

ism, half were in women, but their average age was seventy, and 95 per cent were over fifty.

A few cases have shown such unusual autopsy findings as to alert doctors to a generalized clotting tendency. In one case autopsied at the Johns Hopkins Hospital, for example, there were numerous clots in arteries and veins all over the body, without any actual disease of vessel walls.

But there are other compelling reasons for suspecting the oral contraceptives as a causative factor in these vascular catastrophes. Many of the scientists who have worked with the pill have compared the endocrinologic state induced by these synthetic steroids with pregnancy. While this view is not universally held, there are at least certain parallelisms between normal pregnancy and drug-induced pseudo-pregnancy. As stated above, pregnancy carries with it a definite risk of clotting difficulties, related in part at least to the hypercoagulable state associated with the hormonal alterations undergone by the expectant mother. Both during pregnancy and the taking of oral contraceptives, there is also a reduction in blood-flow velocity in the extremities, which favors the formation of sludge in the vessels of the limbs.

Although the pill buffs tend to ignore them, a substantial number of studies have now been performed to determine whether oral contraceptives affect the clotting capacity of the blood. They have been conducted in such diverse places as Oslo, Norway, and Manchester, England, and in the United States in Washington, D.C., Minneapolis, Brooklyn, Philadelphia, New York, and Seattle. The majority agree on the fact that there are changes from the normal, even in asymptomatic women taking oral contraceptives. These scientists have not all used the same tests, but in general there have been increases in four blood fractions including fibrinogen (the precursor of fibrin, which eventually forms the clot). Blood platelets, in the two studies focusing on this blood constituent (which helps clots to start), were also increased in number. Only one index of blood clotting—the so-called fibrinolytic system—possibly changes in a direction that might impede normal clotting. *All the other changes are such as to encourage the clotting of blood.*

There are other reasons for worry. In several studies in men and women who have been given female sex hormones as treatment for atherosclerosis of the brain or heart, or for cancer of the prostate, there have been significantly more deaths in the treated patients than in the control (untreated) patients, with more strokes, heart attacks, or both.

Studies of blood fats have shown changes in women on the pill that resemble those seen in post-menopausal women, who have a higher risk of heart attacks than younger women. One extremely provocative report involved a Mead Johnson oral contraceptive that was under trial in 7,000 American women. Trials were suddenly halted when British workers giving "massive doses . . . daily and continuously for several months" to dogs reported thromboemboli in the animals.

A number of researchers have been intrigued by the relationship between hard-water areas and the decreased occurrence of hypertension and other cardiovascular diseases. It has even been suggested that a diet deficient in magnesium may be partially responsible for the high incidence of arteriosclerosis in Western nations. In 1966, Doctors John and Naomi Goldsmith reported serum magnesium concentrations to be lower in non-ovulating women and women on Enovid than in ovulating women. The finding calls only for speculation at present, but it supplies another bit of evidence to remind us of the multiple effects of hormonal agents.

With such highly suggestive data, how can one explain the unwillingness of many physicians even to consider the possibility of clotting troubles in some women taking oral contraceptives? One major reason for this apathy is the now famous report of the 1963 Advisory Committee asked by the FDA for guidance in evaluating thromboembolic morbidity and mortality.

The committee decided to focus only on fatal complications, because of the difficulty in tracking down nonfatal cases. (A patient whose lungs were riddled with clots and who survived only because of heroic cardiopulmonary surgery, or who suffered a disabling but nonfatal stroke, thus did not enter into the committee deliberations.)