

sand per annum, on the basis of 32 selected cases without evidence of predisposing cause) and other estimates. They quoted seven such estimates based upon hospital admissions, of which six, not restricted to idiopathic cases, ranged from 0.71 to 1.08. The seventh, for idiopathic cases only (and hence, more nearly comparable to the Vessey and Doll figure) was 0.65. This figure was derived from an unpublished study. In our experience, the proportion of idiopathic cases among patients hospitalized with thromboembolism is only about 15%. It would therefore seem desirable to review the definitions employed before accepting these data as placing the Vessey and Doll findings in question. Furthermore, as Vessey and Doll point out, superficial thrombophlebitis was probably included to an unknown extent in the statistics quoted by Drill and Calhoun, but was excluded from their own study.

The fact remains that in the prospective trials of oral contraceptives quoted by Drill and Calhoun, no excess risk of thromboembolism has been shown. They cited 51 such trials, reported in a previous review by Drill, which uniformly failed to show any increased morbidity. In these studies, detection of thrombophlebitis was not the principal aim and some of them were done before this possible risk had become widely recognized. Careful observation would be needed in order to ascertain, in the case of women who became dropouts from a clinic, whether a medical complication of the medication received, such as thrombophlebitis, might not have been one of the reasons for failure to return to the clinic.

The largest of these studies—in fact the only one with numbers adequate to test the hypothesis—is not in the medical literature; the only reference to it that could be found was a release issued by a voluntary agency. It is described as an extended trial of an oral contraceptive by women who, in order to be eligible for entry to the study, must already have used it for at least two years. Women who dropped out because of thromboembolism or for other reasons before that time were not included, and hence the woman-years of observation during the first two years of use are not relevant to the risk of getting thromboembolism; and yet these person-years have been included in estimating the expected number of cases. In other words, it appears probable that some at least of the women undergoing the first two years of use of oral contraception developed thromboembolism and discontinued use of the method for that reason, so that to base the rate upon those who did complete the first two years produces a spuriously low figure. Another doubtful feature of this study is that of the 58 occurrences of thrombophlebitis self-reported in this study, all but 17 were later rejected as having inadequate evidence for the diagnosis; yet we do not know if similarly strict criteria were followed in other experiences from which the general comparative incidence of thrombophlebitis has been estimated. Finally it should be noted that the authors of this study themselves state:

"This study was not designed to provide a comparative incidence of thrombophlebitis. Such an investigation would require more detailed follow-up examinations than were feasible in order to establish (1) a positive diagnosis of the condition, (2) the existence of recognized contributing causes, and (3) whether the patient was hospitalized. Satisfying these criteria is necessary to provide any meaningful comparison with the only reliable base-line incidence data for this disorder which is limited to idiopathic, hospitalized cases."

It is our opinion that the evidence presented by Drill and Calhoun, which constitutes the main negative evidence published to date, is inadequate to show that the incidence of thromboembolism is either unaffected or reduced by oral contraceptives.

The retrospective study method used by Vessey and Doll, and by ourselves, suffers from two possible biases as applied to thromboembolism. First, women who developed the disease while taking an oral contraceptive might be told by their physicians that the oral contraceptive was responsible, as indeed often happened. Thus, cases might have been more likely than the controls to give an affirmative history of oral contraceptive use. Clearly, the securing of information on contraceptive use from hospital histories would have led to severely biased classifications, but the interview method has, it is felt, largely eliminated this bias. It seems most unlikely that a woman would assert having used several types of contraceptives but deny that she had ever used the orals,