controlled prospective study be initiated with the objective of obtaining more conclusive data regarding the incidence of thromboembolism and death from such conditions in both untreated females and those under treatment of this type among the pertinent age groups" (*37*). Meanwhile, a statistically inadequate mass of scattered observations continues to direct our attention to this as yet unresolved problem.

Final evaluation of this aspect of the study of oral contraceptive preparations must therefore be deferred pending the outcome of such studies.

Studies of Carcinogenesis in Laboratory Animals

The initiation and current development of oral contraceptive agents are almost entirely based on initial findings in experimental animals (*38–40*; *47*, *48*). It is therefore pertinent to consider the results of extensive animal studies concerning the role of these and similar agents, in experimental carcinogenesis and in relation to other endocrinological functions.

The major significance of animal data has been recently emphasized by the finding of neoplastic changes in the breasts of dogs following the prolonged ingestion of Ethynerone, and this finding led to the officially approved cessation of clinical trials with this estrogen-progestogen mixture. The estrogenic component, mestranol, is chemically identical with that contained in most marketed mixtures. The progestogen content of this preparation differs from the marketed mixtures in specific chemical structure. However, all prior studies in this family of progestogens indicate that such structural variations provide only quantitative biological differences, unlike the qualitative changes induced by such structural changes in the corticoid series (*48a*). Hence it is clearly inconsistent to consider the animal data with the new mixture to be of more significance than the huge body of preexisting animal findings with a wide variety of synthetic estrogenic compounds in numerous species of animals, including the dog (*48b*). Either the presently marketed preparations are also to be condemned on the basis of almost certainly expectable animal findings or Ethynerone should not have been condemned.

The essential consideration is whether or not demonstrable carcinogenicity in animals is pertinent to the clinical problem. From a comparative physiological standpoint there is no validity in considering the recent results in dogs to be any more significant than comparable data in mice, rats, rabbits, and hamsters.

The vast amount of experimental data concerning the vital role of estrogens in the pathogenesis and progression of cancer of the breast, uterus, and cervix in numerous species is considered by some to have little or no pertinence to comparable processes in man. This view stems largely from the superficial interpretation of the clinical and epidemiological observations of the past 25 years already discussed. Also, disproportionate emphasis is placed on a few negative experiments (*41–44*), in which no malignancies were observed in monkeys treated for prolonged periods with estrogens or, in the case of one monkey, with estrogen and progesterone. These primate studies, which ranged in duration from 3 months to 10 years, involved a total of 25 Maccacus rhesus monkeys in all, with only 4 of the monkeys treated for 4 years or more. Although no actual malignancies were described, these monkeys almost uniformly did exhibit profound metaplastic changes in the cervix and endometrium and one of them showed a marked endometrial hyperplasia and polyposis (*45*, *46*).

Estrogen administration readily leads to a wide variety of neoplasms under varying experimental conditions in several species. These include tumors of the breast, cervix, endometrium, ovary, pituitary, testicle, kidney, and bone marrow produced in either rats, mice, rabbits, hamsters, and dogs (*49*). These experimental effects are easily and uniformly reproducible and, in view of their multiplicity, do not represent bizarre or rare biological effects. Rather, they are the readily reproducible responses seen in practically all sufficiently tested species of appropriate genetic constitution. However, the human population is so genetically heterogenous, that the role of the genetic factor in man's response to such agents is thus far unknown. From what is known experimentally, however, wide variation in the frequency of response in different genetic groups throughout the world is not improbable (*50*).

A considerable part of what has been stated above relates to estrogens when applied alone. However, we have also already considered the unique histological effects on the endometrium of the estrogen-progestogen combinations presently employed as contraceptives. The question naturally arises as to whether or not the combined use of these two hormonally active agents does not