endometrial glands, and, like progesterone, a pseudodecidual reaction. Both of these effects serve to make the endometrium unable to support implantation.

The third contraceptive effect, which is on the cervix, prevents alterations in cervical mucus that normally occur at ovulation, permitting the ascent of sperm into the uterine cavity. When oral contraceptives are taken, the cervical mucus remains thick and apparently inhospitable to the transmission of sperm. Also, oral contraceptives may affect tubal motility and alter the local ovarian response to gonadotrophic hormones.

When considering the metabolic effects of oral contraceptives, it must be remembered that there are many different formulations of these agents and that data derived from the study of one formulation may not be relevant to another. It is useful to identify the variables upon which the effects may depend:

1. the specific agent(s) employed;
2. the absolute amount of each agent;
3. the proportion between the two agents, if more than one is used;
4. the route of administration, which is usually oral or parenteral;
5. the length of time the patient has used the agent; and
6. the age of the patient.

Recent attention to the importance of these six variables has been expressed in several articles (7, 8) which suggest that a physician should select a specific agent according to the hormonal balance of the specific patient. These observations are based primarily on clinical impressions but they indicate important considerations which warrant further study and examination.

One of the best known metabolic effects of oral contraceptives is their ability to modify carbohydrate metabolism. Although earlier studies demonstrated that estrogen alone may lower the fasting blood sugar levels as much as 20 percent, and that individuals with maturity-onset diabetes may require less insulin with such medication, more recent work with oral contraceptives (9–16) indicates that glucose tolerance is decreased in a significant proportion of normal women on these agents and that diabetic women who take them may require more insulin.

Such alterations in glucose metabolism are similar to those which are observed in normal pregnancy but to a smaller degree. In addition, the effect appears to vary according to the specific formulation used. For instance, some recent investigations with progestogens alone, taken continuously, show very moderate effects. These variations in response depend on the chemical structure of the compound, the amount administered, and the sensitivity of the individual patient.

Increased insulinogenesis occurs with both short-term and long-term use of oral contraceptives and may be related to a parallel effect on growth hormone levels (17, 18) and to increases in blood pyruvate and lactate (19). These effects are more pronounced with combined rather than sequential regimens, and less with formulations which contain no estrogen. Whereas glucose tolerance tests return to normal shortly after the cessation of therapy, insulin levels may remain elevated for some time, suggesting that the hyperinsulinism which occurs with the use of oral contraceptives may serve as a compensatory mechanism for the maintenance of glucose homeostasis. This raises the question of long-term deleterious effects of such agents on pancreatic islet cell function.

Although the functional state of the thyroid gland appears to be essentially unchanged with the use of oral contraceptives and the concentration of free thyroxin is normal (20), it is well known that the PBI is commonly elevated about 20 percent above pretreatment levels with these agents. This effect is thought to be due to the increased protein binding induced by the estrogen. The progestogens in oral contraceptives do not appear to have this effect on PBI levels when administered alone (21). Thyroid tests return to normal 2–4 months after cessation of treatment, while the basal metabolic rate, cholesterol levels and I-131 uptake remain within normal limits throughout the treatment period.

Contraceptive steroids increase the levels of plasma cortisol and decrease the clearance rate of its urinary metabolites (22). These effects, thought to be due to the estrogen, are accompanied by the increased protein binding of aldosterone and cortisol. This later effect on cortisol may relate to alterations in glucose metabolism seen with these agents.