CURRENT ATTEMPTS TOWARDS IDEAL CONTRACEPTION

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It is generally agreed that the development of new contraceptives is an indispensable adjunct to the solution of the world wide and national problems related to the explosive population growth.

Ideal contraception should fulfil certain criteria; it should be effective, safe, inexpensive, reversible, aceeptable and easily applied to various population groups, with no objectionable side effects and it should not interfere with the sexual act. The most recently introduced methods (pills and IUDs) though widely used are still not to the standard to fulfil the above mentioned criteria.

The aim of this communication is to present a variety of research attempts which are hoped to fulfil most of these criteria. The development of these new methods needs the collaboration of several acientists from several disciplines, including reproductive biologists, biochemists, physiologists pharmacologists, molecular biologists, bio-engineers and system analysts working hand in hand with the gynecologists. At the present time, several attempts by scientists from all over the world, are tried, aiming to the development of an ideal contraceptive. A brief account will be given on each :

I.—Steroid Contraceptivss :

1. *Low dose oral progestones*

In the form of chlormadinone 0.5 mg, Lynoestrenol 0.5 mg., Quingestanol 0.25 mg. were tried in a continuous daily dose. (7) Ovulation is not inhibited in the majority of cases (± 60%) as judged by pregnandiol estimation, endometrial biopsies and findings on culdoscopy, but in spite of the occurrence of ovulation, this form of contraception was found highly effective.

The mode of action is possibly a direct effect on the cervical mucous or on an action of the endometrium making it impossible for the fertilized ovum to implant.

This method have the advantage of administering very small doses of steroids and of being given continously and thus needing no special attention from the participants. The main disadvantages are the higher incidence of amenorrhea and irregular bleeding.

2. *Post Coital Pills*

Which could be taken after intercourse. They would presumably inhibit implantation of the fertilized ovum and might have a wide sphere of applicability.

Stilbaesterol and Ethinyl oestradiol were tried in high doses for 4—6 days after exposure and proved effective in preventing pregnancy (9,10). The main disadvantage is the side effects of such high doses of estrogen. Another disadvantage is that in certain communities the post coital pill may turn to be a daily pill.

3. *Once-a-month pill*

Suggestions have been made that it might be feasible to develop a tablet which could be taken once per month instead of regularly throughout the cycle. A pill combining 2 mg. Quinesterol (a long acting estrogen which is stored in the body fat and subsequently released) and 5 mg. Quingestanol (a progestin which has twice the potency of noreethindrone acetate in biological studies). The pill is given on day 25 of the cycle. Its acceptability was reported by Soberon in Mexico and by Greenblatt (3) as good and its effect on preventing ovulation was 57% in the preliminary studies.

4. *Long acting Injectable Preparations*

The once a cycle injectable prepartions combining aestrogen and progestin have been widely experimented all over the world. They proved fully effective in preventing pregnancy. This was our experience with Deladroxate. (5) Its main disadvantage was a 2.4% breakthrough bleeding.

Depo preparations of progestins given every 3, 6, or 12 months are now tried, particularly during the post partum period and their effects on lactation are now evaluated. The main disadvantage is the high incidence of amenorrhea and an increase in body weight. Both are not a problem in the post partum period.

5. *Pellets*

These are being tried now. They are implanted subcutaneously or subfacially and can be removed easily when requested. They contain steroid hormones which diffuse gradually and evenly for months or even years to produce a contraceptive effect. Its introductin implies a small surgical incision besides the menstrual irregularities, mainly amenorrhea.,

II.—Intrauterine Contraceptive Devices

1. *Hormone releasing IUDs*

These were introduced with the idea that expulsion of intrauterine devices could be decreased by addition of a progestin to the device. IUDs mode of silastic were readily expelled by rats and rabbits unless the IUD had melengesterol acetate added in 5 or 10% concentration. The lower concentration lessened the expulsion rate and appeared to act locally. The 10% concentration completelyl prevented expulsion, even of a contral device from the contra-lateral horn. Serial endometrial biopsies after ovariectomy on estrogen primed monkeys demonstrated that the primate uterus also can respond to the local hormone-impregnated in IUDs.

2. *T-cupper devices*

These were introduced and tried in Chile by zipper and Tatum with the idea that the cupper ions in the device act on the enzyme systems in the endometrium, thus preventing bleeding which is a major side effect of intrauterine contraception.

III.—Control of the Time of Ovulation

Clomiphene was tried to fix the date of ovulation and thus making the rythm method more safe.

IV.—Immunologic Methods

1. *Immunization of females against spermatic materials*

(a) *by active immunization* ; was reported in animals and humans. In animals it was demonstrated that antisperm antibodies could be present in the blood serum of immunized female animals, but the effect of such antibodies on fertility is still under experimentation. The failures may be due to the large excess of sperms present in the inseminate which binds all the antibody that may be present in the female genital tract and leaves some sperms unaffected.

(b) *by passive immunization* ; experiments with invertebrates and with vertebrates have shown that the fertilizing capacity of sperm can be destroyed by direct treatment with homologous antiserum. However there has, as yet, been no clear cut demonstration of antifertility action in mammals by systemic administration of an antispermatozoal serum.

2. *Immunologic induction (in males) of aspermatogenesis by auto and isoimmunization with sperm*

Spermantogenesis in guinea pigs is suppressed following injection of homologous or ontologus sperm or testicular extract. So far, the effect is obtained consistently only when an adjuvant of the Freund type is present in the vaccine. Such adjuvants (killed mycobacteria, mineral oil and an emulsifying agent) cannot in their present form be considered acceptable for use in healthy human beings.

3. *Action of antibodies on developing embryos*

Depending on the same principle of the hemolytic destructive effects of the pH antigens on the fetus. Experiments are now done to produce specific antisera directed against various trophoblastic and embryonic tissues. The experiments were successfully true in animals, as evidenced by abscrption of the embryos. This is under trial on humans in Japan where abortion is legalized.

4. *Antihormones*

The antihormone studies has been the subject of much depate and confusion but there is no doubt that antibodies can be produced against protein hormones as against other kinds of proteins.

Inhibition of endogenous hormones by active immunization with the corresponding hormone from another species have not been critically demonstrated, but experiments are reported in which endogenous gonadotrophin is suppressed by means of hetero immune sera. In animals anti L.H. activity was successfully induced and prevented ovulation.

5. *Antienzymes*

These are now experimented. They interfere with the intermediary biosynthetic pathways of steroid hormone production, particularly with regard to corpus luteum function.

V.—Experiments Involving the Tubal Factors

These are now tried aiming at the development of substances which : (1) inhibit the action of the fimbria in egg pick up mechanism ; (2) alter the function of the cilia or the oviductal musculature and thus alter the timing of transport of ovum or sperm ; (3) change the composition of oviductal fluids and advesrly affect ovum or sperm or the process of fertilization.

VI.—Sterilization

1. *Sterilization by temporary occlusion of the Oviduct in female and the vas deferens in males*

Experiments were done in which oviducts of female rabbits were occluded by silicone rubber materials (4) (elastic & elasticon). Occlusion of the medial and midportions of the oviduct prevented pregnancy in a high percentage of cases, while occlusion of the lateral portion failed. Similar work was done to occlude the vas temporarily with even better results. Occusion in the vas was more successful due to the uniformity of its lumen. The effect on the tube and vas was proved to be reversible when the plug was removed.

2. *Sterilization through an operating culdoscope*

VII.—Compounds Interfering with ovum implantation and Development

1. *Alkaloids and Antimetabolites*, were evaluated by John Mc Lean et al., From Yale University (1967) , in experiments carried out in the rabbit and the monkey.

Alkaloids (ergocornine, vinblastine, calcemide) with reported antifertility effect in the rat, antitrophoblastic effect in man or other antim activity were investigated in the rabbit. At the dosage schedule used, ergocornine was ineffective and vinblastine appeared to be teratogenic. The most effective, colcemide, produced complete zygotic destruction after implantation in the rabbit and was evaluated in the monkey by administration on days 24, 45, 66 and 84 of pregnancy. There was no delectable effect on the primate fetus.

Three antimetabolites, a pyrimidine, a ribonucleoside and a purine were also studied. There was surprisingly little effect on the rabbit fetus with 5 fluorouracil or 6-azauridine, the riboneocleoside of 6 azaurcil. The 6 mercaptopurine derivative was effective in producing better destruction early in pregnancy in the rabbit ; it was markedly teratogenic in the middle of gestation and ineffective . Thereafter. When administered on days 28-30 to a Macoque monkey, this compound did not inhibit pregnancy.

Evaluation of these compounds may be of value in contributing to development of post-coital conception control measures, and to knowlege of the possible teratogenic effects of drugs taken during pregnancy.

2. *Synthetic estrogens and antiestrogens* were investigated for post-coital contraceptive effect in the rabbit and the monkey by Morris et al. (1967).

Parahydroxy-propiophenone appeared to have relatively little efiect on implantation or development of the rabbit fetus even at relatively high doses. Clomiphene was also shown to have no effect on preventing pregnancy when administered post coitally. Nor did it appear to have deleterious effects on the fetus.

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