In addition, Kistner has described the marked regression of the glandular elements of the endometrium in patients with endometrial hyperplasia or "carcinoma *in situ*" treated with various forms of progestationally active preparations (*31*). In evaluating the relationship of this finding to our immediate problems, we must recall that practically all known carcinolytic agents, such as X-ray and certain alkylating agents, are also carcinogenic. Hence, these findings further implicate the steroid hormones in the pathogenesis of endometrial cancer and underline the serious limitations of our knowledge of the actual role of these factors in the pathogenesis of these disease processes. One may therefore reasonably question the advisability of unnecessary derangement of such endocrinological relationships in completely normal young women.

These considerations become even more pertinent when one reviews the highly distinctive histological effects of the estrogen-progestogen mixtures on the endometrium. Notable among these effects is glandular atrophy (*1–4*). This appears to be a progressive or cumulative effect attaining its maximal degree after several months of cyclic medication (*1–4*). This change is reflected in progressively decreased menstrual flow during the initial months of therapy and in the failure of bleeding on withdrawal in 1 to 2 percent of the cycles during therapy. Such atrophic changes represent drug-induced pathology since no such phenomena are observed in the endometria of normal young women.

This glandular atrophy is accompanied by varying degrees of stromal modification and in some instances by active decidua formation, a phenomenon not normally observed in the absence of a recently fertilized ovum. Nor are such stromal changes an expected response to the naturally occuring progestogen, progesterone, unless accompanied by the stimulus of nidation. The degree of such decidualization varies substantially with the various dosage and temporal regimens more recently developed. Nevertheless, such tissue is not found in the uterus of a healthy, young, regularly menstruating woman. Its presence in the nongravid uterus is a distinct drug-induced abnormality.

Although the endometrium reverts to an entirely normal-appearing structure after cessation of therapy, (*1, 2*) this provides little assurance as to the future behavior of the previously altered endometrial elements which persist *in situ*—namely the epithelium and the stroma of the basal layers of the endometrium from which the more superficial layers are to be subsequently regenerated throughout the remaining life span. During the prolonged latent period of the action of substances known to be carcinogens in man, such as radioactive ores, X-rays, or aniline dyes, there are frequently no histological changes detectable (*32, 33*).

An instructive lesson regarding the importance of this silent, prolonged, latent period can be learned from studies of the effect of 19-norprogesterone on the ovaries of the mouse. Lipschutz and Iglesias (*31a*) described completely normal fertility after removal of pellets of 19-norprogesterone from Balb A mice after the pellets had been in place for 108 days. However, in a subsequent report these authors described ovarian tumors in 8 of 14 animals which had previously been reported to have had entirely normal ovarian function (*31b*).

We have already emphasized that a prolonged latent period of many years characterizes the behavior of most known carcinogens in man (*32, 33*). Since the longest exposure of any individual to oral contraceptives is 9 years and the greatest bulk of observations is for very much shorter periods of time and only a few years have elapsed since the close of treatment, no data concerning potential delayed effects are as yet available.

Estrogens and Cervical Cancer

The relationship of steroid hormones to the pathogenesis and progression of cancer of the cervix in man is poorly understood. However, the secretory and mitotic activity of the cervical epithelium is clearly responsive to the cyclic changes in ovarian hormone output as well as to exogenous steroid administration. Hence, alterations in these cellular functions are readily induced by the oral contraceptive agents. It is, therefore, universally considered essential that the status of the cervical tissue with respect to the presence of malignant and premalignant change be initially evaluated and closely followed.

In this connection, it is to be emphasized that when initial screening by Papanicolaou smear of a given population is subsequently repeated, the number of positive smears found on rescreening will be a small fraction of the number found initially. Thus, Christopherson *et al.* (*34*) working in Louisville showed that for carcinoma *in*