

All these investigations are, of course, subject to the usual defects of case-control studies, but their statistical inadequacies are very much less than those of the earlier studies already reviewed. Considered together they provide very strong evidence that oral contraceptives are a cause of venous thromboembolism. In conjunction with other investigations (12-15), in which physicians have reviewed their total clinical experience over a period of time, rather than merely singling out particular case histories for special consideration, they provide a good indication that these preparations may also be sometimes implicated in ischemic cerebrovascular disturbances. The evidence for a causal association with coronary thrombosis, however, is weak.

Recent reviews of national mortality statistics for the thromboembolic diseases in the United States and Great Britain (16, 17) have led to the conclusion that trends among women of childbearing age have been paralleled by corresponding trends among men and that vital statistics do not support the suggestion that oral contraceptives cause thromboembolic disease. Vessey and Weatherall (18), however, have shown that the British vital statistics for the venous thromboembolic diseases are fully compatible with the estimates of the small mortality attributable to the use of oral contraceptives provided by the investigation carried out by the Committee on Safety of Drugs (7). No attempt has been made to apply the same calculations to vital statistics for the United States because the British estimates of risk may be totally inappropriate when applied to another country where, for example, spontaneously occurring thromboembolic disease may differ in incidence.

None of the investigations so far described has provided any valid evidence that the risk of thromboembolism is associated with any particular oral contraceptive formulation, nor that the risk is associated with duration of use. Dr. Doll and this author hope to have some additional information shortly on both these points as we are at present updating our investigation (11) by including patients admitted to hospital during 1967. Data obtained from clinical trials where estrogens have been administered to men with coronary heart disease (19) or cancer of the prostate (20) suggest that the estrogen moiety may be at fault and this idea is supported by the recent observation that puerperal thromboembolism is associated with the suppression of lactation by estrogens (21).

The epidemiological investigations thus strongly suggest a causal relationship between the use of oral contraceptives and some kinds of thromboembolic disease, but the case would be greatly strengthened if the physiological or biochemical effects of their use were shown to contribute to some part of the disease process. A vast and bewildering literature has accumulated relating the use of oral contraceptives to changes in various blood clotting factors (8) including platelet function (22). Many investigations have yielded conflicting results which is not surprising when the great variety of preparations tested, the differing laboratory techniques, the varying periods of exposure among the subjects investigated, and in some instances, the small numbers of women studied and the inappropriate controls used for comparative purposes, are taken into account. But even if it is accepted that oral contraceptives do affect blood clotting mechanisms, the significance of any alteration in terms of an increased risk of spontaneous thrombosis is very uncertain.

Other workers (23-25) have demonstrated changes in vessel walls and in venous distensibility and blood flow produced by the administration of oral contraceptives in experimental animals and in man. These findings, which seem to have been neglected by some workers, could be of significance in relation to venous thromboembolism.

Although no definite relationship between oral contraceptives and coronary thrombosis has been established, the work done by a number of groups, especially by Wynn and his colleagues (26, 27), on the effect of oral contraceptives on carbohydrate and lipid metabolism provides some basis for suspecting that such a relationship might exist.

In addition to any further epidemiological information which may yet be obtained from case-control studies, at least four prospective investigations of women using oral contraceptives and control subjects have been, or are in the process of being established. Of these, two are in Great Britain (one organized by the Royal College of General Practitioners and the second jointly by the Medical Research Council and the Family Planning Association), one in the United States (organized by the Kaiser-Permanente Medical Care Program)