1967. During these years numerous accounts have been published in the medical and lay press of individual or small groups of patients who developed thromboembolic disorders while taking oral contraceptives. In the three-and-a-half-year period ending 31 December 1967 the Committee on Safety of Drugs received 1,024 reports of thrombosis or embolism occurring after the use of oral contraceptives or similar preparations. Eighty-eight of these reports referred to a fatal episode.

The Food and Drug Administration (1963) in the U.S.A. reviewed some 350 reports of thrombosis or embolism in women taking Enovid (a mixture of norethynodrel and mestranol, marketed in the United Kingdom as Enavid). As no information was available about the morbidity from these conditions in women not using oral contraceptives, the Food and Drug Administration confined its attention to reports of death. The mortality from thromboembolic disease among users of oral contraceptives was estimated to be 12.1 per milliion women per year, compared with 8.4 per million in the general population, and this difference in mortality rates was not statistically significant. In 1966 the Food and Drug Administration showed that among the five million women estimated to have been taking oral contraceptives in the United States in 1965, 85 deaths from "idiopathic" thromboembolism would have been expected on the basis of national mortality statistics, whereas only 13 such deaths were reported. It was suggested that physicians in the United States were becoming increasingly fearful of reporting adverse reactions because of the risk of litigation. In the same year the Committee on Safety of Drugs was informed of 19 thromboembolic deaths among the 400,000 women who were estimated to have been using oral contraception in the United Kingdom. Ten of the 19 women had no recognized predisposing conditions.

In November 1965 the Committee on Safety of Drugs (Cahal, 1965) published its findings up to the end of August 1965. In the preceding 12-month period 16 deaths from thromboembolism had been reported among users of oral contraceptives. Thirteen deaths would have been expected on the basis of the Registrar General's statistics, and the Committee did not regard the difference as clear evidence of a thrombogenic effect. They did point out, however, that, whereas only two cases of pulmonary embolism would have been expected, eight had been reported. The Committee therefore decided to enlarge the scope of its investigation to include all deaths from thrombosis or embolism in women of child-bearing age recorded by the Registrars General in England and Wales and Northern Ireland in 1966. Protocols for the investigation were considered by the Committee during the last quarter of 1965, and the study began on 1 January 1966.

During 1966 and early 1967 studies were also undertaken by the Royal College of General Practitioners of patients with thromboembolic disease seen in general practice and by the Medical Research Council's Statistical Research Unit of women admitted to hospital. In April 1967 the results of these two studies, together with those of the Committee on Safety of Drugs, were considered by a subcommittee of the Medical Research Council under the chairmanship of Lord Platt, and a preliminary report to the Council was published in May 1967. Though two of the investigations were at that time incomplete it was concluded that there could be no reasonable doubt that some types of thromboembolic disorder were caused by oral contraceptives. From the preliminary results of the investigation by the Committee on Safety of Drugs it was estimated that the risk of death from thromboembolism among women who used oral contraceptives might amount to an excess of three deaths per 100,000 women per year over the corresponding mortality in non-users.

The Royal College of General Practitioners has published a full report of its investigation elsewhere (Royal College of General Practitioners, 1967), and that of the Medical Research Council's Statistical Research Unit appears elsewhere in this issue (Vessey and Doll, 1968). The present communication describes the final results of the investigation of deaths undertaken by the Committee on Safety of Drugs.

SELECTION OF DEATHS FOR STUDY

Transcripts of 499 death certificates relating to women aged 20 to 44 who died in England, Wales, and Northern Ireland during 1966 were obtained by special arrangement with the Registrar Generals. They included certificates