

interference with the cerebral small vessel had occurred at least four days antemortem and before a large clot developed in a major cerebral artery.

Levine and Swanson (21) also presented a differential diagnosis of ischemic strokes in young adults. They basically fall into two classes; the first resulting from atherosclerotic degenerative vascular disease due to diabetes, hypertension and hyperlipidemia, and the second resulting from various rarer diseases. It is likely in the latter class that clues will be found regarding the mechanisms of ischemic stroke in women using hormonal contraceptives. The rarer known causes of ischemic stroke in young adults include: 1) inflammatory-degenerative vascular disorders associated with connective tissue disease, e.g., systemic lupus erythematosus, as reviewed recently by Johnson and Richardson (20), Takayasu's arteriopathy localized to the aortic arch or major branches, and granulomatous angiitis of the central nervous system; 2) embolic disorders due to fat, micro-organisms, tumor, air or thrombi; 3) hematologic-rheologic syndromes, e.g., sickle cell disease or trait, polycythemia and the dysproteinemias; and 4) migraine. The experience of these authors is confirmed by that of Berlin and colleagues (4), Humphrey and Newton (16) and by Louis and McDowell (23) who reviewed also the subject of cerebrovascular occlusions in young adults. Cross and Jennett (10) emphasized also the importance of pregnancy and the puerperium as a cause of ischemic stroke in young women.

EPIDEMIOLOGIC STUDIES RELATED TO STROKE AND THE USE OF ORAL CONTRACEPTIVES

The most definitive statistics currently reported on the association of morbidity and mortality from cerebral thrombosis and the oral contraceptives have derived from the retrospective studies initiated in Great Britain by the Committee on Safety of Drugs and by the Medical Research Council. In December 1964, the Committee on Safety of Drugs began an investigation into reports of deaths from thrombosis or embolism in women who were using the oral contraceptives. In July 1966, the Committee extended its investigation to cover all deaths of women aged 15 to 44 years that occurred in 1966, and in which cerebral thrombosis, coronary thrombosis or pulmonary embolism or infarction was mentioned on the death certificate.

The final results of the Committee on Safety of Drugs' investigation of deaths from pulmonary, coronary and cerebral thrombosis and embolism in women of child-bearing age was reported by Inman and Vessey (18). After exclusions, justified by the design of this type of retrospective study, 309 deaths among non-pregnant married women in England, Wales and Northern Ireland during 1966 were analyzed according to the presence or absence of predisposing conditions and the frequency of use of the oral contraceptives. One hundred and twenty women with adequate history of contraceptive practice were ascertained to have no predisposing condition; 26 dying of pulmonary embolism, 84 of coronary thrombosis and 10 of cerebral thrombosis. The remaining deaths were divided among 175 with predisposing conditions and 14 without sufficient evidence of contraceptive practice. Of the women dying without a predisposing condition, 16 of 26 attributed to pulmonary embolism, 18 of 84 to coronary thrombosis and 5 of 10 to cerebral thrombosis were using the oral contraceptive whereas the expected numbers from the control experience were 4.2, 11.4 and 1.5 respectively. The differences for pulmonary embolism and cerebral thrombosis are statistically significant, ($P < 0.001$) and ($P < 0.01$) respectively. With regard to cerebral thrombosis, five of the six women under 40 years had been using hormonal contraceptives while none of the four over 40 years had taken them. Thus, an association was demonstrated between the use of these compounds and death from idiopathic cerebral thrombosis in healthy British women.

The final report by Vessey and Doll (30) compared the use of oral contraceptives during the month preceding the onset of illness among the cases of idiopathic deep vein thrombosis, pulmonary embolism, cerebral and coronary thrombosis with that among controls admitted (1964-67) to 19 selected general hospitals of more than 300 beds in the area of the Northwest Metropolitan Hospital Board. Married females between the ages of 16 and 40 years inclusive who had relevant thromboembolic disorders without a predisposing condition or having been pregnant within three months were considered cases