CONTRACEPTIVE TECHNOLOGY CURRENT AND PROSPECTIVE METHODS

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Until recently, the scientific basis of most contraceptive methods was the realization that the ejaculate represents or contains the male factor responsible for fertilization. For centuries, mankind attempted to prevent pregnancy by the simple and direct procedure of withdrawing the penis prior to ejaculation; by mechanical devices such as the condom and, later, the diaphragm; by a variety of chemical spermicides introduced into the vagina; and retroactively by postcoital douching. The effectiveness, or lack of it, of these procedures depends on their success in preventing sperm from making their way to the arena of fertilization, the fallopian tubes, on the occasion of a particular coitus. Permanent blockage of sperm passage was achieved by surgical procedures on the male genital organs.

Contraceptive technology caught up with the twentieth century when scientists turned their attention to the ovulatory cycle in the female and the hormonal control of reproduction in both sexes. The principle of periodic abstinence timed to avoid coitus near the day of ovulation was the first method of fertility regulation that had as its basis a modern scientific understanding of the reproductive process. That the rhythm method has never proven to be an effective contraceptive practice does not detract from its significance in focusing upon the ovulatory process as a key event for control of fertility. It was several decades before the necessary knowledge was marshalled to develop effective means to prevent ovulation, but when that moment came, the practice of contraception was revolutionized. The era of hormonal contraception was launched and, with it, the search for different ways to

achieve the regulation of fertility by interfering with specific links in the reproductive chain of events.

Almost without exception, experimental efforts to inhibit fertility can be described as attempts to manipulate a key event in the endocrine control of reproduction. With the gradual elucidation of the normal hormonal requirements of the reproductive process, it becomes apparent that many steps in this sequence are vulnerable to controlled interference.

This report will attempt to review the pertinent studies in this area, to point out types of work needed and to project the kinds of control mechanism that could evolve from present knowledge of reproductive physiology.

DEVELOPMENTS AT STAGE OF CLINICAL EVALUATION

Surgical Sterilization

Present methods of surgical sterilization carry the prospect of irreversibility and, particularly with female sterilization, the requirement of abdominal surgery and hospitalization. Consequently, efforts are being made to develop new and simple means to interrupt or occlude the vas deferens or fallopian tube. Several investigators have achieved success in the use of culdoscopic or peritoneoscopic instruments to interrupt the human oviduct. By eliminating open surgery, these procedures obviate the need for postoperative hospitalization.

Another approach to surgical sterilization that eliminates the need for hospitalization is the trans-cervical instillation of cytotoxic or sclerosing chemicals to cause occlusion of the tubal openings into the uterine cavity. A solution of atabrine has been used successfully for this purpose. Success in 11 out of 12 cases has been reported following monthly instillations into the uterine cavity repeated three times. The investigator is now trying to evaluate the permanency of the chemically-induced tubal closure and eliminate the need for multiple instillation. Other investigators are using the transcervical approach to achieve closure of the tubes by applying a sclerosing chemical or physical treatment directly to the tubal openings. Because the tubal ostia are not readily identified, this research includes the development of new instruments required for visualization and delivery of the treatment. The fallopian tube has a remarkable capacity to recannulize following physical trauma and perhaps the same tendency to recover from chem-

ical insult will be revealed. It will, therefore, require a significant period of observation before the level and duration of effectiveness of these experimental procedures can be established.

Temporary occlusion of the fallopian tube has been attempted by the injection of a liquid silicone polymer (polydimethylsiloxane) that vulcanizes at body temperature to form a pliable plug. Until now, this experimental procedure has been attempted in only a few women scheduled for hysterosalpingectomy so that the contraceptive efficacy has never been tested in human subjects. Animal work suggests that such plugs are readily dislodged by normal tubal motility and can, in fact, be extruded intra-abdominally.

Several foreign materials have been used to cause a partial or complete occlusion of the vas deferens in the male. The insertion of a prosthetic device made of silk thread that partially occludes the vas deferens, and is anchored to its exterior surface, causes in the human male, as in animal species, either azospermia ejaculates or ejaculates containing a high percentage of disrupted spermatozoa (head-tail separation). The effect in man, however, is short-lived so that after several months, restoration of high sperm counts is not infrequent, thus rendering the procedure unacceptable for contraception. Intra-vas devices have been made that are designed to plug the vas completely, but have not been sufficiently tested to permit meaningful evaluation. These are made of polyethylene, polypropylene, silicone polymers or various metals, in shapes including cylindrical, conical, dumbbell shaped or round. The use of a microvalve that could be operated either manually or by magnetic alignment has been mentioned frequently. All of these possibilities share the problem of requiring that the devices be anchored with sufficient pressure to close the lumen of the vas, without causing a pressure necrosis that would result in damage to the organ, thus defeating the purpose of the procedure—easy sterilization.

The application of removal clips or sutures to constrict the vas, and prevent sperm passage, has the same liability, and has not proven acceptable.

Other modifications of the vaso-occlusion procedure include crushing a segment of the vas with a surgical instrument or the intravas injection of a necrotizing fluid (formalin), in each case without opening the scrotum and visualizing the vas. The risk involved in these procedures is not negligible because of the difficulty in isolating the vas deferens from the adjacent spermatic artery.

Vaginal Contraception

A plastic condom has been developed, but not yet subjected to evaluation of clinical effectiveness or acceptability. Its major advantages are ease of manufacture and unlimited shelf-life. Cost is comparable to conventional latex condoms, but could be lower in circumstances of mass quantity manufacture.

Some interest has developed in the use of a dissolving film for applying a spermicidal agent intravaginally but again there are no data to establish effectiveness. This procedure was tested on a limited basis about twenty years ago, then abandoned. Now at least two versions are being developed, using a film that is two inches square that can be either inserted manually into the vagina prior to intromission, or can be introduced atop the glans penis. It remains to be established whether the intra-vaginal distribution of spermicide is sufficiently uniform and complete to assure a high level of contraceptive effectiveness.

Intrauterine Contraception

Several modifications in intrauterine device design, size or material have been suggested. Two experimental devices are made of stainless steel and employ a spring principle in an attempt to reduce the likelihood of spontaneous expulsion. Adequate data are not yet available on the performance of these devices in comparison to those now widely used. However, the problems encountered in removing these devices, when required, have discouraged physicians from using them for their patients.

Other innovations include devices that contain a magnetic material that can deflect a galvanometer needle, a miniaturized radio transmitter or a supply of a chemical or hormonal antifertility agent that can be released gradually into the uterine lumen. Attempts are underway to replace the medium-density polyethylene now used in the manufacture of intrauterine loops with other synthetic materials, including silicone polymers; this is intended to reduce the incidence of bleeding and pain associated with the loop. Most of these are experimental designs that have either been used in only a few women, or used more generally without adequate statistical analysis of efficacy. Evaluation of the double S-shaped loop (Lippes Loop) made of a stiffer polymer than the original has revealed improvement in performance.

Studies in animals have revealed that the intrauterine placement of

certain ionic metals, such as copper, reduces fertility by the prevention of implantation. This interesting finding has been incorporated in the design of a "T"-shaped plastic device that carries a small quantity of copper. The small size of this device, compared to others in use, facilitates the insertion procedure and reduces the risk of uterine perforation or endometrial trauma. Now under clinical investigation, this device appears to have considerable promise. Continuation rates of over 90 per cent for the first year of use have been reported in independent studies in Chile and the US. Pregnancy rates of 0.5 and 1 per 100 women per year have been reported from these two studies. Significantly, the device can be used successfully in women who have never been pregnant. At least one other copper-carrying device is being studied. This, and others that are likely to emerge, will have to be evaluated independently to establish their performance statistics.

Hormonal Suppression of Ovulation

Oral preparations. Pharmaceutical firms continue to investigate different combinations or doses of synthetic progestins and synthetic estrogens in an effort to reduce side effects of antiovulant therapy, while maintaining a high degree of effectiveness. The progestogenic dose has gradually been reduced from over 9 mg in the original preparations to products with 0.5 mg. The dose of estrogen, ethinyl estradiol or its three-methyl-ether, has remained constant at around 0.1 mg, until recently when products with 0.05 mg have appeared. Data are insufficient to evaluate the comparative performance of the various dosage combinations with respect to either efficacy or minor side effects, but it has been established that the risk of thromboembolic disease is less with preparations containing 50 micrograms of estrogen. A product introduced recently contains 500 micrograms of a racemic mixture of the synthetic progestin, norgestrel, and 50 micrograms of ethinyl estradiol. Only one enantiomorph has identifiable biologic activity, so this combination is probably giving antiovulatory therapy at an effective dose of 250 micrograms of the progestin and 50 micrograms of the estrogen.

A series of steroids that are stored in adipose tissue after absorption from the gastrointestinal tract is being investigated for possible one-pill-a-month contraceptive therapy. The investigation is aimed at calibrating the oral dose of the combination that will result in a month-long release of steroid from the adipose tissue at a level that will suppress

ovulation while maintaining an acceptable endometrial bleeding pattern. Until now, the problem of unpredictable endometrial bleeding has not been resolved.

Parenteral preparations. Intramuscular injections of steroids can give a depot effect, adjusted to last a single month or for many months. A widely tested monthly injection regimen has been based on the use of an injectable estrogen-progestin combination that will "wear off" approximately 30 days after administration. For some clinical situations in which the physician wants control of drug therapy not left to the patient's responsibility, this procedure has distinct advantages, but more studies are required to establish the total pattern of safety, efficacy, side effects and reversibility.

The most widely studied compound for injectable hormonal contraception is 6-alpha-methyl-17-alpha-hydroxy-progesterone acetate; several thousands of women have been included in studies in many countries. The regimen investigated most completely is 150 mg injected every 90 days, although studies are also in progress with semiannual injections of 500 mg. With this procedure ovulation is generally suppressed through an interference with midcycle elevation in the production of luteinizing hormone. Ovarian follicle development appears, nevertheless, to proceed so that endogenous estrogen production may not be completely obliterated. The endometrial pattern, however, reveals that the established estrogen-progestin balance is far from normal. As a result, uterine bleeding is totally unpredictable for women on this regimen. Considerable patient variation occurs, but by the end of a year the majority of women have atrophic endometria and are amenorrheic. An extremely low pregnancy rate has been obtained with this procedure. However, considerable delay occurs in the restoration of ovulatory cycles at will. Delays in ovulation of from 12 months to 21 months are not uncommon and the time required for the establishment of a regular ovulatory pattern, post-treatment, is still not certain. To regularize the pattern of endometrial bleeding some clinicians have employed the periodic administration of estrogen either orally or by injection as an adjunct to injected progestin. This requires monthly return visits, or self-administered monthly courses of oral estrogen, so it detracts considerably from the method's simplicity.

The same compound has been tested for antiovulatory activity following absorption through the vaginal mucosa. A novel mode of administration, in the form of a vaginal ring, has been designed for this purpose. The compound is homogenized with a nonvulcanized

form of a silicone polymer, and the mixture is molded in the form of a ring, similar to the rim of a diaphragm. The physical-chemical properties of the polymer are such that the hormonal steroid diffuses from the ring at a relatively constant rate and can be absorbed through the vaginal mucosa. The daily release rate is sufficiently high to provide systemic levels of the hormone that cause pituitary suppression and the inhibition of ovulation. The vaginal ring can be positioned by the woman and left in place for approximately one month. After removal of the ring, endometrial sloughing and bleeding occurs. Subsequently, a new ring can be used for the next month. Thus, a simulated anovulatory menstrual cycle can be induced, similar to that achieved with antiovulatory therapy using oral hormones.

Hormonal Contraception Without Suppressing Ovulation

Oral preparations. A different type of hormonal contraception is now being investigated in several countries. This innovation in hormonal contraception is continuous low-dose progestin therapy that imparts an antifertility effect without added estrogen and without inhibiting ovulation. The basis of the antifertility action remains an uncertainty.

During the investigation of oral progestin-estrogen contraceptives, several investigators concluded that ovulation was occurring in a significant percentage of cycles, even though the antifertility effect was almost absolute. Yet, it was not until 1965 that work was reported implying that ovulation suppression could be dispensed with entirely while still retaining a potent antifertility effect. A synthetic progestin, 6-chloro-6-dehydro-17-alpha-acetoxy progesterone, was given at the low dose of one half milligram daily to a group of nearly 1,000 women with normal cycles. The women were seen at the clinic monthly during the period of investigation, which covered close to 10,000 cycles. Fourteen pregnancies occurred, thirteen of which were ascribed to patient failure to take the medication regularly. Considering only the single so-called "method failure," a pregnancy rate of 0.2 can be calculated. However, when all unintended pregnancies are considered regardless of reason, the pregnancy rate is 2.1. In either event, this is highly effective contraception. However, approximately two-thirds of the patients had some cycle irregularity during the twenty-month study period. With this particular compound, at the dosage employed, problems with cycle control appear to be a serious handicap, but the contraceptive effectiveness of the continuous progestin method seems clearly established. Meanwhile, at least six other synthetic progestins have been placed in

clinical investigations at doses intended to replicate the low-dose effect. Experience is sufficient with three of these compounds to indicate confirmatory results. With one of these, antifertility activity can be achieved with the extremely low oral dose of 40 micrograms daily. It is now evident that the low pregnancy rate reported in the initial study, described above, is not achieved generally with low-dose progestin therapy. Pregnancy rates ranging from two to seven per hundred women per year have been reported, and the extent of irregular bleeding is considerably greater than that first reported.

Although the mechanism remains uncertain by which the uninterrupted daily administration of these progestational agents creates a state of infertility without suppressing the pituitary and inhibiting ovulation, the possibilities can be narrowed down considerably. That the therapy does not generally interfere with ovulation suggests that the mode of action may be on sperm or ovum transport, the fertilization process itself, transport of the zygote or the preparation of the endometrium for nidation. Histologic evidence from biopsy material suggests that endometrial changes are not responsible for the antifertility effect. Sperm transport could be affected at the level of passage of sperm through the cervical mucus, or higher in the female tract. Although the preliminary reports tended to emphasize change in cervical mucus that could create a barrier hostile to spermatozoa, it now appears that these changes are not necessarily correlated with the antifertility effect. Future investigations will be required to establish the effect of microdoses of progestins on such key factors as tubal transport rates of gametes and fertilization itself. The effect of progestins in preventing sperm capacitation in other mammals may very well reveal the mechanism behind the antifertility effect observed in clinical usage.

Parenteral administration. The discovery of the antifertility action of low-dose progestins, based on uninterrupted administration, opens for the first time the possibility of single administration, long-term, reversible control of fertility by hormonal means, in a manner that would allow for maintenance of ovarian function and menstrual cycles. A possible application of this principle is suggested by recent experiments that demonstrate that steroid hormones may be released at low and constant rates from capsules made of various silicone polymers. One such material, polydimethylsiloxane, is already used widely in surgery and is found to be nonreactive when implanted subdermally in human subjects. Capsules containing the synthetic progestin, meges-

trol acetate, have been inserted subdermally in female rats, rabbits or monkeys and biologic evidence of slow and constant release of the hormone has been obtained.

A capsule small enough to be inserted under the skin through a hypodermic needle can be filled with an adequate supply of this progestin to last for more than three years. Capsules that could provide continuous low-dose progestin release for five, ten, fifteen years or longer are well within practical limits. Contraceptive implants of this type could be removed at will and there is no reason to believe that subsequent fertility would be impaired. This form of low-dose progestin contraception, reversible and simple, may very well be one of the next developments in contraceptive methodology. The method is now being evaluated clinically. Its effectiveness for a full year after capsule insertion has been established.

LABORATORY RESEARCH RELATED TO FERTILITY REGULATION

Ovulation Suppression

Although the original hormonal contraceptives (progestin plus estrogen) probably have other biologic effects that contribute to their contraceptive effectiveness, they are basically ovulation inhibitors. The effect on ovulation is subsequent to suppression of pituitary gonadotropin release that, in turn, is the result of an action by the administered steroids on the hypothalamus or higher brain center. Ovulation suppression by means of a primary action at the level of the central nervous system can be achieved experimentally by a number of other pharmacologic agents, including tranquilizers, narcotics and some cardiovascular drugs. Morphine, for example, has been shown to inhibit ovulation in women. A practical application of these observations for the purpose of controlling ovulation seems unlikely, however, because of lack of evidence that the anti-ovulatory effect can be isolated from the general pharmacologic effect of these compounds.

Another possibility for the interference with ovulation through an effect at the central nervous system stems from the growing understanding of how the CNS-pituitary link operates. Humoral substances from the brain that regulate the release by the pituitary of gonadotropins have been identified. They are relatively simple molecules and their precise chemistry is now being established. The possibility is very real of using these releasing factors or analogues that may act as competitive antagonists as a basis for fertility control. Of greater potential

applicability perhaps is the finding that the hypothalamus may produce, in addition to gonadotropin releasing factors, inhibitory substances that provide a physiologically normal means to suppress gonadotropin production. The inhibitor has been found in the brains of infants and prepubertal children, suggesting that it may play a role in holding the pituitary-gonadal circuit in check until puberty.

Direct suppression of gonadotropin production at the pituitary level, or interference with action of circulating gonadotropins, can be achieved by immunologic means. Antibodies to gonadotropins can be induced in experimental animals by immunization. Immunized animals, either males or females, have typical manifestations of gonadotropin deficiency. In the male, spermatogenesis is impaired; in the female ovum maturation or ovulation is prevented. However, several important issues remain to be resolved; a practical application of these experimental findings in human subjects is not imminent. We cannot, for example, envisage now a means of imparting controlled reversibility to a method of fertility inhibition based on active immunization with gonadotropins. Also, our present inability to purify completely luteinizing hormone and follicle stimulating hormone makes it difficult to separate an immunologically induced interference with the gamete-producing function of the gonad from undesirable interference with the gland's hormone-producing function.

Another approach to the inactivation of circulating gonadotropins has been the study of natural plant products. Several plants, one a North American prairie grass, have been reported to have this activity, but years of study have failed to reveal an active and stabile constituent that is devoid of undesirable side effects. In general, the evaluation of plant extracts for antifertility action by means of gonadotropin inactivation or any other route of activity has been discouraging and unrewarding. From time to time, a plant product is described that has a clear antifertility effect in laboratory rodents. Almost invariably these results can be ascribed to a mild estrogenic activity common in many legumes and other plants, an activity that has no practical significance for contraceptive purposes.

It appears, therefore, that control of fertility based on ovulation suppression will, in the foreseeable future, continue to depend on the action of synthetic hormones similar to those now in use as constituents on the widely used oral contraceptive agents.

Remarkably little is known of the various steps involved in the ovulatory process itself. It is as yet not clear what factors cause one

antral follicle to mature and ovulate whereas adjacent follicles of the same size and the same histologic and cytologic appearance become atretic. The specific actions of the gonadotropic and steroid hormones in the gross development of follicles and at the cellular level can be described only in the most general terms. We need to know what initiates the first changes in the follicular apparatus that lead to its growth and development.

The phenomenon of follicular atresia can be recognized if it is reasonably well advanced, but the basic biochemical or endocrinologic aspects of its origin are unknown for any mammal. A great variety of endocrine insults have been shown to induce atresia at all levels of follicular development and other factors may be present that need to be explored in detail. Apparently a definite interrelation is established very early in development among the egg, the corona and the cumulus cells. Increasing evidence indicates that if the egg is not completely surrounded by follicular cells the meiotic process proceeds to diakinesis, and follicular atresia results. A better understanding of atresia could very well contribute information as to the factors involved in normal follicular development and ovulation and their control.

Tubal Transport of Ova

The zygote, or newly fertilized egg, normally spends several days passing through the female reproductive tract before it begins the process of implantation in the uterus. This is a carefully timed sequence that must proceed in phase with preparatory changes occurring in the endometrium. If the zygote arrives too early from the fallopian tube, the uterus is inadequately developed and the zygote will degenerate.

Ovarian steroid hormones have a major regulatory influence on the tubal transport of ova. Estrogens increase the rate of secretion of tubal fluid, stimulate ciliary activity at the upper portion of the tube and increase the peristaltic activity of the tubal musculature. Progesterone generally has the opposite effect on each parameter. Upsetting the proper sequence of hormonal influences, therefore, can disturb the normal passage of cleaving ova in the fallopian tubes. Indeed, this has been demonstrated by many experiments, but no simple unifying idea can be synthesized from the reported observations. Nevertheless, the apparent lability of the regulatory mechanism for normal tubal transport of ova provides an attractive basis for controlled interference with fertility. Indeed, this site of action has been postulated as the basis for the antifertility effect of intrauterine devices.

Studies of tubal transport of ova in rhesus monkeys have shown that the antifertility action of an intrauterine device may occur not only in the uterus but at the tubal level as well. This finding is compatible with the extensive clinical data on intrauterine contraception, which establish that such devices prevent both uterine and ectopic tubal pregnancies. Rapid expulsion of tubal ova occurs in gonadotropin-stimulated monkeys with intrauterine devices, whereas gonadotropin treatment itself does not have this effect. Ova cannot be found in the tubes of monkeys with these devices within 24 hours after ovulation. Because gonadotropin-treated animals tend to have multiple ovulations, an elevated level of ovarian steroids may contribute to the acceleration of tubal ova. That this phenomenon in itself does not account for the rapid passage of ova is shown by the recovery of ova from gonadotropin-treated animals without the devices. In subsequent experiments ova were recovered from the tubes of normally ovulating monkeys, although the precise rate of tubal passage in this situation has not yet been established. Whereas the additive effect of gonadotropin stimulation and the presence of an intrauterine device may be required to demonstrate a dramatic tube-flushing effect within 24 hours, each stimulus alone may influence the tubal transport rate to some lesser extent. Careful timing of tubal transport rates in monkeys with the devices and under different conditions of ovarian function is required to elucidate this issue. Investigations with human subjects have established that sperm may reach the fallopian tubes, but whether fertilization occurs in women using intrauterine devices effectively has not been established, and the recovery of several hundred human ova will be required before this important point can be clarified.

An influence on tubal transport of ova or zygotes may be involved by recent studies on the effectiveness of postcoitally administered hormonal agents in the prevention of nidation in subhuman primates. Pregnancy in the rhesus monkey can be prevented by the administration of an estrogen during the four-day period after mating when the fertilized egg is traversing the fallopian tube. Estradiol, stilbestrol, ethinyl estradiol, mestranol or an experimental compound that is both anti-estrogenic and estrogenic were administered orally following over 300 matings in a colony of rhesus monkeys that normally achieves a 70 per cent pregnancy rate after mating. When the estrogen was administered postcoitally, not a single pregnancy ensued.

In these experiments no direct attempts were made to ascertain the cause for the antifertility action. Accelerated tubal transport is

implicated because, in other species, the relationship has been established between postcoital estrogen treatment and acceleration of tubal transport of ova. Estrogen-induced premature expulsion of the ova from the fallopian tubes has been demonstrated in rats, rabbits and guinea pigs. The effect has now been reported with a variety of compounds, both steroidal and nonsteroidal, but it becomes evident that the common feature of all is their estrogenicity. The data available on the application of this principle to human subjects are too few to permit an evaluation, although it has been reported that no pregnancies occurred in a limited number of rape cases and volunteer subjects treated with stilbestrol or ethinyl estradiol for several days immediately after midcycle insemination. A systematic analysis of the potential antifertility action of postcoital estrogen treatment in the human female is required. Assuming that the activity in animals would carry over to the human, an interesting method of fertility control is suggested. Pills taken orally for a day or two after intercourse would prevent pregnancy even if fertilization had occurred. No disruption of the natural menstrual cycle and no manifestation whatever of the pregnant state would occur. Indeed, no physiologic criterion could be found by which any stage of the process could be classified as a pregnancy.

Biology of the Ovum

The blastocyst remains free in the cornual or uterine lumen for several days before attachment and implantation begin. Although information is not available for lower primates and man, comparative studies of other mammalian species reveal that the zona pellucida remains intact until shortly before embryo attachment begins. It is known further that embryos escape from the zona pellucida by a variety of mechanisms depending upon the species. Such escape is effected only if the ovum is fertilized. Studies in mice reveal that the expanding blastocysts mechanically rupture the zona pellucida. In the rat the zona pellucida is shed during the afternoon of the fifth day after mating or just before embryo attachment. Rupture of the zona in this species is effected also by embryo expansion. In one experiment, a macaque blastocyst, washed out of the uterus eight days after ovulation, still had an intact zona pellucida. Likewise a human blastocyst recovered from the uterine lumen about four days after ovulation was enclosed in the zona. There is no information as to the mechanism of blastocyst escape from the zona pellucida in primates. Whether the trophoblast participates in depolymerizing the zona so as to effect

escape is unknown. If so, as is the case for other mammals, then knowledge of methods of inhibiting deploymerization and thereby preventing the escape of the blastocyst may be a promising target in pregnancy control.

Corpus Luteum Function

The uterine environment is not essential for blastocyst survival, implantation and development inasmuch as in some species ova can be fertilized and cultured *in vitro,* and a human ectopic pregnancy is quite independent of the uterine environment. Nevertheless, in all species studied, a successful intrauterine pregnancy requires adequate progestational preparation and maintenance of the endometrium. It seems likely that the same situation prevails in the human female.

On this assumption, several investigators have sought steroid inhibitors of implantation by examining a variety of compounds for their antiprogestational effect, and a few compounds have emerged that appear to have implantation-inhibiting activity while being virtually devoid of estrogenic activity. In the A-nor-andro-stene series of steroids, at least one compound with an excellent record in biologic assays has been carried to preliminary clinical trial and evidence for antiprogestational activity obtained. Extensive trials in subhuman primates will be required before the antifertility potential of this and related compounds can be established.

In addition, several laboratories have reported antiprogestational or anti-implantation activity for a number of synthetic di- or tri-phenyl hydrocarbons that have been available for a number of years and several of which are used clinically as synthetic estrogens. One (clomiphene), which has excellent antifertility activity in laboratory rats, proved to be remarkably effective for the induction of ovulation in cases of human infertility and is prescribed for that purpose. Another was, in fact, tested as an antifertility agent in women, but without success. Still others, in spite of interesting laboratory findings, have not been evaluated in the human subject. These compounds have been variously described as antizygotic, blastotoxic, antinidational, weak estrogens, antiestrogens or antiprogestational, depending on the assay system used. A systematic analysis should be undertaken of the potential usefulness and safety of this type of compound for human contraception.

Another approach to the elimination of the progesterone needed for nidation has been to interfere with the function of the corpus luteum by pharmacologic means. Several amine oxidase inhibitors with phenyl

hydrazine structure, when studied in the rat, appear to have this effect either directly or through a depressing effect on the pituitary production of luteotrophin. The role of the amine oxidases and their inhibitors in the reproductive process is as yet inadequately investigated. However, this could be one of the more important pharmacologic approaches to fertility regulation, and could explain some of the biologic effects of prostaglandin on reproductive function.

A similar luteolytic effect by inhibition of luteotrophic hormone release is believed to account for the antifertility activity of ergocornine, an antihistaminic of the ergot series, which prevents implantation in the rat or mouse when administered during a limited period of tubal transport of fertilized ova. Future development of this particular compound for contraception is not likely in view of apparent toxicity in clinical trials.

The present disappointments notwithstanding, antifertility action through a luteolytic or antiprogestational effect is one of the more intriguing prospects on the research horizon. In theory, an oral preparation active in such a manner could be taken by a woman either monthly, at the time of the expected menses, or only on the occasion of a suspected fertile cycle as indicated by delay in the onset of menstruation. Efforts along these lines will be stimulated by the growing evidence for the existence, in many species, of a humoral luteolytic substance produced by the uterus and transmitted by tissue diffusion and common blood supply to the ovary. It has been suggested that luteolysis may be a normal physiologic role for prostaglandins. This class of ubiquitous C-20 fatty acid derivatives can be extracted from many tissue sources including seminal fluid, umbilical cord, lung, iris, thymus, kidney, brain and endometrium. Studies in laboratory rodents suggest that the compounds may be luteolytic although prostaglandins may stimulate *in vitro* progesterone synthesis. Whether the prostaglandins can, in fact, suppress corpus luteum function in man remains to be established, although the compounds are now being studied clinically to bring on menstruation when it is a few days overdue. The mode of administration being studied is vaginal tablet.

Myometrial Stimulation

The initiation of myometrial contractions heralds the onset of labor at or near term, or the beginning of a spontaneous or threatened abortion at early stages of pregnancy. Although the steroid hormones can influence uterine contractility and they probably play a role in the en-

docrine control of the myometrium, other factors are undoubtedly involved, not all of which are understood. Oxytocin, for example, is an effective stimulant of the late-gestational uterus, but is ineffective when administered early in pregnancy. On the other hand, some of the prostglandins can initiate myometrial activity in early or late pregnancy, or in the nongravid uterus. This activity led to the testing of prostaglandin F_2-alpha or E_2 as abortifacients, from the 8th to 22nd week of pregnancy. Owing to the fact that the compounds are not effective orally, they were used intravenously for the purposes of study. The initiation of myometrial contraction was usually followed by evacuation of the uterus. It is still not possible to evaluate the potential of this pharmacologic activity. Until now it is not established that an effect on the myometrium can be separated from effects on other smooth muscle; the percentage of cases with incomplete abortions is unacceptably high; and the prospects of serious side effects (respiratory or cadiovascular acute changes, profuse bleeding) are too great to consider the intravenous administration of prostaglandin E_2 or $F_{2\alpha}$ as useful replacement for surgical abortion. Published data are insufficient to evaluate the potential of intravaginal or intrauterine problems encountered following intravenous administration.

Suppression of Sperm Production

The testis, like the ovary, depends upon stimulation by pituitary gonadotropic hormones to perform its normal function of producing sex hormones and sperm. Like the ovary, the testis can be secondarily suppressed by a procedure that stops the production of gonadotropins. The oral progestins, for example, could be effective agents for the inhibition of sperm production. Doses required, however, have the unwelcome effect of inhibiting the secretion of sex hormones by the testis; as a consequence libido and potency are reduced. However, long-acting androgen esters are now available that may provide long-term suppression of spermatogenesis while maintaining libido and general well-being.

Although testosterone and other androgens can suppress spermatogenesis in man, the feasibility of such treatment for contraception depends on establishment of a dosage and mode of administration that would provide the antispermatogenic effect of an androgen without causing the more general metabolic effects such as changes in blood chemistry, stimulation of the prostate and so forth—effects that would give cause for medical anxiety.

Other orally active chemical compounds stop sperm production without interfering with testicular hormone secretion. Several classes of chemical substances have been found to have this effect, but all have accompanying side effects that render them unsatisfactory for contraceptive purposes. One group of such compounds is the nitrofurans, which have had wide use as inhibitors of bacterial growth. They are very effective in stopping sperm production in man, but the doses required cause nausea and headache. In 1960 great promise was seen in another group of compounds, originally of interest for their usefulness in the treatment of intestinal amoebae. The drugs were tested using volunteers among penitentiary prisoners; complete suppression of sperm count was demonstrable. When the drug was discontinued, sperm count returned to normal. With high hopes, trials were expanded to include men in more usual social circumstances. The first unexpected observation was that the drug enhanced the vascular effects of imbibed alcohol. As surveillance of the original prisoner-volunteers continued, it was suspected that the drug was associated with a frequent occurrence of hepatitis, so further investigation was halted.

Another promising compound, a dinitropyrrole, impaired spermatogenesis in the rat for as long as four weeks after a single oral dose. An infertile state could be maintained indefinitely by administering single doses at intervals of four weeks. Sperm production recovered fully when treatment was finally stopped. Subsequent toxicologic findings resulted in the withdrawal of the compound from investigation, but it is possible that a related compound may be discovered that retains the antispermatogenic activity while being devoid of toxicity. The compound fluoracetamide may meet this specification. It suppresses spermatogenesis in rats with no evidence of toxicity. The compound is now being studied in infrahuman primates.

Testicular antigens that can be used for specific immunization to prevent spermatogenesis have been isolated. Indeed, even nonpurified, crude testicular extracts can cause aspermatogenesis in the guinea pig and in the rat. An attempt has been made to immunize human males with testicular extract believed to be purified for the aspermatogenic factor, but the results have not been notable. Immunization with tissue extracts for the purpose of inducing sterility in either the male or female organism seems distant at this juncture. The basic problems of tissue cross-reactions, specificity of antigens, controlled reversibility of the immune response and development of acceptable adjuvants still impede progress in this field.

Fertilizing Capacity of Spermatozoa

Mammalian spermatozoa may have completely normal morphologic appearances and normal motility without possessing the capacity to fertilize ova. This final maturation stage of sperm has been termed "capacitation." Evidence for capacitation has been obtained in a number of mammalian species, including rabbit, rat, hamster, sheep and ferret. From the viewpoint of fertility control research, the intriguing extension of the capacitation concept is an understanding of the manner in which it can be inhibited. Sperm do not capacitate in the uterus of a rabbit injected with progesterone or in the uterus of a rabbit in the pseudopregnant state (progestational condition). In fact, it has been suggested that fully capacitated sperm can lose their fertilizing capacity by exposure to a female reproductive tract that is under progestin domination.

Although the process of capacitation has not been demonstrated as an essential element of sperm maturation in primates, the assumption that it does occur seems reasonable. With the greater availability of infra-human primates for reproductive research, this issue should be clarified before long. In any event, the evidence from other eutherian mammals suggests that interference with sperm capacitation may account for the contraceptive action of continuous low-dose progestin therapy that imparts an antifertility effect without added estrogen and without inhibiting ovulation.

Scientists have not been successful in finding a morphologic or biochemical criterion that can be linked unequivocally with capacitation. Changes in oxygen consumption by sperm, surface-coating proteins or detachment of the acrosome have been implicated, but these phenomena are not proven characteristics of the capacitation process. Ultimately, the proof lies in the actual fertilizing capacity of the sperm. Work on the process of *in vitro* fertilization is, therefore, directly cogent to this problem.

The role of progestin in influencing the ability of sperm to capacitate in the female tract raises the question of a possible influence of this class of hormones while sperm still reside in the male storage system. The effect of progestins in the male at doses below the threshold for inhibition of spermatogenesis has not been systematically analyzed in any species. Although the fertilizing capacity of spermatozoa is dependent foremost on an intracellular component, namely the DNA of the sperm chromatin, changes on the surface coat of the sperm could perhaps control the ability of the sperm to fulfill its role in fertilization.

Whether such changes could be brought about, by hormonal or other means, while the differentiated spermatozoa reside in the epididymis or ductule system, warrants careful study.

Human Seminal Fluid

A primary function of the ejaculate in all species is to act as a carrier of the spermatozoa from the male to the female reproductive tract. However, the chemical complexity of the seminal plasma suggests other and more subtle relation to the function of spermatozoa. The chemical composition of the seminal fluid in man has been analyzed in considerable detail. It is known, for example, that the seminal fluid contains several trace metals, for example, iron, copper, zinc and magnesium. Chelating agents at a concentration of a few parts per million can be toxic to ram, bull, rabbit and human spermatozoa, and the addition of copper or zinc enhances the spermatotoxic activity of many chelating agents. Considerable work has been done on seminal carbohydrates, which appear to be an important source of energy for spermatozoa. In human semen, sorbitol, which may be oxidized to fructose by the enzyme sorbitol dehydrogenase, is also present. Fructose is formed in the seminal vesicles and its formation is dependent upon the secretion of testosterone by the testis. It remains to be explored if mild anti-androgenic substances can influence seminal fluid chemistry at doses below the threshold for other, undesirable, anti-androgenic effects. Even so, the influence of such a change on the fertilizing capacity of spermatozoa is uncertain; the seminal fluid may not be essential to the fertilizing capacity of sperm, according to some studies.

Although such conclusions tend to minimize the significance of the seminal fluids, it remains a distinct possibility that adverse conditions of the fluid medium could influence the spermatozoal surface in a manner that would impair the ability of sperm to reach the fallopian tube or to penetrate an ovum. From experimental data now available, it seems that "an adverse condition" is more likely to be the addition of a deleterious constituent to the seminal fluid than the deletion of something normally present. For example, zinc, which is believed to be essential for normal sperm metabolism, is contributed chiefly by the rat's dorsolateral prostate, yet removal of this organ does not reduce the fertility of the male rat. The possibility of exogenous substances finding their way to the seminal fluid is real. Following the administration of estrogen to the male rat or rabbit, for example, estrogen can be found in the ejaculate. Ethanol and sulfonamides from exogenous

sources have also been found in seminal fluid. A pertinent question, therefore, is whether spermicidal substances might be found that could reach seminal fluid after ingestion or parenteral administration, but that would not have general toxicity.

Pheromones

The study of pheromones provides another approach to the possible development of new agents or methods for fertility control. The term pheromone designates a volatile substance transferred from one individual to another of the same species, which generally in minute amounts evokes some behavioral or developmental response in the recipient.

Investigations in this field have centered largely about insects, but analogous phenomena have been demonstrated in laboratory mammals. One example is the failure of implantation that occurs in a mated female mouse that is placed in the presence of a "strange" male within the first four days, but not later, after mating. The effect does not occur if the female is first rendered anosmic by removal of the olfactory lobes. Also, administration of prolactin or ectopic implantation of a pituitary gland overcomes the block to implantation. Another pheromone-induced phenomenon is the occurrence of pseudopregnancy when several female mice are caged together, but not when they are housed individually. Again the effect is overcome if the olfactory bulbs are removed. Excessive crowding of female mice results in anestrus even when contact between animals is prevented by compartmentation. Both anestrus and pseudopregnancy are overcome by the introduction of one or more males, direct contact being again unnecessary for this effect.

Among the insect pheromones, those concerning the control of reproductive behavior and gametogenesis are of special interest. In the honeybee a pheromone normally derived from the queen has been isolated and identified that inhibits oogenesis in workers. The manner in which this substance acts to suppress ovulation is uncertain. Also, only occasional, and rather incomplete, investigations have reported on the possible action of these or of chemically related substances in mammals. From other information concerning the action of hormones of mammalian origin on lower organisms, including insects, it is not unreasonable to expect the reciprocal situation to pertain with respect to physiologic processes that are basically similar.

POSSIBLE MEANS OF FERTILITY CONTROL— DISTANT OR NEAR

The foregoing is a fairly comprehensive review of topics in reproductive biology that have some apparent relation to fertility regulation. From these areas of research, as well as some others, it is possible to compile a list of potential methods to regulate fertility that have a realistic basis in terms of present knowledge.

For Use By Female

1. *Once-a-month anti-ovulant pill.* Now under limited clinical evaluation; this is a modification in the manner of using estrogen-progestin combinations. The steroids used are absorbed from the gastrointestinal tract, stored in adipose tissue and released gradually over a month.

2. *Once-a-month anti-ovulant injection.* Now in clinical investigation; this is a modification in the manner of using estrogen-progestin combinations. Long-acting steroid esters are injected at a dose calibrated to last one month.

3. *Once-a-month vaginal ring.* Preliminary trials completed; this procedure is based on anti-ovulatory action of a synthetic progestin released from an elastomer and absorbed through the vaginal mucosa.

4. *Long-term anti-ovulant injection.* Extensively studied in clinical trials, this procedure is based on the anti-ovulatory action of a synthetic progestin without estrogen. Microcrystallized suspensions of the steroid are injected in doses that will last three or six months.

5. *Long-term anti-ovulant implant.* Not yet studied clinically, this procedure would provide chronic release of estrogen-progestin to suppress ovulation and menstruation.

6. *Continuous low-dose progestin.* This provides an antifertility effect without inhibiting ovulation or the normal endometrial cycle.

   a. Pill or oil-filled capsule taken orally: several compounds are under investigation.
   b. Subdermal implant: provides for continuous absorption from an elastomer at a constant rate. One version now proven to work for one full year. Studies continuing to improve and simplify the method.
   c. Removable vaginal ring: provides for continuous absorption and may act locally on cervical mucus glands or systemically to give the low-dose progestin antifertility effect.

d. Long-acting injection: requires the development of a preparation that would provide a depot effect that gives constant, low absorption below level that will affect pituitary or endometrium.

e. Skin-contact absorption: requires the development of highly potent progestin, active at levels that could be absorbed through the skin—from a finger ring, for example or by adding to a cosmetic.

f. IUD-released: provides for continuous absorption and may act either locally in the uterus, or systemically to give the low-dose progestin antifertility effect.

7. *Long-term luteotrophin injection.* Requires a better understanding of the trophic control of the human corpus luteum. The purpose would be to lengthen the postovulatory phase of the cycle to perhaps 90 days so that a woman would have fewer ovulations per year.

8. *Corpus luteum maintenance by injection of* LT-RF *releaser.* Requires identification and purification of LT-RF active in human female. Objective same as in (7).

9. *Monthly oral preparation to cause luteolysis.* At least two compounds, active orally, have been claimed as having luteolytic activity in animals, and possibly in humans. Taken regularly, the drug would bring on menstruation whether or not the cycle had been fertile.

10. *Monthly injection to cause luteolysis.* This would be an application of the proposed uterine luteolytic factor. If active in the human, it will probably require injection since preliminary work indicates a peptide structure. Objective would be as in (9).

11. *Vaginal tampon to cause luteolysis or uterine contraction.* This would be a method to apply substances, such as prostaglandins, that are not orally active. Used regularly, the method would bring menstruation whether or not the cycle had been fertile.

12. *Nonregular use of injection or oral preparation.* A variation in the use of the monthly injection or oral preparation would be to instruct the woman to do nothing for contraception but on the infrequent occasion of a fertile cycle, as indicated by a delay in menstruation, to use a luteolytic method.

13. *Once-a-month anti-progestational pill.* To be taken regularly at the time of the expected menses, to interfere with luteal maintenance of early decidua and bring on endometrial sloughing whether or not

the cycle has been fertile. Several compounds are available with a potential for this activity are available.

14. *Precoital progestins.* At least one compound has been used that appears to cause a rapid change in the cervical mucus, making it impossible for sperm to penetrate.

15. *Postcoital estrogen or anti-estrogen taken orally.* On the basis of limited human use, this procedure is claimed to be effective in preventing pregnancy following isolated exposures. Presumably, it affects the rate of ovum transport. Several compounds are active in animals.

16. *Postcoital antizygotic agent taken orally.* Work is required to seek compounds that would appear in the tubal fluid at adequate concentration to be toxic to the zygote without manifesting general toxicity.

17. *Immunization with sperm antigens.* The objective is to prevent deposited spermatozoa from achieving fertilizing capacity in the female tract. Success has been reported in animals, but considerable basic work, including safety studies, are needed before human trials are feasible.

18. *Injection of passively transferred antibodies to* HCG. This procedure would be employed on the occasion of a missed period, during the time that HCG stimulation of the corpus luteum is required to maintain a nascent implantation. Animal studies establish the feasibility of the approach.

19. *Immunization with steroid-binding proteins.* Recently described tissue-specific intracellular binding proteins can be derived from the uterus. Active antibody production would prevent estrogenic changes from occurring in the uterus without interfering with the ovarian cycle.

20. *Improved methods to detect ovulation.* This is feasible on the basis of simplification in the method to detect either LH or progesterone, in urine, saliva or blood (finger-prick sample).

21. *Reversible tubal occlusion.* Instead of sectioning the fallopian tube, a removable plug would be introduced, either trans-cervically or through an abdominal approach.

22. *Simplification of tubal ligation operation.* Now being tested by several surgeons, the tube is sectioned or electrocoagulated by a peritoneoscopic or culdoscopic instrument.

23. *Intrauterine infusion of cytotoxins.* Intrauterine infusion of cytotoxins has been reported as a means of inducing sterility. The safety and permanency of the procedure need further study. The objective is to occlude the intramyometrial portion of the fallopian tube.

24. *Oral or parenteral preparation to assure multiple births at will.* Purified human pituitary gonadotropin can stimulate multiple ovulations; at least one synthetic compound has similar activity. Fine adjustment of dosage, on the basis of ovarian function tests, would provide assurance of multiple births, if desired.

25. *Sex determination at will by immunization with Y-sperm antigen.* There is some evidence that specific antigens from Y-sperm may be identifiable. If so, women could be immunized against this antigen to inactivate Y-sperm and assure female sex determination. No similar approach to male sex determination can be envisaged.

26. *Sex determination at will by artificial insemination.* There have been occasional claims of success in separating X- and Y-spermatozoa in an ejaculate by physical means (centrifugation, electrophoresis, sizing, column diffision). By using only Y-bearing gametes in artificial insemination, male zygotes could be assured. No confirmed procedure has yet been established, however.

For Use By Male

1. *Subdermal implant to suppress spermatogenesis.* Release of an androgen from a capsule of silicone rubber can be achieved at a low and constant rate for several years. This can provide a basis for gonadotropin suppression at levels of androgen therapy that may be medically acceptable.

2. *Periodic injection of long-acting androgen.* Testosterone enanthate, or other esters, can suppress sperm production while providing androgen replacement therapy. Depot injections can remain active for three to six months.

3. *Subdermal implant of progestin.* Low doses of progestin, below the threshold for pituitary suppression, can prevent maturation of epididymal sperm in some animals. A similar activity in the human male would prevent fertility without suppressing spermatogenesis.

4. *Oral tablet of synthetic spermatogenesis inhibitor.* Several compounds that act directly on the testis to prevent spermatocyte maturation have been reported. In animals, some compounds require continuous administration; others can be given for a few days each month. A nontoxic compound of this type is being sought.

5. *Oral tablet to alter biochemical constitution of seminal fluid.* Although no specific compound has yet been identified that can influence

fertility by this mechanism, the possibility of this type of action exists. The appearance of exogenously administered substances in seminal fluid has been reported.

6. *Immunization with testis or sperm antigens.* This procedure can cause aspermatogenesis in animals. Purification of antigens, control over reversibility, mode of immunization remain as problems to be investigated for human application.

7. *Reversible vas deferens occlusion.* The use of a liquid silicone rubber that vulcanizes into a pliable plug at body temperature has been attempted in animals.

8. *Reversible vas deferens ligation.* Procedures are being tested to modify the procedure for surgical vasoligation, in a manner that would improve prospects for reversibility.

For Use By Either Male or Female

1. *Immunization with gonadotropin-releasing factors.* The isolation of these substances, probably polypeptides, may provide a basis for specific LH or FSH suppression so that gamete production in either the male or female could be prevented.

2. *Immunization with enzymes specific for normal reproductive function.* There is evidence that specific iso-enzymes can be identified in gonadal or placental tissue. Although this work is at a preliminary stage of development, it could lead to a source of highly specific antigens.

3. *Oral administration of chemical inhibitors of releasing factor production.* Monamine oxidase inhibitors, prostaglandins and other biologic amines interfere with reproductive function in either male or female. These substances may act by interfering with the function of neurosecretory cells in the CNS.

4. *Immunization with purified gonadotropins.* In either male or female animals gonadotropin antibody formation leads to the expected result of gonadotropin deficiency. In some animals, LH immunization prevents the maintenance of early pregnancy.

5. *Oral administration of antigonadotropic drugs.* Several antigonadotropic agents, either synthetic chemicals or natural plant products, have been reported. Taken regularly, an active and safe preparation of this type could prevent sperm production in the male or interfere with reproductive function in the female in a number of ways.

6. *Topical application of pheromones.* Laboratory experiments demonstrate that volatile agents produced by one animal can influence reproductive functions in another. The role of such substances in human reproductive physiology remains to be established.

DISCUSSION

Karl A. Smith: As Dr. Segal predicted I was familiar with most of what he had to report in his paper. However there was one new piece of information for me, and this had to do with the *contragestational* pill, which would take the form of an antiprogesterone or a synthetic progestagen. I was most pleased to hear Dr. Segal report on what he describes as a more intelligent approach to contraception, and I hope that before long some of these new lines of approach will reach fruition.

Despite these prospects, I still think that we lack a great deal of basic knowledge. For instance we still do not know fully the effects on the ovaries of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in the pure form and in varying doses; nor do we know their effects on the uterus—their specific sites of action and their mode of action. We know very little about the phenomenon of ovulation, and its mechanism. It may be that, armed with such knowledge, we could find simpler means of contraception than are at present available for interfering with ovulation. For instance, a specific anti-enzyme could perhaps be used in place of a progestagen we now use in the manner of a workman using a pneumatic hammer to crack a peanut.

Again, notwithstanding the information we have from Dr. Segal, it seems to me that we are still not too sure about the principal sites and modes of action of the oral contraceptives; for example we are told that the low dose progestagens work by interfering with the viscosity of the cervical mucus, but we do not seem to know how exactly this is brought about. In another area, what do we know about the mechanism of capacitation of spermatozoa? I maintain that a better understanding of this phenomenon could lead to the development of several antifertility drugs for the use of males.

I would like to hear more about the mode of action of the intrauterine device; and about the possible profound social and religious implications and ramifications of the use of the prostaglandins.

In conclusion I would say that we need to have more and better methods of contraception and birth control, having in mind the prob-

lems related to the use of the methods at present available, which are in turn related to such things as a lack of knowledge of reproductive physiology by the masses of the people who try to use these methods. These considerations have important implications for the acceptability and effective use of contraceptives.

Wilson H. Grabill: In talking informally with Dr. Segal about his paper I asked him if some improved device could be developed to instantly detect impending ovulation (rather than rely on repeated measurements of unreliable temperature changes and so forth). Two gains would seem to follow such a device: (a) help the Catholics with their unsafe rhythm method and (b) help families predetermine sex of a next child, insofar as coitus early or late helps to get a boy or girl. He replied that better yet would be something to cause prompt ovulation rather than leave it to normal timing. So, his paper perhaps should have included something about methods to foster ovulation rather than just methods to prevent or nullify conception.