

have been conducting experiments on the effects of ovarian hormones in men and postmenopausal women, since they represent the vascular-problem prone groups. Although the results of these studies are not necessarily applicable to the young girl taking oral contraceptives, they do show generally that progesterone has little effect on lipids and that the estrogens lower blood total cholesterol and the "light" (Beta) lipo-protein levels (15).

Less information is available for the premenopausal female using the oral contraceptives. A review of these studies can be divided into the four lipid groupings. Again it should be noted that these published reports involve different drugs, different dosages, and different durations of treatment in varying types of women and accordingly cannot always be compared or the results combined. In 1966 Wynn and Door reported an elevation of free fatty acids in the blood of women taking oral contraceptives (16). More recently (1969) they have been unable to confirm this finding (17). Three other investigators have found normal free fatty acid levels in women using the oral contraceptives (18-20).

The second lipid group is the phospholipids. All of the reports demonstrate an elevation of this group (21-23). This is a heterogenous group of many subtypes of phospholipids. The medical meaning of these reported elevations is only open to speculation. Bolton and co-workers have studied patients with arterial occlusive disease and they have found abnormal blood platelet function (important in blood clotting) which is presumably due to an elevation of the blood phospholipid lecithin (24). Whether the elevation of this lipid in the users of the oral contraceptive is related to their proneness to blood clotting diseases is not known at this time.

The third lipid fraction to be considered is cholesterol. Pincus in his original observations on the oral contraceptive could not demonstrate any change in blood cholesterol (25). Several earlier investigators confirmed this report (18, 19, 23, 26, 27). More recently, four research teams have found elevated cholesterol levels in their subjects using oral contraceptives (25, 28-30). This discrepancy of results can be partially explained on the basis of the different drugs that have been used in these investigations.

There is almost unanimity of opinion among the nine investigating groups measuring blood triglyceride levels in women taking a variety of different oral contraceptives. All but one (27) of the reports demonstrate a significant elevation of this lipid (19, 21-23, 26, 28-31). Indeed Zorrilla and his co-workers have produced similar elevations by giving women only the estrogen component of the oral contraceptive (32). Since these lipids are carried on blood proteins, and since we have already described the ability of estrogens to alter the liver's production of blood proteins, these lipid alterations may be a result of disturbed liver function.

Hazzard and associates have also been concerned with the mechanism by which the oral contraceptive alters blood lipids. The level of blood triglycerides are dependent upon two processes: (1) production in the liver which is mediated by insulin, and (2) a breakdown or destruction at body fat depots which is under the control of fat enzymes. They have investigated both processes and their results suggest that there is both an increased rate of synthesis or production of triglycerides as well as a decreased rate of enzyme destruction at fat depots in a woman taking an oral contraceptive (31). It is apparent that the three metabolic areas under review today (liver-lipids and carbohydrates), are interrelated, and a primary alteration produced in one may manifest itself in the other two.

The medical importance of these blood lipid changes falls into two areas. First, for the patient with an abnormal blood lipid pattern, the oral contraceptive may make her even more abnormal. Zorrilla and associates have reported two women whose blood lipids were elevated before receiving an oral contraceptive and who then developed extremely high and dangerous levels of blood lipids (33). deGennes and colleagues have also reported a patient who had a congenitally high blood lipid pattern and who then developed a stroke while receiving an oral contraceptive (34). Again, as with liver disease, the woman who has a minor abnormality before using the oral contraceptive may develop a major one when she takes the drug. It is important for the physician to know his drugs and his patients before combining them. An interesting observation has recently been reported by Glueck and associates from the NIH. They treated a group of four women having abnormally high blood lipid levels with an isolated progestin and the blood lipids decreased (35). The different responses between premenopausal and postmenopausal women, between estrogens and progesterones, and between normal and abnormal women must all be considered in any study.