The Role of Progesterone in Human Endometrial Cancer

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SUMMARY

The administration of progestational agents to patients with metastatic endometrial carcinoma has resulted in an objective remission rate of approximately 32%. Remissions lasting from 1 month to 9 years have been achieved. In general, patients with well-differentiated histology are more likely to respond than those with undifferentiated carcinomas. Patients with pulmonary or osseous involvement have a higher response rate than those with abdominal or local recurrent disease. It appears clear that endometrial carcinoma is another target-organ carcinoma which will respond to manipulation of the hormonal environment of the host.

Although carcinoma of the endometrium when confined to the uterus responds well to surgical and radiation therapy with a 60% 5-year cure rate in Stage I (2, 14, 20), the management of recurrent carcinoma or those cases beyond local control initially has presented a difficult problem. This is particularly true in patients with distant metastases, with the pulmonary area the most common site of dissemination. Endometrial carcinoma has long been associated with the presence of endocrine abnormalities in the host, most commonly in relation to the ovary, where evidence of excessive or unopposed estrogen production has been postulated as a predisposing factor in the development of uterine cancer. Ovarian pathology such as the Stein-Leventhal syndrome (6), cortical stromal hyperplasia (17, 19), Leydig cell hyperplasia (15), ovarian hilar rests resembling Sertoli and Leydig cells (6), thecomas (19), and feminizing ovarian neoplasms (11) have been described in coexistence with endometrial carcinoma, and numerous theories of cause and effect between the lesions have been postulated. Large doses of estrogen have been demonstrated to induce endometrial hyperplasia and carcinomatous alterations in rabbits (1, 12, 16). Abnormalities of the endometrium, such as cystic and adenomatous hyperplasia and anaplasia, interpreted as evidence of excessive estrogen stimulation have been noted in patients who later develop endometrial carcinoma (4), and vaginal smears reflecting estrogen influence after castration have been recorded in these patients (14).

An attempt to modify the course of incurable uterine cancer was a logical outgrowth of the demonstration that the growth of certain malignant tumors arising in organs under endocrine control could be altered by hormonal manipulation of the host. It is well recognized that endometrial carcinoma is often a well-differentiated tumor retaining marked histologic similarity to the parent tissue. There is evidence that such tumors in postmenopausal women may show evidence of secretory activity and squamous metaplasia, suggesting response to a progesterone-like substance, while in premenopausal patients, secretory activity in the tumor tissue may resemble that in adjacent normal endometrial tissue but is slower and less complete in its evolution (2). The profound effect of progesterone on the maturation of normal endometrium and the apparent sensitivity of this tissue and its well-differentiated neoplastic offspring to hormonal stimuli motivated the choice of large doses of progestational agents for therapeutic trial in disseminated endometrial cancer. Since our original publications describing unequivocal and often prolonged remissions (7-9) in patients treated in this manner, many more patients have been treated by us and others, receiving a variety of progestational agents; they have shown responses similar to those observed by us in approximately 25-30% of cases.

The type of patient demonstrating the most impressive response has been characterized by a long hiatus between the original treatment and the recurrence of endometrial cancer, a well-differentiated adenocarcinoma or adenocanthoma histologically, and pulmonary metastases, with or without local recurrence in the pelvis. In favorable cases, pulmonary nodules have regressed within at least 2 months of the initiation of therapy, have disappeared within 4-6 months, and have remained in abeyance as long as 4.5 years. Pelvic recurrences have been much less impressive in their response, although decrease in disease for several months has occurred. In most instances these areas have been heavily irradiated prior to the institution of hormonal therapy. We are currently treating a few patients with extensive pelvic disease who have received no prior therapy, but it is too early to record results. In 1 patient, extensive hepatic metastases causing obstructive jaundice due to the involvement of the biliary ducts have shown gratifying regression with marked clinical and chemical improvement. Osteolytic lesions in a few cases have been reported to recalcify. Symptomatic relief of pain and debility has occasionally been striking.
and sustained, even in the absence of demonstrable objective regression.

It is an accepted fact that the progression of metastases in endometrial carcinoma may be very leisurely, even in the absence of therapy. In our series, however, patients failing to respond objectively to progestational therapy have succumbed to their disease within several months, in contrast to the responders, many of whom have enjoyed prolonged remissions of several months' to several years' duration.

Several progestational agents in varying dosages have been utilized in the course of this study by us and others. Aqueous progesterone, progesterone in oil, 17α-hydroxyprogesterone caproate and 6α-methyl-17α-acetoxyprogesterone have all been demonstrated to induce responses in this disease. Dosage in the range of 500 mg of 17α-hydroxyprogesterone caproate, given twice weekly i.m., or its equivalent in other preparations, appears adequate to induce remissions. Larger doses, up to 5 gm weekly, have not improved the percentage response rate. These agents are well tolerated, and the only complications we have observed have been an occasional sterile abscess at the injection site and occasional fluid retention. Table 1 shows the over-all response collated from 65 different investigators.

The following case reports are illustrative of the types of responses seen in favorable cases:

Case I.—R. W. (Massachusetts General Hospital 845077), a 61-year-old woman, 3 years before admission to this study had a panhysterectomy for adenocarcinoma of the endometrium with metastases to 1 ovary. Local vaginal recurrence in April, 1954, was treated by X-ray therapy, 3300 r. Shortly after this course multiple nodular densities in both lungs were demonstrated, which increased over the ensuing 2 months. For this reason, she was referred for treatment with progesterone. In June, 1954, she was placed on progesterone in oil, 50 mg, 3 times weekly. X-ray study at the time of institution of treatment showed multiple bilateral densities. Three months later, X-ray examination disclosed definite regression of the metastatic nodules, and 1 year later all the densities had disappeared. During the next 4 years, while she remained on continual therapy on the same dose schedule, no further change on the X-ray films was demonstrated. At the end of this time an increase in hilar densities, which enlarged slowly, was noted. Progesterone in oil was discontinued in September, 1958, to determine whether she might have a withdrawal response, similar to that sometimes seen in patients with carcinoma of the breast on withdrawal of hormonal therapy to which they have previously shown a response. No such change occurred, however. In July, 1959, because of a further increase in hilar disease and the appearance of a nodule in the right lower chest, she was placed on 17α-hydroxyprogesterone caproate, 500 mg twice a week. In 6 months the nodule disappeared, the hilar mass shrank about 1.0 cm, and the chest X-ray did not change until December, 1962. From December, 1962, until the present (July, 1965) pulmonary disease has gradually increased. Over the last 6 years she has had submucosal palpable nodularity at the apex and anterior surface of the vagina, which has not changed during this period. Smears of vaginal secretions have been persistently negative for malignant cells. At present she is in fair health.

Case II.—E. G. (Pondville Hospital 45685), a 70-year-old woman, developed adenocarcinoma of the uterus in 1953 which involved most of the myometrium and ⅙ of the cervix. She was treated with hysterectomy and bilateral salpingo-oophorectomy. In 1959, peculiar shadows were noted on a routine chest film. They had progressed markedly by September, 1960, and were accompanied by a hacking cough. There was no evidence of recurrent carcinoma elsewhere. Since the lung lesions were typical of those seen in other cases of endometrial carcinoma, she was placed on 17α-hydroxyprogesterone caproate, 500 mg i.m. twice weekly. Within 2 months, her chest X-ray was virtually clear and remains so 22 months after institution of therapy. She is being maintained on 500 mg of Delalutin once weekly and is completely asymptomatic.

Case III.—M. B. (M.G.H. 1115849), a 53-year-old woman, had a total hysterectomy in 1955 for adenocarcinoma of the endometrium. Vaginal recurrence in February, 1959, was treated with 6000 r. This therapy was repeated in January, 1960, but vaginal bleeding persisted. An additional 2000 r in October, 1960, stopped the bleeding and reduced the size of the vaginal disease. In December, 1960, she complained of dyspnea, and pulmonary metastases were noted for the first time. Therapy with 500 mg of 17α-hydroxyprogesterone caproate twice weekly was instituted, and within 2 months the multiple pulmonary lesions had disappeared. Coincident with this there was complete relief of dyspnea. Initially, there was further shrinkage of the vaginal disease, but this rapidly recurred with bladder invasion and she received pelvic perfusion with methotrexate and 8-azaguanine in August, 1961, and with 6-fluorouracil in January, 1962. Throughout this period her chest film remained negative. Her dose of Delalutin was increased to 2.5 gm twice weekly without any effect on the progression of the pelvic disease. After 2 months, the dose was again lowered to 500 mg twice weekly. Her chest film remained negative 18 months after institution of hormonal therapy, while the pelvic disease continued to progress. Death occurred in 1962, from metastatic disease.

There is little question that the administration of moderately large doses of a variety of potent progestational agents may exert a marked influence on the progression of carcinoma of the endometrium in some patients, placing

<table>
<thead>
<tr>
<th>Area of metastasis</th>
<th>Response (%)</th>
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<tbody>
<tr>
<td>Abdominal</td>
<td>24.2</td>
</tr>
<tr>
<td>Local</td>
<td>34.5</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>30.6</td>
</tr>
<tr>
<td>Pulmonary with Osseous</td>
<td>53.8</td>
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<tr>
<td>Osseous</td>
<td>14.3</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>37.5</td>
</tr>
</tbody>
</table>

* The data for this table were collated from 165 cases reported by 65 investigators.
this disease in the category of hormone-responsive tumors. The mechanism of action of this therapy is not clear at present, but there is evidence to favor both a local effect and a central effect mediated via 17-α-hydroxyprogesterone caproate, with marked gross clinical changes, including decrease in the size of the uterus, and abatement in blood loss and vaginal discharge (18). Such gross alterations were not paralleled by histologic changes toward a more mature type of tumor. These authors also observed tumor regression following direct application of the agent to the tumor. Kistner (10) has demonstrated that prolonged administration of progestational agents can induce hyperplastic endometrial glands to regress and convert actively proliferating stroma to decidua—further evidence of action at the site of application.

Postulation of mediation via the pituitary gland is suggested by the observations by Sherman and Woolf (15), who demonstrated a fall in elevated titers of luteinizing hormone in 4 patients with endometrial carcinoma receiving 17-α-hydroxyprogesterone caproate. Studies of luteinizing hormone on our own patients are under way in an attempt to verify this observation. Studies in patients with hypogonadism and high follicle-stimulating hormone (FSH) levels receiving large doses of 17-α-hydroxyprogesterone caproate failed to demonstrate a decrease in FSH excretion (3). Our patients have shown no alteration in FSH values during progestational therapy.

A 3rd speculative route of effectiveness lies in the possible conversion of administered progesterone in whole or in part to one of its active steroid products, i.e., androgen, estrogen, or corticoid. Although progesterone is known to be a precursor of all of these compounds, there is no evidence on clinical grounds in these patients that such a conversion has occurred.

Elucidation of the reason for the effectiveness of this therapy in a small percentage of patients must await more sophisticated measures of various urinary hormones and careful histologic and possibly histochemical studies of serial biopsy material on previously untreated cases. Until such data are available the utilization of progestational agents must remain an empirical but often strikingly effective mode of therapy, much as does the hormonal management of carcinoma of the breast.

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REFERENCES

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