minor nature may result in profound changes in biologic activity. Some of the effects of the progestins mimic changes seen in pregnant women. This is not unexpected. During pregnancy the estrogenic hormones are increased 100- to 1,000-fold and progesterone is increased approximately tenfold. Many of the important physiologic and metabolic alterations seen in normal pregnancy are due directly or indirectly to these naturally occurring hormones, and comparisons have been made between these effects and those occurring in response to the synthetic progestins. Secretion of thyroid hormones, for example, is increased by approximately 25 to 40 percent above prepregnancy or pretreatment levels, yet the functional status of the thyroid remains unchanged in either case. The cause for this change is related to the known effect of estrogen in inducing increases in thyroxine-binding protein. Protein-bound thyroxine is rendered biologically less active. "Free" thyroxine remains within the normal range. Circulating levels return to normal values after pregnancy and after discontinuance of oral contraceptives respectively. Both natural and synthetic estrogens cause an increase in cortisol-binding protein. This is reflected in an increase in adrenal corticosteroid hormone secretion similarly in pregnant women and in women on oral contraceptives. Adverse effects on thyroid or adrenal function have not appeared in short-term or long-term use of oral contraceptives.

Gonadal steroid hormones are known to modify carbohydrate metabolism. Similarities in the diabetogenic effects of pregnancy and oral contraceptive drugs have been noted, particularly in women with a known genetic predisposition to diabetes. Our work with diabetic mothers and their offspring over the course of the past 15 years has led us to conclude that pregnancy does not alter carbohydrate metabolism significantly in normal women. In genetically predisposed mothers diabetes may be temporarily unmasked, or permanent diabetes may be precipitated. In women with pre-existing diabetes the disease is usually aggravated during the course of gestation. As a rule insulin requirements which are elevated during pregnancy return to the prepregnancy dosage or approximately that dosage thereafter. It is not yet clear which of the women showing a transient abnormality in carbohydrate metabolism during pregnancy will ultimately develop overt diabetes in later life. Our studies and others—O'Sullivan in Boston, as well as several prospective and retrospective studies—would indicate that approximately one-fourth of the group showing reduced glucose tolerance during gestation and improvement after delivery progress to permanent diabetes within 5½ years. Far less is accurately known regarding the potential diabetogenic effects of oral contraceptives despite a very large number of carefully conducted research studies in this specific area. Many of these have shown that glucose tolerance is impaired in genetically predisposed women taking oral contraceptives. Evidence is not as convincing that the progestins produce abnormalities in glucose tolerance in the absence of a diabetic diathesis. On the basis of our own studies of subclinical diabetic pregnancies I can attest to the difficulties in separating these subjects from normals. In the early prediabetic stage, the disease is virtually asymptomatic, histories are frequently poor and laboratory tests are lacking in specificity or sensitivity at this particular stage of the disease.