The Effect of Estrogen on the Serum Glucuronidase Activity of Patients with Breast Cancer*

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A relationship between estrogen and the β-glucuronidase activity of the uterus was first suggested by Fishman (2, 5). He reported that a decreased glucuronidase activity of the uterus in the mouse followed ovariectomy and that this activity was markedly increased by subsequent treatment of the animals with estrogens. A similar estrogen-β-glucuronidase relationship for other sexual tissues has been suggested by the following observations: (a) Fishman and Anlyan (4) reported a greatly increased glucuronidase activity in the human mammary gland during lactation and in breast carcinomas; (b) Odell, Burt, and Bethea (11) observed an increase in the glucuronidase activity in the cervix of women during pregnancy and in both the cervix and the vaginal fluid of untreated lower genital tract carcinoma. Kerr, Levvy, and Campbell (8) have suggested that the increased glucuronidase activity effected by estrogens and present in malignancies is a generalized phenomenon, in that they have observed an increased β-glucuronidase in a wide variety of tissues in which mitosis has been stimulated. Fishman and Anlyan (4) also observed an increased glucuronidase activity in a number of cancers involving nonsexual tissues; they point out, however, that in none of these cases is the increase in glucuronidase activity as great as that found in the mammary carcinoma.

There is no direct evidence that an increase in the β-glucuronidase activity of the blood occurs when a high level of estrogen is present in the body or in the presence of malignancies. Two indirect indications of such a relationship have, however, been observed: (a) Fishman (8) and McDonald and Odell (9) all reported a rise in the blood levels of β-glucuronidase during pregnancy and obtained curves which paralleled the increased estrogen production that has long been known to occur in pregnancy; and (b) Fishman, Odell, Gill, and Christensen (6) have recently reported that the daily administration of 5-25 mg. of stilbestrol to post partum women caused a significant reduction in the rate at which the blood glucuronidase level fell from the high ante partum levels.

The data presented in this paper offer the first direct evidence that the administration of estrogens can cause an increase in the glucuronidase activity of blood serum. These data were obtained during the course of studies on the metabolic effects of estrogen therapy on patients with advanced breast carcinoma.

METHODS

This report includes all the blood glucuronidase data of the mammary cancer patients thus far studied by us. These patients were selected in accord with the suggestions of the Subcommittee on Steroids and Cancer of the Therapeutic Trials Committee of the A.M.A. (1947). The patients selected thus all had advanced breast cancer and were at least 5 years post-menopausal.

During their course of therapy, eight of the patients were treated daily with 3 mg. ethinyl estradiol administered orally, and six of the patients were similarly treated with 15 mg. of diethylstilbestrol.1 Control blood samples were drawn prior to the initiation of therapy and at intervals thereafter. In addition, a number of assays were carried out on blood samples from individuals being examined in the University of Minnesota Cancer Detection Center. These latter patients were of about the same age as those receiving the estrogen therapy and offered a means of comparing the serum glucuronidase levels of healthy individuals with those of patients with breast cancer.

1 The hormone preparations used in this study were supplied through the Therapeutic Trials Committee of the American Medical Association by the Abbott Research Laboratories, Schering Corporation, and Winthrop-Sterns, Inc.

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Serum glucuronidase activity was determined by the method of Fishman, Springer, and Brunetti (7).

RESULTS

Pre-therapy serum glucuronidase levels.—The blood serum levels of $\beta$-glucuronidase activity of patients with mammary cancer and of the non-cancerous controls are shown in Table 1. It is seen that no significant difference exists in the values for the cancerous and noncancerous females. The data do, however, indicate significantly higher serum glucuronidase levels for men than for women in this age group.

Serum glucuronidase levels during estrogen therapy.—In Figures 1 and 2 are shown the serum glucuronidase levels obtained during the course of therapy with diethylstilbestrol and with ethinyl estradiol, respectively. It can be seen that a significant increase in serum $\beta$-glucuronidase activity up to the present time. The average maximum serum glucuronidase attained is about 1,700 units per cent, which level represents an increase of more than 100 per cent over pre-therapy levels. One patient on stilbestrol therapy (Patient J. G., Fig. 1) for over a year still shows an average serum glucuronidase value of 1,600 units per cent (1,800—2,000), a value which represents an increase of 300+ per cent over her pre-therapy determination. There appears to be no obvious relationship between the progress of the malignancy and the

<table>
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<td>THE $\beta$-GLUCURONIDASE ACTIVITY OF SERA OF CONTROL AND MAMMARY-CANCEROUS PATIENTS</td>
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<tr>
<td><strong>GLUCURONIDASE ACTIVITY OF BLOOD SERUM (UNITS PER CENT)</strong></td>
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<tr>
<td><strong>RANGE</strong></td>
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<tr>
<td><strong>No. of patients</strong></td>
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<td>Untreated patients:</td>
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<tr>
<td>Male controls</td>
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<td>Female controls</td>
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<td>Patients with mammary cancer not treated with estrogen</td>
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<td>Estrogen-treated patients:</td>
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<td>Average pre-therapy levels for patients with mammary cancer</td>
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<td>Maximum values attained on stilbestrol therapy</td>
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<td>Maximum values attained on ethinyl estradiol therapy</td>
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Fig. 1.—The effect of stilbestrol therapy on serum $\beta$-glucuronidase levels of mammary cancer patients
serum glucuronidase levels during estrogen therapy.

DISCUSSION

While there seems to be a somewhat greater serum β-glucuronidase activity in the patients with the mammary cancers than in the normal controls, this difference is not statistically significant for the patients thus far studied. This observation is in agreement with the report of Fishman and Anlyan (4) that there was no consistent increase in the serum glucuronidase levels of their patients with mammary carcinomas.

It is obvious from the data presented in this paper that estrogen therapy administered to patients with mammary cancer causes an increase in the level of serum β-glucuronidase activity. This increase is usually quite marked within 3–4 weeks and is apparently maintained as long as the estrogen therapy is continued. No significant difference was observed in the group treated with stilbestrol, as compared to that receiving ethinyl estradiol as the estrogenic substance. It is hoped to determine the importance of the cancerous mammary gland in this response to estrogen by studies on the serum glucuronidase activity of other patients being treated with estrogens.

While we have had occasion to make observations on only two patients with mammary cancer on testosterone therapy, in neither of these cases was there any significant effect on the serum glucuronidase activity. One of these cases was treated with 100 mg. testosterone 3 times a week for 14 months, at the end of which time her serum glucuronidase was only 880 units per cent, whereas after 2 months on stilbestrol therapy her serum glucuronidase had attained a level of 1,900 units per cent (Patient B. R., Fig. 1).

The apparently greater serum glucuronidase activity in men than in women in the post-age-50 group is difficult to explain by either the tissue growth (8) or the metabolic conjugation (9) hypotheses elaborated for tissue glucuronidase by these authors.

On the basis of data presented in this paper it would seem desirable to determine the effect of age and sex on serum glucuronidase activity levels.

SUMMARY

1. No significant difference in the serum β-glucuronidase levels of normal women and women with mammary cancers was observed.
2. Male control patients have a significantly higher serum glucuronidase activity level than do women in the post-age-50 group.
3. Estrogen therapy causes a marked rise in the β-glucuronidase activity in the sera of patients being treated for mammary cancer. The average maximum values for all patients studied was more than twice as high as the pre-therapy levels.
4. No difference could be observed in the serum β-glucuronidase response for the diethylstilbestrol and the ethinyl estradiol-treated groups.

ACKNOWLEDGMENT

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