

for further study. Two carefully matched hospitalized control patients of the same age, marital status, parity and without evidence of predisposing conditions were selected for each case and the complete "triads" of interviewed idiopathic cases and matched controls were analyzed.

All records were reviewed which were coded under Rubrics 331-334, in order to detect cases of cerebral thrombosis not coded under Rubric 332. Abstracts of the records were reviewed by a neurologist without knowledge of the patients' contraceptive practices. Nineteen cases were accepted, of whom four had angiographic evidence of arterial occlusion. Eleven (58%) had been using hormonal contraception during the month before they became ill whereas 3.5 (18%) would have been expected on the basis of a control experience ($P < 0.001$). The authors estimated that the risk of developing a cerebral thrombosis or other intracranial ischemic stroke syndrome, in the absence of any known predisposing cause, is about six times higher when oral contraceptives are used than when they are not.² Oral contraceptives were used by 3 of the 4 patients in whom the diagnosis was proven arteriographically. They also concluded that clinical, angiographic and postmortem evidence from their own and other series indicate that the thrombosis or occlusion affects the cerebral arteries rather than the cerebral veins.

A recent analysis of oral contraceptive use and mortality trends from thromboembolism in the United States was reported by Markush and Seigel (25). They compared the mortality rates during 1962-1966 among women aged 20-44 years with the rates for men and women in comparable age groups in previous years. They analyzed overall trends of mortality attributed to cerebral thrombosis and embolism (ICD 332) and could not find evidence of a general increase in women in the recent period or of an increase in females relative to males. Possibly improvements in the treatment of primary diseases such as hypertension and renal disease have compensated for an increase that would otherwise be seen. Also, as mentioned above, stroke in pregnancy is included under Rubric 332 and one might expect a downward trend in mortality from this type of stroke with decreasing birth rates. Nevertheless, an increased trend in mortality attributed to ICD 332 was detected for white females aged 25-29 and negro females aged 25-34.

Greene (15) analyzed also U.S. cerebrovascular mortality with regard to temporal trends before and after the introduction of the oral contraceptives. The results including ratios of white male to female mortality in the child-bearing ages are consistent with the above-mentioned findings.

DISCUSSION

The purpose of this review of both clinical reports and statistical evaluations of the association of oral contraceptives with cerebrovascular disease is to ascertain whether or not an etiologic relation exists and also to gain clues as to possible biological mechanisms which might be operating. The available clinical data are consistent with an etiologic relation. The clinical reports suggest also that an unusual type of stroke, namely that involving the vertebrobasilar area of the brain, is occurring in about a quarter of the young women now experiencing stroke while using hormonal contraceptives. A close temporal association between the use of oral contraceptives and the onset of migraine-like headache has also been reported. These headaches often occur prior to cerebral ischemic infarction. The clinical evidence suggests that various neurological syndromes, seemingly related to vascular alterations with or without thrombosis, are related to use of the oral contraceptives.

The results of retrospective epidemiologic studies of mortality and morbidity from idiopathic cerebral thrombosis in Great Britain indicate a statistically significant association with the use of oral contraceptives. It is not possible with the existing data to estimate with assurance the magnitude of the increased morbidity and mortality risk of stroke among women using these compounds but it may be in the neighborhood of sixfold judging by findings of Inman and Vessey (18) and Vessey and Doll (30).

²This relative risk is estimated from a ratio of cross-products, i.e., proportion of oral contraceptive users among cases (58%) x proportion of non-users among controls (82%) divided by the proportion of non-users among cases (42%) x proportion of users among controls (18%).