

, from the experience of the control subjects selected to match the patients with venous thromboembolic disease, was 0.7.³

IV. DISCUSSION

pulmonary embolism and deep vein thrombosis

Retrospective studies of hospital patients are always open to bias, and the present study is no exception. Both the affected and the control patients were selected from larger groups by procedures that were certainly not random, and information about the use of oral contraceptives was obtained by inquiry of the patient and so was dependent on the accuracy of her memory. The evidence, however, suggests that these sources of bias have not materially affected the results.

Firstly, women were selected for inclusion only for objective reasons, and any subsequent decision to exclude them for subjective reasons—for example, the presence of doubtfully significant predisposing disease—was taken in ignorance of their contraceptive practice. Secondly, the proportion of women with deep vein thrombosis or pulmonary embolism who used oral contraceptives was greater when the diagnosis was firmly established than when the diagnosis was less certain—and the contrary would be expected if diagnosis and referral to hospital were biased by knowledge of the women's contraceptive practice. Thirdly, the proportion of control women who said they were using oral contraceptives (9%) was close to the proportion of married women estimated to use them: (1) from knowledge of available supplies (approximately 11% at ages 15 to 44 years in 1966⁴); and (2) from the experience of women of general practice lists (7% at ages 15 to 49 years in 1965–66⁴). Fourthly, the proportion of women treated for pulmonary embolism who said they were using oral contraceptives (54%) is close to that recorded among women aged 20 to 49 years who died of pulmonary embolism in England, Wales, and Northern Ireland in 1966 (62%, Inman and Vessey, 1968). We conclude, therefore, that the method of investigation has not materially biased the results and that the association between the use of oral contraceptives and the development of deep vein thrombosis or pulmonary embolism is real.

Two considerations suggest that the association reflects cause and effect. Firstly, we have been unable to find any evidence of a third factor which could account for the association by being related to both. Many factors which use the disease or influence the use of contraceptives were excluded by the sign of the study. Two—previous attacks of thromboembolism and obesity—were not excluded; both were found more commonly in affected patients, but neither was particularly associated with the use of oral contraceptives. Others were either unrelated to the disease or the relation was so weak that it could have had no material effect on the results. Secondly, there is evidence that oestrogens can cause thromboembolism in other circumstances (Daniel, Campbell, and Turnbull, 1967; Oliver, 1967; Bailar, 1967; Schrogie and Solomon, 1967).

Further evidence should eventually be obtained from examining trends in the incidence of the condition and its geographical distribution, particularly as the use of oral contraceptives has become more common than it was in 1966. The evidence, however, will not be easy to interpret, as the use of oral contraceptives is only one of many potential causes of thrombosis, and changes in the prevalence of the other factors may mask its effect.

If, as we now conclude, the use of oral contraceptives is a cause of venous thromboembolism, three questions arise. How big is the risk? Is it concentrated in a particular section of the population? And is it attributable to any one component?

The results of our study are quantitatively similar to those obtained by the Royal College of General Practitioners (1967) and the Committee on Safety of Drugs (Inman and Vessey, 1968).

In the first of these studies the data relate mainly to superficial phlebitis, and it may be noted that the total morbidity from all types of thromboembolic disease was approximately 2 per 1,000 women per year and that the risk of venous thrombosis or pulmonary embolism in women who were taking oral contraceptives was increased approximately threefold. Only six women aged 15

³ This number is less than that expected among nine patients with "cerebral thrombosis" because those with coronary thrombosis were, on average, older.

⁴ Medical Research Council (1967).