follow-up examination nine months later was normal. An unusual case of bilateral middle cerebral occlusion was recently sent to us by a colleague and is illustrated (Fig. 5) but not included in the group of 8 assessed for 1966.

DISCUSSION

It would appear that there are now more than 100 well established cases of cerebrovascular complications associated with the use of oral contraceptives. That the number represents only a small fraction of the actual complications appears almost certain because, as pointed out by Inman and Vessey, in Britain only 15 per cent of the deaths of women who were taking oral contraceptives were reported independently as users to the Committee on Safety of Drugs. In the United States, the Food and Drug Administration has suggested that physicians are becoming increasingly reluctant to report adverse reactions because of the risk of litigation. The weight of evidence leads to the inevitable conclusion that a relationship can be found between the use of oral contraceptives and disability or death from cerebrovascular occlusion in the absence of any predisposing conditions.

It is well known that ovulation may be suppressed by the oral administration of progestogens. Of the substances in common use today, the majority are combined products of estrogen and progestogen taken throughout the entire treatment. More recently, sequential products have been available. In this method estrogen alone is administered for fifteen to sixteen days followed by five to six days of combined estrogen and progestogen. In the authors' experience and in the experience of others (9), cerebrovascular complications occurred with either type.

There are conflicting reports on the alterations of clotting mechanisms in individuals who are receiving oral contraceptives (3, 7, 16, 20, 25). Most of the work involves complex testing technics, but much of the data indicates that the administration of estrogen has an influence on the fibrinolytic enzyme system and tends to decrease the breakdown of fibrinogen. Such a change would permit spontaneous thrombosis to occur at an increased rate, much as in the pregnant state (16). In addition, it has been found that the intravenous administration of progesterone increases the platelet count significantly in human beings and in lower animals (17). Egeberg and Owren (7) reported a marked increase in blood coagulability in women on oral contraceptives, evidenced by a uniform increase in the antihemophilic globulin activity (factor VIII) up to 2 to 3 times the pretreatment level. A slight increase in the proconvertin factor (VII) was also noted, and increases in prothrombin factors IX and X have also been reported (3, 5, 7, 20).

There is now general agreement that the pathophysiologic mechanism is an alteration in blood coagulability chiefly through an increase in several prothrombin factors. There is no evidence that there are predisposing conditions in either the veins or arteries themselves (1, 8, 12, 15). In none of the cases coming to necropsy has evidence been found that there are inflammatory or degenerative changes involving the intima or any other vessel coats that might provoke the formation of a thrombus.

Some authors such as Vessey and Doll, while convinced of the high occurrence rate of cerebral thrombosis as a complication of contraceptive ingestion, have not had the opportunity of establishing with certainty the diagnosis of occlusion. In only 2 of the cases of cerebral ischemia studied by them was there opportunity to obtain angiographic confirmation. The present report provides the objective proof of cerebrovascular occlusion that has left several earlier clinical reports open to criticism. The highly significant increase in hormone-related arterial occlusions in 1966 as compared with 1960 (TABLE I) reveals not only an eightfold increase but shows that one-eighth of all women in the specified age group who came to angiography for any reason had demonstrable vascular occlusion. More recently an even