26. Ryder, N. B. and Westoff, C. F. Use of oral contraception in the United States—1965, Science 153:1199, 1966.
27. Salmon, M. L., Winkelman, J. Z. and Gay, A. J. Neuro-ophthalmic sequelae in users of oral contraceptives, JAMA 206:85, 1968.
28. Shafey, S. and Scheinberg, P. Neurological syndromes occurring in patients receiving synthetic steroids (oral contraceptives), Neurology 16:205, 1966.
29. Thromboembolic phenomena in women, Proceedings of a Conference, Chicago, Sept. 10, 1962, Copyright 1962, G. D. Searle & Co., Chicago.
30. Vessey, M. P. and Doll, R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A Further Report. Brit Med J 2:651, 1969.
31. Walsh, F. B., Clark, D. B., Thompson, R. S. and Nicholson, D. H. Oral contraceptives and neuro-ophthalmologic interest, Arch Ophthal 74:628, 1965.

APPENDIX 3

Report of the Task Force on Carcinogenesis

R. Hertz, M.D., Chairman

INTRODUCTION

It has been repeatedly demonstrated that the steroid substances used in oral contraceptives produce a wide variety of tumors in 5 species of experimental animals (10, 13, 17, 22, 31, 32). It is also known that all physical and chemical agents that are carcinogenic in man are also carcinogenic in animals (24). Moreover, these carcinogenic agents frequently produce tumors in the same organs in animals as they do in man. Hence there is a distinct interrelation between animal and human carcinogenic responses.

Steroid carcinogenesis in animals usually requires prolonged administration of hormone at relatively high dosage (13). Such administration of estrogen has elicited a carcinogenic response in rodents and in dogs but not in monkeys (6, 11, 36). It is therefore essential to ascertain whether such experimental findings in rodents and in dogs have any pertinence to the question of a potential carcinogenic effect of steroid contraceptives in women. To date, no properly devised prospective or retrospective study providing conclusive data bearing on this question has been completed.

In consideration of available animal studies and in the light of certain physiopathological considerations it is deemed advisable to focus our interest on the potential effects of steroid contraception on the epidemiology, pathogenesis, and clinical course of cancers of the cervix, endometrium, and breast in women.

CERVICAL CANCER

An extended body of data provides an adequate background for the consideration of the major epidemiological aspects of cancer of the cervix (3, 5, 9, 25, 43, 44). However, despite a broad area of common agreement regarding morphological criteria for cytological and histological diagnosis of cervical cancer, it is clear that in practice wide differences of interpretation of pathological and normal material are frequently encountered (16, 29, 30, 33, 35, 38). Nevertheless, evidence of a variety of cervical epithelial aberrations of indecisive prognostic significance has emerged (4, 41). The complexity of interpreting the true impact of steroid hormonal effects on the occurrence and behavior of these epithelial changes is manifest. This difficulty is augmented by attempts at comparison of such hormonally responsive changes with those seen in the newborn or during pregnancy (34, 39). In addition, certain diagnostic procedures such as punch biopsy will in some cases remove all evidence of disease, thereby frustrating any reliable prognostic interpretation.

Nevertheless, Barron and Richard (1) have provided a mathematical model for the quantitative assessment of the proportion of cases to be expected to progress from "dysplasia" to "carcinoma in situ" in a given test population. The Task Force considers this model to be eminently applicable to the problem at hand and recommends its use in the evaluation of the validity of further data presented for consideration in this area. Seigel and Corfman (40) and