

without added estrogen and without inhibiting ovulation. The basis of the antifertility action remains uncertain.

During the investigation of oral progestin-estrogen contraceptives, several investigators concluded that ovulation was occurring in a significant percentage of cycles, even though the antifertility effect was almost absolute. Yet it was not until 1965 that work was reported implying that ovulation suppression could be dispensed with entirely while still retaining a potent antifertility effect (10). In this early study, a synthetic progestin, 6-chloro-6-dehydro-17-alpha-acetoxy-progesterone was given alone at the low dose of 0.5 mg. daily to a group of nearly 1,000 women with normal cycles. The women were seen monthly during the period of investigation, which covered close to 10,000 cycles. Fourteen pregnancies occurred, thirteen of which were ascribed to failure of patients to take the medication regularly. Considering only the single so-called "method-failure," a pregnancy rate of 0.2 per 100 women per year can be calculated. When all unintended pregnancies are considered regardless of reason, the pregnancy rate is 2.1 per 100 women per year. Approximately two-thirds of the patients had some irregularity in the cycle during the twenty-month study period. The studies were subsequently expanded to include observations on 50,000 cycles, with more than 600 women observed for over two years. In this broader experience, 159 method failures were reported, giving a pregnancy rate of roughly 2 per 100 women years of use (7).

With this particular compound at the dosage employed, problems with control of the cycle appear to be a handicap, but the contraceptive effectiveness of the continuous progestin method seems clearly established. As a consequence, several other synthetic progestins have been placed under clinical investigation at doses intended to replicate the low-dose effect. Experience is sufficient with two of these compounds to indicate confirmatory results. With one of them, norgestrel, anti-fertility activity can be achieved with a daily oral dose of 0.075 mg. (4). More than 1,000 women have been observed for approximately 7,000 cycles, including over 400 women for at least one year. The ten reported pregnancies suggest a pregnancy rate of 1.6 per 100 women per year. Similar results have been achieved with respect to both control of cycle and fertility control with the use of 0.5 mg. daily of megestrol acetate (1). An innovation in the study of this compound is the use of an oil-filled gelatine capsule instead of a tablet, with the aim of achieving more uniform absorption and reduction of a cyclic irregularity. A cooperative statistical evaluation involving thousands of subjects in several countries is now in progress.

Although the mechanism by which the uninterrupted daily administration of these progestational agents creates a state of infertility without inhibiting the pituitary and suppressing ovulation remains uncertain, the possibilities can be narrowed down considerably. That the therapy does not interfere with ovulation suggests that the mode of action may be transport of sperm or ovum, the fertilization process, transport and development of the zygote, or the preparation of the endometrium for nidation. Histologic evidence from biopsy material suggests that endometrial changes are not responsible for the antifertility effect. Sperm transport could be affected as it passes through the cervical mucus or higher in the female tract. Although the preliminary reports tended to emphasize changes in cervical mucus that could create a barrier hostile to spermatozoa, such changes are not necessarily correlated with the antifertility effect. Future investigation will be required to establish the effect of continuous progestins at doses that do not inhibit ovulation on such key factors as tubal transport rates of gametes and the process of fertilization.

b) Parenteral Administration-The discovery of the antifertility action of low-dose progestins, based on uninterrupted administration, opens up for the first time the possibility of singly-administered, long-term, reversible control of fertility by hormonal means, in a manner that would allow for maintenance of ovarian function and menstrual cycles. A possible application of this principle is suggested by experiments demonstrating that steroid hormones may be released at low and constant rates from capsules made of various silicone polymers (3, 13). One such material poly-dimethylsiloxane, is already used widely in surgery. Capsules containing the synthetic steroid, megestrol acetate, have been inserted subdermally into female rats, rabbits, and monkeys, and biologic evidence of slow and constant release of the hormone has been