given to dogs and other animals, produce breast carcinoma. In many, but not all experiments the dosage was large on the basis of human therapy.

Against:

Although estrongens have been increasingly employed for a long time and there has been increasing use of oral contraceptives for 6 years, there has been no increase in mortality from breast carcinoma.

The FDA files contain only one case of breast carcinoma occurring in a patient taking oral contraceptives.

Carcinoma of the breast is less prevalent in multiparous than in nulliparous women, although each pregnancy induces an elevation in endogenous estrogen.

All this evidence has been carefully considered by the committee.

At the present writing, it seems that if the oral contraceptives are at all carcinogenic for the human breast, they cannot be very potent and the occurrence of breast carcinoma from this cause must be extremely rare. Nevertheless, caution and prolonged surveillance are in order. Whenever the oral contraceptives are employed, not only the pelvic organs, but the breasts as well must be examined at periodic followup.

Other Cancers:

Malignant lesions in the pituitary, kidneys, ovaries and bone marrow have been found in animals after treatment with certain sex hormones, but at present there are no human corollaries.

Animal Studies:

Sex steriods, particularly estrogens, have been shown to produce malignant lesions and to affect adversely the existing tumors in the mouse, rat, rabbit, hamster, and dog. These neoplasms have occurred in various organs, such as the cervix, endometrium, ovary, breast, testicle, pituitary, kidney, and bone marrow. The observations in animals given progesterone and the newer progestogens have been contradictory; however, these agents alone and in combination with other sex steroids have promoted neoplasia or metastatic growth in a few instances. A recent example is a 52-week study of six dogs that received massive doses of a combination of mestranol and ethyneron (MK-665, an experimental progestogen). Four of the dogs developed mammary lesions; one was a carcinoma in situ with early invasion; the second was a carcinoma in situ; the third represented atypical hyperplasia; and the fourth was a benign intraductal papilloma. Animal studies in which certain susceptible strains and species are used and in which the dosage is excessive and continuous, cannot be directly transferred to human beings. There is, nevertheless, a warning that an altered endocrine environment in human tissues might result in an abnormal expression or potentiation of growth, as in experimental animals. In fact, there has always been the suspicion that experimental animal and human tissues follow the same biological laws in this regard, but conclusive data are not available. A great difficulty in obtaining a reliable answer involves the prolonged period of latency in human beings exposed to known carcinogens. Future epidemiologic studies must take full recognition of this fact.

Statistical Considerations

A substantial change in the incidence of certain diseases such as cancer may be difficult to detect even with very large samples. For example, in a study of the incidence of breast cancer with 4-year followup of women aged 20 to 39 years, a sample of about 15,000 to 20,000 women, or 60,000 to 80,000 person-years, would be required to have a reasonable (that is, 90 percent) chance of detecting (at the 95-percent probability level) a twofold increase in risk. Naturally a control group of almost similar size would have to be studied in order to detect this change. Changes in the incidence of cervical cancer could be detected with samples of about the same size; changes in the incidence of endometrial cancer would require samples about six to eight times as large as those for breast cancer. No studies approaching this magnitude have been reported. Since duration of exposure is a critical factor, only those women exposed for prolonged periods provide pertinent information. There are no scientific data to justify the imposition of a time limitation for the oral contraceptives.