

The effects of these hormones on water metabolism are complex. Water can be retained or lost in association with sodium, potassium, phosphate, and nitrogen as part of anabolic or catabolic actions. Water can also be retained or lost in association with sodium and chloride in the expansion or contraction of extracellular fluid volume; these effects also are separate. Furthermore, the effects may be biphasic or even triphasic during hormone administration.

MINERALS

Several investigators (19, 65, 66) have shown no effect of oral contraceptives on levels or intestinal absorption of calcium, but a decrease in magnesium excretion has been demonstrated with a parallel decrease in serum magnesium levels. The data suggest that suppression of ovulation is associated with a poorly understood alteration in magnesium metabolism. Concern has been expressed over the observation that there is an association between soft water supplies and increased levels of cardiovascular disease in certain geographic regions. These interesting observations warrant confirmation.

Oral contraceptives have also been noted to increase serum copper and zinc levels (29, 125), as well as serum iron and total iron-binding capacity (25). The significance of these observations is not known, but estrogens have been known for some time to increase serum copper and ceruloplasmin levels (57).

KIDNEY

In proportion to the widespread use of oral contraceptives, remarkably little is known about their effects on renal function. These agents have been shown in recent years to be the cause of hypertension in certain women and this effect appears to be mediated in part through alterations in the angiotensin-aldosterone-renin system. It may also be mediated in part through the development of asymptomatic pyelonephritis developing secondary to ureteral dilatation, which is known to occur with these agents.

Ureteral dilatation is the only well-documented effect of oral contraceptives on the excretory system (111). Such dilatation disappears after medication ceases and it has been postulated to be due to progestins rather than estrogens. Comparable studies in the rabbit (115) demonstrated no ureteral dilatation but did show that these agents result in the disappearance of elastic fibers from the ureters.

LUNG

Recent studies (108, 162) show that oral contraceptives and allied agents exert a variety of effects on the respiratory system. First, progesterone, through some unknown effect on the respiratory center, increases alveolar ventilation and produces decreases in the arterial $p\text{CO}_2$. This effect is seen during pregnancy and in the luteal phase of the menstrual cycle. The presence of an ethinyl group on the progestin prevents this effect. Second, contraceptive steroids cause an increase of bronchial resistance; early work suggests that this effect may be mediated by an increase in histamine, a potent bronchial constrictor. Third, estrogens alone appear to inhibit gas transfer to a small degree. Fourth, stilbestrol or ethinyl estradiol in large amounts will produce progressive pulmonary lesions characterized by an accumulation of macrophages in capillaries, migration of macrophages to the alveolar interstitium and diffuse interstitial pneumonitis. Last, fibrosis of the pleura and the interstitial tissue of the lung was shown to develop after several months of treatment.

The relation between these effects and those of oral contraceptives in women has not been elucidated.

CENTRAL NERVOUS SYSTEM

Ovarian steroids are known to be essential to production of normal expression of sexual behavior in female animals. In man evidence of the essential role of these substances in the control of sexual activity is still lacking. The few reported studies suggest that an increase in either sexual desire or sexual activity in women as well as Rhesus monkeys coincides with the days preceding ovulation, while the second half of the menstrual cycle is characterized by a decrease or lack of sexual interest.

One study (117) reports a reduction in male sexual behavior in subhuman primates attendant upon the administration to the female of both sequential