

carcinogenicity of estrogen in other species cannot be transposed directly to man. Suspicion lingers, however, that the results in laboratory animals may be pertinent to man. Many difficulties arise in epidemiological elucidation of this suspected relation. The principal obstacle is the long latent period between the administration of the known carcinogen and the development of cancer in man. Thus far, no properly devised prospective or retrospective studies provide an adequate solution to this problem.

There are 3 target areas, the cervix, endometrium and breast, that might potentially be affected by the oral contraceptives. It has been known that estrogen produces epithelial changes in the human cervix. The prognosis of these changes is obscure and their etiologic relation to carcinoma is unknown. A recently published study of women attending Planned Parenthood Clinics in New York City has revealed a higher prevalence of cervical epithelial abnormalities than the investigators called carcinoma in situ among women using oral contraceptives than in those using the diaphragm. Neither the authors nor the Advisory Committee on Obstetrics and Gynecology of the Food and Drug Administration believes that this study proves or disproves an etiologic relation between the oral contraceptives and these cervical changes.

There is no available data to indicate that the oral contraceptives cause endometrial carcinoma in women.

Although estrogen causes epithelial changes in the human breast, its carcinogenic effect on that organ has never been proved. Even in women with frank mammary carcinoma, estrogen produces variable changes. For example, ovariectomy leads to regression of metastatic breast carcinoma in approximately half of premenopausal women with the disease. It may, however, either cause regression or stimulation of similar tumors in premenopausal women. The reason for this peculiar effect of estrogen on metastatic tumors of the breast is not clear. Furthermore, diagnostic uncertainty surrounds precancerous lesions of the breast; it is not known whether exogenous steroids significantly affect this stage of the disease.

Currently available data on death rates from genital and mammary cancer in women do not clarify the problem of association between steroids and carcinoma. The long latent period of action of known carcinogens (10 years) and the length of time between diagnosis and death eliminate vital statistics as a source of information about this association until the mid-1970's or later.

The massive program of prophylaxis launched against cervical cancer in this country has accomplished a steady decline in deaths from the disease. The common practice of repeating cervical smears, annually or semiannually, in women taking oral contraceptives has contributed to the decline, but it has clouded the question of the effect of oral contraceptives on cervical cancer. There are some who believe that the massive prophylactic program, now common practice in the United States will make exceedingly difficult, if not impossible, an adequate epidemiologic study on the relation of oral contraceptives to cervical cancer. Since there is no method of early detection of mammary carcinoma comparable in efficacy to that of the cervical Papanicolaou smear, the problem of possible carcinogenic effect of the oral contraceptives on breasts is worrisome and unresolved.

Lacking conclusive information about the applicability of existing animal data to women and valid direct observations in human studies, the potential carcinogenicity of the oral contraceptives can neither be affirmed nor excluded at this time. Suspicion, however, continues and has been enhanced by the recent cytologic studies of the cervix. It is, therefore, necessary that a major effort be expended to solve this problem. In the meantime, clinical surveillance of all women taking oral contraceptives must be vigorously continued.

The decisions of the Food and Drug Administration concerning oral hormonal contraceptives are based on efficacy and safety. In the first instance, the issue is clearcut. The second, however, requires a carefully considered approach. Although the Kefauver-Harris Amendments of 1962, under which the Food and Drug Administration derives its current authority, indicate the term "safe" has reference to health of man, nowhere do they define safety. The Commissioner of the Food and Drug Administration pointed out the obvious in 1964 to a Committee on Government Operations of the House of Representatives, namely, that no drug can ever be absolutely safe, therefore, benefit must be weighed against risk in evaluating the safety of the drug.