

expected to have been doing so from the experience of the control series (Table VI). Even though the number of women dying from cerebral thrombosis is so small, this difference between the two groups is statistically significant ($P < 0.01$). The data are too few for detailed examination by age and parity, but it is noteworthy that five of the six women under 40 years had been using oral contraceptives, while none of the four over 40 years had taken them.

Class B.—The principal predisposing conditions which caused 17 of the deaths from cerebral thrombosis or embolism to be allocated to class B were as follows: hypertension (9), previous cerebrovascular accident (2), recent surgery (2), and other conditions (4). A post-mortem examination had been performed on only seven of these patients and only two death certificates were signed by a coroner. Details of the use of oral contraceptives were not available for one patient, but none of the remaining 16 had taken them (Table VI). One patient had been taking Metrulen-M for a week only before her death.

When classes A and B are combined there is a small excess of users of oral contraceptives among the women who died.

Oral contraceptive preparations used by women who died

Of the 39 women allocated to class A in all three diagnostic groups who had been taking oral contraceptives at the onset of the terminal illness, the preparation then in use was ascertained for 34. Similar information was not available for the control subjects, so a comparison was made with national sales statistics provided for the year 1966 by Intercontinental Medical Statistics Limited. There was no suggestion that the risk of thromboembolism was associated with any particular oestrogen-progestogen combination.

The duration of treatment had been recorded for 35 of these 39 patients. There was some suggestion that those who died from coronary thrombosis had been using oral contraceptives rather longer on the average (mean 16 months) than those who died from pulmonary embolism (mean 12 months) or cerebral thrombosis (mean 6 months).

DISCUSSION

The frequency of thromboembolic disorders is inversely related to their severity. Superficial venous thrombosis in young women is a common condition. Deep venous thrombosis and pulmonary embolism are much less common and death from thrombosis is comparatively rare. In the investigation carried out by the Royal College of General Practitioners (1967) two-thirds of the patients had suffered only from superficial venous thrombosis and no conclusions can be drawn about the more serious conditions.

The serious forms of thromboembolic disease such as deep venous thrombosis or pulmonary embolism leading to hospital admission can be studied more easily. Objective diagnostic criteria can be applied and the diagnosis can often be supported by special investigation. The work of Vessey and Doll (1968) has shown that conclusions can be drawn from the investigation of a comparatively small number of carefully selected patients who have been treated in hospital.

The present study was initiated in direct response to the receipt of "random" reports to the Committee on Safety of Drugs of episodes of thromboembolic disease in women using oral contraceptives. At the time the study began there was no important difference between the number of reported deaths and the number expected on the basis of national mortality statistics. However, the hypothesis that there was no relation between the use of oral contraceptives and fatal thrombosis depended on the assumption that there had been almost complete reporting of thromboembolic deaths. That this assumption is untenable has now been demonstrated.

In spite of widespread publicity in both the medical and the lay press, particularly in 1965, only 8 of the 53 deaths of known users of oral contraceptives in the present study were reported independently to the Committee on Safety of Drugs. Only two of these eight deaths were reported by the patient's general practitioner, though he was almost invariably aware that she had been taking oral contraceptives.

Before attempting to draw any firm conclusions from the other results of this investigation it is important to consider the sources of bias which might have influenced the data on which they are based.