adverse or beneficial, of these contraceptive pills on endometrial malignancy (table 14).

There are numerous studies which suggest a preponderance of estrogenic influence, either endogenous or exogenous, in women who subsequently develop endometrial adenocarcinoma. A cause-and-effect relationship has by no means been established. All women receiving estrogen therapy must be followed with the utmost care and thoroughly investigated at the slightest suspicion; the advice to administer a progestogen periodically to women receiving estrogen, in order to allow periodic "withdrawal" bleeding on the basis that it "prevents" endometrial cancer, is not valid either on a theoretical basis or on the basis of the very limited number of postmenopausal patients so treated.

The use of progestogens in the treatment of adenomatous hyperplasia and carcinoma in situ of the endometrium is under investigation in several centers. At the present time no conclusions can be drawn. There is clinical evidence of some palliative benefit, but not cure, from the administration of large doses of progestogens in about one-third of the patients with metastatic endometrial cancer.

Breast Cancer

The mortality rate of cancer of the female breast in the United States has remained remarkably stable since 1930 (table 15). The incidence of cancer of the breast rises with age. Inasmuch as contraceptors are in the younger age groups, very large samples will be necessary to detect an association if one exists.

In the published reports of women receiving contraceptive pills for variable periods of time there are no observed cases of breast cancer. The FDA files contain one recent instance of a woman, age 44, with a history of previous cystic disease of the breast, who was shown to have a scirrhous carcinoma of the breast after 7 months of cyclic estrogen-progestogen. In the limited data available, with the preponderance of relatively young women and the uncertainty as to the completeness of followup breast examinations, no conclusions can be drawn as to the relationship between the use of the contraceptive pills and cancer of the breast.

The animal studies, to be mentioned later, and certain clinical observations indicate the need for a high index of suspicion and continuing alert observation and studies. The acceleration of growth of certain existing breast cancers by the administration of estrogens has been noted. Many instances of breast cancer have been reported in males receiving large doses of estrogens for prostatic cancer; although this is not proof of the inciting of breast cancer by estrogens, it is strongly suspicious. Any relationship of progesterone or the progestogens to breast cancer is not clear. One recent clinical study of breast biopsies in a limited number of women on the contraceptive pills revealed an increase in the amount of intralobular and perilobular fibrosis as compared to controls. The significance of this is not certain and the finding needs confirmation to accept.

Other Malignancies

Malignant lesions in the pituitary, kidneys, ovaries, and bone marrow have been found in animal studies after treatment with certain of the sex hormones, but at the present time there are no human corollaries. The FDA files contain one instance of malignant melanoma found during the administration of contraceptive pills; this is favorably coincidental, but the alterations of melanin distribution during pregnancy and in some patients receiving contraceptive pills are well known and therefore a relationship cannot be entirely dismissed.

Animal Studies

Sex steroids, particularly estrogens, have been shown to produce malignant lesions and to adversely affect existing ones in the mouse, rat, rabbit, hamster, and dog. These neoplasms have been in various organs and organ systems such as the cervix, endometrium, ovary, breast, testicle, pituitary, kidney, and bone marrow. The observations in animals using progesterone and the newer progestogens have been contradictory; however, these agents alone and in combination with other sex steroids have promoted tumor formation or not prevented it in a few instances. A recent example is a 52-week study of six dogs which received massive doses of a combination of mestranol and ethynerone (MK-665—an experimental progestogen)—four of the dogs developed mammary lesions; one, a carcinoma in situ with early invasion; one, a carcinoma in situ; one, an atypical hyperplasia; and one, a benign intraductile papilloma. The decision of the FDA to discontinue clinical trials of this agent and advise further animal studies was a correct one.