the epileptic state might be expected from this cause. Conversely, some epileptic patients whose attacks primarily occur premenstrually have been relieved of their attacks.

There is no evidence that ENOVID is etiologic in the production of uterine fibroids, although pre-existing fibroids frequently increase in size while ENOVID is being given. Discontinuance of therapy ordinarily results in a regression.

That several hundred instances of peripheral thrombophlebitis and embolism, including fatalities due to embolic phenomena, have occurred in women receiving ENOVID has received considerable attention. The possible causal relationship of ENOVID administration to these incidents has received considerable study and has been reviewed by four committees of recognized authorities.

Any relationship between a state of "hypercoagulability" and thromboembolic disease still remains undetermined. In any event, presently available data do not establish—or exclude—the possibility that ENOVID produces hypercoagulability as defined by increases in components or acceleration of clotting kinetics. A number of blood coagulation factors are known to be modified during normal pregnancy. These include fibrinogen, fibrinolysin, prothrombin, factors VII, VIII and X, and other complicated measurements of the blood coagulation mechanism. ENOVID also produces changes in these factors in the same directions as those observed during pregnancy. Although the significance of these changes is presently unknown, additional studies are in progress.

ENOVID was first distributed commercially in June 1957. As of June 1963, somewhat more than 400 thromboembolic episodes have been reported among ENOVID users with thirty-seven fatalities in the United States as a result of the development of pulmonary embolism. On further investigation some of these cases and fatalities were unrelated to thromboembolic disease or the histories revealed definitive and generally-recognized causes for the development of the reported condition. Among the fatalities, more than one-third could be classified as idiopathic or having no clear cut (precipitating) etiologic factor.

Available medical and statistical evidence relative to the incidence of thromboembolic episodes in non-medicated and nonpregnant women of childbearing age is singularly sparse and not completely reliable. Studies are in progress to attempt to rectify this defect in knowledge of the incidence of thrombophlebitis and pulmonary embolism in this segment of the female population. The *expected* incidence of thromboembolic episodes in "healthy" young women is difficult to determine from the available data but there is evidence that in such women in the age range of 20 to 44 years, not subjected to trauma and not pregnant, 926 cases of thrombophlebitis per million per year will occur, that among these sixty cases of pulmonary embolism will be seen and that 7.9 will die as a result of thrombophlebitis or pulmonary embolism.

A recent panel survey (February-August 1963, J.A.M.A. *185*:776 [Sept. 7] 1963) in analyzing the 1962 fatalities by age groups did not find a statistically significant increased rate of fatalities in any age group. Since the possibility of a real increase especially in the older age group remains this should be carefully weighed by the physician prescribing ENOVID. Further data will be evaluated and reported.

There is abundant evidence in the literature to support the concept that the incidence of thrombotic episodes increases with age, with parity, with obesity, with a history of previous occurrences, with a history of varicose veins or other vascular abnormality, with trauma or unusual activity, and with restricted movement combined with an interference with the dependent circulation (long automobile or airplane trips). Similar causal or contributory factors have been noted in the histories of many of the cases reported as occurring during ENOVID administration. Women subject to such exposure or exhibiting these characteristics should be considered as being at risk of thrombosis.

## *Side Actions*

The most frequently encountered side action to ENOVID therapy is nausea, less commonly vomiting.

It is also apparent that side actions are more prevalent in the first cycle of treatment and that they fall sharply on continuation of therapy. After the third cycle the incidence is low.

Nausea may be controlled by instructing the patient to take the tablet with meals or with a glass of milk at bedtime or by recommending that an antacid or an antinauseant preparation be taken with the tablet of ENOVID.

Spotting or breakthrough bleeding may occur; usually this is evidence of inadequate dosage. This type of bleeding is usually controlled by increasing the daily dosage of ENOVID. The first increment of such additional dosage should be taken as soon as spotting is noticed. This increased dosage may be required for only four or five days after which the original schedule may be resumed.

The menstrual flow associated with ENOVID therapy is usually typical of the individual patient although it may be scanty or, less commonly, more profuse. In uncommon instances an endometrial cast may be produced.

Vaginal bleeding occasionally occurs after several months of the cyclic use of ENOVID therapy. When this is observed careful search for the presence of an organic lesion is indicated. Patients on long-term ENOVID medication should have annual or more frequent pelvic examinations.

Amenorrhea is a phenomenon encountered occasionally in instances when ENOVID is prescribed cyclically. The term is used to describe an absence of menstrual flow during the periodic omission of ENOVID to permit the patient to menstruate. In spite of the fact that no menstrual flow occurs in the missed or amenorrheic period, this phenomenon does not preclude ovulation during the following cycle. Sometimes ovulation may occur as early as nine or ten days after medication is so stopped. Thus, it is most important to instruct the patient to begin to take the ENOVID tablets for another twenty days and to begin taking them again no later than one week after the last tablet was taken.

Sodium retention with edema is encountered and usually may be treated satisfactorily by salt restriction or controlled by judicious selection and use of a diuretic agent. For this reason, however, ENOVID should be used with caution in patients with cardiac or renal disorders or hypertension.

As previously stated ENOVID may be used for the treatment of premenstrual tension and may prove successful. However, an aggravation of premenstrual tension occurs occasionally, presumably as a result of the sodium retention to which reference has been made.

The occurrence of chloasma has been reported. The degree of pigmentation varies widely and persists, usually at a stationary level, throughout the course of medication. On discontinuing medication the pigmentation usually disappears but, as in the postpartum patient, it may persist for varying lengths of time.

An occasional patient may experience photosensitivity dermatitis or urticaria. Miscellaneous cutaneous conditions occurring during administration