These effects on detoxification are not the result solely of the enxyme-inducing potency of these drugs, since steroids are known to serve as substrates for the microsomal drug-metabolizing enzyme system in the liver. The drugs, therefore, compete with various exogenous substances for oxidative transformation by the enzyme system. The dual role played by sex steroids as both inducers and competing substrates makes it difficult to analyze the effect of oral contraceptives on the ability of the liver to detoxify specific agents (85, 89).

A recent review (143) of the hepatic toxicity of oral contraceptives concludes that these agents produce their effects through modifying permeability of the liver cell rather than causing parenchymal cell damage and that their use is probably not detrimental to the hepatic function of otherwise healthy women.

CARBOHYDRATE METABOLISM

Ovarian steroid hormones have been known for some time to modify carbohydrate metabolism. Early workers reported a decrease of glucose tolerance in diabetic animals treated with estrogen, but others (79, 80) demonstrated amelioration of diabetes in estrogen-treated rats; they attributed this effect to the induction of islet cell hyperplasia. Similarly, in human subjects, contradictory effects of gonadal steroids on carbohydrate metabolism are reported. Several (54, 167)) have shown that estrogens may lower the fasting blood sugar levels by as much as 20 per cent and that individuals with onset of diabetes in maturity may show lower insulin needs when estrogens are given. More recent work (82) has shown that estrogens such as mestranol, administered alone as well as in combination with norethynodrel, can cause a decrease in glucose tolerance. Androgens generally produce deterioration of carbohydrate metabolism in mammals (54, 96).

Explanation for these inconsistencies appears to depend on the chemical structure of the compound, the amount administered, and the individual sensitivity to the metabolic actions of these agents (12).

The preponderance of evidence indicates that glucose tolerance is diminished in women taking oral contraceptive drugs (61, 129, 132, 133, 157, 159, 186). Evidence of the abnormality is more pronounced with the oral than with the intravenous test. Similar findings with respect to greater frequency of abnormality in the oral, compared with the intravenous, test are seen in gravid women (16).

The impairment of glucose tolerance is more pronounced in women predisposed to diabetes and in those with latent or overt diabetes. These effects are well recognized in association with pregnancy. In studies in which a comparison can be made between the diabetogenic influences of pregnancy and oral contraceptives, the so-called diabetogenic effects of the drugs were shown to be of a lesser degree (12).

In nondiabetic subjects increased insulinogenesis is observed following both short-term and long-term use of oral contraceptives (159, 160). Effects are more pronounced with combined than with sequential regimens. In long-term use, the tendency is for glucose tolerance to return to normal while insulin levels remain elevated, suggesting that hyperinsulinism may serve as a compensatory mechanism for maintaining homeostasis of glucose.

Wynn and Doar (185) tested 67 subjects before and during oral contraceptive therapy (Group A) and 24 subjects during and after treatment (Group B). Glucose tolerance decreased significantly in approximately three-fourths of the subjects in Group A and improved in virtually 100 per cent of Group B after treatment was stopped. In contrast, there was a significant elevation of plasma insulin levels during therapy in Group A subjects in response to a glucose load, whereas insulin response was not significantly different in Group B subjects on or off treatment. These findings support the concept that increased insulinogenesis is essential for prevention of hyperglycemia in subjects receiving steroid contraceptives and raise the question of the capacity of pancreatic islet cells to sustain hyperactivity during long-term use of these agents.

In latent diabetic subjects or in women with overt diabetes, insulin response to steroidal contraceptive agents appears to depend upon the functional state of pancreatic beta cell activity. Gershberg (62) found a transient rise in immunoreactive insulin secretion in potentially diabetic patients during the first two months of treatment with oral contraceptives, but after three months glucose tolerance was impaired and insulin secretion returned to initial levels