threne, into one horn of the uterus using a beeswax control in the opposite horn. Endometrial hyperplasia, the overgrowth pattern developed in the methylcholanthrene treated horn within 6 months, carcinoma in situ within 9 to 10 months and invasive carcinoma within 12 months. However, the cancer developed only in the presence of ovarian steroids since in castrate rabbits the methylcholanthrene was unable to exert its carcinogenic effect, and this exemplifies what I mentioned before. However, when progestational steroids, such as Delalutin or Depo-Provera which are potent progestins, were administered to ovarian intact animals, carcinoma did not develop in the methylcholanthrene treated uterus. We produced it with methylcholanthrene with the ovaries in. We take the ovaries out, we cannot produce it. This observation suggested that the progestational agent may have marked protective effects on the development of endometrial cancer.

The same "protective-anti-estrogenic" effect of synthetic progestins was evident in a report of Kistner in 1958, when we were interested in the effect of these agents on endometriosis. In this clinical study 12 human females with endometriosis were treated by pseudo-pregnancy, that is, giving them the same hormones obtained in pregnancy because pregnancy improves endometriosis. Large doses of estrogenic substances, either diethylstilbestrol (60 mg. daily), ethinyl estradiol (0.60 MG., not micrograms, daily, or estradiol valerate (35 mg. daily) were given for 3 to 7 months. It should be noted that the dose of ethinyl estradiol, the estrogen in some of the bills, given to some of these individuals were six times the amount of estrogen in the contraceptive pill (0.1 mg.) that is, containing 100 micrograms and 12 times the amount contained in the newer versions which contain only 0.05 mg. The progestins administered were: Delalutin in increasing doses from 62.5 mg. to 500 mg. over a period of the first 12 weeks and norethyodrel 9.85 mg. and mestranol (the 3-methyl ether of ethinyl estradiol) 0.15 mg., the original Enovid-10 tablet. The latter was given daily in increasing doses up to 40 mg. daily, and in some of the patients we originally treated for endometriosis we gave up to 120 milligram of Enovid daily because of "breakthrough" bleeding. I really thought at that time that I could obtain a better decidual effect in the endomethiosis by a higher dosage.

After 12 weeks these patients were receiving an additional 0.60 milligram of estrogen in the Enovid tablet in addition to the 0.60 milligram given as ethinyl estradiol. These patients were, after 12 weeks of therapy, receiving 24 times the amount of estrogen contained in the present low-estrogen pill, 24 times. The endometrial growth pattern was observed by sequential biopsies or curettage. Endometrial hyperplasia did not develop in any patient. As a matter of record, the endometrium gradually progressed through a decidual pattern (as seen in pregnancy) to that of atrophy.

As a result of these observations we then began to study the effects of the synthetic progestins on spontaneously occurring endometrial hyperplasia.

In other words in the endometriosis study it was somewhat by serendipity that we found that where we should be getting hyperplasia, an overgrowth, with the amount of ethinyl estradiol we were giving, we