PHARMACOLOGY OF REPRODUCTION AND FERTILITY

By Louis Fridhandler[1] and Gregory Pincus
The Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts

Introduction

This review is mainly concerned with reports published from 1962 to mid-1963 dealing with specific agents that may affect fertility. Within the confines of the space allotted, no exhaustive coverage of this field can be contemplated. Relevant areas such as hypothalamic-hypophyseal interactions are scarcely reviewed here. For recent reviews of this and related subjects see *Control of Ovulation*, C. A. Villee, Editor (1).

The 1959 review of Jackson (2) on "Antifertility Substances" is of interest. A more recent review of much of the pertinent literature in this field is that of Jöchle (3) who covered the work up to early 1962. A publication of the U. S. Department of Health, Education and Welfare (4) lists the titles of research projects concerned with birth and population control to late 1962.

The contribution that overpopulation makes to economic and ternal difficulties in many parts of the world has stimulated activity in this field; much of it inevitably from the point of view of applied research. Following the conclusive demonstration of the effectiveness of Enovid as an oral contraceptive (5), other effective agents have been devised, and research is continuing on such questions as their economic and esthetic acceptability, side-reactions and, through long-term use, effects on health.

Oral Contraceptives—Progestins

Of special importance in young women is the assurance of resumption of fertility upon cessation of therapy. In clinical trials with progestational agents, no report of posttreatment decrease of fertility has appeared, while there continues to be recorded evidence of at least normal fertility after withdrawal of medication. Confirming earlier reports, e.g., Pincus, Rock & Garcia (6), are those of Goldzieher et al. (7) and Watts & Diddle (8) who used norethindrone. Watts & Diddle noted continued normal cervical cytology, 17-ketosteroid excretion and blood cholesterol even in women treated for more than two years. There was a normal pregnancy rate after withdrawal. Goldzieher et al. noted that in women treated cyclically with norethindrone for less than 12 cycles there was a normal endometrial histological picture during the first posttreatment cycle. In those treated for 12 to 25 cycles, there were some residual changes in the endometrium with persistence of glandular regression. Women who discontinued therapy to become

[1] Present address: Harbor General Hospital, Torrance, California.

pregnant were successful in 62 per cent of the cases in the first posttreatment cycle. This is claimed to be a significantly higher figure than for groups of women discontinuing other forms of contraception. Kistner (9) reported on the prolonged use of synthetic progestins (Enovid, Norlutin, Deluteval and Depo-Provera) for the treatment of endometriosis. After treatment, no abnormalities of endometrial, ovarian or pituitary function were observed, and uncomplicated pregnancies occurred in a high percentage of the women.

Reports continue to appear on the generally enthusiastic acceptance by patients of the orally active progestins for contraceptive purposes (10–14). The rejections occur because of persistence of some of the well-documented side-effects.

Oral contraceptives—safety.—The idea that therapy with synthetic progestins creates a hormonal environment that mimics pregnancy may have received additional support in the finding of Brownrigg (15) that a patient with endometriosis treated with high doses of norethynodrel (40 mg/day) for a long period of time developed a syndrome resembling toxemia of pregnancy. This report is relevant as well to the general question of possible hazards to health, a subject discussed by Venning (16). He concluded that norethynodrel therapy is as safe as pregnancy, but without the hazards associated with the presence of the fetus and placenta and the process of parturition. Minogue et al. (17) presented a case and discussed the literature concerned with the question of association of thromboembolism and norethynodrel therapy. Egeberg & Owren (18) carried out a direct study of blood coagulability in five healthy women on Enovid therapy. They found an increase in certain coagulation factors. In a similar study, Sobrero et al. (19) found no significant alteration in these factors. The general conclusion is that incidence of thromboembolic disease as such is not affected by Enovid therapy (20).

Synthetic progestins and ovarian function in humans.—The question of how ovarian hormonal function is affected by long-term use of ovulation inhibitors was explored by Shearman (21). The modes of action of the synthetic progestins in experimental animals appear to be through effects on the hypothalamic centers controlling pituitary function (22). Ovulation inhibition by direct effects on pituitary or ovary have not been excluded. In the human, their mode of action is not established (23). Brown et al. (24) used norethisterone and its acetate in women. They found no suppression of urinary pituitary gonadotropin excretion in the subjects during administration of the drugs. With adequate dosage, ovarian hormone excretion was suppressed throughout the cycle. At lower levels follicular hormone production persisted, but there was no ovulation or corpus luteum formation. If given only in the luteal phase, there was no effect by either drug on luteal function. Taymor & Klibanoff (25) studied ovulation suppression by norethindrone acetate in women. Their findings suggest that below a critical dose level ovulation may still occur. They offer the suggestion that even if ovulation does occur, the effect of the drug upon endometrial function may still pre-

vent pregnancy. Consistent with this idea is the work of Holmes & Mandl (26). They found that in rats doses of norethynodrel sufficient to induce sterility did not consistently block ovulation. However, they made no direct study of ova so that a pseudo-ovulation in the rat is not excluded. The pituitaries of treated rats were heavier than those of controls. Their findings have not been confirmed by Munshi (27) who used another strain of rats.

Goldzieher et al. (28) also found evidence of ovulation in a small percentage of women taking 10 mg norethindrone daily. This is at variance with the results of Swartz et al. (14) who found none.

Newer oral ovulation inhibitors in humans.—Pincus et al. (29) noted that ethynodiol diacetate was a very efficient antifertility agent at rather low dosage. This provided adequate control of menstrual cyclicity with minimal side effects. The low dosage offers potential advantages such as greater physiological safety and lower cost to the patient. Mears (30) has reported data on another new clinically effective oral contraceptive, Volidan (6α-methyl-6-dehydro-17-acetoxyprogesterone plus 0.05 mg ethinylestradiol). David etal.(31) claim that 17α-acetoxy-6-methyl pregna-4:6-diene-3,20-dione is the most potent antiovulatory compound yet reported. Retrosteroids as a source of antifertility agents have been explored by Scholer (32). Other papers concerned with the clinical use of orally active progestins include the following. Swyer & Little (33) have proposed the postponement of menstruation as a means of quantitating oral progestational activity of the synthetic progestins. Lynestrenol (17α-ethinyl-17β hydroxy-estr-4-ene) has been evaluated as an ovulation inhibitor in a clinical study by Szontagh et al. (34). Studies of the endometrial effects of synthetic progestins have been offered by Maqueo et al. (35), Swyer (36), and Rubio (37).

Synthetic progestins in animal experiments.—The action of the synthetic progestins in experimental animals continues to be of great interest. Overbeek et al. (38) found Lynestrenol to be an effective ovulation inhibitor in the rat with no effects on nidation. The rat estrous cycle is inhibited by an acetophenone derivative of 16α,17α-dihydroxyprogesterone (39). These authors claim this drug to be devoid of androgenic and estrogenic activities, and normal fertility was regained 60 days after cessation of treatment. Munshi (27) gave norethynodrel to mice and rats with the expected suppression of estrous cycles. The ovaries were smaller than in control animals and no corpora lutea were evident. Twenty-one days after cessation of treatment the ovaries resembled those of the controls. No effect on mouse adrenals and pituitaries was noted. Treatment of mice for 108 to 176 days with implanted pellets of 19-norprogesterone resulted in sterility during treatment with subsequent recovery of fertility (40). Unexpectedly, ovarian tumors were discovered in these animals. The authors discuss their data with regard to the implication that failure of progestational homeostasis may be significant in ovarian tumorigenesis.

Kincl & Dorfman (41) studied the antiovulatory effects of a large number of steroids in the adult estrous rabbit. Two routes of administration were

studied, subcutaneous and gavage. Eckstein & Mandl (42) administered heavy doses of norethynodrel to immature female rats and found that the ovarian sensitivity to exogenous gonadotropins may have been somewhat enhanced, A study with some analogous inplications is that of Evans & Dutt (43) who reported the induction of reproductive activity in anestrous ewes by the use of oral progestins and pregnant mare's serum.

Nonsteroidal Ovulation Inhibitors

Several nonsteroidal substances have been claimed to act as ovulation inhibitors. A derivative of dithiocarbamoylhydrazine (Ayerst 61122) which seems to inhibit gonadotropic hormone secretion in women was found by Tyler (44) to be an apparently effective ovulation inhibitor. The use of the same or a similar compound by Bell et al. (45) also inhibited ovulation, but excretion of gonadotropins was not affected. Parkes (46) has reviewed additional clinical studies in Britain with this type of compound. Kontracep is a commercial preparation of unknown composition which is claimed to be an orally active contraceptive. A critical study by Banik (47) failed to reveal evidence that it interfered with any of the aspects of reproduction studied.

Purshottam (48) noted that a number of tranquilizers, including alkaloids of the reserpine group, were effective ovulation inhibitors in immature mice. He believes that the effectiveness of exogenous gonadotropins in inducing ovulation in immature animals is dependent on the presence of an intact hypophysis contributing a factor essential to follicle rupture. He suggested that the tranquilizers exert their antiovulatory effect through the central nervous system by influencing the release of this factor. Hopkins & Pincus (49), however, demonstrated that reserpine interferes with the ovulation-inducing activity of HCG in hypophysectomized, immature rats.

The well-known effect of barbiturate in preventing ovulation was used by Strauss & Meyer (50) to investigate the time during which release of pituitary hormone is most effective in inducing ovulation. They concluded that ovulation depended on release of pituitary hormone during a "critical period" between 2:00 and 4:00 p.m. on the day before ovulation was expected.

Aron & Asch (51) found atropine inhibited ovulation triggered by coitus in the rat, indicating a mechanism involving a cholinergic factor in the triggered ovulation.

The Stimulation of Ovulation

Whereas finding means for reducing the birth rate is an urgent problem for the world, the converse problem of the correction of subfertility is of little importance to international economic and political stability. It is, however, of the utmost urgency to the individuals involved. Swyer (52) recently reviewed critically the literature concerned with stimulation of human ovulation by various means such as gonadotropins and nonsteroidal agents. Rosemberg et al. (53) and Gemzell (54) reported evidence of ovulation in women after administration of human pituitary FSH and HCG.

Greenblatt et al. (55, 56) with apparent success administered clomiphene to anovulatory patients in the hope of stimulating ovulation. The evidence for ovulation included a number of successful pregnancies. They concluded that clomiphene is useful not only for induction of ovulation but for correction of certain menstrual disorders. A rather undesirable effect noted was the high incidence of ovarian cysts in the treated women. Laberge & Rock (57) claimed that ovulation was stimulated in some women by the monobenzyl ether of stilbestrol.

Studies on induction and control of ovulation in experimental animals have been carried out as well. Multiple ovulations were stimulated in the adult monkey (Macaca mulatta) with the use of human gonadotropin preparations (58). Dziuk & his collaborators (59, 60) induced ovulation in swine with HCG after withdrawal of the administration of synthetic progestins.

Superovulation generally has not increased fecundity in experimental animals, and Wilson & Edwards (61) confirmed this by their data obtained with superovulated mice. Increased death rate of litter members and failure of implantation contributed to a fecundity lower than that of controls.

Interesting effects by propylthiouracil and thyroxine were noted on superovulation in immature mice (62). Thyroxine reduced, and administration of propylthiouracil increased, the number of ova shed. Results seemingly at variance with the above were obtained by Thorsøe (63), who found that thyroidectomy in rabbits inhibited coitus-induced ovulation.

Nikitovitch-Winer (64) found that infusion of median eminence extracts directly into the pituitary was very effective in inducing ovulation in rats. These experiments were designed to shed light on the nature of the hypothetical hypothalamic humoral substances that may stimulate the anterior pituitary to release the ovulating hormone. For earlier data on the induction of ovulation with median eminence extracts consult the work of Harris (65).

Interference with Zygote Progress

A number of agents have been found effective antifertility substances in the female by mechanisms which do not necessarily involve inhibition of ovulation. The effects may be directly on the developing zygote or on the genital tract. The distinction is not always clear as to which effect is responsible for the inhibition of pregnancy.

Thus, Davis (66) was able to terminate an already established pregnancy in the rat with large doses of northynodrel. Lucey & Behrman (67) found that thalidomide interfered with pregnancy in the monkey. They suggested that the embryo was killed prior to implantation. Lutwak-Mann & Hay (68) noted that thalidomide given to rabbits caused degeneration of the embryonic disk of rabbit blastocysts recovered $6\frac{1}{2}$ days after mating. They also reported effects on the embryonic disk of other agents given to the mother.[2]

The ergot alkaloid ergocornine has been found to interfere with preg-

[2] For the teratogenic activity of thalidomide and other agents, see page 226 ff.

nancy postcoitum. The studies of Shelesnyak (69) in women, and those of Zeilmaker & Carlsen (70) in the rat indicate an interference with luteal function. Zeilmaker & Carlsen have suggested the primary action to be an inhibition of pituitary LH secretion.

Duncan & his collaborators (71, 72, 73) have studied three nonsteroidal, orally active antifertility agents designated by Upjohn Co. as U10520A, U11100A (derivatives of diphenyldihydronaphthalene), and U11555A (a derivative of 2,3-diphenylindene). Their contraceptive activity is confined approximately to the preimplantation period of zygote development. They are effective in rats, guinea pigs and rabbits, but not in hamsters. Gonadotropin inhibition is apparently *not* seen at therapeutic doses, but there is evidence of antiestrogenicity.

Deanesly (74) found that estradiol benzoate given to guinea pigs after mating inhibited pregnancy and that, contrary to general belief, the effect is due not to retention of ova in the tubes but to their expulsion. In a relevant study by Greenwald (75) pregnancy was interrupted in the rabbit by estradiol cyclopentyl propionate given immediately after mating. The author suggested that the effect was due to disturbances of tubal egg transport.

Serotonin can interrupt pregnancy in mice at all stages. Reports by Robson & Sullivan (76) and by Lindsay et al. (77) showed that in early pregnancy progesterone and prolactin can preserve the pregnancy against the effects of this drug. In late pregnancy progesterone is much less effective and prolactin is ineffective in reversing this serotonin action.

Investigation of the role of histamine in pregnancy led to the finding by Kameswaran et al. (78) that antihistamines interrupt rat pregnancy, possibly by affecting the blood flow through the placenta.

Cutting (79) found paludrine, an antimalarial, to diminish fertility in mice. The effect was observed only in females and was all or none; i.e., there was either complete inhibition of pregnancy or the litters were normal.

Aminopterin was evaluated by Goetsch (80) as an abortifacient and was rejected because of toxicity to the mother and incomplete effectiveness, probably leading to congenital malformations.

Martin et al. (81), in a study of antiestrogens, showed them to interrupt early pregnancy in mice. These compounds also possess some estrogenic activity as well, and they were not able to decide from their data whether the interruption of pregnancy was due to their antiestrogenic or their estrogenic activity. Emmens (82) found that estradiol and the antiestrogen, dimethylstilbestrol, appeared to inhibit implantation markedly when administered to mated rabbits on days five to seven or days seven to nine. The animals were examined on days nine to eleven. Also effective at high dosage was 17-ethinyl-19-nortestosterone (norethindrone).

Cholesteryl chloride reduced fertility in rats (83). In males the weights of accessory glands were reduced, and in females the experiments suggested that the agent interfered with implantation.

Banik & Pincus (84) surveyed a number of steroidal antiprogestins for

their effects on implantation of fertilized eggs in rats and mice. Four of the nine compounds tested significantly interfered with implantation in both species, while two were active only in mice. Single injections on day one of pregnancy were sufficient and were more effective than single injections on day three.

Pincus et al. (85) studied a number of nonsteroidal compounds for their possible effects on implantation in mated mice. One stilbene derivative inhibited implantation when administered on day one of pregnancy, and was even more effective when given for three consecutive days. Systemic administration of carbonic anhydrase inhibitors to mice, rats and rabbits failed to affect implantation. Diamox placed directly into the uterus did prevent implantation.

Spector (86) found that administration of a monoamine oxidase inhibitor to female rats inhibited fertility. He suggested that there was interference with two reactions prerequisite for fertility, estrus and implantation, and that fertility was suppressed by the drug through its anti-inflammatory properties which inhibit these processes.

Barnes & Meyer (87) gave ethamoxytriphetol, MRL-37, and clomiphene orally to pregnant rats at various stages of pregnancy. When given early enough there was inhibition of implantation. Treatment during days eight to twelve killed some embryos, but given during days thirteen to seventeen the drugs did not affect the embryos. Administration of any of the three compounds for 21 days caused abolition of the regular estrous cycles. Three weeks after withdrawal of treatment normal fertility was apparently resumed.

Prahlad & Kar (88) critically tested *m*-xylohydroquinone for its possible anti-implantation effect. They found none. It was also found that this agent had no antiprogestational nor antifertility effects in women (89).

Male Fertility

As in the past, investigations of the pharmacology of male fertility have not been as extensive as investigations in the female.

The compound mentioned above, *m*-xylohydroquinone, was tested in male rats (90). There was no effect on genital organs, and fertility was unaffected in spite of long-term administration.

The administration of reserpine to male rats caused deterioration of the testes at the interstitial level (91). There were regressive changes in sexual behavior and in the central nervous system. (Fertility was apparently not tested, but must have been diminished or abolished.)

Boccabella et al. (92) found testicular function and histology to be severely affected in rats after treatment with serotonin. Since simultaneous treatment with a vasodilator prevented the morphological changes, it was concluded that the serotonin effect was the result of testicular ischemia. PMS failed to prevent the damage caused by serotonin.

Interest has continued in the effects of radiomimetic alkylating agents on

testicular physiology, especially spermatogenesis. Fox et al. (93) administered single injections of busulphan, tretamine and isopropyl methanesulfonate to male rabbits. After 10 or 11 weeks, the rabbits were aspermic. Certain alkylators which sterilize male rats did not suppress sperm count nor interfere with sperm motility in the rabbit. It is of special interest that continued small doses of tretamine maintained male rabbits in a state of sterility. Hemsworth & Jackson (94) examined the effect of busulphan on the developing gonads of young male rats in utero and post partum. When administered to the mother in early pregnancy, there was apparently a selective destructive effect on the male fetal sex cells. Treatment of the male neonatal rat also resulted in selective destruction of germ cells, and the sensitivity of these cells decreased rapidly with age of the neonatal rat.

Steinberger (95) concluded from his studies with rats that the alkylator, triethylenemelamine, has a rather specific action on the formation of Type A spermatogonia with a minimal effect on the primary spermatocytes. Monoyer (96) in a study of the effects of busulphan (Myleran) in male rats reached essentially similar conclusions. Jackson et al. (97) found that intraperitoneal injection of busulphan did not affect the subsequent maturation of Type A spermatogonia present at time of treatment, but that these were not replaced. Sterility ensued, but after withdrawal of treatment, normal fertility was ultimately restored.

Three bis(dichloroacetyl)diamines have been administered orally by Drobeck & Coulston (98) to male rats, monkeys and dogs; they inhibited spermatogenesis completely. Complete recovery was attained after withdrawal even after long periods of aspermia. The drugs seemed to be highly specific in their effect on the germinal epithelium. The general picture of the effects was fundamentally similar in the three species tested, but the minimal effective dose varied considerably from drug to drug and among the species.

The bis(dichloroacetyl)diamines were given to human male volunteers by Heller & Moore (99). They concluded that sperm production was inhibited without suppression of pituitary or testicular hormone production. An undesirable side-effect was that the subjects could not tolerate ethanol while under treatment. Recovery of sperm production and return to normal testicular histology were noted after the drug was discontinued.

Blye & Berlinger (100) and Patanelli & Nelson (101) studied the effects of 1-(*N*,*N*-diethylcarbamolylmethyl)2,4-dinitropyrrole (ORF-1616) in adult male rats. Spermatogenesis was severely inhibited with resultant sterility. Again, fertility was recovered after the drug was discontinued. The effects were confined to the germinal epithelium, and spermatocytes and young spermatids were the most sensitive germ cells. Patanelli & Nelson (101) noted that this type of drug depends for its antispermatogenic action on the presence of pituitary gonadotropin. The situation in this respect appears similar to that previously observed with nitrofurans, thiophenes and bis(dichloroacetyl)diamines. Blye & Berliner (100) noted further that ORF-

1616 has antispermatogenic activity in guinea pigs and rabbits as well as in rats.

Methoxychlor in the diet of weanling male rats at a level of 1 per cent resulted in pathological effects on testes, seminal vesicles and prostate (102). The suggestion was that the estrogenicity of this compound inhibited pituitary gonadotropin secretion.

An odd effect by ACTH on spermatogenesis was noted by Ruponen & Näätänen (103). Atrophy of the germinal epithelium was induced in both young and adult rats although young animals were more sensitive to the hormones. Regressive changes in histology of the prostate and seminal vesicles indicated disturbances in androgen production. The authors suggest that the effects are related to the antianabolic activity of the glucocorticoids released from the stimulated adrenals.

Sperm production was decreased in rabbits by administration of progesterone and synthetic progestins (104). Libido was reduced under this regimen.

Any interference with gonadotropin secretion or activity can be expected to affect testicular development. Hayashida (105) was able to inhibit both spermatogenesis and development of secondary sex organs in male rats by treatment with anti-sheep-ICSH antiserum. Treatment was begun while the rats were still immature.

Even after allowing a long-term post-hypophysectomy regression period, Boccabella (106) was able to restore spermatogenesis with testosterone propionate in rats.

A new attempt has been made to develop a contraceptive based on inhibition of hyaluronidase. Schoysman & Wesel (107) claimed that oral administration of an inhibitor of that enzyme resulted in infertility in rats. There was no effect on sperm morphology or motility. They concluded that sperm penetration of egg or cervical mucus was prevented. Trials in humans were encouraging but inconclusive.

The Bruce Effect

Though not immediately relevant to pharmacology, the work of Bruce & Parkes (108–111) on the blocking effect of odors of strange males on pregnancy in female mice ("Bruce effect") is of potentially great interest. This illustrates the existence in the CNS of very sensitive discriminatory mechanisms capable of controlling reproductive performance. An unidentified odorous substance appears to inhibit luteotrophic hormone production by the anterior pituitary.

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