Lack of Effect of Human Growth Hormone and Ovine Prolactin on Cancer in Man

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SUMMARY

Human growth hormone increased the urinary calcium excretion by an average of 64 mg/24 hours in the subject without cancer. This complicates the evaluation of the observed increases in urine calcium resulting from the administration of growth hormone to patients with metastatic cancer.

Human growth hormone did not increase the urinary calcium excretion of six patients with metastatic breast cancer who were in remission. In five patients who did not respond to hypophysectomy, growth hormone increased the excretion of calcium to the same extent as in the control group.

The combined administration of estrogen and growth hormone in two women with estrogen-sensitive mammary cancers did not measurably exacerbate tumor growth.

It was concluded that, for the short periods of administration used in this study, neither human growth hormone nor ovine prolactin measurably increased the activity or rate of growth of metastatic cancer of the breast and prostate.

There are ample experimental data suggesting that hypophyseal hormones influence certain phases of cancer induction or growth. As early as 1932, Ball and Samuels (8-13) demonstrated that, in the rat, hypophysectomy decreased the growth rate of spontaneous, induced, and transplanted tumors.

Ball and Samuels (6) and Talalay et al. (27) proved that this type of inhibition was not due to the caloric restriction accompanying hypophysectomy. Moon and collaborators then clearly implicated growth hormone as one of the factors favoring the chemical induction of cancer (17) and increasing the rate of appearance of a variety of spontaneous tumors (16, 18-20).

In man, however, there is only fragmentary evidence that growth hormone can influence the induction or growth of cancer. Archer (1) pointed out that patients with panhypopituitarism had a decreased incidence of cancer, but his sample was small. Mustacchi and Shimkin (22) in a more extensive study were unable to confirm this and also reported that the incidence of cancer in patients with acromegaly did not differ from that of the general population.

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The well documented action of prolactin in both lactation and galactopoiesis suggests its possible relation to human breast cancer. Furthermore, Mühlbock (21) has suggested that prolactin facilitates the induction of breast cancer in sensitive strains of mice without the intervention of the milk factor. Its relevance to carcinoma of the prostate is suggested by the observation that 125I-labeled prolactin has been shown to localize in the rat ventral prostate (26) and in one study to synergize with testosterone in promoting the growth of the ventral prostate (12).

With the clinical use of hypophysectomy for the palliation of patients with metastatic cancer of the breast and prostate, it has become pertinent to assess the significance of the removal of growth hormone and prolactin to the remissions obtained. However, the measurement of changes in the rate of tumor growth in man is difficult. Pearson et al. (25) correlated the degree of hypercalciuria with the growth rate of osteolytic metastases in patients with breast cancer. They demonstrated, by this index, that estrogen administration could increase osteolysis and, by inference, the rate of tumor growth. Since the increases in urine calcium were of large magnitude, were temporally correlated with estrogen administration, and were in a direc-
tion different from that observed when estrogen is given to women without cancer, the conclusions of these investigators seem valid. Subsequently, Pearson and co-workers, employing this index, reported that beef growth hormone (24) and human growth hormone (23) stimulated metastatic mammary cancer. In these instances, the conclusions were based upon changes in urinary calcium excretion of lesser magnitude than those observed with estrogen.

It was the purpose of this study to evaluate the effect of human growth hormone and ovine prolactin in patients with metastatic breast cancer and prostate cancer. We shall report our observations with these hormones and compare the effect of human growth hormone on the calcium excretion of subjects without cancer and of those with metastatic osteolytic breast cancer.

HGH was administered to eleven patients with metastatic carcinoma of the breast, of whom ten had been subjected to either hypophysectomy or hypophyseal stalk section. Of these ten patients, nine demonstrated lack of pituitary function as measured by the absence of gonadotropin in the urine and marked suppression of thyroid and adrenal function. Six of the eleven patients were in remission, and five had failed to respond to therapy. The patients either had been hypercalciuric before surgery or were hypercalciuric during the study with HGH.

To evaluate the changes in urinary calcium produced by HGH in the patients with metastatic breast cancer, we have examined the effect of HGH in seventeen studies in fourteen subjects without cancer. The pertinent data for the control group are listed in Table 1.

**TABLE 1**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Growth hormone (mg/24 hr)</th>
<th>No. days</th>
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<tbody>
<tr>
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<td>34</td>
<td>F</td>
<td>5</td>
<td>6</td>
</tr>
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</tr>
<tr>
<td>5</td>
<td>38</td>
<td>F</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>F</td>
<td>5-10</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>69</td>
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</tr>
<tr>
<td>8</td>
<td>49</td>
<td>M</td>
<td>5-10</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>F</td>
<td>5-10</td>
<td>10</td>
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<tr>
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<td>F</td>
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<td>4</td>
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<td>11</td>
<td>14</td>
<td>F</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>M</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>13</td>
<td>12</td>
<td>M</td>
<td>5-10</td>
<td>18</td>
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</tr>
<tr>
<td>15</td>
<td>10</td>
<td>M</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

**Diagnosis**
- Cushing's syndrome
- Hypopituitarism
- Hypopituitarism
- Hypopituitarism
- Hypopituitarism
- Hypopituitarism
- Osteogenic
- Osteogenic
- Osteogenic
- Growth failure
- Normal
- Dwarfism
- Achondroplasia
- Agammaglobulinemia
- Dwarfism

**MATERIALS AND METHODS**

The growth hormone (HGH) was prepared by a number of methods from human pituitary glands removed at autopsy. Each lot was shown to be active by a rat bioassay technic (11) and by its capacity to cause nitrogen retention in man. The preparations were free of corticotropin, thyrotropin, gonadotropins, and prolactin by bioassay. In the human subject, no stimulation of the thyroid or adrenal glands was observed.

The ovine prolactin was distributed by the Endocrine Study Section of the National Institutes of Health and was assayed at 15 I.U. per mg. of dried powder by the pigeon crop-sac method. This preparation was similarly shown to be essentially free of other tropic hormones.

HGH was also given to three men with carcinoma of the prostate, and the serum acid phosphatase was used as the criterion of response.

The HGH was given intramuscularly in divided doses for at least 6 days. The period of study was interposed between adequate control periods. Six of the studies in the patients with breast cancer were performed on a complete metabolic balance regimen. The patients with breast cancer received 200 mg. or less of calcium daily in the diet. The data regarding dose of HGH and length of administration are shown in Tables 2 and 3.

Prolactin was administered to six men with cancer of the prostate and five women with cancer of the breast. The material was given intramuscularly in divided doses. The doses employed and the time of study are recorded in Tables 2 and 3.

Urinary calcium was measured by the Tisdall-
Kramer method (28). Standard metabolic balance technics were used. Serum acid phosphatase was determined in the Clinical Pathology Department of the Clinical Center by the method of Bessy, Lowry, and Brock (8).

RESULTS

Since a proposed criterion of increased rate of growth of osteolytic metastatic mammary cancer is an increased rate of osteolysis manifested by augmented urinary calcium excretion, it was necessary to determine the effects of HGH in the subject without breast cancer. In Chart 1 the average 24-hour increment in calcium excretion resulting from HGH has been plotted above the zero line for each subject in the control group and in the group with breast cancer. The average 24-hour urinary calcium excretion during the control period has been charted below the zero line. Since the effect of growth hormone frequently persisted for several days the values for the 3 days following HGH were not included in these averages.

Calcium excretion increased by an average of 6.4 mg. daily in the control group, ranging from no change to an increase of 16.4 mg/24 hours. The comparative data for the patients with breast cancer differ significantly from the control group.

TABLE 2

PATIENTS WITH METASTATIC BREAST CANCER

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Status of disease*</th>
<th>Growth hormone (mg/24 hr.)</th>
<th>Prolactin (mg/24 hr.)</th>
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<tr>
<td>16</td>
<td>51</td>
<td>R</td>
<td>5</td>
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<td>6</td>
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<tr>
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<td>52</td>
<td>R</td>
<td>5</td>
<td>15</td>
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<td>49</td>
<td>R</td>
<td>5</td>
<td>96</td>
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<td>27</td>
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<td>R</td>
<td>50-100</td>
<td>12</td>
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<tr>
<td>28</td>
<td>47</td>
<td>R</td>
<td>50</td>
<td>6</td>
</tr>
</tbody>
</table>

* R = in remission.
  A = advancing disease.

TABLE 3

PATIENTS WITH CARCINOMA OF THE PROSTATE

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Status of disease*</th>
<th>Acid phosphatase (mg/100 ml.)</th>
<th>Growth hormone (mg/24 hr.)</th>
<th>Days of admin.</th>
<th>Prolactin (mg/24 hr.)</th>
<th>Days of admin.</th>
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<td>A</td>
<td>50 -70</td>
<td>5</td>
<td>6</td>
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<tr>
<td></td>
<td>R</td>
<td>1 - 1.5</td>
<td>5</td>
<td>6</td>
<td>75</td>
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<td>30</td>
<td>71</td>
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<td>65</td>
<td>A</td>
<td>2 - 3</td>
<td>.6 - .8</td>
<td>50</td>
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<tr>
<td></td>
<td>R</td>
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<td>10</td>
<td>50</td>
<td>6</td>
</tr>
</tbody>
</table>

* A = advancing disease.
  R = In remission.

† Bessy, Lowry, and Brock (8).
  In each instance, remission followed orchietomy.
The low urinary calcium excretion during the control period in patients 16 to 21 reflects a phase of bone repair, since five of these patients had responded to hypophysectomy and 21 to oophorectomy. In only two of these patients was there a small increase in urinary calcium excretion in response to HGH. In contrast were patients 22 to 26 in whom the relatively high excretion of calcium indicated a failure to respond to one of the surgical procedures. HGH in these subjects resulted in significant increases in calcium excretion averaging 98 mg. daily, a response that was in the control range. In no instance did HGH induce a measurable change in the excretion of phosphorus or the serum concentrations of calcium phosphorus or alkaline phosphatase.

Although changes in the main pattern of patients with cancer cannot be used as evidence for the success or failure of any maneuver designed to alter tumor growth, it is nevertheless important to record that HGH did not perceptibly alter the pain pattern in the patients with metastatic cancer.

The increased excretion of calcium in the control group could not be linearly correlated with the urinary calcium excretion before HGH ($r = 0.11$). Since all these subjects were studied on metabolic balance it can be stated that the effect of HGH on urinary calcium was independent of the anabolic effect of the growth hormone.$^2$

$^2$The effects of growth hormone in these subjects will be reported elsewhere.

Since we were unable to obtain evidence that growth hormone could alter the growth of mammary cancer we attempted to obtain an effect by giving estrogen and growth hormone concomitantly after hypophysectomy to two patients with presumed estrogen-sensitive cancers. Patient #17 was studied 2 years following oophorectomy and demonstrated hypercalciuria with osteolytic bone disease. The administration of ethinyl estradiol, 0.05 mg. daily for 4 days, resulted in a marked increase in calcium excretion (Chart 2). She later underwent hypophysectomy with relief of hypercalciuria improvement of pain and subsequent regression of disease. During the postoperative period HGH and the combination of ethinyl estradiol and HGH led to only small increases in calcium excretion.

In Chart 3, a similar study is shown. This patient with hypercalciuria and hypercalcemia responded to oophorectomy. Following relapse, hypophysectomy resulted in a decrease in calcium excretion and x-ray evidence of healing of bone. During the postoperative period, neither HGH, ethinyl estradiol, nor a combination of the two affected the excretion of calcium. Both of these patients could be classified as having estrogen-sensitive cancers on the basis of the response to ethinyl estradiol and the response to oophorectomy. In each case, there was a demonstrated effect of either exogenous estrogen or removal of the main source of estrogen on osteolysis.

Ovine prolactin did not cause hypercalciuria.
Chart 2.—Effect of HGH and estrogen on breast cancer

Chart 3.—Effect of HGH and estrogen on breast cancer
or increase in pain in any of the patients with breast cancer. Three of the patients with carcinoma of the prostate received HGH and five were given prolactin. In only one instance was there a suggestion of an increase in acid phosphatase levels, and this was brief. In the absence of either a sustained response or a greater increase we could not consider this a positive response.

DISCUSSION

An increased urinary excretion of calcium and a negative calcium balance were observed in acromegalic patients by Bauer and Aub in 1941 (7). Recent studies have demonstrated that HGH induces an increased loss of calcium in the urine in man (9, 13). In the latter study, one injection of 30 mg of HGH resulted in an increase of urinary calcium of 120–150 mg/24 hours. As in our studies, the serum levels of calcium, phosphorus, and alkaline phosphatase were unchanged.

Although the mechanism of this effect is not clear it is a consistent response to HGH. It was noted even in patients 7, 8, and 9, in whom an anabolic effect did not occur. Since the growing child is normally in positive calcium balance, these effects may represent the response to excessive amounts of HGH and are thus the counterpart of the hypercalciuria of acromegaly.

Such a response to HGH, however, precludes the use of an increased excretion of calcium as an index of an increased rate of osteolysis mediated by tumor growth unless the responses are of a much larger magnitude than those normally obtained. Such responses were not seen in our study or in the studies reported elsewhere (23, 24). Of considerable interest was the finding that, in those patients who were in remission, HGH did not increase the calcium excretion. Apparently, the osteoblastic response in the areas of tumor involvement was great enough to prevent the hypercalciuric effect of HGH. However, it is particularly in this group of patients who have responded favorably to pituitary ablation that HGH might be expected to stimulate tumor growth if its role were a significant one. Pearson and Ray (23) similarly noted that HGH resulted in a rise in urinary calcium excretion in only the two patients who had failed to respond to hypophysectomy but that it was without effect on the calcium excretion in the three patients who were in remission.

There is other evidence to support the view that the anterior pituitary hormones, growth hormone and prolactin, are not important factors in supporting the growth of breast cancer. If they were, the results of hypophysectomy should be consider-erably better than those of adrenalectomy. This did not prove to be so in Atkins’ series (2), and Pearson and Ray (23) noted the same incidence of remissions after hypophysectomy as after adrenalectomy. They did, however, observe longer remissions after hypophysectomy. A comparison of the incidence of remissions reported for adrenalectomy with that reported for hypophysectomy reveals the results to be approximately the same (10). Furthermore, if HGH and prolactin played significant roles, then hypophysectomy should yield worth-while improvement in the adrenalec-tomized-oophorectomized subject. In two series (14, 23) such improvement was rarely observed.

One hypothesis that has been entertained is that HGH and estrogen synergize in their growth-promoting activity for breast cancer. The observed results of combined estrogen and HGH administration do not support this view, and two similar studies have been reported elsewhere (25).

In view of the many experiments in animals cited above is it possible to reconcile these essentially negative studies in man? There are many points of difference in the two types of studies; e.g., the animals receive the hormones for an appreciable part of their life span, but the patients received HGH and prolactin for relatively brief periods. Susceptible strains of animals are used for testing, and the end-point is easily measured. Since the evidence for stimulation in man depends on one facet of the metabolic activity of the tumor, osteolysis, slight degrees of stimulation of tumor growth could remain undetected. Furthermore, the effect of growth hormone in animals lies in the influencing of the rate of induction or ease of transplantability of tumor, whereas the criterion of effect in the present studies is an alteration in the rate of growth of the tumor.

From our data, however, it can be concluded that if HGH or prolactin exerts any influence on the rate of growth of breast cancer, it must be of a low order of magnitude when compared with the prompt responses elicited by estrogen in patients with estrogen-sensitive cancer.

There is a curious phenomenon which occurs after hypophysectomy that has been noted by others (23) and by us. Following hypophysectomy, further remissions of breast cancer have not been obtained either with estrogens or androgens. Furthermore, estrogen is ineffective in exacerbating the disease in those patients who are in remission. One is impressed that, after this procedure, the cancer has become hormone-insensitive or more autonomous. This cannot be the case, of course, in those patients who respond to hypophysectomy but whose subsequent relapse is followed by resistance to estrogen or androgen therapy.
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