Experience Behind Enovid-E®— New, Low-Dosage Form of "The Pill"

Each tablet of ENOVID-E contains:

norethynodrel	2.5 mg.
mestranol	0.1 mg.

ENOVID-E should not be confused with other dosage forms of ENOVID:

	5-mg. tablet*	*10-mg.* tablet*
norethynodrel	5.0 mg.	9.85 mg.
mestranol	0.075 mg.	0.15 mg.

*Note that one-half of a 5-mg. tablet or one-fourth of a 10-mg. tablet cannot be substituted for ENOVID-E.

The responsibility of leadership. "In the last eight years oral contraception has become a reality, and this undoubtedly represents as great a medical landmark as the introduction of antibiotics."[1]

ENOVID opened the era of oral contraception and "has led the field."[2] Because of its worldwide impact, those associated with the development of ENOVID have long felt a responsibility to study this drug and its effects with a thoroughness and persistence that are almost unprecedented. As a result, few drugs in any category[3] have ever been subjected to clinical tests as exhaustive as those already undergone by ENOVID. And there is no question that ENOVID is "the most thoroughly studied synthetic progestogen."[4]

After 35,000,000 cycles, the consensus. Intensive exploration of the organic and physiologic effects of ENOVID, during and after longer and longer periods of administration, is slated to continue indefinitely. But certainly the voluminous evidence produced by almost a decade of clinical study, together with experience in more than 6,100,000 women for more than 35,000,000 cycles, permits these conclusions:

- The response to prolonged use of ENOVID appears to be remarkably similar to the response to the natural ovarian hormones. In the mass of data now on hand, there is no evidence that long-term inhibition of ovulation with ENOVID impairs post-treatment fertility, harms subsequent children, delays or extends the menopause, or results in thyroid, adrenal or pituitary dysfunction.
- Experience indicates that endocrine function typical for the individual patient prior to use of ENOVID returns promptly after it has been discontinued.
- There is no doubt that ENOVID is virtually 100 per cent effective for extended suspension of fertility.

The lowest contraceptive dose with more than five years of confirmation. While certain phases of ENOVID research will require continuing study for many years to come, one important phase was brought to a successful conclusion earlier this year: the determination and clinical confirmation that 2.5 mg. of norethynodrel will afford the contraceptive effectiveness assured by the 5-mg. and 10-mg. tablets of ENOVID. The introduction of ENOVID-E—2.5 mg. of norethynodrel and 0.1 mg. of mestranol—represents the culmination of this study.

In the initial clinical tests of ENOVID for conception control, the 10-mg. tablet was employed. It was soon determined that a tablet containing half the ingredients in the original 10-mg. tablet was equally effective in preventing ovulation and conception. Clinical trials of a 2.5-mg. tablet were initiated[5] in August 1958, in Puerto Rico, where the original ENOVID study[6] had begun more than two years earlier. These were the first tests of a low-dose oral contraceptive.

A tablet offering half the contents of the 5-mg. tablet was shown[7] to have insufficient mestranol for original support of the endometrium. But the 2.5-mg. dose of norethynodrel proved successful when combined with 0.1 mg. of mestranol. (The marked lowering of the norethynodrel-to-mestranol ratio in the 2.5-mg. tablet should be noted, since it means that one-fourth of the 10-mg. tablet or one-half of the 5-mg. tablet *cannot* be substitued for the combination now available as ENOVID-E.)

By the end of 1959, clinical evaluation of the 2.5-mg. tablet was in progress in the continental United States and other countries as well as Puerto Rico. The expanded clinical test program included a variety of ethnic groups in clinic and private practice. By September of 1963, 2,946 women had already participated in ENOVID-E trials for from 1 to 46 cycles, for a total of 33,416 cycles. (See Tables 1 and 2.)

In no instance in any of the clinical trials[5,6,8,10-28]