An Approach to the Control of Carcinoma of the Endometrium

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With carcinoma of the cervix coming under increasing control because of the accuracy, applicability and increasing acceptance of the routine Papanicolaou smear, it would appear that carcinoma of the endometrium has become a more critical problem.¹ It is not clear whether this apparent increase in the prevalence of endometrial carcinoma is due to an aging population, better nutrition or specific dysfunctional reproductive factors, but there is little doubt that this disease has not received the attention from researchers and clinicians alike that would seem indicated.

The efficiency of the Papanicolaou smear in the detection of carcinoma of the cervix is demonstrated by the fact that this cytologic method can disclose the minutest focus of carcinoma in situ and even dysplasia of this region in the transformation zone of the cervix, as well as an overt cancer of the cervix. At the same time, it must be acknowledged that the cytologic smear, taken in the conventional manner, which may be regarded as 95 percent accurate in cancer of the cervix, is only 75–80 percent accurate for cancer of the endometrium in most laboratories. Furthermore, there are only a few experts who can claim much accuracy in the use of the cytologic method for the detection of precursors of endometrial cancer. The opportunity for discovery of preclinical disease is clearly the key to better control of this malignant disease.

Adenomatous Hyperplasia and Carcinoma in Situ

Adenomatous hyperplasia, a typical precancerous lesion, may be a focal or general change, with its greatest prevalence in women of perimenopausal age with dysfunctional bleeding. Characteristically, histologic examination of curettings shows the glands to be crowded and frequently back to back; there is pseudostratification of the glandular epithelium and, in the most intense form, a characteristic pallor or eosinophilic stain reaction of these glands with intense proliferation of the glandular epithelium, forming buds and islands within the gland lumen. We prefer the term adenomatous hyperplasia rather than carcinoma in situ for this intense variety because of the impure criteria for invasion in the endometrium, unlike that in the case of cervical cancer, and also because in young women this lesion is frequently reversible by the administration of progestins. We have reserved the term carcinoma in situ for those lesions of undoubted invasion of the stroma, high differentiation and confinement to a local area of the endometrium; in the past this lesion was called adenoma malignum. (Figs. 1, 2, 3, 4.)

Patients with adenomatous hyperplasia are at high risk for later invasive carcinoma of the endometrium, as the illus-

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tration of our prospective study shows.² (Fig. 5.)

The Menopause and the High Risk Patient

Although young women who have the so-called syndrome of the cystic ovary and oligoamenorrhea may present with adenomatous hyperplasia in their reproductive years, such a lesion at this time of life is susceptible to reversal by the administration of progestins or the induction of ovulation. Most precursors of endometrial carcinoma are in fact seen in women in the perimenopausal era, and they are encountered in the course of the diagnostic curettage necessary for the exclusion of organic lesions of the endocervix and endometrium during the investigation of dysfunctional bleeding. Most precursors of endometrial carcinoma are those who have:

1. Obesity
2. Diabetes
3. Infertility
4. Irregular menses and failure of ovulation
5. Adenomatous hyperplasia
If we are to identify high risk patients we must turn our attention more intensively to menopausal women and devise a method of screening them by histologic sampling. Of course, we must do a curettage on every individual with abnormal bleeding during menopause so that we may rule out the presence of current organic disease. In addition, it may be necessary to screen all menopausal women with or without symptoms by the introduction of methods of histologic sampling. Of course, we must do a curettage on every individual with abnormal bleeding during menopause so that we may rule out the presence of current organic disease. In addition, it may be necessary to screen all menopausal women with or without symptoms by the introduction of methods of histologic sampling which will be as complete as diagnostic curettage under anesthesia and which can be done with a local anesthetic or no anesthetic at all.

A method that could be performed with minimal discomfort on an out-patient clinic or office basis has now become technically feasible. It is possible that aspiration techniques may enable us to obtain histologic samples which are virtually the equivalent of those produced by the diagnostic curettage under anesthesia. Surely we can now perform more diagnostic and therapeutic techniques formerly done under anesthesia by local anesthesia on an ambulatory basis. I think we have come to the era when we must take advantage of these advances and direct them toward the screening of all menopausal women, with special attention to those who are at high risk. Indeed, it is possible to construct a treatment protocol for menopausal patients with dysfunctional bleeding based upon the histologic findings at curettage. (Fig. 6.)

The Technique of Early Diagnosis

The perimenopausal era may begin with irregularity of the menses or epi-
sodes of amenorrhea, but any excess of flow or episode of intermenstrual bleeding should be considered an indication for further surveillance. The two conventional methods for investigating such abnormalities are the following:

(1) The cytologic sample taken through a cannula from the endometrial cavity. This method is the only way of obtaining a cytologic sample that insures a modest degree of accuracy in the diagnosis of carcinoma of the endometrium.

(2) The fractional curettage. Curettage of each separate sector of the uterus is done independently: first, the endocervical canal and second, each wall of the uterine cavity and the fundus. This technique enables the physician to identify and evaluate the extent of any existing malignancy and to discriminate between endocervical and endometrial cancer.

It is obvious to all experienced operators that carcinoma of the endometrium will come away in fragments that are somewhat gray and almost necrotic looking while normal endometrium and even cystic glandular hyperplasia of the endometrium will come away in strips of thinner or greater thickness. Of course, tissue must be subjected to laboratory examination, but one should not hesitate to request that the large samples of tissue obtained from a probably malignant endometrium be subjected to the frozen section technique, as lesions can be accurately diagnosed with this technique if further treatment is to be given promptly. No menopausal patient should receive treatment for menstrual abnormality without diagnostic curettage.

Problems of Treatment

As a result of the publication of selected series with results appropriately favorable at an 80–90 percent rate of five-year control, a misapprehension has developed that all cancers of the endometrium are of low grade and easily cured. We have been hampered by the lack of an appropriate staging utilizing the three parameters of virulence which are accessible to us, namely: (1) the size of the uterine cavity; (2) the lack of differentiation of the tumor; and (3) the involvement of the cervix. Our clinical staging formula\(^3\) has utilized these characteristic factors. (Fig. 7.)

Fig. 8. High risk patients and choice of treatment of Stage 0.
This information will help us resolve the problem of whether to utilize hysterectomy and bilateral salpingo-oophorectomy, or adjuvant radiotherapy or even more radical treatment. Our own protocol of treatment according to our classification is as follows:

**Stage 0**. (Adenomatous hyperplasia and carcinoma in situ.) Choice of treatment for adenomatous hyperplasia (Fig. 8) may be based on age, health and reproductive status of the patient.

**Stage 1.** Hysterectomy without preoperative radiation. It can be shown that tumors in small uteri that are well differentiated have a rate of cure that is above 90 percent and it is very difficult to improve upon this figure by any adjuvant treatment.

**Stage 2.** Those with larger uteri or undifferentiated tumors will benefit from preoperative radiation. Either the Stockholm technique of radium packing or external radiation, for larger uteri, followed by hysterectomy at an appropriate four-week interval is indicated.

| STAGE | Description |
|-------|-------------|
| STAGE I | Uterus normal size |
| STAGE II | Uterus mildly enlarged up to 2½ months or 10 cm, depth |
| STAGE III | Uterus markedly enlarged over 3 months or 10 cm, depth |
| STAGE IV | Contiguous organs involved or distant metastases |

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This figure illustrates the high risk patient decision-making process.

**HIGH RISK PATIENT**

- **Observe Only**
- **Infertility** → **Restore Ovulation**
- **Premenopausal**
- **Others** → **Cyclic Progestin**
- **Perimenopausal**
- **Good Operative Risk** → **Hysterectomy**
- **Postmenopausal**
- **Poor Operative Risk** → **Observe**

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Stage 3. In those instances where the tumor has reached the cervix, or by lack of differentiation suggests it is deep in the myometrium, the use of preoperative radium followed by radical hysterectomy, if the patient is surgically fit, may offer us an improvement in the cure rate. Patients less favorable to surgery will require radiation treatment via endometrial and cervical patterns, followed by simple hysterectomy.

Stage 4. Treatment must be individualized.

Using this method of staging, the physician can take advantage of the possibility of obtaining a high cure rate for tumors of low virulence with less aggressive treatment without depriving the patient with a more virulent tumor of the possibility of a more suitable radical treatment. It is well known that patients with metastatic cancer of the endometrium can occasionally be palliated for long periods of time by the administration of large doses of progestin. It has been demonstrated that approximately one third of patients with pulmonary metastasis will have their disease arrested by this modality.

Hormonal Relations

There has been great interest in the possibility of an endocrinopathy in the background of patients with carcinoma of the endometrium because of observations concerning obesity, nulliparity and infertility in many of these patients; secondly, the frequency of prior failure of ovulation and dysfunctional bleeding; and thirdly, the obvious proliferative effect of estrogen upon the endometrium in all age groups.

Appropriately sensitive laboratory animals have been shown to develop carcinoma of the endometrium with estrogen administration, but much of the evidence in humans has lacked control and in general has been circumstantial and derived from clinical observation of failure of hormonal homeostasis. That adenomatous hyperplasia may be induced by prolonged estrogen administration is no doubt clear and the observation that postmenopausal women with granulosa-theca cell tumors of the ovary that are functioning also produce coincident adenomatous hyperplasia, carcinoma in situ and true endometrial cancer is also provocative. With the demonstration by Kelley and Baker that metastatic endometrial cancer could be arrested by progestin, the stage was set for closer scrutiny of this problem with newer metabolic technology. Newer steroid technology has opened new areas of research with respect to steroid sensitivity of endometrial carcinoma. The study of the estrogen metabolism in postmenopausal women and the protein receptor sites for estradiol in the endometrium of women of this age group with carcinoma of the endometrium reveals sensitivity to estrogen that could be significant.

This relates to the problem of long term estrogen treatment on a prophylactic basis for asymptomatic postmenopausal women for the alleged advantages of the preservation of cosmetic youthfulness, prophylaxis against coronary sclerosis, and the prevention of osteoporosis in old age. It would appear that firm evidence that such prophylaxis is indeed successful is incomplete, if not absent, and one must remember that benign tumors of breast and uterus may be reactivated after the menopause by the administration of estrogen. In addition, the occasional induction of hypertension, the increase that has been demonstrated in thromboembolic phenomena in patients on estrogen, and the demonstrated capacity for this steroid in some individuals to induce adenomatous hyperplasia must be considered when one weighs the advantages and disadvantages of such long-term treatment in asymptomatic women.

Summary

There are still problems to be solved regarding the most efficient approach to
the diagnosis and treatment of carcinoma of the endometrium, but we have every right to expect that with the recognition of women at high risk we can reduce this disease to a minimum and possibly eradicate mortality from it to a very high degree. The approach to this state of control depends upon the following factors:

1. Recognition of adenomatous hyperplasia and carcinoma in situ of the endometrium as true precursors of invasive endometrial cancer.

2. Recognition of the high risk menopausal patient, through a histologic sampling of patients at the menopause with or without dysfunctional bleeding.

3. Further research into the technology of obtaining histologic samples in all menopausal women on an ambulatory basis without anesthesia as a means of screening for the precursors of endometrial cancer.

4. Adoption of a staging formula that will allow us to understand on a clinical basis the order of virulence of any endometrial cancer that comes to treatment so that we may not overtreat the patient with a less aggressive tumor and thereby penalize her with an excess of complications or, on the other hand, undertreat the patient with a highly virulent tumor and penalize her by a lower rate of cure than might be obtained by more radical treatment.

5. The appropriate recognition of the place of surgical and radiotherapeutic treatment and combinations thereof that are most appropriate for the treatment of the individual patient.

6. Recognition of the menopause as the time of life when high risk patients may be identified.

7. Caution in hormonal treatment in the perimenopausal or postmenopausal era until evidence of their efficacy supersedes evidence of their possible etiologic role in endometrial aberration.

When these criteria are fulfilled there is little doubt that we will be able to control cancer of the endometrium in somewhat the same fashion that we are beginning to control cancer of the cervix.

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