

undertaken by the Committee on Safety of Drugs, (7) only 8 of the 53 deaths found to have occurred in women using oral contraceptives were independently reported to the Committee by the responsible physicians.

In 1966, Drill (8) reviewed the results of 6 major clinical trials of oral contraceptives covering many thousands of woman-years of exposure. On the basis of various morbidity statistics, he calculated that a total of 105 cases of thrombophlebitis would have been observed among the participants in these studies if oral contraceptives were unrelated to the disease. In fact, only 28 cases were noted and Drill concluded that oral contraceptives had no thrombogenic effect. Unless, however, oral contraceptives protect women from thrombophlebitis, an alternative explanation for these results is that such factors as patient selection, losses to follow-up, and the inevitable inadequacy of the data used to calculate expected numbers of affected individuals preclude any definite conclusions.

In 1966, American (6) and British (9) groups came independently to the conclusion that the best way to obtain adequate data on the thromboembolism problem within a reasonable length of time would be by means of case-control studies, and the results of 3 British investigations have now been published.

In one study, organized by the Royal College of General Practitioners, (10) 29 family doctors interviewed women aged 15 to 49 who had consulted them for an episode of thromboembolic disease and the results were compared with those obtained from 2 control groups matched for marital status and, broadly, for age and parity. The data were too few for any conclusions to be drawn about cerebral or coronary thrombosis, but the results indicated that the risk of venous thrombosis or pulmonary embolism, ("venous thromboembolism") was increased sixfold in women who were pregnant or in the puerperium and threefold in women who used oral contraceptives. (9) Three quarters of the women with venous thromboembolism suffered from superficial thrombophlebitis of the legs and the estimates of risk therefore relate principally to this condition.

In a study carried out under the auspices of the Committee on Safety of Drugs and reported by Inman and Vessey (7), inquiries were made by the Committee's medical field staff about the use of oral contraceptives by women aged 20 to 44 certified as dying in England, Wales, and Northern Ireland during 1966 from pulmonary embolism, coronary thrombosis, and cerebral thrombosis. The results were compared with those obtained for control women selected from the same doctors' practices as those in which the fatalities occurred. It was found that, irrespective of age, the risk of death from pulmonary embolism or cerebral thrombosis was increased about eight times in previously healthy women using oral contraceptives. In absolute terms, however, the mortality rate attributable to the use of these preparations was substantially lower among those aged 20 to 34 than among those aged 35 to 44, there being an excess of 1.3 and 3.4 deaths per 100,000 users per annum, respectively, in these two age groups.

The situation in regard to coronary thrombosis was much less well defined in this investigation and the existence of an association with oral contraceptives has not been established. There was, however, some suggestion that oral contraceptives might be of etiological significance in coronary thrombosis in women under 35.

Vessey and Doll (11) carried out an investigation of married women aged 16 to 40 admitted to hospital during 1964 through 1966 with thromboembolic disease without evident predisposing cause. Control patients matched for age, parity, date of admission, and absence of any factor predisposing to thromboembolism were selected and all participants in the investigation were interviewed in their homes. From these data it was calculated that the risk of hospital admission for deep vein thrombosis or pulmonary embolism is about 9 to 10 times greater in previously healthy women who use oral contraceptives than in those who do not. By using national sales data for estimating the frequency of use of oral contraceptives in the general population, it was estimated that about 1 in every 2,000 women using oral contraceptives is admitted to hospital each year with "idiopathic" venous thromboembolism in comparison with about 1 in every 20,000 women not using them.

Evidence was also obtained in this study to support the suggestion that cerebral thrombosis may rarely be caused by oral contraceptives, but no relationship was found between their use and coronary thrombosis.