Non-atherogenic causes of stroke were reviewed since atheromata almost never could be documented as the direct cause of stroke in the autopsied women succumbing while on oral contraceptives. Furthermore, only rarely have strokes due to atheromatosis been reported in persons under thirty years of age. Non-atherogenic stroke develops in women during pregnancy or the puerperium, in women having migraine and in women with various systemic connective tissue diseases and especially system lupus erythematosus. Each of these conditions seems to be related closely to physiological or histological alterations of the vasculature of the brain. Few women who died while using hormonal contraception have had careful studies of the brain, and especially of its vasculature. The single reported autopsy revealed significant and impressive alterations of the small and medium-sized vessels.

Animal experimental studies of vascular effects of oral contraceptives are limited but those of Danforth and coworkers (12) in rabbits revealed an increase in the amount of muscle, a decrease in the amount of collagen, marked fragmentation of the reticulum, apparent loss of elastic tissue and a marked loss of acid mucopolysaccharides in large vessels. Qualitatively similar changes were found in pregnancy. Manalo-Estrella and colleagues (24) showed that these changes disappeared at variable rates after withdrawal of antiovulatory agents or the termination of pregnancy. The mucopolysaccharides return to normal within a day while other alterations revert at a slower rate. Cutts (11) demonstrated, in rats, that long-term administration of estrogen predisposes to vascular lesions resembling polyarteritis nodosa. It is tempting to speculate that oral contraceptives induce changes analogous to those in pregnancy and thus may alter the composition or architecture of cerebral blood vessels as suggested by Crocker (9) in considering fibromuscular dysplasia of the renal arteries found predominantly in multiparous women.

The review by Dugdale and Masi (13) of coagulation studies in women using hormonal contraception suggests that estrogen contributes to increased platelet function and accelerated clotting whereas progestin contributes to increased fibrinolytic activity. A few studies comparing the effects of high dose with low dose oral contraceptives did not show any great differences in platelet function, coagulation or fibrinolysis.

In order to understand the effects of the oral contraceptives on the vascular system and the blood clotting system it is necessary to consider the complex alterations in the endocrine system induced by these compounds as reviewed by Corfman (7). It is invalid to conclude that any changes occurring in women taking the oral contraceptives are entirely due to the estrogen or progestin without considering how these hormones alter the general endocrine and physiologic balance of the body.

SUMMARY AND CONCLUSIONS

1. A review of the major clinical reports of cerebrovascular occlusion in women using the oral contraceptives reveals a notable increase in the number of instances of cerebrovascular disease in healthy women of child-bearing age that have appeared since the introduction of the oral contraceptives.

2. Young women suffering from stroke while using the oral contraceptives almost always have some warning, usually significant headache, prior to the onset of the paretic event. In about one-fourth there is ischemia or infarction in the vertebral and basilar arterial system, a location which was previously considered rare in young healty women.

3. Cerebral arteries rather than veins are primarily involved. Limited angiographic and autopsy studies suggest intrinsic vascular alterations in addition to possible derangement of the hemostatic mechanisms.

4. Controlled retrospective studies of young women with cerebral thrombosis without a predisposing cause indicate a statistically significant etiologic relation with the oral contraceptives. There is a sixfold estimated increase in the risk of both morbidity and mortality.

5. Available statistical evidence concerning the overall mortality from cerebrovascular disorders in the general population of women of child-bearing age since the time of introduction of the oral contraceptives until 1966 indicates no significant change. There is neither a decrease which one might anticipate due to the decreased number of pregnancies and deliveries in the general population, nor an increase which might have been evident if the risk from the oral