DISCUSSION

Since Jensen and Jacobson (1962) demonstrated that rat uterus can accumulate and retain estradiol, a number of investigators have contributed to the concept that the uterus contains estrogen receptors. The uptake of $^3$H-estradiol in the uterus has been found to be competitively inhibited by estradiol and a number of estrogenic and antiestrogenic compounds (Korenman 1968). Estradiol in higher doses of 10 ug has been shown to inhibit the uptake of $^3$H-estradiol in the uterus of mouse and rat (Terenius 1965, Korenman 1968). Norethynodrel has been shown to inhibit the uptake of $^3$H-estradiol in the same manner (Eisenfeld and Axelrod 1965).

A careful study of the effect of pretreatment of mice with norethynodrel has shown that it can produce a stimulatory or an inhibitory effect on the uptake of $^3$H-estradiol in the uterus and this depends upon the dosage of norethynodrel used and the time of pretreatment. Norethynodrel pretreatment in the doses of 0.01, 0.1, 1.0 and 5.0 ug for a period of 4 hours produced stimulation in the uptake of $^3$H-estradiol. The maximum stimulating effect was exerted by a dose of 1.0 ug of norethynodrel at 4 hours. Prolongation of the time of pretreatment with norethynodrel for 8 or 18 hours resulted in the waning of this effect for all other doses except the 1.0 ug dose. This dose continued to produce a
stimulatory effect on the uptake of $^3$H-estradiol when pretreatment was given for 8 and 18 hours. However, the extent of $^3$H-estradiol uptake was lower at 8 and 18 hours as compared with the uptake seen at 4 hours. A dose of 50.0 ug of norethynodrel produced an inhibition of the uptake of $^3$H-estradiol in the mouse uterus.

The results presented in this dissertation show for the first time that a progestational steroid like norethynodrel, not only inhibits the uptake of $^3$H-estradiol and acts as its competitive inhibitor, but also stimulates its uptake. Saucier, Banerjee, Brazeau and Hsain (1970) in a recent study showed that administration of 100 ug norethynodrel per 100 gm body weight to rats 15 minutes before and 15 minutes after the administration of $^3$H-estradiol produced a reduction in the uptake of $^3$H-estradiol. These authors concluded that norethynodrel produces a competitive inhibition of the uptake of $^3$H-estradiol.

Eisenfeld and Axelrod (1965) using a high dose of norethynodrel 220 ug/100 gm body weight) reported that norethynodrel acts as a competitive inhibitor of estradiol uptake which has been confirmed by Saucier et al (1970). The present results are in agreement with the above studies, when a relatively high dose of norethynodrel (50 ug) is used for the pretreatment. The findings of stimulation of $^3$H-estradiol uptake by relatively small doses of norethynodrel have a similarity to some of the earlier reports (Laumas 1967; Laumas and
Farooq unpublished observations, Eisenfeld and Axelrod 166; Kraye & Black 1970) in which small doses of estradiol were shown to cause a stimulation in the uptake of \( ^{3}H \)-estradiol. Kraye and Black (1970) made a detailed study of the effect of estrogen priming on the uptake of \( ^{3}H \)-estradiol by the mouse uterus. It was seen that 0.03 ug estradiol pretreatment for 3-6 hours produced a maximal stimulation of \( ^{3}H \)-estradiol uptake.

In the present study, the stimulation of \( ^{3}H \)-estradiol uptake with norethynodrel priming may be due to two possibilities. Firstly, it may be due to the inherent estrogenic activity of norethynodrel. Norethynodrel has been reported to possess 7% of the estrogenic potency of estrone(Drill, 1966; Edgren, Jones and Peterson, 1967). The second possibility may be due to the estrogenic metabolites of norethynodrel which may be exerting a mild estrogenic effect on the uterus as also noted with very small doses of estradiol. Arai, Golab, Layne & Ficus (1962) isolated 17\( \alpha \)-ethynyl-19-norandrost-4-ene-3\( \beta \), 10\( \beta \), 17\( \beta \)-triol as one of the major urinary metabolites of norethynodrel, which has been found to possess estrogenic activity (Bialy, Layne & Ficus, 1965). It is possible that the mild estrogenic activity of this metabolite of norethynodrel stimulates the uptake of \( ^{3}H \)-estradiol in the uterus. Yadava and Laumas (1969) studied the metabolism of U-C\(^{14} \) glucose in the rabbit uterus after prolonged administration of
norethynodrel and found an increased rate of synthesis of lipid, RNA and protein. This observation further confirms the estrogenic properties of norethynodrel and its metabolites, since estrogens are known to increase lipid, RNA and protein synthesis in the uterus (U1 & Mueller 1963).