1961

# Ideal anti-fertility agent

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Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

April 1, 1961

Omaha, Nebraska

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# Introduction

Conception may be defined as the fertilization of the ovum, and contraception as any means taken to prevent this fecundation. Anti-fertility agents and birth control serve as synonyms for contraception. This thesis will attempt to trace contraception from its origin to the present time, with emphasis on the most recent advances in the field-oral contraceptives. It should be noted that no attempt will be made to discuss contraception on a moral or religious basis.

## Historical Backround of Contraception

Contraception is ancient discipline. Man's attempt to control the size of his family, first by infanticide, then by abortion, and then by contraception goes back beyond recorded time. In the early Egyptian papyri there are prescriptions on how to prevent impregnation. (1) Thus the act of contraception is not a new concept in the morals and mores of man.

No evidence still in existence indicated when the very primitive or even the prehistoric woman became sufficiently conscious of her own person and powers to desire, or even achieve any measure of birth control. That definite contraceptive means were employed in the prehistoric past is probable, for today a number of extremely primitive races possess their own type of crude knowledge on this subject, and make it evident that earlier races of the same grade probably did also. However, abortion and infanticide are the early and more barbarous equivalents of contraception, since the personal needs and health of the women are less likely to have been realized than the simple desire to reduce

the number of unnecessary babies.

According to Smith (16) the inhabitants of Futuna did not consider killing the child as being shameful-this was accomplished by pressing the body with heavy stones thereby crushing the baby, or (after birth), by burying them alive in the sand.

A number of authors also speak of an island race of primitive Australians who employed the Mika operation, which consists of the slitting, with a stone knife, of the urethra by the lower side of the penis. This operation is paralleled by a much more elaborate sterilization of girls by the tearing off of the cervix and slitting of the vagina down to the anus. A full account of this latter operation is given by Garson. (17)

The Sanskrit books of the Sixth Century were one of the earliest historical documents to reveal sex instruction and the art of contraception. Some of the advice given is as follows: (15)

> "1. The women who will drink for three days after the fourth (purification day) a decoction of Chitrake (Ceylon lead-wort Plumbargo zeylonice) boiled with rice water, will never have children."
> "2. The women who will drink for three days after the fourth a decoction of Kallamba plant and the feet of jungle

flies, will never have children."

"3. The women who will eat every day for a fortnight mashas of molasses (Jugri) which is three years old will be barren for the rest of her life."

A contraceptive measure still greatly in vogue came into use in Italy in the Sixteenth Century- sheaths, made of linen, isinglass, and caecum of a lamb.

In the Nineteenth Century a method of birth control called the sponge method came into use. A piece of soft rubber sponge was tied to a piece of string or ribbon and inserted just before the sexual intercourse took place, and was withdrawn again as soon as it had taken place. (15)

The most important medical advance in the second half of the Nineteenth Century was inaugurated by Dr. Mensinga who described the convenient rubber caps used by the female. (18)

In the pursuit of information concerning the historical methods of contraception, it was interesting to note the lack of such information. For example, in W.J. Robinson's "The Limitation of Offspring," a chapter entitled: "The Best, Safest, and Most Harmless Means for the Prevention of

Conception" was followed by blank pages. And under the title of "Means for the Prevention of Conception Which are Disagreeable, Uncertain, or Injurious," another series of blank pages followed. (15) The author's reason for doing this, and my reason for including this now, is to illustrate the type and extent of the censorship that existed then and to a certain degree at the present time. This perhaps accounts, in part, for the lack of information on primitive methods of birth control.

The methods used in the Twentieth Century and at the present time will be dealt with in a subsequent chapter.

Much work has been done on a physiologic approach to birth control. Experiments thus far have primarily involved laboratory animals, with a few including human results. The following material is a brief scan of the research that has been done in the realm of physiologic contraception.

The search continued for the ideal contraceptive, and with the advent of oral agents, a new concept was supposedly introduced. Evidence that fertility can be controlled by the administration of hormonal

agents became available as early as 1921, when Haberlandt (19) showed that the transplantation of ovaries from pregnant laboratory animals into mature females of the same species caused the later to be sterile for limited periods. This author ascribed the result to the presence of corpus luteum hormone in the transplanted ovaries. Later Scaglione (21) observed that temporary sterility in female laboratory animals is produced by implantation of male gonads and by injection of testicular extracts. Parkes and Bellerby (22) injected corpus luteum extract into mice and rats and observed inhibition of ovulation and extrus for prolonged periods.

Evans et al., (23) demonstrated that purified lactogenic hormone will induce functional activity of corpus lutea. He stated, "Since corpus lutea secreteprogesterone, which inturn inhibits pituitary release of L.H. it is easy to see why ovulation rarely occurs during lactation." Three articles by Byrnes and Meyer (24, 25, 26) indicate that in certain respects the effects of estrogen and progesterone are additive in inhibiting gonadotropic hormone secretion by the pituitary, and that amounts

of these agents required are small and within physiologic limits. This principle is perhaps one of the reasons for the effectiveness of Enovid, a drug which will be discussed subsequently.

As to the use of estrogens alone, in 1932 Moore and Price (27) administered estrogen continuously to rats over a period of time and demonstrated that the gonadotropic potency of the pituitary decreased.

Haberlandt (28) administered corpus luteum extracts I.M. or orally to laboratory animals and observed temporary sterility.

Musser (29) stated that primary dysmenorrhea can be prevented in any cycle by preventing ovulation and that the administration of large daily doses of estrogen, beginning four days after the start of menstruation, will prevent ovulation. This author goes on to suggest that the administration of 1 mg. of diethylstilbesterol could be given orally, beginning on the first day of menstruation, in such a way as to have a fertility control effect, and that progesterone could be given to bring about menstruation.

Heckel et al., (30, 31) administered testosterone propionate-50 mg. three times a week-to men and observed a fall in sperm count which approached

zero level in a matter of days and which was maintained as long as the treatment continued. In the work described the aspermic conditions were maintained as long as three months or more. After cessation of treatment, recovery of sperm production occurred rapidly and sometimes reached higher levels than previously existed-a rebound phenomenon.

These observations add strength to the view that testosterone and estrogen produce effects in the male and female which are similar.

Prior and Ferguson (32) administered the antibactericidal drug nitrofuran (20% in the diet) to rats and observed a complete aspermia within a week. Similar results were obtained with furacin by Friedgood et al., (33, 34) who observed the effects in man in connection with cancer therapy. Nelson (35, 36) administered furadroxyl to rats and observed complete aspermia in four weeks. In all cases spermatogenesis returned to normal or higher levels following termination of treatment.

Train et al., (37) in a study of utilization of desert plants of the Southwest, reported that certain American Indians used an infusion made from the desert plant Lithospermum ruderale as

an oral agent for the control of fertility, the women drinking a cup of this concoction once daily during periods when they wished not to conceive. Cranston (38) performed a series of experiments on mice and found that a fluid extract with normal diet rapidly induced suppression of the estrous cycles in addition to lowering birth incidence in breeding females. Cranston suggested that the active factors derived from the herb act directly on the pituitary gland, suppressing release of the gonadotropic hormones. Suppression of the estrous cycles with Lithospermum has also been observed by Drasher and Zahl (39), Plunkett et al., (40), Noble et al., (41, 42), and Weisner and Yudkin (43). Zahl observed that whereas the sex organs go into a state of quiescence and increased fibrosis, removal of the herb materials from the diet causes an immediate return to normal estrous and reproduction.

Laszlo and Henshaw compiled a list of more than 100 plant extracts which are reported to affect human reproduction. (44)

Another approach which has been utilized is the anti-hormonal method. Since gonadotropins are protein in character, they may accordingly be

expected to induce antibody formation when used as antigens. Parked and Rowland (45) studied the inhibition of ovulation in the rabbit using anti-gonadotropic serum. They found that after administering this serum I.V. to rabbits, immediately after mating, ovulation did not occur.

The anti-enzyme approach is another, at least theoretical, method of birth control. Many enzymes are involved in the reproductive process, but so far as is known, attempts to develop an anti-enzyme which would break a link in the reproductive chain have been carried out only in relation to one enzyme-hyaluronidase, which is present at highest levels in semen. Sieve (46) has used phosphorylated hesperidin (believed to act by preventing dispersion of follicular cells around the ovum, thereby preventing fertilization) in human beings-300 couples-for the specific purpose of fertility control, and he reports clear-cut, positive results. Hesperidin was given three times daily in amounts of 100-200 mg. in tablet form, to both males and females. Ten days were allowed for the substance to reach saturation in both the man and the woman, after which no other contraceptive protection was utilized.

Periods of protection varied from 3 to 30 months and 220 couples bore normal offspring after termination of the agent. Only two couples developed pregnancies during the periods of protection, and each of these admitted negligences in maintaining saturation of the agent.

In a search for the "ideal contraceptive" - one that does not require the cooperation of the individual-Morris J. Baskin began a series of experiments. Based on the knowledge that spermatozoa produce immune bodies as shown by Metcnikoof in 1898, Landsteiner in 1899, McCartney in 1923, Fogelson in 1926, and many others, Baskin attempted to use this method in the following manner; a specimen was obtained via intercourse with condom, 1 cc hexylresorcinol added, and the entire amount injected into the woman's buttocks. Three injections seven days apart were given. The study was begun in 1929 and concluded in 1932. There were no constitutional symptoms, and only local pain at the site of injection. 19 out of 20 cases were immunized-no pregnancies-with the other case failure attributed to insufficient amount of semen injected. Baskin concluded that no case became pregnant as long as

her blood showed a definite immunity to the spermatozoa based on a slide test with and without the immunized serum. (2)

This above method has not come into common use despite the apparent excellent results, perhaps because its long term side effects are not known, and the problem of weekly shots poses a problem of inconvenience.

Thus as has been shown there have been many attempts to find the "ideal contraceptive." A furt er discussion of methods is presented in a subsequent chapter-most of which are methods currently in use and thus not primarily of historical interest.

## Present Methods of Birth Control

The present day methods of birth control are multiple-orthodox remedies, suppositories, tablets, cervical and uterine stems and rings, douching, diaphram, spermicidal jelly or cream, condom, surgery, oral drugs, and combinations of one or more of the methods.

Philosophers and sociologists have proposed two remedies: one is that the poor should not marry, or marry late in life; the second advice is abstinence or coitus interruptus. The first remedy is obviously not a practical or realistic approach, and can be dismissed rather rapidly. The second method, that married people should abstain from sexual intercourse is advice which also has no realistic basis, and to give advice which is impossible to follow is the acme of fatuity. (1)

Coitus interruptus or withdrawal, when practiced habitually, may produce organic and psychic reactions. The relatively high percentage of failure with this method is attributed to escape of viable sperm prior to ejaculation, and to the uncertainty of control of ejaculation. (5)

It is generally agreed that conception does

not usually occur at certain phases of the menstrual cycle. Through many centuries many so-called safe periods have been promulgated, but none have been scientifically supported. (5) A theory was developed soon after 1928 when a human ovum was removed from the fallopian tube at laporotomy-a theory of supposed fertile and non-fertile days in the menstrual cycle. (5) One objection to this theory is that it proposes a consistent and regular ovulatory cycle which does not exist in most women. Furthermore, contraception based on abstainence during the fertile period can not be depended on for reasons other than irregularities in the menstrual cycle. Even if the exact time of ovulation were able to be predicted accurately, the survival time of the ovum and the time consumed in traversing the fallopian tubes are not definitive. Also the extended periods of viability for sperm in the upper portion of the female genital tract complicate any attempts to define a safe period. Thus, I think it may be justly concluded that the "safe period" is impractical and experience to date has proved it undependable.

The belief that pregnancy cannot occur during lactation has little foundation since there is no

uniform pattern in the resumption of menstruation during the lactation period. Since ovulation may recur prior to menstruation the menstrual cycle alone cannot be relied upon as a guide to the re-establishment of fertility. Thus, lactation offers only minimal protection.

There is also considerable variation in the level of fertility during the climacteric period. Conception has been known to take place many months following the cessation of the menstrual cycle. Thus this period is also not a "safe period."

A spermicidal agent to be dependable must be effective from the moment of application. Most suppositories require time to melt after insertion in the vagina-also the greasy type of suppository is not miscible with the body secretions and thus may not readily release its active ingredients. The average foam tablet requires moisture for its dissolution-a moisture which is not always available in sufficient quantities in the vagina. Furthermore, there is no certainty that the tablet or suppository will be placed in the vagina to assure protection at the cervix.

Most gynecologists agree that the cervical and

uterine stem rings are dangerous and undesirable. (5) These devices act by blockage of the sperm so that they do not reach the cervical canal, and also by irritation. The rigid stems may cause perforation of the uterus, and the continued presence of a foreign body in the cervical canal may cause endocervicitis and also could act as a ladder for an ascending infection.

Douching, though a common employed contraceptive device, is impractical and inefficient. Even when used immediately after coitus, the sperm already have been deposited and may have entered the cervical canal out of reach of the douching fluid. The use of caustic fluids in the douche solutions may produce irritation of the mucosa or toxic absorption may give rise to a systemic effect.

Thus far the discussion has been limited to methods which are used today, or have been used in the recent past, and are considered illogical, unrealistic, and/or impractical. Nevertheless, many of these methods are still being used. A contraceptive device to be good and useful must be effective in preventing conce tion, but must not alter fertility upon withdrawal or discontinuation of the method.

The following methods are those which have been shown to possess these qualities.

Acceptable methods for the prevention of conception depend upon certain principles. The objective is to prevent the union of sperm and ovum-or as has been recently advocated, the prevention of ovulation, nidation, and the production of sperm. These latter methods will be discussed further in a separate chapter. This purpose can be accomplished, first, by a mechanical barrier which permits normal intercourse with a deposition of semen in the vaginal tract, but prevents sperm from entering the cervical canal. The sponge would be a crude example of this type of occlusive device. The cervical cap, vault pessary, and the vaginal occlusive diaphragm are more frequently used devices. Another principle involves the destruction of the sperm before they have an opportunity to reach the cervical canal. The most satisfactory carrier for the spermicide is a water-soluble jelly or cream. If the base is properly selected for the physical characteristics it will also act as a mechanical barrier. (5)

The contraceptive device which has been found in clinics and in private practice to be both

effective and acceptable is the individually fitted vaginal occlusive diaphragm used in conjuction with a spermicidal preparation. The diaphragm of all mechanical devices, is the most practical because it is easy for most women to use. This isolates the cervix from the coital canal and also holds the jelly or cream against the cervix.

The condom or sheath in combination with a spermicidal jelly or cream is frequently prescribed for newly married couples or where a mechanical barrier is impractical. However, as a regular method it has disadvantages. The condom is frequently unacceptable to the husband because of inhibitions due to the time required for application. For most men, and for many women as well, there is also a definite blunting of sensation.

There is also the surgical approach to birth control-a permanent device. The vasectomy for the male and tubal ligation for the female are the two surgical methods presently employed for permanent birth control and sterilization. However, these methods do not fit the criterion of allowing fertility upon "withdrawal." There is also the inconvenience of a surgival procedure, plus the everlasting

and permanent nature of the method. Theoretically, the seminal vesicles are empty of sperm within a few months, but cases have been reported of their persistence for a year. Also, it is not unusual for the cut ends of the vasa to join up by means offa channel through the intervening scar tissue. (77) Thus even these methods are not 100% effective in preventing conception.

This now leaves oral contraceptives as the most recent and perhaps most useful of the contraceptive agents. The use of progestational steroids and other drugs for conception control provides potentially relative simple form of family planning. On the other hand it also initiates for the first time the use of anti-fertility measures which can theoretically have constitutional actions. Until now the conception control measures used have been medications or devices, which as far as we know, do not possess other than local effects. Oral conception control, on the other hand, takes advantage of the fact that one of the normal physiologic functions requisite for reproduction can be altered. A separate chapter has been devoted to a discussion of the current methods of oral contraception, and

other methods which although not currently in use, are being advocated.

## Oral Contraceptives

The physiologic mechanisms of pregnancy inhibit ovulation for the duration of the gestation. It is accepted that the production of ovarian hormones by the corpus luteum of pregnancy is primarily responsible for the physiologic inhibition of ovulation. Since the pregnancy corpus luteum is known to regress at about four and one-half months of gestation, it is considered that the placental hormones exert a similar action for the balance of the pregnancy.

The administration of progesterone or estrogens will inhibit ovulation most probably in the same manner as do these hormones during pregnancy-that of inhibiting the elaboration of the gonadotropic hormones by the anterior pituitary gland. (47) However, the parenteral administration of progesterone is painful and the use of other progestins or estrogens is characterized by a change in rhythmic ovarian physiology or a pharmacologic activity for a varying period of time followed by a loss of activity-commonly called "escape." (47)

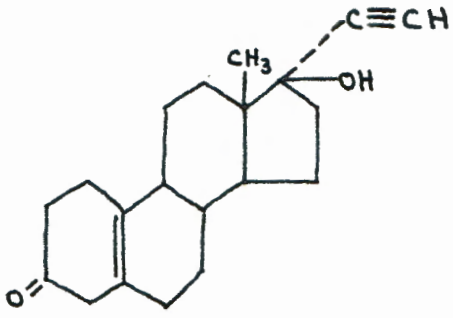
A synthetic progestin which is safe, orally effective, and not characterized by "escape" would

seemingly be of value as an oral contraceptive. On this basis the drug Enovid was developed.

A more detailed discussion of Enovid will be presented since this drug, at the present time, is the only F.D.A. approved oral contraceptive available.

Norethynodrel, a synthetic steroid, is chemically 17-ethynyl 17-hydroxy 5 (10)-estren 3-one, manufactured under the trade name of Enovid, (Searle), with ethynylestradiol, a 3-methyl-ether, added. In a ten mg. tablet of Enovid, 0.15 mg. is ethynylestradiol. (48)

Norethynodrel has three main properties: first it has progestational action when administered orally; second it has inherent estrogenic effects; and third it inhibits the pituitary gland, and it is also androgenic. (9)




The human pharmacological actions of Enovid on the endometrium, gonadotropin excretion, testes,

and on vaginal desquamation were determined by a number of workers.

A secretory endometrium was produced by women on 10 mg. of Enovid orally which was indistinguishable from that produced normally. (6) This was best demonstrated in women who possess an adequate supply of endogenous estrogen, but do not develop a secretory (progestational or luteal) endometrium. If this latter quality is not present it is necessary to prime the patient with estrogen two weeks prior to the giving of Enovid. (11)

Pincus (49), Kupperman and Epstein (50) reported a sharp reduction in gonadotropin excretion by the human being during Enovid administration.

Pincus (49) also reports a reduction in the sperm count during Enovid administration as well as testicular atrophy following prolonged administration. Heller (10) and his co-workers find that Enovid produces azospermia in the male but that within a relatively brief period after discontinuance of the drug the sperm count returns to, or exceeds pre-treatment levels. These observations seem to be able to be explained on the basis of a decreased gonadotropin secretion by the anterior pituitary

gland.

Normally there is an abrupt shift in vaginal smears as the progestational phase of a menstrual cycle begins. Rock, Garcia, and Pincus (11) observed 69 menstrual cycles and their vaginal smears under the influence of Enovid. Since the abrupt normal shift in cell distribution is accepted as evidence of ovulation, this test is circumstantial evidence of non-ovulation under Enovid influence. These authors noted only 4% with evidence of shift to the progestational type of vaginal smear as compared with 97% in the controls. Also the smears of 15% were equivocal while 81% did not show evidence of ovulation but only an irregular maintenance of the proportion of cornified cells.

The ovary is placed on physiologic rest while the drug is administered for the purpose of contraception. There is no destruction of ova since the actions of the drug inhibit the production of gonadotropic hormones and, thus, the ovaries produce no mature ova.

Thorough studies have been made and are being made at the present time in the clinical evaluation of Enovid. In 1956 a study was initiated by the

Family Planning Association of Puerto Rico to determine the efficacy and safety of Enovid for ovulation control. Approximately 900 women have been observed since this study began in 1956. The women chosen for this study were from the low income bracket living in a housing development project in a slum area. The control group was similarly chosen. Enovid was given in 10 mg. doses beginning the fifth day after menses began and continued for 20 days and then stopped. For statistical purposes, the expression of results is in patient years-adding the number of those patients who have been taking Enovid more than two months. (For an explanation of "patient years" as a statistical expression, see chapter 5 page 43.) Including those volunteers who neglected to take the medication as directed, the pregnancy rate for the first 30 months of the study was 2.7% per 100 women years whereas the same women prior to this program had a rate of 61.2% per 100 women years. There were no pregnancies in those who took the medication as directed. The results in all studies are summarized in Table one. (12)

Table One

| Investigators | Number of Patients* | Total Women Years | Total Number of Cycles | Remarks |
|---|---|---|---|---|
| Rock, Garcia, Pincus, and Paniagua (53) | 364 | 421.7 | 5,483 | 66 patients for 24-38 cycles |
| Laragne and Nicola (54) | 121 | 77.4 | 1,007 | 64 patients for 9-12 cycles |
| Satterthwaite (55) | 181 | 151.5 | 1,970 | 80 patients for 12-21 cycles |
| Morris (56) | 47 | 15.0 | 196 | 47 patients for 1-10 cycles |
| Banks, Rutherford, and Coburn (57) | 20 | 9.0 | 120 | 20 patients for 6 cycles |
| Tyler (58) | 164 | 127.0 | 1,651 | 70 patients for 12-22 cycles |
| TOTALS | 897 | 801.6 | 10,427 | |

*None of these patients became pregnant while taking Enovid

As far as the safety of the drug is concerned, a vast study has been made. Evidence pertinent to this has resulted from the observation that women who withdrew from ovulation control, regardless of the reason, were at least as susceptible to conception as non-participants and such pregnancies proceeded to the delivery of infants which were normal in every respect. (12) An additional evidence of safety is supplied in the results of long term high doses (40 mg. daily) of Enovid used in the treatment of endometriosis by Kistner (51) who observed no toxic effects in these women and when the medication was stopped normal menstrual rhythm was re-established.

The fact that normal women ovulate and menstruate regularly following Enovid therapy indicates that there is no discernible untoward effect on gonadotropin activity of the anterior pituitary gland. Neither is there any evidence of adverse effect on the elaboration of other anterior pituitary hormones.

That there is no adverse effect on the ovum producing capacity of the ovaries following Enovid administration has been demonstrated by Rock and

his co-workers. (52) This determination was made by actual count of the number of primordial follicles in the ovaries of Enovid-treated and untreated patients. In no instance was there any significant variation from the normal count.

Pregnancies according to the number of tablets missed: (7)

| No. of tablets missed | No. Preg. | Rate/100 women years |
|---|---|---|
| 0 | 1(?) | 0.2 |
| 1-15 | 5 | 7.7 |
| 6-19 | 11 | 43.3 |

Thus if the regimen is followed faithfully practically 100% contraception occurs. It is also clear that the rate of conception is proportional to the number of tablets missed. Analysis of the data indicates that no habituation to the medication occurred-that is pregnancies occurred at the same rate in the long term users as in the short term users.

There are a multitude of reasons given for the withdrawal from the use of Enovid. These reasons are tabulated in Table two. (7)

In three projects 28.2% to 41.8% of those withdrawing did so because of reactions; in the fourth

Table Two

Reasons for Withdrawal

| | San Juan | | Humacao-R | | Humacao-P | | Haiti | |
|---|---|---|---|---|---|---|---|---|
| Reason | No. | % | No. | % | No. | % | No. | % |
| Reactions | 64 | 28.2 | 5 | 41.8 | 10 | 32.3 | 3 | 7.3 |
| Not Interested | 36 | 15.9 | 1 | 8.3 | 0 | 0.0 | 17 | 41.5 |
| Pregnant | 12 | 5.3 | 1 | 8.3 | 1 | 3.2 | 3 | 7.3 |
| Unrelated illness | 16 | 7.0 | 0 | 0.0 | 0 | 0.0 | 2 | 4.9 |
| Husband opposed | 5 | 2.2 | 0 | 0.0 | 0 | 0.0 | 1 | 2.4 |
| Moved | 34 | 15.0 | 3 | 25.0 | 6 | 19.3 | 9 | 22.0 |
| Sterilized Male or Female | 29 | 12.8 | 1 | 8.3 | 6 | 19.3 | 0 | 0.0 |
| Separated | 20 | 8.8 | 0 | 0.0 | 6 | 19.3 | 2 | 4.9 |
| Miscellaneous | 11 | 4.8 | 1 | 8.3 | 2 | 6.5 | 4 | 9.7 |
| Total Withdrawal | 227 | | 12 | | 31 | | 41 | |
| Total No. of Subjects | 438 | | 117 | | 126 | | 149 | |
| Percent Withdrawal | | 51.8 | | 10.3 | | 24.6 | | 27.5 |

project, lack of interest was the prime cause of withdrawal. Between them these two reasons account for 32-50% of the withdrawal. Since the reactions are in a large part psychogenic, means for dealing with them might be devised. It has been shown that a placebo or an antacid pill will relieve up to 90% of these reactions. (7) The lack of interest is due chiefly to the lack of motivation among an economically low level group.

The high withdrawal rates can also be explained on the following facts: other methods of contraception were available, frequent moving, improved economic conditions making limitation of a family less desirable, and difficulties in initiating a new method.

An analysis of reactions is given in Table Three. (59)

In the physicians brochure, published by the Searle Company, a series of statements are made in answer to anticipated questions concerning Enovid: (60)

"1. Is the method contraceptively effective? yes

2. Does it cause any significant

Table Three

Analysis of Reactions to Enovid

| | |
|---|---|
| Total Number on Enovid | 221 |
| Total Number on Enovid having reactions | 38 |
| Percent having reactions | 17.43% |

| Symptoms | Number | Percent |
|---|---|---|
| Dizziness | 29 | 76.12 |
| Nausea | 26 | 68.16 |
| Headache | 18 | 47.14 |
| Vomiting | 17 | 44.28 |
| Abdominal Pain | 9 | 23.26 |
| Weakness | 7 | 18.16 |
| Diarrhea | 1 | 2.24 |

abnormalities of the menstrual cycle? no

3. Does it adversely affect the reproductive tract and adnexae? no
4. Does it have physiologically adverse effects generally? no
5. Does it affect the sex life of the subjects adversely? no
6. Does it impair fertility upon cessation? no
7. May a low dosage level of the drug be used? yes
8. Is the method acceptable? yes, but to an extent which varies with the motivation, economic situation, and other factors."

It is recommended by the Searle Co. and stated by the F.D.A. that when Enovid is prescribed for cyclic administration over prolonged periods, a total period of twenty-four months should not be exceeded until continuing studies indicate that its present lack of undesired actions continues for even longer periods.

As far as clinical effectiveness is concerned,

a comparison with various other methods of contraception is tabulated in another portion of this paper.

Tyler and Olson studied five steroid compounds as anti-fertility drugs. (8) The drugs used were:

1. Norethindrone (19-nor-17 alpha-ethinyl testosterone) known as Norlutin.
2. Norethynodrel (17-ethinyl estraenolone) known as Enovid when estrogen is added.
3. 17-alpha-hydroxyprogesterone caproate (17-AHPC) known as Delalutin. (an I.M. preparation)
4. 17-alpha-acetoxyprogesterone
5. 9-alpha-bromo-11-ketoprogesterone (BKP)

These two authors discovered on a preliminary study that ovulation was often suppressed by the progestational compounds, but that this suppression was not invariable. However, there was a relatively consistent distribution of the pattern of endometrial development so that it seems unlikely that normal implantation could occur in such endometria. Furthermore, the potent progestational compounds often altered the quality of cervical mucus to make it less receptive to spermatozoa. There seemed to be considerable individual variation among women in susceptibility to inhibition of ovulation.

A contraception study was initiated utilizing the above named progestational compounds as the

measures. 715 patients requested the method-241 (34%) actively used the methods and the remainder discontinued it. Reasons for discontinuing were side effects and patients moved away. The 241 patients represent a total of 3,622 patient months of use. For 1,488 patient months, which are excluded, use of the compounds was associated with another method. With 474 patients who discontinued use 948 patient months could be included in the overall figures, as indicated in Table Four; thus this study encompassed a total of 2,134 and 948 or 3,082 months of use. 22 pregnancies occurred during this time or 8.6 per 100 women years compared with an average of 4% with standard methods as the diaphragm and jelly. (8) These 22 pregnancies were divided into those occurring among patients admitting to regular use-7, and those who admitted to irregular use-15. Of further note is the fact that there were proportionately more pregnancies during trials with the less potent compounds than there were with use of norethynodrel and norethindrone. Utilizing the figure of 7 pregnancies occurring with the regular use of the drugs, a rate of 2.7, which compares favorably with standard

methods. See Table Four.

Another significant point in relation to the use of this method is the relative importance of the estrogens in the compounds employed. The two most effective agents, norethindrone and norethynodrel, both have estrogenic activity, the latter having 0.150 mg. of 3-methyl ether of estradiol in each tablet of 10 mg. Tyler and Olson (8) further state that this amount of estrogen alone will inhibit ovulation, and they are conducting further studies at the present time to determine the relative occurrence of this as well as the frequency of other findings observed when patients received the combined substances. These rates may not be strictly comparable to the Indianapolis study, since most figures counting "women years" of exposure include only those who have used some method at least one full year successfully.

## Table Four

241 Active Patients 474 Discontinued

| Compound | Months Used Alone | Months With Other | Months Used Alone | Months With Other |
|---|---|---|---|---|
| Enovid | 1,008 | 869 | 495 | 372 |
| Norluten | 563 | 257 | 202 | 188 |
| Delalutin | 74 | 47 | --- | 28 |
| Progesterone and Estrogen | 364 | 213 | 94 | 181 |
| BKP | 152 | 102 | 157 | 157 |
| Totals | 2,161 | 1,488 | 948 | 926 |

Pregnancy Rate - 15 pregnancies - 5.9 Irregular use

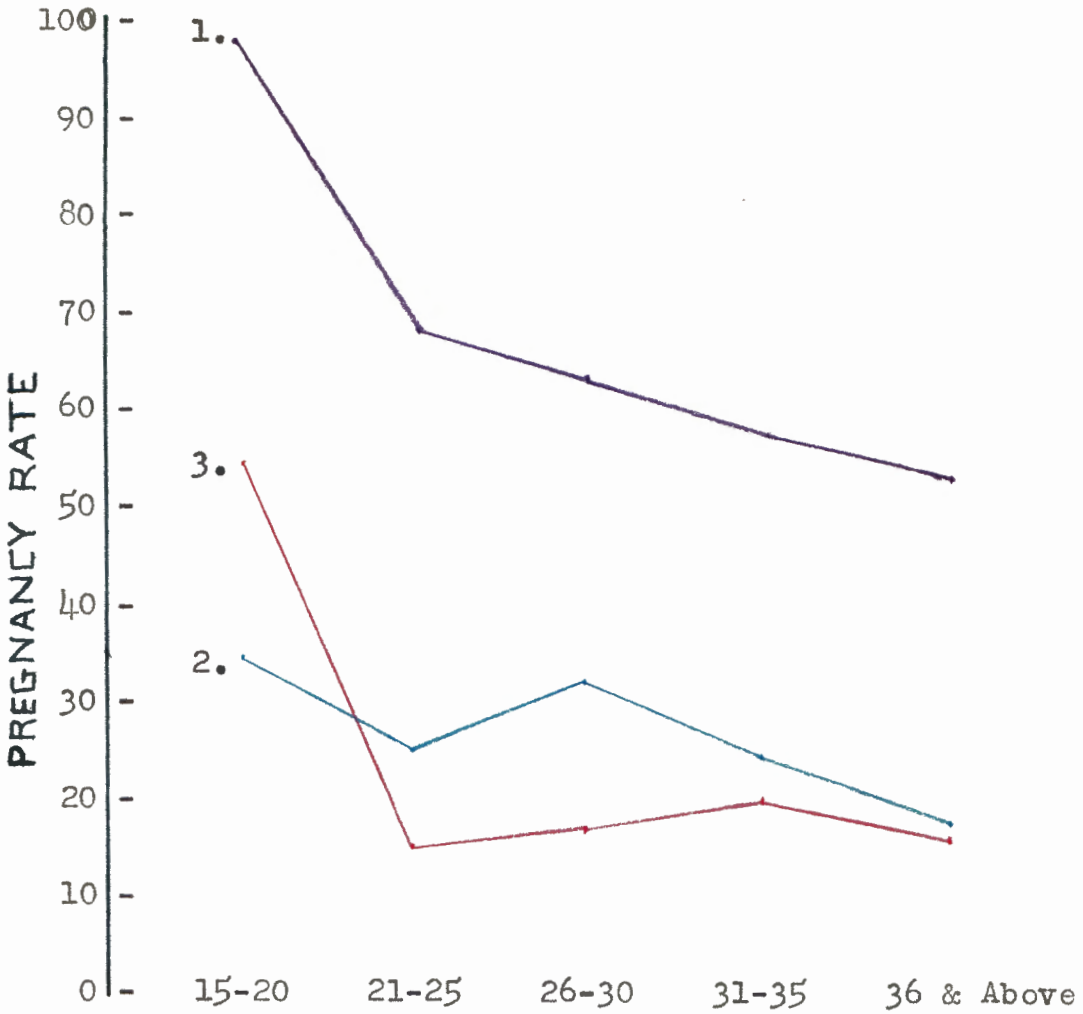
Pregnancy Rate - 7 pregnancies - 2.7 Regular use

A series of animal experiments on white rats by Samyal (61) from 1950-1955 demonstrated the contraceptive effect of Pisum Sativum (the common field pea). This effect was due to the inhibition of the peripheral action of progesterone and consequent prevention of nidation of a fertilized ovum. The active principle of this compound was found to be m-xylohydroquinone.

Samyal (62) conducted a field trial on humans for the effectiveness of this compound. This group consisted of a low income and lower middle class group of people. Doses of 300-350 mg. were taken orally by women twice each month on the 16th. and 21st. day of menstruation, and the pregnancy rate was found to decrease. Graph A shows this decrease in a tabulated form.

Advantages of this oral contraceptive were two-fold. Apart from the prevention of nidation of a fertilized ovum by preventing progesterone preparing the lining of the uterus for the reception of the fertilized ovum, it acts as a spermicide by being excreted into the cervical secretions. The author further stated that this oral contraceptive requires no preparation, no intelligence on the

Graph A




Age-Grouping Curve

1. Preclinic rate.
2. Clinic rate all calculated.
3. Clinic rate, two months eliminated.

part of the user, and there is no cause for repugnance even with the fastidious subjects. There is no risk of abortion, permanent sterility, or deformity in babies born in failure cases. (62)

There were two series of cases: during the first four months of the first series one capsule 150 mg. was administered each month orally 8-10 days before the expected onset of the next menstrual period. From the fifth to the twelfth month of the first series two such capsules were given each month. Subsequently in the first series and throughout the second series, two capsules were given each month, each containing 300-350 mg. The timing of the administration was chosen with the expectation of preventing the lining of the uterus from being prepared for nidation-approximately the 16th. and 21st. day, with the patients who were not menstruating taking the capsules approximatley every fortnight.

The premedication pregnancy rates were calculated as follows: from the total number of years of married life, there were subtracted 3/4 year for each live birth or still birth, and 3/8 year for each miscarriage. The total number of pregnancies

times 100 was then divided by the net number of non-pregnant years married. This rate was 65 per 100 couples per year. See Table Five for a summary of results.

To summarize the results given in Table Five, the pregnancy rate was reduced from 65 to 31 or 52% reduction when the second capsule was taken at home. When the capsules were taken under observation the rate was 20 or 69% reduction, and when in addition the third and later months were considered, the reduction was 83% or a rate of 11. (62)

C. Gamble (63) undertook to study the toxicity effect of this drug and demonstrated that it is not at all toxic to the human system.

For a comparison of this drug as an oral contraceptive with other oral contraceptives and other contraceptives in general, please refer to another portion of this paper.

Table Five

| | First Series | Second Series |
|---|---|---|
| Patients | 473 | 254 |
| Patient Months | 2,167 | 1,465 |
| Pregnancies | 56 | 24 |
| Pregnancy Rate | 31(27) | 20(11) |
| Excluding Months of Amenorrhea | | |
| Patients | 473 | 254 |
| Patient Months | 1,567 | 934 |
| Pregnancies | 48 | 21 |
| Pregnancy Rate | 37(32) | 27(12) |

(The second figure in parenthesis is omitting the first two months.)

## Clinical Effectiveness of Contraceptives

Tietze (64) stated that the consideration of the effectiveness of contraceptive methods requires distinction on three levels of effectiveness: physiologic, clinical, and demographic.

Physiologic effectiveness may be defined as the measure of protection against unwanted pregnancy affored by a specific contraceptive method under ideal conditions-used consistently and according to instructions without omissions or errors of technique-thus according to the scientific method. This measurement would be higher than that observed clinically due to the rarity of such conditions.

Clinical effectiveness is the measure of protection achieved by a group of couples using contraception more or less consistently with some degree of care and skill. I believe it is evident that this type of effectiveness would be higher among the more intelligent segments of the population. It is also higher among those who follow the method because of their own initiative rather than those who have been persuaded to do so; and also higher in cities than in rural areas. (64) These considerations should be taken into

account before evaluating the effectiveness of a contraceptive method.

Demographic effectiveness is a more inclusive concept. It is the reduction of conception among all couples who have been instructed in the use of a contraceptive method, including those who fail to use it as well as those who discontinue the use after a shorter period of time. Thus demographic effectiveness would include clinical effectiveness plus all other factors which may promote or discourage continued reliance on the method, including also the availability and acceptance of other forms of birth control.

A more efficient approach to the study of effectiveness of a contraceptive than the percentage of failures or successes was developed by Raymond Pearl (65) in the early 1930's. This is the pregnancy rate per 100 years of exposure computed by the following formula:

$$\text{Rate} = \frac{\text{Total number conceptions} \times 1200}{\text{Total months of exposure}}$$

Stix and Notestein (66) found that pregnancy rates without the use of contraception have generally been found within a range from 6-100 per

100 years of exposure, after the first pregnancy, according to the experience of couples who later resorted to contraception. An average of 80 approximates the general average. It is important to know these facts so that a true evaluation of a contraceptive method maybe ascertained.

The most comprehensive data that was found on the effectiveness of contraception as practiced by the general population, was a sample of about 2,000 white Protestant couples interviewed in Indianapolis in 1941 and 1942. The period of married life covered by the histories of these couples was 12 to 15 years, with the median age of the wives at marriage 21. The sample included a total of almost 12,700 years of exposure-152,300 months-with use of various contraceptive methods, and 1,567 pregnancies during this period. The pregnancy rate for all methods combined was 12 per 100 years of exposure. (67) This calculated is: Rate= 1567 x 1200/152,300. Refer to Table Six.

A statistical analysis by the Ortho Products Co. (5) revealed similar results as the Indianapolis study. Table Seven shows the breakdown of these

Table Six

Years of Exposure, Number of Accidental Pregnancies, and Pregnancy Rate, by Method and Level of Income.

| Method | Total | High | Medium | Low |
|---|---|---|---|---|
| Years of Exposure | | | | |
| All Methods | 12,692 | 2,820 | 5,160 | 4,712 |
| Diaphragm | 971 | 283 | 355 | 333 |
| Condom | 2,705 | 587 | 1,212 | 906 |
| Withdrawal | 546 | 151 | 123 | 272 |
| Douche | 3,870 | 688 | 1,577 | 1,625 |
| All Other | 4,600 | 1,131 | 1,893 | 1,576 |
| Accidental Pregnancy | | | | |
| All Methods | 1,576 | 226 | 506 | 835 |
| Diaphragm | 39 | 8 | 9 | 22 |
| Condom | 183 | 34 | 73 | 76 |
| Withdrawal | 53 | 4 | 15 | 34 |
| Douche | 815 | 120 | 269 | 426 |
| Others | 477 | 60 | 140 | 277 |
| Pregnancy Rate | | | | |
| All Methods | 12 | 8 | 10 | 18 |
| Diaphragm | 4 | 3 | 3 | 7 |
| Condom | 7 | 6 | 6 | 8 |
| Withdrawal | 10 | 3 | 12 | 13 |
| Douche | 21 | 18 | 17 | 26 |
| Others | 10 | 5 | 7 | 18 |

(Others-means including all combinations of methods.)

Table Seven

| | Diaph. with Jelly or Cream | Diaph. with Gel | Gel Alone | Cream Alone | Vaginal Tablet |
|---|---|---|---|---|---|
| Total Women | 271 | 269 | 458 | 137 | 649 |
| Total Months of use | 2,843 | 2,971 | 3,728 | 633 | 2,836 |
| Pregnancies Planned | 17 | 21 | 37 | 1 | 10 |
| Pregnancies: Incorrect Use Irregular Use Subst. Method | 13 (4.8%) | 14 (5.2%) | 15 (3.3%) | 3 (2.2%) | 11 (1.7%) |
| Pregnancies Claimed Constant Use | 10 (3.7%) | 8 (3.0%) | 10 (2.2%) | 1 (0.7%) | 5 (0.8%) |
| Pregnancy Rate: | 9.7 | 8.9 | 8.0 | 7.6 | 6.8 |

results, giving some information as to combination of methods not given in Table Six.

Dickinson and Morris (68) reveal another method of expressing clinical effectiveness of a contraceptive method as indicated in Table Eight.

Comparing the pregnancy rate for oral contraceptives with the rates given in Tables Six and Seven, the rate for oral contraception-8.6, which includes all pregnancies is at least comparable with the best methods as indicated by the clinical effectiveness. And when comparing the oral methods excluding the pregnancies resulting from not following instructions, a pregnancy rate of 2.6 is calculated. Since irregular use of the hormones destroy its effectiveness as a contraceptive, it is as though no device is used at all. According to Rock and his coworkers, a pregnancy rate of 0.0 is obtained if directions are followed explicitly. (53) Table One further illustrates this possibility in actual case evidence.

Millman and Hartman (69) investigated a series of various compounds as to their oral anti-fertility properties. Their results are given in Table Nine. These

Table Eight

| Method | Percent of Effectiveness |
|---|---|
| Diaphragm and Jelly | 85-95% |
| Condom | 70-95% |
| Withdrawal | 35-80% |
| Jelly Alone | 70-90% |
| Foam Powder | 55-95% |
| Douche | 16-70% |

Table Nine

Typical Results in Assay of Oral Control of Fertility

| Class | Agent | % Inhibition of Fertility |
|---|---|---|
| Antimetabolites | Aminopterin | 81 |
| | Desoxypyridoxine | 70 |
| Antienzymes | Ph. Hesperidin | 0 |
| | Arbutin | 0 |
| | Esculin | 0 |
| Antispermatogenics | Furadroxyl | 100 |
| Antihistamines | Benadryl | 0 |
| | Pyranisamine | 0 |
| Botanicals | Lithospermum | 31 |
| | V. Prunifolium | 0 |
| | Y. Santa | 0 |
| Synthetics, drugs | Sulfathiazole | 0 |
| | Thiouracil | 67 |
| | Xyloquinone | 20 |

(Mice, rats, guinea pigs, and rodents)

results, however, are from laboratory animals and their application to human beings may be seriously questioned.

An estimation of the cost per month of the various contraceptive agents available for public use has been tabulated in Table Ten. The cost of the various agents per month were calculated on the basis of ten applications per month. The low cost of Pisum Sativum does not reflect the added expense of shipping, packaging, etc. which would be necessary if the product became available for general use. The cost of a device for anti-fertility perhaps influences its selection as much as its clinical effectiveness, if not more.

Table Ten

Cost of the Contraceptive Agents

| Agent | Gross Cost | Cost/Month |
|---|---|---|
| Diaphragm | $3.00/each | $ .25 |
| Jelly (Ortho-gynol) | $2.25/136 Gm.** | $ 1.00 |
| Jelly Alone (Preceptin) | $2.00/70 Gm. | $ 1.50 |
| Cream (Ortho-cream) | $2.25/115 Gm. | $ 1.00 |
| Foam Tablets (Norform) | $ .98/6 | $ 1.60 |
| Condoms | $1.80-6.50/12 | $ 1.50-5.50 |
| Suppositories (Lorophyn) | $1.47/12 | $ 1.20 |
| Enovid | $ .50/each | $10.00 |
| Pisum Sativum* (m-xylohydroquinone) | $ .02/each | $ .04 |

*Cost is for raw material only.

**5 Gm. per application-cost per month based on 10 applications per month.

## Future Approaches to Fertility Control

There are many points in the reproductive process that could be attacked in order to prevent conception and thus control fertility. Among those which may be particularly vulnerable, according to Nelson (70) are: spermatogenesis, transport of sperm, formation of seminal fluid, maturation of ova and ovulation, action of the hormones on the uterus, transport of sperm to the upper end of the tube, maturation of sperm in the female reproductive tract, sperm entry into ovum, and embryonic development.

Experience to date has suggested that the most vulnerable point in spermatogenesis is the meiotic division, which is undertaken by the primary spermatocyte in its process of chromosomal reduction. Certain drugs, nitrofurans and related compounds, which interfere with important phases of carbohydrate metabolism, very effectively inhibit in a reversible fashion the meiotic division without in any way appearing to influence the other testicular functions. However, high doses have an adverse effect in men. When used in therapeautic doses it has a slight but scarcely significant action. (71)

A safe, but not entirely practical method of interfering with spermatogenesis in man is through the use of steroid hormones, via their inhibition of secretion of the gonadotropic hormones. Estrogens are the most effective, but are contraindicated due to their interference with the endocrine function of the testes. The androgens are also effective as anti-fertility agents. However, these hormones have the disadvantage of requiring constant maintainance of high levels of the hormone which not only is expensive, but is not without danger. (30)

Although no means of preventing the metamorphosis undergone by spermatids in the process of sperm formation is known to be effective in the case of the human being, it is thought that this complex phenomenon is a very vulnerable point. According to Featherstone et al., (72) and Steinberger (73) the spermatid-spermatozoon transformation involves important metabolic processes which should not be too difficult to interfere in and thus constitutes another potentially vulnerable point of attack.

The transport of sperm although a seemingly vulnerable point has not been investigated to any

great degree so that information concerning this aspect of conception control is not readily available.

It has been shown that a reduction or increase in the seminal fluid content of one or more constituents will have marked deleterious effects upon the capacity of sperm to effect entry into the ovum. For example, Hagg, Goldzieher, and Werthessen (74) have shown that an excess of certain substances-silver-binding-are related to a significant reduction in fertility, at least in stallions.

- The inhibition of the action of estrogens and/or progesterone on the endometrium in a direct fashion, thus preventing nidation of the ovum has already been discussed in a limited degree. (Pisum Sativum studies). The studies of Velardo et al., (75) in which the administration of pregnandione and prenanediol inhibited the normal response of the endometrium to progesterone, bear directly upon this means of interfering in the conception process.

Studies with certain of the anti-metabolites have shown that recently implanted embryos are highly vulnerable to the effects of substances that interfere with fundamental anabolic processes.

Particularly effective have been azaserine, 6-mercaptopurine, and aminopterin. The mechanisms whereby these substances destroy the young embryo appear to be one in which the compound competes with the naturally occurring materials that are important to the embryo. However, the use of these drugs is not without danger to the mother, and if the embryo is not killed, the fetus may develop serious anomalies. (76)

Hormones are complex and not simple compounds in their action. The delicate endocrine balance of the organism is easy to disturb; it is not always easy to re-establish it, and it is never easy to predict the full nature and ramifications of that disturbance. Therefore, it will take much investigation and experimentation to rule out the possibility of undesired side effects when these many drugs that have been mentioned as potential fertility control agents are used.

There have been many interesting approaches to the problem of "an ideal contraceptive," and perhaps only time will tell if any of these will eventually prove out to be acceptable.

## SUMMARY

The foregoing thesis undertook the task of reviewing the literature on the subject of birth control, with special attention to the latest developments in this field-oral contraceptives.

Man has gone a long way from the prehistoric period where contraception was based on infanticide and abortion to the present era where the simple act of taking a pill will prevent conception.

The many theoretical approaches to a method of contraception were reviewed: hormonal, including plant extracts; anti-metabolites; anti-hormonal; anti-enzyme; immune bodies; and anti-spermatogenics.

The many present day methods of contraception were also reviewed: orthodox remedies, vaginal suppositories and foam tablets, cervical and uterine stem rings, douching, diaphragm, spermicidal jelly and cream, condom, surgery, oral agents, and the various combinations thereof.

A more detailed discussion of Enovid was presented-the only oral contraceptive available for public use. Included also is a study of other oral agents that have been used in experimental studies,

and their results. A new agent extracted from the common field pea-Pisum Sativum-and known as m-xylohydroquinone, has been found to possess anti-fertility properties, and has been shown to be a very promising agent in the studies thus far completed.

A section of this thesis is devoted to the subject of clinical effectiveness of contraception, in an attempt to place the relative merits of the various agents on a statistical basis. Tables and graphs are included to illustrate the relative effectiveness of the anti-fertility agents available.

There are a multitude of experiments going on at the present time utilizing new theories and new methods in the search for the "ideal contraceptive." Some of these theories have been reviewed in brief, in order to give some insight into future possibilities.

An idea as to the cost of the methods available has also been presented.

Thus a review of the historical, present, and future methods of contraception have been presented, with a discussion of advantages and disadvantages of the various agents,along with a statistical

comparison of their clinical effectiveness.

It should be evident by the multiplicity of methods available, that no one agent has been found which satisfies the criteria of an "ideal contraceptive." To satisfy this title, the agent would have to be safe, effective, rapid in action, rapid in reversibility, simple in action-without disrupting complex balance systems of the body, low cost, acceptable, and pure. Thus, it is perhaps easy to see why such an agent has not been found to date, but this is not to say that such an agent will not be developed in the future.

## CONCLUSION

The most effective contraceptive method in wide use at the present time is the diaphragm. Of the oral agents, Enovid is the only one available for general use and based on the clinical data to date it is very effective-perhaps approaching 100% in its effectiveness. However, the potential long term side effects of this drug caution against its use. M-xylohydroquinone may be the answer in the search for an oral agent, since no toxic or side effects have been observed in its limited clinical studies. The use of this compound must, thus, be considered. The search for the "ideal contraceptive" continues.

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