Moderate changes in liver function tests are seen in many women on oral contraceptives who are symptom-free. Bromosulfophthalein excretion is diminished in a significant portion of women with almost all formulations and this effect appears to be dose-dependent (23); the dye is retained in the plasma primarily as a conjugate. Elevated BSP levels are related to a concomitant alteration in bile transport, an effect shared by all steroids which have an alkyl group at the 17-alpha position. These agents inhibit the glucuronyl transferase system which participates in the transfer of conjugated bilirubin from the liver cell to bile.

Another alteration in liver metabolism which is commonly observed is an increase in transaminase values in up to 20 percent of patients (24, 25), and a small proportion of subjects experience a slight elevation in alkaline phosphatase levels. After cessation of treatment, all of these values return to normal over a period of time.

Jaundice occurs in about 1 woman in 10,000 on oral contraceptives. In such patients, nausea, malaise, and itching precede clinical jaundice by several weeks. Liver function tests show increased bilirubin and moderately elevated transaminase levels; liver biopsies demonstrate canalicular and hepaticocellular bile stasis. Patients with such jaundice appear to fall into three major groups (26). The first group is women who have recurrent cholestasis of pregnancy; their livers seem unusually sensitive to contraceptive steroids. The second group are those who have cholestasis without evidence of hepato-cellular damage: this effect is similar to the jaundice produced by anabolic steroids and probably results from a direct effect on bile secretory apparatus. The third group shows frank hepatocellular injury or hypersensitivity.

Oral contraceptives affect a variety of enzyme systems (27) and produce increases in beta-glucuronidase and isocitrate dehydrogenase and decreases in lactic dehydrogenase, alkaline phosphatase, and transaminase. One author (28) describes alterations in serum naphthylamidase isozymes as one of the most sensitive indicators of disturbances in liver function and another (29) establishes a correlation between increases in glutamic oxalacetic transaminase levels and histological demonstration of liver cell damage. This latter effect is thought to be due to the progestogen rather than the estrogen in oral contraceptives and represents one of the few examples of the implication of the progestogen. In most studies of the effects of oral contraceptives on liver function, estrogen is considered to be the active agent.

Another effect on enzyme systems is the decreased ability of the liver to extract cortisol from the blood (31). The related elevation in transcortin levels produces an increase in unbound cortisol. As already stated, such an effect on cortisol levels is probably related to the effects of oral contraceptives on glucose metabolism and raises concern over the possible effect of these agents on pituitary function.

It has been observed recently (30) that oral contraceptives appear to participate in the development or enhancement of hypertension in certain women. This effect may be related to the fact that estrogens increase serum-renin substrate levels, through the stimulation of the hepatic biosynthesis of related enzymes. Oral contraceptives also increase aldosterone levels. These effects may compromise the ability of the renin-angiotension-aldosterone hormonal system to respond to normal physiological stimuli.

Another class of effects of oral contraceptives relates to lipid metabolism. Several studies (32, 33) show that these agents increase plasma levels of nonesterified fatty acids, and produce increases in phospholipids and triglycerides. They have a particular effect on low density lipoproteins, changing the proportion between high density and low density lipoproteins to stimulate the proportion observed in adult males. Since lipid synthesis requires the presence of insulin, observed changes in lipid levels may be mediated through the effect of estrogens on plasma concentrations of insulin. Although no specific clinical alterations have been attributed to these changes in lipid and lipoprotein levels they are appreciable and warrant close observation and study.

In summary, oral contraceptives have a variety of metabolic effects in many women who use them. Considerable attention has been placed in recent years on their effects on glucose and lipid metabolism, liver function and blood pressure. It is not possible at this point in time to state with certainty which alterations in function, if any, have a permanent effect on the health of