A Review of the Status of Endometrial Cancer

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SUMMARY

The histogenesis, pathogenesis, and endocrine background of endometrial cancer are reviewed. The histogenesis can be traced in graded steps through phases which have been designated as: 1) cystic hyperplasia, 2) adenomatous hyperplasia, 3) anaplasia, and 4) carcinoma in situ. A similar sequence of events has been observed in experimental animals when endometrial cancer was induced by the use of methylcholanthrene.

The pathogenesis of endometrial cancer is closely related to anovulation. The occurrence of endometrial cancer in postmenopausal women, anovulatory young women, and in patients with estrogen-secreting ovarian tumors, exogenous estrogen administration, and autonomous endometrial polyps provides the evidence that anovulation is the primary pathogenetic factor. The concept that estrogen stimulates the appearance of endometrial cancer is at best equivocal and requires further statistical evaluation.

Patients with endometrial cancer are very prone to a “habitus” consisting of obesity, diabetes, a diabetic glucose-tolerance curve, and hypertension.

BASIC FACTS

Before examining the evidence for the histogenesis, pathogenesis and endocrine background of endometrial carcinoma, it would seem appropriate to document briefly the fundamental clinical characteristics of the fully developed, invasive stage of this tumor (21, 6).

The incidence is approximately 0.0119% per year in the female population: this constitutes roughly ¼ or less of the incidence of squamous cell carcinoma of the cervix. With respect to age incidence, the range is from the 3rd to the 9th decades of life with the peak incidence around the age of 57. Seventy-five % of these tumors appear postmenopausally.

The major clinical manifestation leading to the detection of endometrial carcinoma is painless uterine (vaginal) bleeding. Characteristically, the bleeding from this tumor is a mucoid bloody discharge although the quality and quantity of bleeding is variable.

From the gross pathologic standpoint there are fundamentally 2 types of endometrial adenocarcinoma, the diffuse and the discrete. The discrete varieties often present as polypoid masses of either the pedunculated or sessile types, and may arise from any part of the uterine lining. Discrete tumors are localized to the endometrium in roughly ½ of the cases but more frequently have already invaded the myometrium at the time of their discovery. The diffuse variety, as its name implies, involves the entire uterine cavity and, although widespread throughout the endometrial layer, may be confined to it. These tumors are usually pale, soft, and friable and their surfaces are usually covered with mucus with, frequently, an admixture of blood.

The spread of this tumor (5) is slower than that of cervical carcinoma and is primarily by direct extension into and through the myometrium and by lymphatic vessel invasion. Occasionally, the tumor will have penetrated the myometrium and burst out on the serosal surface, and from this site it may implant on the serosa of the viscera of the pelvis and abdominal cavity. It sometimes extends into the broad ligaments. Lymph-node metastases are found in about 20% of cases, ovarian metastases in 4%, and the commonest distant sites are the lung and liver. Table 1 indicates the extent of the spread of endometrial cancer at the time of discovery in almost 300 cases (3).

From the microscopic standpoint these tumors are adenocarcinomas which at the time of discovery may be well, moderately, or poorly differentiated. Characteristically, the glands are closely packed and they compress and displace the endometrial stroma. The glands are composed of large pale cells with acidophilic cytoplasm and large vesicular nuclei. The epithelium tends to bulge into the lumens in papillary projections. Squamous metaplasia of the glandular epithelium is a frequent occurrence and has given rise to the separate category of adenocanthoma. The squamous epithelium is usually benign in appearance and numerous studies have shown that adenocanthomas are no different from adenocarcinomas in their prognosis or response to therapy. The appearance of squamous cell nests in an adenocarcinoma is of histologic interest only and for all practical purposes these tumors should be regarded as one.

Table 2 indicates that histologic grading of adenocarcinoma of the endometrium is of some prognostic value. As with most of the common tumors, histologic grading is
of less importance in relation to the selection of therapy than is clinical staging. The recently proposed International Classification of the clinical stage will probably provide a better basis for comparison of the effectiveness of therapy.

**INTERNATIONAL CLASSIFICATION OF CORPUS CANCER**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Adenomatous hyperplasia or carcinoma in situ</td>
</tr>
<tr>
<td>I</td>
<td>Carcinoma confined to the corpus</td>
</tr>
<tr>
<td>II</td>
<td>Carcinoma involves the corpus and cervix</td>
</tr>
<tr>
<td>III</td>
<td>Carcinoma outside the uterus but not outside the true pelvis</td>
</tr>
<tr>
<td>IV</td>
<td>Carcinoma has extended outside the true pelvis or has obviously involved the mucosa of the bladder or rectum</td>
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</tbody>
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Through a combination of factors, i.e., the slow growth and spread of the tumor and its tendency to bleed, leading to early discovery, the prognosis (15) of adenocarcinoma is comparatively good. With modern therapy, including hysterectomy and salpingo-oophorectomy, radium and X-ray, and various combinations of these, the 5-year salvage rates vary from 78 to 94%. When therapy fails the commonest causes of death are uremia (40%) and pyelonephritis (25%) due to ureteral compression by tumor and fibrous tissue.

**HISTOGENESIS OF ENDOMETRIAL CARCINOMA**

The development of our knowledge of the precursors of squamous cell carcinoma of the cervix has brought the opportunity, to eradicate this tumor with the methods now available. Certainly, the lessons learned from studies of carcinoma in situ of the cervix deserve application to other tumors, not only from the practical standpoint of their discovery at stages when complete cures can be effected, but also from the theoretical standpoint of our fundamental knowledge of the causes of cancer. Although the evidence is as yet fragmentary, the pioneer studies of Hertig (7, 8, 18) indeed show that adenocarcinoma of the endometrium goes through a stage when it can be recognized histologically but at a point prior to its invasion of connective tissue—in other words at an in situ stage. In a retrospective study of biopsy specimens taken from patients during a 15-year period prior to the appearance of invasive carcinoma, a sequence of events could be observed which can tentatively be regarded as the developmental changes leading to adenocarcinoma.

A. **Cystic hyperplasia**.—This is one of the earliest changes in this developmental process. It appears to be a reversible stage, since only 1.5% of patients with cystic hyperplasia ultimately develop cancer.

B. **Adenomatous hyperplasia**.—If cystic hyperplasia persists for years, it undergoes a gradual transformation. The cysts tend to collapse and leave radially symmetrical projections of smaller glands at their periphery. Small satellite glands appear around the cysts. These smaller glands crowd closely together and become irregular in size and shape and may form a rather complex glandular tissue. The epithelium lining these glands is dark-staining, due to a basophilic cytoplasm and small dense nuclei. This adenomatous transformation is often found side by side with cystic hyperplasia.

C. **Anaplasia and carcinoma in situ**.—As time passes, the cells lining the glands of adenomatous hyperplasia undergo a transformation. They become larger and paler staining, owing to the acquisition of abundant acidophilic cytoplasm and to the enlargement of the nuclei, which are now vesicular. The cells are not only enlarged but lose their polarity. Instead of lining up in an orderly fashion they grow in a haphazard manner in all directions, and frequently bulge in papillary projections into the lumen of the gland. This change has been called anaplasia because it gives these glands the same cytologic appearance as those in obvious endometrial cancer. It is this similarity that allows us to recognize the in situ stage. The cellular alteration is best recognized by comparing the anaplastic gland with its neighbors, whose cells often retain the dark-staining reaction of benign endometrial growth.

When anaplastic (pale-staining) epithelium lines many glands (10–30) in a low-power microscopic field, the neoplasm has reached the stage of carcinoma in situ (designated severe adenomatous hyperplasia or Stage 0 cancer by some investigators). Not only do the epithelial cells resemble cancer cells, but the glands have come to be "back to back." This tiny focus of neoplastic cells has not yet grown to the point of invasion of lymphatics or blood vessels and hence fulfills the requirements of the definition of carcinoma in situ. Great care must be taken to distinguish this neoplastic change from benign inflammatory or secretory changes in endometrial glands. As with cervical carcinoma in situ, this precursor in the endometrium may be found alongside an invasive cancer, and the peak incidence occurs several years before the peak incidence of invasive carcinoma.

In summary, the stages in the development of endometrial carcinoma appear to be: cystic hyperplasia, adenomatous hyperplasia, anaplasia, and carcinoma in
situation. Fortunately, a few patients on whom multiple biopsies were taken over long periods of time have been observed to go through all of these stages. This same progression has been noted in animals developing carcinoma upon exposure of the endometrium to methylcholanthrene. However, although the evidence is good, confirmation of this developmental process should be sought in carefully worked out prospective studies. The regular discovery of adenocarcinoma of the endometrium in its in situ stages would provide us with the possibility of eradicating this tumor by simple surgical procedures.

ESTROGEN AND ENDOMETRIAL CARCINOMA

For many years there has been controversy over the question of the role of estrogen in the genesis of endometrial carcinoma. This question probably arose in the first place because of the early recognition that in some way cystic hyperplasia bears a relationship to endometrial cancer (12, 13). A variety of types of evidence have been brought to bear on this question and will be briefly considered.

A. Ovarian tumors and endometrial carcinoma.—Probably one of the major arguments for the viewpoint that estrogens materially affect the incidence of endometrial cancer comes from those studies of the association of endometrial cancer with so-called “estrogen-secreting” tumors of the ovary, including granulosa cell tumors and thecomas. In a series of 75 such ovarian tumors Mansell and Hertig (11) found a concomitant adenocarcinoma of the endometrium in 15% of the cases, an incidence greatly in excess of that for the female population in general. In addition, carcinoma in situ was found in 9% of these endometria. The results of this study are presented in Table 3.

Several studies of a similar type have indicated essentially the same high incidence of endometrial cancer in patients with granulosa-theca cell tumors.

In spite of this, the argument of Larson (10) must be taken into consideration. These small series from gynecologic pathology departments may represent a special selection of “interesting cases” referred to these clinics. Emge (1) collected 753 cases of “feminizing” tumors throughout the country and stated that 25 (an incidence of only 3.3%) had a coexisting endometrial cancer. Larson reviewed the literature and among 919 granulosa-theca cell tumors found a concomitant endometrial cancer in 44, an incidence of 4.8%. If the incidence from these latter studies is to be believed, it is clear that the coexistence of ovarian and endometrial tumors is little higher than the 5% expected incidence of double primaries in patients with tumors of any organ. Until the discrepancies between these 2 types of studies is resolved at a statistical level, it seems best to reserve judgment on the significance of the endocrine relationship between ovarian tumor and endometrial cancer.

B. Ovarian cortical stromal hyperplasia and endometrial cancer.—Hyperplasia of the connective tissue of the ovarian cortex was first described in 1941 by Smith (16), who noted that this anatomic change in the ovary was often associated with adenocarcinoma of the endometrium. Since this original description several authors have confirmed a statistical relationship between ovarian cortical stroma hyperplasia of the ovary and adenocarcinoma of the endometrium and have added evidence of a relationship to carcinoma of the breast (20). The association of these conditions is beyond doubt, but the answers to such problems as the cause of the stromal hyperplasia, its endocrine secretory capabilities, and why it is so often associated with endometrial and breast cancer have remained undetermined.

Cortical stroma hyperplasia is macroscopically manifest by an ovary that is only slightly larger than the normal postmenopausal ovary. It is more convoluted, may even be nodular, and has an amber or yellow-brown color. On section, the yellow-brown cortical rind is observed to be considerably thicker than normal. Microscopically, this thickened cortex stains blue with hematoxylin and eosin, owing to the relatively scant amount of cytoplasm in these cells and the crowding and prominence of nuclei. In some ovaries whorls and nodules of this tissue bulge down into the medullary connective tissue, and in others they expand outward onto the surface. Sudanophilic material has been observed in a patchy distribution in the stroma cells, and capillaries appear to be more numerous in this altered cortical stroma than in normal ovaries. Since these are generally postmenopausal ovaries, primordial ova, follicles, and corpora lutea are generally absent, but corpora albicantia may be numerous.

Rarely, the stroma cells undergo a focal change to what appear to be “luteinized” theca cells. These cells accumulate in small clusters and are characterized by the presence of large round or oval nuclei, abundant granular acidophilic cytoplasm and sharp cell membranes. They were found in 15 of 638 cases examined by Woll et al. (22) and were 4 times more frequent in the group associated with endometrial carcinoma. This alteration has been referred to as “thecomatosis.”

Another rare finding in these ovaries are foci of granulomatous inflammation, referred to as “cortical granulomata.” These are variable in appearance but generally are composed of a central giant cell, surrounded by histiocytes, with a peripheral rim of lymphocytes. Cortical granulomata were found in 30 of the 638 cases recorded by Woll et al. (22) and were 7 times more frequent in the endometrial carcinoma group.
The degree of thickening of the cortex and the extent of the stromal hyperplasia are quite variable from one individual to the next.

In summary, the normal mature ovary contains a moderate amount of cortical stroma which at the time of the menopause appears to have 2 alternatives: a) to atrophy and fibrose; or b) to remain active and increase in size. It may be that cortical stromal hyperplasia is more a persistence of active stromal tissue into the menopausal period than an actual increase in the amount of this tissue. Cortical stromal hyperplasia is predominantly a condition of the postmenopausal ovary. It is extremely rare in women before the 4th decade and uncommon before the 5th decade. The incidence rises and reaches a peak shortly after the menopause and declines in the older age groups. In noncancerous women, the percentage of individuals with this lesion is about 40% and changes very little from the 4th to the 8th decade.

Table 4 illustrates the high incidence of cortical stromal hyperplasia in patients with carcinoma of the endometrium when compared to a control group. An average of 44% of women beyond the age of 30 who did not have endometrial carcinoma had this lesion, whereas it was found in 84% with carcinoma.

Novak and Mohler (14) reported a similar result. Using a grading system of 0–3+ for the extent of the hyperplasia, they observed that in 63 patients with cancer, 54% had significant stromal hyperplasia, while the remaining 46% did not. Of 63 patients without cancer (autopsy cases) 21% had significant stromal hyperplasia, and 79% had little or none.

The frequent association of these 2 lesions is well-established. Is cortical stromal hyperplasia causally related to endometrial cancer? The above statistics reveal that cortical stromal hyperplasia is not found in every case of endometrial cancer, and that not every case of cortical stromal hyperplasia is associated with endometrial cancer. This suggests a negative answer to the question.

Does cortical stromal hyperplasia increase the incidence of carcinoma of the endometrium by virtue of secretion of estrogen? This question cannot be answered until it has been clearly proved: (a) that cortical stroma secretes estrogen; and (b) that estrogens precipitate the appearance or stimulate the growth of human endometrial carcinoma.

It was originally suggested by Smith that the cortical stroma cell secretes estrogen. Experimentally, luteinizing hormone, in combination with amounts of follicle-stimulating hormone (FSH) too small in themselves to initiate the follicular secretion of estrogen, causes the nonfibroblastic cells of the ovarian stroma to secrete estrogen. Tumors derived from ovarian cortical stroma, particularly thecomas, are known to secrete estrogen, and the theca cells of granulosa cell tumors are apparently capable of estrogen secretion. Of particular importance is the fact that the ovarian cortical stromal cell possesses the potential of transforming into cells of known estrogen-secretory function normally.

Further evidence on this score can be derived from urinary estrogen excretion studies. Using the Smith and Smith technic of hydrolysis, extraction, and bioassay, Jessiman and Moore (9) found that young women excrete 20–900 IU of estrogen/day ($T_0$ values, acid hydrolysis). With zinc hydrolysis, 50–700 IU/24 hr additional were found ($T_m$ values). In normal postmenopausal women, the urinary estrogen levels were considerably lower. The $T_a$ values were between 25–50 IU/24 hr, and the $T_m$ values between 50–100 IU/24 hr. Even though no definitive values could be given for women with ovarian cortical stromal hyperplasia, Jessiman noted that high levels are common but not invariable. Of great interest is the fact that in postmenopausal women with cancer of the breast, estrogen activity ($T_a$) in the range of 50–125 IU/24 hr may be observed, with $T_m$ values as high as 5000 IU/24 hr. The latter figure is more than 40 times that expected.

Smith and Emerson (17) have suggested the alternative possibility that the adrenal glands may be the source of the very high $T_m$ values in patients with mammary cancer following castration or in the menopausal period.

Therefore, the known biologic potential of the cortical stroma cell and the high urinary estrogen values in some cases are strong presumptive evidence in favor of the idea that cortical stromal hyperplasia is associated with increased estrogen secretion. Nevertheless, as Engle (2) has pointed out, there is no direct evidence that the ovary with cortical stromal hyperplasia is secreting estrogen. Progress in this field will depend upon the direct demonstration of the precise endocrine activity, both qualitative and quantitative, of this abnormal ovary.

C. Exogenous estrogen and endometrial cancer.—There are numerous individual case reports of endometrial carcinoma in patients who have received exogenous estrogen therapy for varying periods of time (4). Some observers have ascribed the tumor to the estrogen administration. Obviously the main problem here is again the question of causal relationship or coincidence.

Speert reviewed 56 cases of endometrial cancer and found that estrogen therapy of 1.5–6 years duration preceded the diagnosis of cancer in 7 (12.5%) of these patients.

Larson commented on the fact that 1000 women with inoperable breast cancer received massive estrogen therapy for 3 months to 2 years and none developed endometrial cancer.

Individual case reports and the latter 2 studies are unimpressive in the establishment of a cause and effect relationship. It seems wise to reserve judgment on the question of whether or not exogenous estrogen causes
PATHOGENESIS OF ENDOMETRIAL CANCER

In the reproductive period of life the endometrium is a constantly changing tissue. It is the only tissue of the body that undergoes necrosis normally and is rebuilt again on a monthly basis. Histologic examination of the endometrium during the menstrual cycle reveals that the cyclic changes (proliferation, secretion, and necrosis) occur in the superficial ⅓ of the endometrial lining and that the basal ⅔ does not undergo these changes. It has a rather constant and "inactive" histologic appearance and remains behind while the larger surface layer is sloughing. It is from this basal layer that the new endometrium regenerates each month. It is also from this basal layer that carcinoma of the endometrium arises when the appropriate biologic background exists. One might consider this basal layer as the "growth" layer of the endometrium.

The basic condition which is associated with the development of adenocarcinoma of the endometrium is the failure of ovulation over long periods of time. Evidence that this is the case is readily obtained from an analysis of the clinical conditions associated with carcinoma of the endometrium.

1. The menopause.—Seventy-five percent of all endometrial cancers occur in postmenopausal women. The peak incidence for this tumor is between the ages of 50 and 60, an average of some 10 years after the cessation of ovulation.

2. Failure of ovulation in young women.—When cancer of the endometrium develops in premenopausal women, there is frequently a history of long periods of amenorrhea and menorrhagia. These patients usually do not have regular menses but have neither irregular bleeding with long intervals or excessive bleeding at irregular intervals. These patients are anovulatory.

3. Endogenous estrogen excess.—Patients with ovarian tumors that secrete estrogen, thecomas and granulosa cell tumors, may have a higher incidence of endometrial cancer than the remainder of the female population. In patients with these tumors the amount of estrogen excreted in the urine on a daily basis falls considerably below that of the normal menstrual cycle, yet it is often enough to suppress pituitary secretion of FSH and to prevent ovulation. The duration of anovulation depends on the continued secretion of hormone by the tumor, which may extend for long periods of time.

4. Exogenous estrogen administration.—A few patients who have been given estrogenic substances, usually stilbestrol or some related material, for many years on a therapeutic basis have ultimately developed endometrial carcinoma. Here again, the basic consideration may be a suppression of ovulation by the exogenous hormone.

5. Endometrial polyps.—The origin of adenocarcinoma of the endometrium within endometrial polyps is a special case of the general rule. The benign endometrial polyp arises from the basal or "growth" layer of the endometrium. The core of all benign polyps is composed of this tissue, even though in some polyps the surface layers respond to the cyclic changes in the ovaries. The core, and in many instances the entire polyp, usually does not undergo cyclic changes and remains "static" for long periods of time. As far as this small focus of tissue is concerned, the patient might as well be anovulatory, since it ignores the hormone fluctuations anyway. Thus, some patients with endometrial cancer will have normal regular menses, but these are exceptions to the rule. The origin of the endometrial cancer, however, is from the same, unstimulated growth layer of the endometrium, which in this instance has isolated itself from its hormone environment and is focal.

Therefore, in all conditions where the incidence of adenocarcinoma is actually or reportedly high, the tumor is preceded by the presence of inactive basal endometrium for long periods of time, most frequently as a result of the cessation of ovulation. However, it should be emphasized that this is only a predisposing factor and not an etiologic factor. Some more fundamental change, which at present is unknown, must be added to the predisposing factor in order for cancer to appear. This is obvious from the fact that not all patients who are postmenopausal or anovulatory, have estrogen-secreting ovarian tumors, are given exogenous estrogens, or have endometrial polyps develop endometrial cancer. In fact, the overwhelming majority do not.

OBESITY, DIABETES, AND ENDOMETRIAL CARCINOMA

Of great interest clinically is the fact that patients with endometrial cancer are very prone to a "habitus" which consists of obesity, diabetes or diabetic glucose-tolerance curve, and hypertension (19). Almost 50% of patients with endometrial cancer are obese, 10% have clinical diabetes, over 50% have a diabetic glucose-tolerance curve, and over 50% have hypertension. The presence of this "habitus" should alert the clinician to the possibility of the presence of endometrial cancer. Whether or not these metabolic changes are in any way directly connected with the development of cancer remains to be determined.

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