

steeply and steadily for both males and females in the three age groups 35-44, 45-54, and 55-64 over the ten-year period. The rise in mortality from this cause was greater in females than males for all but the 15-24 year age group, in which there was little or no rise. No explanation for this finding is readily available.

In the lower two age groups, death rates from cerebral embolism and thrombosis (rubric 332) fluctuated widely with no definite trends. The actual number of deaths at these ages was very small, such that an excess of five to ten deaths from one year to the next caused a large relative increase in the death rate. In the older three age groups, death rates from cerebral embolism and thrombosis were stable from 1956-66 with the male rate uniformly higher than the female rate. The lack of a rise in female deaths at reproductive ages from cerebral embolism and thrombosis fails to support an association between the use of oral contraceptives and these conditions, barring the possible concealment of an effect by a lowering of pregnancy rates, as suggested above.

It is possible that such deaths are often coded to other cerebrovascular causes or that the frequency of fatal cerebrovascular complications of oral contraceptive use is so low in relation to other cerebrovascular diseases as not to be evident in mortality statistics. In any case, the analysis of these data does not warrant any conclusions regarding the influence of oral contraceptives on cerebrovascular mortality.

D. EFFECTS OF THE ORAL CONTRACEPTIVES ON BLOOD CLOTTING

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Hemostasis can be thought of as occurring in stages: initial control of bleeding, which is effected by platelets; secondary control of bleeding, which is a function of clotting; and clot removal by fibrinolysis as the tissue heals. The concept of hypercoagulability arose as a natural outgrowth of clinical situations characterized by the inappropriate formation of intravascular clots. Its definition on laboratory grounds has proved more difficult.

Using the above outlined concept of normal hemostasis, it is logical to think that intravascular clot formation could arise because of excessive platelet adhesiveness of aggregability, an increased tendency of blood to clot, or insufficient removal of fibrin because of inadequate fibrinolysis. This approach has been used by numerous investigators in the study of clinical hypercoagulability. The processes of intravascular clot formation in arteries and veins are different. Platelet adhesion to damaged endothelium (or foreign surfaces) appears to initiate the formation of an arterial thrombus; in veins, clotting plays the major role. Both arterial and venous thromboses have been attributed to the use of oral contraceptives.

A large number of reports is available, describing the results of investigations of the coagulation and fibrinolytic system. A smaller number of reports deals with aspects of platelet function. The present report attempts to summarize these studies, which cover observations made by 41 investigators on about 1000 patients receiving oral contraceptives. Approximately 412 patients were studied during the first three cycles (short term group); 530 women were studied after more than 3 months of cyclic oral contraception (long term group). These results are compared with studies of hemostasis in approximately 650 pregnant women and on smaller groups receiving either estrogens (165 subjects) or progestins alone (104 subjects).

Since these reports come from widely scattered laboratories, methods have varied greatly, particularly in studies of the fibrinolytic system. The reviewers have attempted to group together comparable tests even though the methods used may have differed. Readers are referred to the original articles for methodologic details.

In all articles selected for this review there was an adequate number of appropriate control subjects. In all the tables the results will be given in terms of change from normal based on the normal values given by each investigator.

PLATELETS

In Table 1 we have summarized the rather scanty data on platelet number and function. Adhesion and aggregation, which are pertinent to the problems of arterial thrombus formation, deserve most attention.

The *in vitro* tests have been grouped under three headings: tests in which