

Appendix 5

An appraisal of certain problems involved in the use of steroid compounds for contraception

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The growing acceptance of various steroid compounds as contraceptive agents has been attended by extensive controversy.

Such controversy has been mainly concerned with the nature of the immediate and delayed effects of these preparations. This communication aims to identify certain questions which merit consideration and to appraise the currently available data bearing on these problems.

Such a discussion becomes all the more imperative because of piece-meal and inadequate treatment of these matters in the lay and scientific press and in official statements of responsible governmental agencies. Meanwhile, the distribution of steroid compounds as contraceptives has become an accepted function of numerous public health agencies despite the lack of appropriately designed epidemiologic studies concerning many of their important potential effects.

The following are selected for discussion:

1. Will the prolonged use of steroid contraceptives affect the incidence or the pathogenesis of such malignant tumors as cancer of the breast, endometrium, or cervix?
2. Do these substances increase the frequency or predispose to the occurrence of thrombophlebitis or thromboembolism?
3. Does the prolonged exposure of the ovarian ova to steroids alter their reproductive or genetic potential?

Three types of steroid contraceptive regimens are currently employed: (a) Estrogen-progestogen combinations given cyclically; (b) estrogen and progestogen given in sequence on a cyclic basis, (c) progestogens given continuously. According-

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ly, it is imperative that we consider the properties of each of these classes of compounds when administered both singly and in combination.

For example, certain effects of the estrogen-progestogen combinations constitute characteristic responses to estrogen. These include: (a) A rise in thyroxin-binding and cortisol-binding protein in the plasma, (b) a tendency to fluid retention as manifested by varying degrees of weight gain and edema, (c) alteration in bromsulphthalein clearance by the liver (4a), (b), and (d) the subjective symptoms of nausea and malaise (1-4) and fullness of the breasts. These effects are not produced by even massive doses of progestogens and are readily reproducible with all varieties of natural as well as synthetic estrogens. Such effects clearly indicate that the estrogen administered exceeds normal endogenous estrogen production despite the presumed drug-induced suppression of endogenous estrogen formation. Moreover, available data concerning normal estrogen secretion rates in women (5, 6) show that the total endogenous estrogen would not equal in biological activity for man the estrogenic doses contained in currently employed contraceptive mixtures (6a). Hence the net biochemical and biological effect of such combinations is characteristic of hyperestrinism.

It is therefore highly pertinent to consider what is known about the relationship between the levels of endogenous and exogenous estrogen and various neoplastic processes both in man and in animals.

First, however, certain salient features of the carcinogenic response in man must be described. Of major importance is the fact that all known human carcinogens exhibit a prolonged latent period. Table I lists most of the agents which can be considered with some certainty to be capable of producing malignancies in man. It is especially