Of all the tissues of the body the endometrium is especially remarkable in that under normal stimulation by estrogen it proliferates faster than most malignant tumors do. In contrast, by inducing differentiation of endometrial cells, progesterone acts to stop the proliferation provoked by estrogen. Consequently, it seems logical that when progesterone action wanes, unopposed estrogen will stimulate the endometrium to proliferate excessively. The problem of precancerous states of the endometrium is closely related to such a type of unopposed excessive proliferation, and in contrast to the development of tumors in other organs, it is easy to expect from what has been said how hormonal stimulation is so important for the development of endometrial cancer.

Let us now examine the types of endometrial proliferation that develop from either endogenous or exogenous hyperestrogenism and attempt to classify these types according to their biological behavior as either benign proliferations or facultative or obligatory precancerous growths.

A. The etiology of precancerous conditions (Table I)

The glandular epithelial cells of the endometrium are the most sensitive to the unopposed estrogen stimulus and respond to the proliferative pressure in 3 ways: first, by cystic dilatation of the glandular lumina; second, by increase in tortuosity of the glands; and third, by the formation of papillae that protrude into the glandular lumina. The stimulus for proliferation may also affect the stromal cells, either alone or with the glandular epithelial cells.

I. PRECANCEROUS LESIONS IN THE ENDOMETRIUM

a) facultative:
irregular Proliferation
circumscribed and diffuse glandular - cystic Hyperplasias

b) relative obligatory:
adenomatous polyps
circumscribed adenomatous Hyperplasias
juvenile adenomatous Hyperplasias
diffuse adenomatous Hyperplasias
true stromal Hyperplasia (rare)

II. EARLY CARCINOMA OF THE ENDOMETRIUM

The first response of the endometrium to a persistent, unopposed stimulation by estrogen for more than 14 days, as with a persistent follicle, is the irregular proliferation. We recognize this condition histologically by its...
intensely proliferating glands, which have different diameters and which are irregularly distributed in a stroma of variable cellularity. The height of this endometrium may vary greatly. These changes are characteristic of the anovulatory cycles and consequently occur predominantly during the climacterium.

If the unopposed stimulation by estrogen persists, then the irregular proliferation gradually develops into the glandular-cystic hyperplasia. On the one hand, the severity of morphologic changes depends upon how long and how continuous the estrogen stimulation has been, and on the other hand, depends upon individual differences in cell responsiveness to estrogen. The most common hyperplasia to develop is the homologous type, in which both the glands and stroma proliferate; from this type we can distinguish a heterologous type of hyperplasia. Because of the rapid proliferation of glandular and stromal cells (high mitotic counts), the most common form of homologous hyperplasia is the cystic hyperplasia, in which the glands are dilated but not increased in number. The epithelium of the enlarged glands is uniformly high, either pseudostratified or genuinely multilayered. The nuclei of the cells are elongated, rich in chromatin, and contain several large nucleoli of dense ultrastructure. Mitoses are increased and often arrested by the excessive estrogen stimulation in either prophase or metaphase [29].

That explains the occurrence of the so-called «clear cells» in the glandular epithelium [15, 32].

The synthesis of DNA is greatly increased [12], and the nuclei when measured, are found to be enlarged [30].

The cytoplasm of the epithelial cells is scanty but rich in RNA, and contains lipid granules [4]. Acid mucopolysaccharides accumulate at the apical margins of the epithelial cells. The activity of alkaline phosphatase is directly proportional to the level of estrogen. The acid phosphatase and esterase are decreased [26].

Electron-microscopically four different types of glandular cells may be distinguished: those with short microvilli, expanded Golgi apparatuses and abundant lipid granules; those (the dark cells) that are dense with numerous ribosomes and have elongated microvilli; those with cilia, and those (the «clear cells») that are arrested in mitosis [37].

When the increased levels of estrogen persist unopposed for prolonged periods, the glandular-cystic hyperplasia progresses to an adenomatous hyperplasia. Here the proliferation in the cystically dilated glands evolves into glandular budding, sprouting and growth, whereby the newly formed glands may be small with miniature alveoli. The larger glands are lined by an epithelium of several layers which form papillae that project into the glandular lumen.

Although the chromatin-rich nuclei of the epithelial cells are still elongated, they begin to show irregular shapes and a markedly increased synthesis of DNA. The cytoplasm is sparse but basophile due to the abundant RNA. Structural changes characteristic of differentiation are lacking. The histochemical reactions remain similar to those of glandular-cystic hyperplasia. As the glands sprout and grow, the stroma between them continuously diminishes, so that eventually some glands impinge on their neighbors. In the gusset-shaped remnants of stroma between the proliferating glands, foam-cells appear in over 50% of all adenomatous hyperplasias. These cells contain lipids that emit a green autofluorescence, and histochemically give reactions typical of cholesterol esters [6].

These probably are formed from degraded products of estrogens they have stored [7]. These foam-cells are never associated with inflammatory processes. They are altered stromal cells and are always related to hyperestrogenism. For that reason they have prognostic value as accurate indicators that hyperestrogenism has persisted for a long time. The more numerous the foam-cells are, the more rapidly the hyperplasia evolves into neoplasia and adenocarcinoma. Only about 30% of the cases of glandular-cystic hyperplasia disclose foam-cells.

When high levels of unopposed estrogen persist, the glands in adenomatous hyperplasia continue to grow, producing multicentric groups of glands that assume neoplastic qualities. The glands of these groups appear strikingly clear and lightly stained, primarily be-