LH, but the development of radio-immune techniques for measuring these biologic products undoubtedly will lead to progress in this field.

Most oral contraceptives produce a contraceptive effect by preventing ovulation through the suppression of the hypothalamic-pituitary system. Not all the agents seem to produce this effect in the same way but, in general, the immediate effect of dominantly estrogenic compounds is to reduce FSH, whereas the effect of progestins is to suppress the midcycle peak of LH without significantly altering the basal LH level. Prolonged administration of estrogens or estrogen-progestin combinations causes marked reduction in both FSH and LH (27, 53, 76, 107, 146). Many animal experiments employing various species (51, 76, 94) support the concept that oral contraceptives exert their effect by blocking estrogen receptor sites in the hypothalamus and pituitary with reduction of gonadotropin release and suppression of ovulation.

Resumption of ovulation after cessation of oral contraceptives is usually prompt, within 4 to 8 weeks in most cases. In a few women, however, amenorrhea persists for 6 months or longer (14, 21, 47, 49, 78, 114, 152, 153). Some believe that this phenomenon simulates the occasional period of extended anovulation that may follow pregnancy or lactation. Recovery after long-term suppression has been described (53). The pituitary recovers first (FSH first, then LH), followed by the ovary, and then the endometrium, which may require as long as three months to regain its normal histologic appearance and enzymatic activity. Although the small group examined showed resumption of ovulation rather promptly, clinical studies continue to report anovulation and amenorrhea from weeks to months after discontinuation of oral contraceptives. Several authors have outlined means of evaluating and treating women with this condition.

Pregnancy may be considered to be the prime indicator of adequate pituitary and ovarian function. While clinical observers agree that most women conceive "promptly" after the discontinuation of oral contraception, valid statistical information is scanty. To be sure, a number of investigators have reported the percentage of women who conveived among those who discontinued, or the distribution of pregnancies by number of months required for conception, or even conception rates per 100 woman-years of exposure. None of these measures is satisfactory. The first completely neglects the duration of follow-up. The second ignores the women who did not conceive. The third fails to take into account that the conception rate declines with time.

The closest approximation to the life table is the percentage of women who conceive during the first cycle after discontinuation. Some such figures have been reported, but they are so far out of line with earlier experience as to raise serious questions as to the completeness or accuracy of the information furnished to the investigators by their informants (67, 130, 169).

Pregnancy outcome was deemed satisfactory in these studies with no significant increase in abortion, prematurity, or developmental anomalies (9, 140). Continued study of this problem should be undertaken, however, since as noted below, there is evidence from laboratory animals that the suspension of ovulation is associated with fetal anomalies once fertility is restored.

Suppression of ovarian function secondary to pituitary suppression by oral contraceptives is evidenced by low estrogen excretion during treatment (107, 115). Flowers and associates (53) found estrogen levels during prolonged use of oral contraceptives to be much lower than those in normal cycles. The endometrium was found to be atrophic with reduced enzymatic activity.

Whether oral contraceptives have direct ovarian suppressive effects is controversial. One group (84) gave contraceptive steroids to amenorrheic women; their subsequent response to human gonadotropins showed no inhibition of the ovarian reaction. This observation supports the contention that the major suppression is at the hypothalamic level. Direct effects of oral contraceptives on ovarian weight and on histological and ultrastructural changes are suggested by some studies (172).

Oral contraceptives in higher doses (5 and 10 mg. of progestins) tend to decrease or stop lactation in many women in the first or second cycle of use (141, 149). Smaller doses are reported to have no significant suppressive effect on lactation (86), but radioactive tagged norethynodrel is excreted in breast milk (101).