by the administration of estrogen which look exactly like cancer and the pathologist cannot distinguish it from invasive cancer. But as soon as the estrogen is taken away or a progestin is administered this cancer-like lesion disappears.

But these lesions, as I just said, are readily reversible if endogenous progestin is given, if the patient is permitted to ovulate and her own progesterone is secreted, or if exogenous progestins—as used in the pill—are administered.

In 1956 Kistner, Duncan and Mansell—Kistner, R. W., Duncan, C. J., and Mansell, H., Obstetrics and Gynecology, 8:399, 1956—administered large doses of estrogen—synthetic Tri-p-Anisyl Chloroethylene-TACE—to 44 normally ovulating human females for ovulation suppression in the treatment of endometriosis—this is a disease that occurs because the woman menstruates regularly into her body cavity. It causes pain, infertility gets better if women get pregnant, unfortunately many of them are infertile and they can't get pregnant; it is a disease that sometimes has a cancer potential, and it may be a very debilitating disease. But if a woman doesn't ovulate she doesn't get the disease, and if she ovulated and has a disease the disease will improve if ovulation is suppressed. Therefore, we set out to suppress ovulation with that particular estrogen which is now in the pill in the treatment of dysmenorrhea—painful periods—and premenstrual tension. Dysmenorrhea—painful periods—occur in women who ovulate and do not occur in women who do not ovulate. Severe degress of hyperplasia, and anaplasia—this is one phase between beyond hyperplasia—were produced in 90 days, yet as soon as the estrogen was discontinued and ovulation occurred, the abnormal endometrial patterns disappeared. Obviously, this is due to the secretion of endogenous progesterones by the woman's ovary.

Wellenbach and Rakoff had already shown in 1953 that progesterone had a similar protective effect in animals. (Wellenbach, B. L. and Rakoff, A. E., J. Albert Einstein Med. Center, 2:3, 1953). They produced extensive endometrial hyperplasia in oophorectomized adult hamsters within 4 weeks by the administration of 100 micrograms of estradiol once weekly. They found almost complete regression of the hyperplasia within 4 weeks after discontinuing the estrogen and obtained, I believe more important, a more rapid regression when progesterone was given. If progesterone was given along with the estrogen, hyperplastic changes were virtually prevented.

A similar experiment was reported by Kistner and associates in 1962 (Kistner, R. W., Baginsky, S., Craig, J. M., and Bigler, P., Surgical Forum, Vol. 13 American College of Surgeons, 410, 1962). They induced endometrial cancer in adult rabbits by the insertion of a known carcinogen—if you want to produce cancer in a rabbit use a very potent carcinogen such as methylcholanthrene, or one of the coal tars. It can be produced with estrogen but it takes a long time. If one wants to produce cancer in the rabbit in a shorter period of time use a potent carcinogen such as methylcholanthrene.

Fortunately the rabbit's uterus looks like rabbit ears. There are two of them and it comes built in for investigators because you have to have a control on the opposite side. So we induced endometrial cancer in adult rabbits by the insertion of a known carcinogen, methylcholan-