

to permit evaluation. The findings of this study are in general agreement with those previously reported from Great Britain.

These studies together establish an etiologic relation between thromboembolic disorders and the use of oral contraceptives. Quantitatively they suggest that the mortality from thromboembolic disorders attributable to the oral contraceptives is about three per 100,000 women per year adding slightly less than 3 per cent to the total age-specific mortality in users of these drugs.

*(f) Carcinogenesis*

Much indirect evidence suggests that steroid hormones, particularly estrogen may be carcinogenic in man. These data are derived from experiments on laboratory animals in which long-term administration of estrogen resulted in cancer in five species. Although all physical and chemical agents that are carcinogenic in man produce malignant tumors in experimental animals also, evidence of the 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 the epidemiological elucidation of this suspected relation. The principal obstacle is the long latent period between the administration of a known carcinogen and the development of cancer in man. Thus far, no properly devised prospective or retrospective studies have provided an adequate solution to this problem.

The Committee has focused its attention on three target organs: cervix, endometrium, and breast. Estrogens may produce a variety of epithelial changes in the human cervix of uncertain prognostic significance. A study of women attending the Planned Parenthood Clinics in New York City has revealed a higher prevalence of epithelial abnormalities that the investigators considered to be carcinoma in situ among women using oral contraceptives than in those who use the diaphragm. The Committee believes that this study does not prove or disprove an etiologic relation between the oral contraceptives and these cervical changes. The epidemiological and diagnostic problems inherent in these studies are discussed in the Task Force Report.

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 in the clinical course of the disease. For example, ovariectomy leads to regression of metastatic breast carcinoma in approximately half of premenopausal women. Exogenous estrogens cause either regression or stimulation of similar tumors in menstruating women but induce regression in about half of post-menopausal women. The reasons for these paradoxical effects of estrogen on breast cancer are not clear.

In accordance with suggestions in the last report, the Food and Drug Administration has required mandatory testing for all currently licensed and investigational hormonal contraceptives on monkeys throughout their lifetimes and on dogs for 7 years. Thus far the presently licensed compounds have not produced tumors in these two groups of laboratory animals. Two estrogen-progestin combinations have, however, induced mammary tumors in beagles. Because these two compounds offered no clear therapeutic advantage over previously available hormonal contraceptives, clinical investigation was discontinued. This decision still leaves unresolved the question of similarity in hormonal induction of mammary tumors in a highly susceptible canine strain and in man. Continued testing of the presently available drugs is indicated.

Currently available data on death rates from genital and mammary cancer in women in the United States 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 cancer in this country has accomplished a steady decline in deaths from the disease. The common practice of repeating cervical smears, annually or semi-annually, 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.

Since there is no method of early detection of mammary carcinoma compara-