mittee to review and analyze this situation and to determine if the use of Enovid resulted in an increase in the incidence of death from thromboembolic conditions. This consitutes a report of the efforts of the Committee to resolve the questions involved. The Committee was composed of representatives with broad interests but especially experienced in the fields of gynecology and obstetrics, vascular diseases, thromboembolism, hematology (especially coagulation), and statistics; and epidemiology.

The Committee has not been unmindful of the complexity of the over-all considerations involved in this area. These incude not only the medical implications but also those involving the biological, psychological, social, philosophical and religious aspects. The relationship of all of these to the population explosion must be of interest to all intelligent citizens. Nevertheless these factors were not permitted at any time to cloud the immediate issues which constituted the commission of the Committee.

Background material was obtained from the Food & Drug Administration and G. D. Searle & Company. The representatives of both organizations were completely co-operative throughout this study. More than 350 case reports of both thromboembolism and death from the files of both sources were reviewed by the members of the Committee together with much additional data. After this it was concluded that because of the impossibility of obtaining solid comparable statistics regarding thromboembolic complications as they occur in the usual population groups, it was essential to concentrate on deaths where the documentation is more complete and valid.

The coagulation balance

The possibility of the production of changes in the coagulation balance which might significantly add to the risk of thrombosis or embolism was carefully considered. The pertinent literature on this point was reviewed and special studies designed to answer certain questions were carried out in the laboratories of member of this Committee.

In assuming the responsibility of trying to establish whether the use of Enovid affects blood coagulation adversely to a degree capable of resulting in thromboembolic disease, the Committee, after reviewing the available literature and recent unpublished experiments performed by members of the Sub-committee (attached appendix), accepted the following basic facts:

1. Enovid produces some uterine changes similar to those occurring in pregnancy. Therefore it was essential that the coagulation changes during pregnancy be reviewed. The gravid woman develops significantly increased concentrations of the following plasma clotting components: Factors VII (proconvertin), X (Stuart), VIII (AHF),* IX (PTC), fibrinogen, and platelets. Less definite evidence regarding Factors II (prothrombin) and the fibrinolytic components has been reported. Virtually nothing is known as yet regarding parallel changes in Factors XI (PTA) and XII (Hageman). Factor V (AC-globulin) is unaffected. Although thrombotic phenomena were not searched for or carefully analyzed in the studies during the antepartum period upon which these findings were based, overt thromboembolism was not strikingly impressive. This is not surprising since thromboembolism complicating pregnancy occurs 4–6 times more frequently in the immediate post-partum state than during the gravid state.

2. These facts having been established in pregnancy, comparable studies in subjects receiving Enovid were sought. In a small series of subjects, one laboratory had reported an increase in Factor VIII activity and lesser increase in Factor VII (1) Less impressive changes in other clotting parameters have also been reported (Rapaport) (2) and Hanstell). (3) Eleven women receiving Enovid and eleven healthy women were studied concurrently. Levels of Factor VIII activity, one stage prothrombin times, plasma recalcification times, and platelet numbers were not significantly different in the two groups. (Spittell, Owen, Thompson, and Bowie (Personal communication to the Committee). In order to attempt to determine a possible relationship between elevated levels of Factor VIII and hypercoagulability, experiments were performed by adding semi-purified Factor VII to *in vitro* clotting systems. Significant shortening of plasma partial thromboplastin times below the normal range was not produced when the levels of AFH ranged between 100 and 850 percent of normal. Nei-

* Alexander. B., personal communication with Committee.