despite hyperglycemia. In women with overt diabetes, glucose tolerance deteriorate promptly and immunoreactive insulin levels decreased at the half-hour and one-hour periods of the test.

Gold and his associates (64) showed that oral contraceptive-induced hyperglycemia demonstrable both during fasting and after glucose loads was accompanied not only by increased secretion of insulin but also by a significant increase in resistance to exogenous insulin. These findings accentuate the hyperglycemic potency of steroid contraceptives more strikingly than do studies performed in nondiabetic subjects. Whether prolonged administration of steroid contraceptives can result in exhaustion of the insulinogenic reserve and thus induce diabetes in women who are not genetically predisposed has not yet been ascertained.

Growth hormone secretion is known to be influenced by sex steroids. Frantz and Rabkin (56) demonstrated an elevation in HGH levels in response to estrogen, and Spellacy (156) showed significant increases also during a hypoglycemic stimulation test after administration of oral contraceptives. Gershberg (62) found elevation in potentially diabetic subjects of HGH levels that increased progressively during three months of treatment with medroxyprogesterone acetate. The importance of persistent elevation of HGH produced by oral contraceptives is unknown. A causal relation might be postulated between the increases in HGH and induced hyperglycemia and between increased insulin resistance and compensatory increases in circulating insulin.

Blood pyruvate levels are strikingly increased during oral contraceptive treatment. Elevated levels are demonstrable in the fasting state and after either oral or intravenous glucose tolerance tests in both obese and nonobese subjects (46). These effects can be produced with estrogen alone. The question of whether this is a direct effect of the estrogens or an effect secondary to increases in other circulating hormones such as cortisol, growth hormone, and thyroxin has not been ascertained.

These investigators (46) also studied the venous lactate-pyruvate ratio during infusion of sodium 1 (+)—lactate solution. Since conversion of lactate to pyruvate is obligatory for lactate metabolism, infusion of the stable solution was used to provide information about whether elevated levels of blood pyruvate and lactate in patients on oral contraceptives resulted from an increased rate of production or impaired removal of these metabolites. Close correlation of fasting blood lactate levels and the calculated endogenous production rate of lactate was observed in women on oral contraceptives and in controls, suggesting an increased rate of production. The authors further suggest that these metabolic alterations are caused by increased cortisol activity, probably at the hepatic level.

Substantial increases in plasma triglyceride levels are demonstrable during treatment and they remain elevated for months after discontinuation in long-term administration (60). This effect may have some bearing on the increases in plasma insulin levels previously described. In preliminary reports, Wynn and Doar (187) suggested that there was a slight increase in the nonesterified fatty acid levels in patients receiving progestational agents; in a subsequent study (186), however, with better matched controls, the same investigators found no significant differences in NEFA levels that could be related to treatment.

### THYROID FUNCTION

In women receiving combined steroid contraceptives the PBI level is elevated approximately 25 to 40 per cent above pretreatment levels. Thyroxine-iodine (T4 by column chromatography) values are similarly increased and T3 resin uptake values are diminished. All demonstrated changes appear to result from estrogen-induced increases in thyroxine-binding globulin (TBG). A significant rise in the PBI can be induced with ethinyl estradiol in amounts as small as 0.01 mg. (3). Progestational agents alone do not alter the PBI or the triiodothyronine red blood cell uptake (77).

All of these effects can be explained on the basis of increased protein-binding induced by estrogen. The basal metabolic rate, cholesterol levels, and 1–131 uptakes remain within normal limits. Concentrations of "free" thyroxine remain within normal range, suggesting that the functional status of the thyroid is unchanged (69). In addition, a normal response of the thyroid gland to small doses of TSH is maintained in patients on prolonged cyclic combination therapy (110).