

and combination contraceptive steroids, the effect being more pronounced with the latter. This remarkable effect is mediated through some unexplained mechanism, possibly an alteration in female sexual pheromones.

No definite conclusions can be drawn from data about the effect of oral contraceptives on human sexual behavior. One study (122) indicates that libido was reduced or lost in about one-third of patients receiving oral contraceptives. Other investigators (87, 88, 119, 176a), however, report an increased desire and greater satisfaction from sexual intercourse. In these situations it is difficult to separate the actual effect of the contraceptive steroid on sexual perceptivity from the effect brought about by an absence of fear of an unwanted pregnancy.

In lower species, progesterone is known to increase and estrogen to decrease the threshold for seizures induced by electric current (90, 164). The combination of agents used as contraceptives tends to lower the threshold, and the effect appears to be dependent on the ratio of progestin to estrogen. The recently reported increase in frequency of epileptic seizures in patients with documented epilepsy in the immediate premenstrual period implies that the observations made in lower species may be applicable to man (113, 176).

No information is available regarding the relation between contraceptive steroids and central nervous system excitability. Pregnanolone, a metabolite of progesterone, is a potent hypnotic; in the cat it is more effective as a hypnotic on the basis of weight than is pentobarbital. On the other hand, several synthetic progestins such as norethynodrel have minimal hypnotic properties.

The effect of contraceptive steroids upon thermoregulatory centers still remains to be elucidated. There is circumstantial evidence that at least progesterone increases body temperature by a central action. The exact mechanism is not known.

Depression has been identified as a side effect of contraceptive steroids, but its relative frequency varies markedly from study to study. Close examination of the data (7a, 62a, 69a) indicates that the depressive episodes encountered are usually not related to the pharmacologic effects of contraceptive steroids but are peculiar to the population under study. Brief periods of depression are not infrequent among young housewives with many small children.

Depression is more frequently associated with women of higher educational background. Thus, one investigator (87) studying a small population in a predominantly academic community in which the mean level of education was 15.4 years detected symptoms of depression in 34 per cent. In general, women who suffer from depression before and during the menstrual period seem more susceptible to depression while on contraceptive steroids. Recent observations (69a) indicate that depression and loss of libido are more likely to occur with compounds containing larger quantities of progestins and that the lowest incidence of these side effects is observed with the sequential preparations. The incidence in the former group was 28 per cent, whereas that in the latter was only 5 per cent. Another study (119) covering 72 clinic patients followed for 15 months reports no increase in depression attributable to the medication.

The incidence of headache among patients attributable to contraceptive steroids ranges between 3 and 11 per cent (129a). This kind of headache often has features associated with migraine, and changes in the pattern of pre-existing migraine headaches have been reported (180a). The tendency for migraine to occur when the concentrations of gonadal steroids change is well recognized. It is also known that women with pre-existing migraine headaches tend to develop their attacks while off medication, in contrast to patients without pre-existing headache who are more likely to complain of migraine headaches during the period of medication. It must be stressed that most studies have drawn their samples from selected populations, often with characteristics that make the evaluation of this side effect difficult if not impossible. Evidently, more studies are required to ascertain the true incidence of these phenomena.

SKELETAL MATURATION

In recent years there have been several reports of the use of estrogen to prevent excessive height in otherwise normal girls through the induction of premature epiphyseal closure. Both estradiol valerate (179, 180) and stilbestrol (177) have been used for this purpose, and the endocrinologic basis for this treatment has been reviewed (182). The effect is said to be mediated by direct