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EDITORIAL—ORAL CONTRACEPTIVES AND THROMBOEMBOLIC DISEASE

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The first report in the medical press of a woman developing a thromboembolic disorder while taking an oral contraceptive preparation appeared in 1961 (1). In that same year, two young Los Angeles women using oral contraceptives suffered fatal pulmonary embolisms (2). Since that time hundreds of similar case histories, relating both to fatal and nonfatal illnesses, have been published in medical journals, and thousands more have been reported to the Food and Drug Administration in the United States and the Committee on Safety of Drugs in Great Britain. The majority of these reports relate to deep-vein thrombosis in the lower limbs or pulmonary embolism, but the occurrence of coronary thrombosis, cerebrovascular accidents, mesenteric and other arterial thromboses, and the Budd-Chiari syndrome has also been described.

All these conditions also occur in young women who do not use oral contraceptives and in themselves the case reports provide no significant evidence that oral contraceptives are a cause of thromboembolic disease. A number of attempts have, however, been made over the years to assess the problem in a methodical way.

In 1962 at a conference sponsored in Chicago by G. D. Searle and Co., (3) a comparison was made between the reported incidence of episodes of thromboembolic disease in users of Enovid and the incidence in the general population estimated from the results of a number of different studies. The participants recognized the considerable inadequacies of the data available to them, but concluded that there was no evidence that Enovid was a cause of thromboembolic disease.

In 1963, a committee appointed by the Food and Drug Administration (4) reviewed about 350 reports of thromboembolic disease in women using Enovid drawn from their own records and from those of the manufacturer. On this occasion, existing statistics about the morbidity from thromboembolism in the general population were considered to be unreliable, and the Committee concentrated on reports of death. Among Caucasion women using Enovid, deaths from thromboembolic disease were estimated to be 12.1 per million annually compared with 8.4 per million in the general population calculated on the basis of national mortality statistics. This difference was not statistically significant, but the Committee took into account the limitations of the data and said that carefully planned, controlled prospective studies were necessary before reliable conclusions could be drawn.

In 1965, the Committee on Safety of Drugs (5) reviewed their findings in Great Britain for the previous year. Sixteen deaths from thromboembolic disease had been reported among women using oral contraceptives, whereas on the basis of national mortality statistics, about 13 deaths could have been expected if the use of these preparations was unrelated to the disease. The Committee concluded that there was no evidence that oral contraceptives had a thrombogenic effect, but they did draw special attention to the fact that 8 of the 16 reported deaths were from pulmonary embolism whereas only 2 such deaths would have been expected.

Quite apart from the absence of comparable control data in any of the investigations just outlined, each one also depends on *reported* episodes of thromboembolism for the calculation of morbidity or mortality rates in users of oral contraceptives. The assumption is, therefore, that all, or nearly all, of the episodes affecting women using oral contraceptives are reported by the responsible physicians. That this assumption is, in fact, untenable has since been demonstrated both by the Food and Drug Administration and by the Committee on Safety of Drugs. Thus in 1966, the Food and Drug Administration (6) showed that, among the 5 million women estimated to have been using oral contraceptives in the United States in 1965, about 85 deaths from "idiopathic" thromboembolism would have been expected on the basis of the national mortality rates even if the contraceptives had not produced any extra fatalities. In fact, only 13 such deaths were reported. Similarly, in 1966 in the special investigation of mortality from thromboembolism in young women

NOTE.—Numbered references at end of article.