregnancy and foreshadowing an increasing degree of control of pregnancy among teenagers within the next decade.

III. RISKS AND BENEFITS OF THE PILL

From all this we may conclude that the introduction of the pill, a technological innovation, has brought about significant changes in contraceptive

TABLE I. Women Using Oral Contraceptives Currently or At Last Intercourse,
Selected Years 1965-1975 (%)^{a, b}

Subgroup	1976	1975	1973	1971	1970	1965
White married women aged 15-44 (current method)	NA	27.1	25.9	NA	23.9	18.9
Black married women aged 15-44 (current method)	NA	NA	26.3	NA	22.1	12.4
White sexually active unmarried women aged 15-19 (method) at last intercourse	30.4	NA	NA	13.4	NA	NA
Black sexually active unmarried women aged 15-19 (method) at last intercourse	35.3	NA	NA	13.6	NA	NA

^a Sources: White married women, Westoff and Jones (1977, Table 1); Black married women, Westoff (1976, Table 1); unmarried women 15-19, Zelnik and Kantner (1977, Table 12).

^b NA, not available.

practices and in fertility levels in *all* socioeconomic and ethnic groups. The results are extraordinary considering the fact that news stories about health risks associated with the pill began in 1962 and have been published almost continuously since 1969. In fact, the pill has been subject to more intensive evaluation of risks than any other drug, and there have been more stories in the media questioning its safety than any other commonly used medication. Yet the number of women using the pill continued to increase at least until 1975 (Table I).

We do not need a conspiracy theory to explain this phenomenon affecting millions of persons. The more direct explanation is also the more plausible. The pill has two attributes that differentiate it sharply from other methods and both meet basic needs of many sexually active persons that no other method meets as well:

First, the pill is the most effective method of preventing pregnancy currently available. As Ryder (1973) has shown, the standardized 12-month failure rate for IUDs is twice as high as the pill, the rate for condoms is three times as high, the rate for diaphragms is four times as high, and the rate for foam, rhythm, and douche are more than five times as high.

Second, because the pill is coitally independent, it makes possible a greater

degree of freedom and spontaneity in sexual relationships than methods that need to be applied at the time of intercourse. The pill was first adopted in the 1960s by younger couples, who have higher rates of coital frequency than older couples. But older persons were not far behind. Even in 1965, pill users in all age groups had higher monthly rates of coital frequency than users of other methods.

These factors are important not only for analytic purposes but also because they suggest several of the key criteria with which to evaluate any new methods that may be developed. They also suggest that the evaluation framework that has been utilized thus far and has kept the pill in the headlines for years is highly selective and does not reflect adequately the needs and purposes of persons who use contraception. The framework for almost all of the published articles and news stories about the pill is a framework for comparing medical risks and medical risks alone. Those risks should not be ignored, and accurate information about them should be widely disseminated. But medical risk does not take into account two other aspects of the contraceptive experience that people evidently find salient: efficacy in preventing unwanted pregnancy and facilitation of a more satisfactory sexual relationship. Accurate information about these factors should also be widely disseminated. In the last 15 years in the U.S., we have seen conclusive evidence that low-income persons share these values with the more affluent.

The medical risk framework carries with it an implicit assumption that other methods of contraception could be substituted for the pill, thus rendering the risks from the pill unnecessary. This assumption is true for some persons, but not for all. It is a particularly class-bound assumption, which ignores the difficulties low-income women had with traditional contraceptives before the advent of the pill and their quite different experience with it subsequently. Those who advocate replacing the pill with the diaphragm, the condom, or other coitally related methods may be speaking for themselves, but on the record of the last 15 years, they are not addressing the needs of the bulk of low-income women in the U.S. They have every right to make that choice for themselves, but they should be careful to avoid imposing their values on others.

Even within the narrow framework of medical risks, Tietze and his colleagues (1976, 1977) have shown that except for older women who smoke, the known risk of mortality from using any method of fertility control, including the pill, is low—lower than the risk of death from automobile accidents or from childbirth. For smokers over 40, use of the pill carries an almost three times higher risk than that which would be expected from childbirth and much higher risk than all other methods. For nonsmokers over 40, the risk from the pill, while higher than other methods, is still relatively low and lower than from childbirth.

If all married users under age 40 abandoned the pill and used no other method except abortion, there would be millions of additional abortions. If they substituted instead the diaphragm or other traditional methods, there would be additional abortions, possibly doubling the 1976 U.S. total. It does not seem

realistic to expect that many women now using the pill will choose these alternatives or that our society is prepared at this time to make available that many additional abortions (Tietze *et al.*, 1976).

IV. CHALLENGE TO RESEARCH

We need a more comprehensive framework for weighing the total benefits against the total risks of any particular method. We also need methods that have fewer risks than the pill. It is now 17 years since the pill was first marketed, 15 since the first report on the pill's association with thromboembolism, 8 since Senator Nelson made headlines with the pill, and at least 5 since the health risks of the pill became a principal concern of many health and women's groups. During that period our government's investment in the search for new contraceptives reached a peak of 2.2% of total governmental expenditures for medical research in 1973, and declined in 1974 to 1.7% (Greep *et al.*, 1976, Table 11.9). During that period, there have been thousands of columns in newspapers and magazines and hundreds of hours of Congressional testimony about the risks of the pill from women's and health groups. Yet, there has been almost no demand for an expanded research program expressed in either the testimony or the media stories. The omission is persistent, and puzzling. It seems evident to me that responsible concern over the safety of the pill must be coupled with concerted support for research to discover suitable alternatives. It is time for all of us to demand a high-priority research program that is capable of producing contraceptive methods that are safe and practical for human beings in the last quarter of the 20th century.

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GONADAL HORMONES AND HUMAN BEHAVIOR

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I. INTRODUCTION

Among popular medical beliefs is a collection of tales about hormones and their effects on human behavior. Premenstrual tension is believed to be caused by "raging hormones." Old age in males and females supposedly entails the disappearance of sexuality because of the decline in hormone levels, and a 70-year-old who copulates is a dirty old man or woman. "Machismo" is thought to be dependent on the male hormone testosterone. Homosexuality is supposedly caused by hormonal imbalance. Gender identity—one's affiliation with her/his sex—is believed to be controlled by hormone levels. These beliefs—to distinguish them from other outright superstitious fallacies—are shared by large segments both of the intelligent lay public and of the medical profession.

Unfortunately (or perhaps fortunately), careful examination of the available data will show that we have reliable evidence only to establish one important principle about the relationship between hormones and human sexuality. That is, androgens are very important for the expression of male sexual behavior. All the rest is a mixture of conjecture, prejudice, clinical impressions, speculation, extrapolation from findings on animals, and conclusions based on inadequate

data. In this chapter I shall discuss our present knowledge about human behavioral endocrinology, particularly as it relates to sex differences, and point out the large amount of information that we still need to acquire. It is hoped that in the near future government and other research funding agencies will more readily support studies on the role of hormones in human sexuality.

II. THE MALE

In rats, as in all other vertebrate species that have been studied, castration sooner or later results in the disappearance of mating behavior, and replacement with testosterone or certain other androgens will maintain or restore the behavior. Now it turns out that this is one of the few situations where there is a clear-cut evolutionary continuity between hormonal effects on behavior in animals and in the human species. In a study still in progress on treatment of hypogonadal human adults with testosterone enanthate (the first double blind study of its kind), we found the following: as blood testosterone levels rose and fell with time after each injection, there followed, with some delay, a parallel rise and fall in some parameters of sexuality (Davidson, J. M., Camargo, C., Smith, E. R., and McNeil, M., unpublished data). We have looked at a variety of measures, including spontaneous sexual feelings and erections, sexual activity—autoerotic or heterosexual, nocturnal erections, and orgasms from different sources. The particular measures affected by testosterone treatment differed in the different men, which is to be expected in view of their different personalities, relationships, and life circumstances. However, each individual showed some effect, and the effects varied with the dose. Figure 1 shows data from two men: total number of erections from whatever cause are plotted against the level of testosterone in the blood. The relationship between the behavior and the hormone is clear; the delay for behavioral effects is probably about a week and there is a definite quantitative relationship between dose and effect. All of this corresponds to findings in animals (Davidson, 1972).

These findings do not imply, however, that the levels of testosterone in blood of normal males are correlated with the amount or quality of sexual behavior or experience. In fact, we could find no such correlations in normal populations of rats and others have found none in human males (Monti *et al.*, 1977). It also does not mean that homosexuals have low levels of androgen; the balance of evidence to date is clearly against that (Tourney *et al.*, 1975). It does not mean that sexual offenders should automatically be treated with antiandrogens. The use of cyproterone in Europe for this purpose is based on inadequate research to date, apart from possible questions of ethics. Likewise, testosterone treatment should not be regarded as a solution to most problems of hyposexuality. In fact, low testosterone levels may well be consistent with enjoyment of sexual activity. However, testosterone does have powerful influences and should be used to help

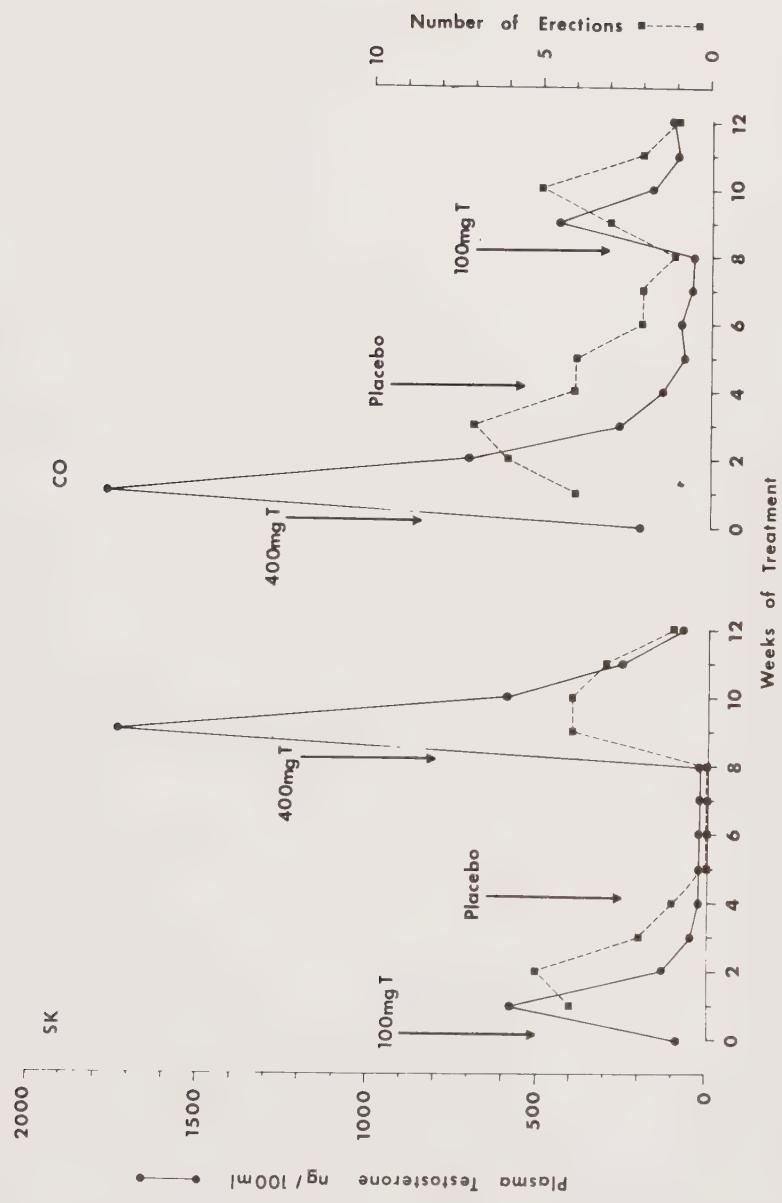


Fig. 1. Blood testosterone levels and total reported erections, from all causes, in two hypogonadal males treated (double blind) with 100 or 400 mg testosterone enanthate or a placebo. Treatments given once every four weeks.

androgen-deprived males to restore their impaired sexuality, along with counseling or other psychological treatment.

III. THE FEMALE

A. Cyclicity and Behavior

And now for something completely different. With the evolution of the human species, a surprising change is found from the absolute dependence of the subprimate female's sexual behavior on estrogen and progesterone and the relative dependence of primate females. The usual expression among behavioral endocrinologists is that women have become "emancipated" from dependence on estrogen and progesterone. The term evokes themes of liberation, but it is appropriate in light of the capacity of the human female to continue an apparently normal sex life after removal of her ovaries or their postmenopausal atrophy. Yet there are a multitude of reports about variations in women's sexuality throughout the menstrual cycle and about effects of contraceptive pills on libido. Are there indeed effects of ovarian hormones more subtle than the dramatic shifts encountered in the male following castration and replacement therapy? Is it possible that postmenopausal and ovariectomized women may somehow compensate for the loss of hormones, but the hormonal fluctuations in intact cycling women still may have significant effects?

The literature on cyclicity of sexual behavior in women can be used to provide support for anyone's pet hypothesis about the relationship between hormones and female sexual activity or experience. Peaks have been reported at midcycle, and before, after, and during menstruation, and there are studies that report no significant variation. The best-known study (Udry and Morris, 1968) showed a major peak in coital and orgasmic frequency at midcycle, a lesser premenstrual peak, and a trough during the luteal phase. These results have been used (in combination with other data on effects of contraceptive progestational agents and rhesus monkeys experiments) to support the notion that progesterone may suppress sexual activity in the female via an aversive olfactory stimulus from the progestin-treated woman to her (male) sexual partner (Udry *et al.*, 1973). The force of this highly speculative notion has been somewhat decreased by the recent report of Goldfoot *et al.* (1976), who could not replicate Michael's findings on pheromonal (chemical) signals from the rhesus monkey's vaginal secretions functioning as sex attractants. Furthermore, the findings of Udry and Morris (1968) have been reanalyzed to show that their data actually demonstrated a postmenstrual rather than a midcycle peak (James, 1971). The only clear-cut conclusions one can arrive at from surveying this literature are (a) the studies show a multitude of methodological inadequacies, and (b) there are all kinds of nonhormonal common-sense explanations for the different patterns of cyclic variations in women, such as abstinence during menstruation, or desire to avoid or to have sexual activity close to ovulation.

B. Premenstrual Behavior

The literature on menstrual cyclic fluctuations in nonsexual behavior and experience is hardly more enlightening as to the actions of ovarian hormones. In this case, however, at least we are dealing with a real phenomenon (and one that may be related to reported effects on differences in sexual behavior throughout the cycle). Depending on the method of evaluation, 15-95% of American women can be regarded as showing the "premenstrual syndrome" (Paige, 1973). The correct figure is probably closer to the higher estimate, but however it is figured, the percentage represents far too large an amount of suffering to be passed over lightly.

The evidence of premenstrual symptoms has been used historically to excuse women from certain responsibilities, as well as to discriminate against them in the allocation of positions of societal status. It is not often admitted in this context that many men also go through periods of anxiety and depression, but these episodes are less predictable than premenstrual tension. It should be pointed out, anyway, that there is no evidence that the overall performance of women on the job is impaired by premenstrual symptomatology. Furthermore, though crime, accident, and suicide rates are higher in women in the premenstruum, they are still lower than those seen in the noncycling male (Tavris and Offir, 1977).

The cause of premenstrual tension, as of postpartum depression, could be decreased estrogen or progesterone or the preceding peaks in either or both types of hormone. In the growing literature on this subject, many careful measurements of hormone levels in combination with careful psychological evaluations are not yet available. Thus replicated findings are rare and we cannot derive clear-cut conclusions. Yet several recent studies have reported correlations between elevated estrogen and/or progesterone levels and general psychologic symptoms (Backstrom and Mattson, 1975) and migraine headaches (Epstein *et al.*, 1975). Behavioral endocrinologists have demonstrated that androgen acts on the brains of rats and several bird species to directly influence sexual and other behavior, and there is similar evidence for estrogen and progesterone in various animal species. This mechanism is often assumed also to apply to ovarian hormones in women, but this is still highly debatable.

Among the reasonable alternative interpretations of premenstrual tension are some that, while retaining the idea that hormones are responsible, postulate that they act extracerebrally, via production of various bodily effects. It is often thought that physical discomfort from water retention is responsible. Though ovarian hormones are known to affect water and electrolyte balance, probably by influencing secretion of the adrenal hormone, aldosterone (see DeMarchi, 1976), several studies have failed to find correlations between cyclic physiologic symptoms and the manifestations of water retention, e.g., feelings of swelling (Moos *et al.*, 1969; Backstrom and Mattson, 1975).

Physiological effects other than fluid retention may be involved in the development of premenstrual tension, including hormonal effects on such important behavior-influencing enzymes as monoamine oxidase (Klaiber *et al.*, 1972). But whether hormones are indirectly involved or not, serious consideration must be given to the possibility that the major determinants of the premenstrual syndrome are psychological, if only because in some societies women do not seem to experience it (Paige and Paige, 1978). In this context, anxiety about menstruation or more covert forms of conditioning of psychological to physiological events may be involved. In one of the most striking studies, hysterectomized women with intact ovaries (and therefore normal hormonal cycles) did not show cycles of premenstrual symptomatology (Beumont *et al.*, 1975). However, only a small number of women were studied and there were no data as to whether these subjects had premenstrual tension before hysterectomy, so that this study needs to be replicated. The conclusions were that the expectation of menstruation is responsible for the symptoms. Application of this idea to women in general seems questionable, since some have premenstrual tension at times when they are not aware of their position in the cycle, but they may be responding to subconscious physiological cues. Another interpretation of the findings of Beumont *et al.* is that the presence of the uterus has behavioral effects due to unknown mechanisms. These could be related to findings in various animal species that hysterectomy prolongs luteal function, thereby affecting hormone production.

Finally, it is important to emphasize that to expect a purely psychological or purely physiological origin of these problems is to ignore the inextricable and pervasive nature of the psychophysical interactions that underlie all human behavior. Research should be pursued in an emotionally neutral atmosphere without any imputations of value to either psychologic or physiologic interpretations.

IV. HORMONES AND THE SEXUAL DIFFERENTIATION OF BEHAVIOR

Another view of the role of hormones in human behavior, growing out of a formidable body of animal research, is widely debated today. Sexuality and sexually differentiated behaviors are believed by many scientists to depend not on hormonal action in the adult, but rather on whether the brain is exposed to androgen at critical periods in embryonic development. This "organizational" effect of androgenic hormones, well demonstrated in animals, is presumed to fix the brain structurally and/or functionally in a male or female direction. We are even beginning to see small anatomical differences between male and female brains of animals, which may be related to such effects (Raisman and Field, 1973; Greenough *et al.*, 1977; Gorski *et al.*, 1977).

The major support for extrapolation of these findings from animals to humans comes from the work of Money and Ehrhardt (1972). They found that prenatal

exposure of girls to androgen, resulting from disease or medication, had the effect of masculinizing certain aspects of the female behavior, particularly "maternalism" and the more aggressive forms of play. Although alternative interpretations for the data are available, they did find significant effects on non-sexual gender identity-related behaviors. However, there were no significant changes in the sexual behavior of these girls during development or after reaching young adulthood.

In fact, it makes little sense to look for early androgen effects on differentiation of human sexual behavior, since, unlike male and female animals that have very different mating patterns, we are realizing more and more that human male and female sexual behavior does not differ very much. Masters and Johnson (1966) demonstrated clearly that the physiological aspects of the sexual response are very similar in both sexes, at least in terms of the changes in myotonia and vasocongestion that they studied. Erection has its parallels in women in clitoral erection and pelvic vasocongestion. Other sex differences in the arousal value of visual and other exteroceptive stimuli, sexual fantasy, incidence of masturbation, etc., seem to be disappearing or at least diminishing (Schmidt and Sigusch, 1973), since the earlier studies reported by Kinsey *et al.* (1953). Thus these differences are probably largely culturally rather than biologically conditioned.

Among the major remaining differences in sexual behavior between the sexes are those related to orgasm: particularly multiorgasmia without loss of arousal in many women. But we are beginning to hear reports that multiorgasmic males exist, though they are rare, and perhaps many men can be trained to achieve this capacity as they learn to delay ejaculation in the face of intense genital stimulation.

If then males and females are not basically different in their sexuality, how could such similar behaviors have such different biologic determinants, only males appearing to require hormones in adulthood? Is it, however, possible that the hormonal requirement is in fact similar for adults of the two sexes, both requiring androgen? The view that adrenal androgen is the libido hormone in the human female is held by many clinicians and some scientists. Unfortunately the evidence is poor. It comes from reports on women ovariectomized and/or adrenalectomized for malignancies and from treatment of anorgasmic women with large doses of testosterone. But there are other suggestive indications: Human females do experience a major growth in sexuality at the time of puberty, and we know that adrenal androgens do increase at that time, having important morphological effects such as growth of pubic and axillary hair. The lack of scientifically sound comprehensive studies again points up the need for government encouragement and support of research in this difficult and sensitive area.

V. IS BIOLOGY DESTINY?

Thus we see that, regarding the role of hormones in human sexual behavior, a sizable mythology coexists with a minute assemblage of established facts. The

tremendous success of molecular biology in recent times has engendered great hopes for biomedical solutions to human problems. But how can one believe in the simplistic view that by understanding biology we shall automatically learn to understand all human behavior? The important dimension of human sexuality is the nature of personal experience, which is not accessible to the methodology of laboratory science. Biological processes, behavior, and experience are engaged in a mutually interactive transactional system in which each component influences all the others. Understanding sexuality and sex differences involves understanding the sexual scripts by which people live (Simon, 1973) and their relationship to biology.

Biological factors themselves should be viewed not as determinants, but as constraints that can be overcome. The paraplegic who learns to enjoy sex is an example of the transcendence of the biologic constraints on sexuality. So are those rare individuals who can fantasy to orgasm. In this context, the biological differences in sexuality between the sexes appear to be only small constraints on the working out of mutual sexual problems. In this as in other areas of human behavior, however, the extent to which biological factors are important need not be regarded as preordained. Not only does each individual have her or his own bisexual script, but if he or she is not satisfied there is the possibility of creating a new one. To paraphrase John Lilly (1973), what one wishes to experience one can experience, within limits to be found experimentally or experientially. These limits are further beliefs to be transcended.

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EPILOGUE

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The message in this book is sent out to three types of people in particular: (1) medical and health-related professionals who prescribe the use of sex steroid hormones for contraception and/or estrogens for relief of menopausal symptoms, (2) scientists who investigate sex steroid hormones and seek contraceptive agents, and (3) the women who might use these hormones and the men who are concerned that they do.

To health professionals, the appeal is to confront the risks associated with the use of these hormones and not to minimize the potential importance of these risks to the women who use them. Besides careful attention to the individual's medical history, the health professional should seek an open *dialogue* on alternative contraceptives or the choices in taking replacement estrogens for menopausal symptoms. The most important but often omitted points of such a dialogue are to listen sensitively and to admit freely and willingly when knowledge is lacking. Moreover, health professionals can contribute in the development of alternative contraceptives and treatment for menopausal symptoms. They can dare to ask: What kinds of methods are now lacking for human sexual relationships? What kinds of methods would be safer than hormones? How should new contraceptives be tested for safety?

To research scientists, the appeal is to give more than lip-service to social needs in developing research goals. Only recently have basic scientific researchers begun to search for the relevance of their scientific interests. One strategic goal of biomedical science should be to seek knowledge for the improvement of health. There are many scientists with the tools and ability to investigate reproductive processes for alternatives to contraception and menopausal estrogen therapy. If only one of the multiple projects each investigator undertakes were directed to such aims, great insight into these problems might be gained. Why does only one follicle ovulate? How does that follicle ovulate? What keeps the other follicles from developing? What could prevent fertilization? Implantation? How can sperm be incapacitated? An added challenge to the researcher is to determine if treatment with systemic hormones or daily drugs might be avoided altogether. What kinds of methods are safer than hormones or systemic drugs?

Finally, to the women who might use the hormones, there is a need to educate and to communicate. More women must become confident in their understanding of their own basic physiology, anatomy, health, and diseases, confident enough to ask questions and to question the answers they receive. This does not require a lot of technical information, but does thrive on the ability to ask questions until the existing available information is understood. Each woman is the ultimate protector of her own health, for only she can know all about herself. Women must learn how to get the advice and counsel that is responsive to their particular needs. Furthermore, women must communicate not just with women, but with doctors, health agencies, and scientists. Ways must be found to direct the development of future contraceptives and alternatives to estrogens that are safe, effective, and appealing to use. Men who care must be heard, too, so that they may also have a choice and share in the responsibility of contraception and the welfare of themselves, their partners, and their offspring.

GLOSSARY

acrosomes: subcellular structures in sperm cells modified from the Golgi apparatus

adenocarcinoma: malignant tumor originating in glandular epithelium

adrenalectomized: removal of the adrenal glands

aldosterone: steroid hormone produced by the adrenal, active in regulating the salt and water balance in the body

amenorrhea: absence or suppression of menstruation from any cause other than pregnancy or the menopause

ampulla: dilated portion of oviduct between the isthmus and the funnel-shaped opening

androgen: sex steroid hormone (such as androstenedione or testosterone) produced especially in the testes, but also in the ovary and male or female adrenal cortex and usually characterized by its ability to stimulate the development of sex characteristics in the male; also: a synthetic compound such as methyltestosterone having similar biological activity

anorgasmic women: women who do not experience an orgasm

anovulation: inability to release an egg from the ovary

antispermatic compounds: compounds that act against sperm

antral cavity: fluid-filled cavity in developing ovarian follicles

atresia: death of an ovarian follicle

atypia: abnormality, irregularity

autoimmune disease: self-destructive disease due to malfunction of the immune system

basement membrane: membrane beneath endo- and epithelial cells

blood-testis barrier: myoid layer between germ cells and the blood vessels

bursa: saclike structure

cervix (cervix uteri): narrow, lower end of the uterus

cholesterol: steroid found in all animal fats and oils, in bile, blood, brain, milk, yolk of egg, etc.

chromatin: nuclear material carrying the genes for inheritance

collagenases: enzymes that break up collagen, part of connective tissue

corpus luteum: reddish yellow area of hormone-producing tissue that develops from the Graafian follicle on the ovary after release of the egg (ovulation)

cuboidal cells: cube-shaped epithelial cells

depolymerization: breakdown of a compound into similar, simpler molecules

desoxycorticosterone: steroid hormone extracted from the adrenal cortex and active in regulating the salt and water balance in the body

desquamation: peeling off of cells in the form of scales

dysmenorrhea: painful menstruation

embolization: obstruction (as of a blood vessel)

endoderm: germ layer in the embryo that gives rise to epithelia in pharynx, respiratory tract, digestive tract, bladder, and urethra

endometrium: mucous membrane lining the uterus

- endoplasmic reticulum*: subcellular cytoplasmic system of tubules fashioned from unit membrane
- enzyme*: catalytic proteinaceous substances produced by living cells
- epididymis*: highly coiled duct, 4–5 m in length, which leads from the testes to the ductus deferens
- epithelium*: tissue covering external and internal surfaces of the body
- estradiol-17 β* : naturally occurring estrogenic steroid
- estrogen*: sex steroid hormone (such as estradiol, estriol, estrone) produced especially in the ovaries and usually characterized by its ability to promote ovulation as well as the stimulation of secondary sex characteristics in the female
- extracerebral*: outside the cerebral hemispheres
- exteroceptive stimuli*: stimuli coming from outside the body
- feedback*: return to the input of part of the output of a system
- fimbria*: fingerlike projections on the free margin of the oviduct adjacent to the ovary
- flagellation*: whiplike process of movement of cellular extensions
- follicle (Graafian follicle)*: vesicle in the ovary enclosing a developing egg
- FSH (follicle-stimulating hormone)*: hormone of protein and carbohydrate produced by the anterior pituitary that can stimulate growth of ovarian follicles in the female and stimulate the sperm-forming cells in the male
- genome*: one haploid set of chromosomes with the genes they contain
- germinal epithelium*: cell layer that produces germ cells in the embryo
- glycoproteins*: compounds of protein and carbohydrate groups
- GnRH (gonadotropin releasing hormone)*: peptide hormone produced in cells of the brain that can stimulate the release of FSH and LH by the anterior pituitary
- gonadal dysgenesis*: failure of the gonads to develop
- gonadal ridges*: cell areas in the embryo from which gonads develop
- gonadotropins*: hormones that stimulate the gonads
- granulosa cells*: cells that surround the developing egg
- gynecomastia*: excessive development of male mammary glands, even to a functional state
- hirsutism*: excessive growth of hair of normal or abnormal distribution
- hyaluronic acid*: cementing substance in tissues
- hydrogel*: gel that has water as its dispersion medium
- hypertension*: abnormally high arterial blood pressure
- hyperplasia*: abnormal or unusual increase in the number of cells of a tissue
- hypothalamus*: part of the diencephalon of the forebrain forming the floor and walls of the third ventricle
- infarction*: production of an area of coagulation necrosis in a tissue resulting from an obstruction of the local circulation
- inhibin*: water-soluble hormone secreted by the testes that is supposed to restrain the stimulating effect of the pituitary upon the seminiferous tubules of the testes
- interstitial cells (Leydig cells)*: cells in the testes that produce testosterone
- isthmus*: contracted part or passage connecting two larger structures or cavities
- LH (luteinizing hormone)*: same as interstitial cell-stimulating hormone (ICSH); a hormone of protein and carbohydrate produced by the anterior pituitary and which in the female stimulates the development of corpora lutea and in the male the development of the interstitial cells
- libido*: sexual desire
- luteal function*: functions of the corpus luteum
- luteal phase*: period in the menstrual cycle after ovulation when the corpus luteum predominates

- meiosis:* cell division during which each daughter cell receives half the number of chromosomes in the parent cell
- menarche:* first menstrual period of a woman's life
- menses:* menstruation, menstrual period
- mucin:* mucopolysaccharide or glycoprotein, the chief constituent of mucus
- multiparous:* (1) having borne one or more previous babies; (2) giving birth to more than one baby at a time
- mutation:* permanent transmissible change in the character of an offspring from those of its parents
- neoplasia:* cellular alterations involved in the formation of tumors and especially malignant tumors
- nulliparous:* never having borne a child
- osteoporosis:* abnormal diminution of density of bone due to failure of bone forming cells to lay down bone
- ostium:* opening into a tubular organ
- ovarectomy:* removal of ovaries
- ovulation:* to produce eggs or discharge them from an ovary
- pituitary:* hormone-producing gland attached via the infundibulum to the rest of the brain; the anterior lobe produces various hormones that influence other hormone-producing glands, directly or indirectly impinging on most basic body functions
- placenta:* organ within the uterus that establishes exchange of nutrients between the fetus and the mother
- plasmins:* enzymes with particular ability to dissolve fibrin clots
- portal vascular system:* blood vessels that loop from the hypothalamus to anterior pituitary and return to the hypothalamus
- primordial follicles:* egg cells in their earliest stages of development
- progesterone:* hormone produced by the corpus luteum whose function is to prepare the uterus for the fertilized ovum
- progestin:* name originally given to the crude hormone from the corpus luteum—now used for certain brands of synthetic progesterone
- prolactin:* glycoprotein that produces mammary development and lactation
- prostate:* walnut-sized gland in male reproductive system; surrounds male urethra and adds secretions to semen
- prostaglandins:* family of biologically active lipids found in most tissues and in high concentrations in human seminal fluid; regulates smooth muscle and exerts influences upon the implantation process
- releasing factors:* substances from the hypothalamus that stimulate the release of hormones from the pituitary
- rete testis:* portion of the duct in the male reproductive system that transports sperm from testis to epididymis
- RNA:* ribonucleic acid—a substance involved in protein synthesis in the cell
- scrotum:* outer sac or pouch that houses the testes
- semen:* thick, white secretion of the reproductive organs of the male; composed of spermatozoa in their nutrient plasma, secreted by the prostate, seminal vesicles, and various other glands
- seminal vesicles:* portion of the male reproductive system that forms part of the semen; located posterior to urinary bladder and joins with vas deferens to form ejaculatory duct
- seminiferous tubules:* tubules in the testis that produce sperm
- steroids:* group of compounds that resemble cholesterol chemically
- stigma:* bulging area on the surface of the follicle where ovulation will take place

- target tissues:* tissues acted upon by hormones secreted into the bloodstream to act elsewhere in the body
- testosterone enanthate:* male sex hormone that, when administered in oil, exerts a prolonged action
- theca interna:* steroid-secreting cells of ovarian follicles
- third ventricle:* one of the chambers filled with cerebral spinal fluid found in the forebrain
- tunica albuginea:* fibrous connective tissue covering the ovary or testes
- tunica vaginalis:* serous membrane covering the testis
- urethra:* tube leading from the urinary bladder to the exterior of the body
- vas or ductus deferens:* tube in the male reproductive system that transports sperm from the epididymis to the urethra
- zona pellucida:* translucent membrane in the ovarian follicle

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