Dose Responses of R3230AC Mammary Tumor and Mammary Tissue to Estrogen: Enzymes, Nucleic Acids, and Lipids

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Summary

The effect of several dose levels of estradiol valerate on the activities of 6 enzymes and the levels of nucleic acids and certain lipids was studied in a transplantable lactating mammary adenocarcinoma, R3230AC, as well as in the mammary glands of the same tumor-bearing animals. Estrogen treatment caused a dose-related increase in the activities of glucose-6-phosphate dehydrogenase, malate dehydrogenase (decarboxylating), and phosphoglucomutase in the neoplasm, whereas it decreased the activities of glucosephosphate isomerase and isocitrate dehydrogenase in that tissue. Glycerocephosphate dehydrogenase activity decreased markedly as the dose of estrogen increased. The tumor contained elevated levels of free fatty acids and triglycerides as well as slightly decreased DNA levels, these changes being related to the dose of hormone administered.

All enzyme activities increased in the mammary glands following treatment with estrogen. Cholesterol, but neither free fatty acids nor triglycerides, increased as the dose of estradiol valerate increased. Both RNA and DNA levels likewise rose relative to the dose of the hormone. Enzyme activity of mammary tissue expressed in terms of DNA concentration indicated that only glucose-6-phosphate dehydrogenase and malate dehydrogenase (decarboxylating) activities remained elevated at the higher doses of hormone, whereas both glucosephosphate isomerase and glycerocephosphate dehydrogenase activities decreased at these doses. In a similar manner, free fatty acids/mg DNA and triglycerides/mg DNA decreased by high doses of estrogen, but cholesterol/mg DNA remained constant. The lipid metabolism as well as the similarities and differences of the responses of normal and neoplastic tissue to estrogen are discussed.

Introduction

The R3230AC mammary adenocarcinoma is a hormone-responsive, autonomous transplantable neoplasm of the Fischer rat. We have recently reported the growth and morphologic characteristics of this tumor and its responsiveness to treatment with various hormones (12). Biochemical investigations indicated that the estrogen-induced lactational response of the tumor was accompanied by marked increases in the activities of glucose-6-phosphate dehydrogenase, malate dehydrogenase (decarboxylating), and phosphoglucomutase, but not of isocitrate dehydrogenase or glucosephosphate isomerase activities. These estrogen-induced elevations in enzyme activity were prevented by actinomycin D, suggesting that estrogen treatment stimulated DNA-mediated RNA synthesis, i.e., de novo protein synthesis (13). Since these responses occurred following treatment with a high dose of estradiol valerate (10 mg/kg/week) and, since hormonal responses are dose-related, it was deemed worthwhile to investigate the effects of several dose levels of estrogen on the biochemical responses of the carcinoma.

One approach to a better understanding of neoplastic tissue is a comparative investigation with a similar tissue of the tumor-bearing host. It has been employed successfully in studies of hepatomas, leading to the discovery of tumors with biochemical properties quite similar to the biochemical properties of the normal liver (20, 27, 28). This approach was utilized in these studies and this report contains data obtained by simultaneous assays of normal mammary tissue from the same tumor-bearing animals.

Because of the lactational changes observed in the neoplasm following estrogen treatment, and to gain additional information concerning lipid metabolism, quantitative measurements of cholesterol, free fatty acid, and triglyceride levels were made. In addition to the enzymes studied previously, glycerocephosphate dehydrogenase activity was measured. The activity of this nicotinamide adenine dinucleotide (NAD)-linked enzyme may reflect changes in lipid metabolism, since glycerocephosphate serves as an important precursor for the synthesis of glycerocephosphatides and triglycerides (14, 22). Nucleic acids were also measured to determine any alterations in cell number, as reflected by DNA, and protein synthesis, as reflected by RNA.

The data presented here demonstrate both similarities and differences in the responses of normal and neoplastic mammary tissue to estrogen. Treatment with estradiol valerate caused a dose-related elevation in glucose-6-phosphate dehydrogenase, malate dehydrogenase (decarboxylating), and phosphoglucomutase activities in the tumor and these changes were accompanied by increased levels of free fatty acids and triglycerides as well as a marked decrease in glycerocephosphate dehydrogenase activity. All of the enzyme activities measured in the mammary glands were elevated by hormone treatment; however, DNA levels also increased relative to the dose of estradiol valerate. Relative to the DNA concentration, only glucose-6-phosphate dehydrogenase and malate dehydrogenase (decarboxylating) activities increased in mammary tissue following estrogen treatment, and all other parameters decreased. These data are dis-
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Effect of Various Doses of Estradiol Valerate on Growth of the R3230AC Tumor and Uterus and Ovary Weights in the Fischer Rat

<table>
<thead>
<tr>
<th>Dose of estradiol valerate (mg/kg/week)</th>
<th>Δ carcass weight (gm)</th>
<th>Tumor weight (gm)</th>
<th>Uterus weight (mg)</th>
<th>Ovary weight (mg)</th>
<th>T/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>+35.6</td>
<td>3.36 ± 0.43</td>
<td>228.8 ± 25.6</td>
<td>43.3 ± 2.8</td>
<td>1.00</td>
</tr>
<tr>
<td>0.001</td>
<td>+39.6</td>
<td>3.44 ± 0.57</td>
<td>234.6 ± 15.2</td>
<td>41.5 ± 2.2</td>
<td>1.02</td>
</tr>
<tr>
<td>0.01</td>
<td>+36.3</td>
<td>3.70 ± 0.34</td>
<td>280.0 ± 9.9</td>
<td>34.3 ± 2.9</td>
<td>1.10</td>
</tr>
<tr>
<td>0.1</td>
<td>+33.9</td>
<td>2.12 ± 0.39*</td>
<td>342.6 ± 11.7a</td>
<td>32.1 ± 2.8*</td>
<td>0.63</td>
</tr>
<tr>
<td>1.0</td>
<td>+33.6</td>
<td>1.36 ± 0.29*</td>
<td>499.0 ± 30.2ab</td>
<td>45.6 ± 4.9</td>
<td>0.40</td>
</tr>
<tr>
<td>10.0</td>
<td>+34.3</td>
<td>1.68 ± 0.40*</td>
<td>557.4 ± 17.5ab</td>
<td>55.6 ± 4.6*</td>
<td>0.50</td>
</tr>
</tbody>
</table>

* Carcass weight = total weight - tumor weight.
† Mean ± S.E.
* * Tumor weight treated/tumor weight control.
* * * Significantly different from control values, P < 0.05.

Materials and Methods

Female Fischer rats, weighing 90–100 gm and divided into groups of 10 animals, were implanted with the R3230AC tumor by sterile trochar technic (10, 11). Estradiol valerate, dissolved in sesame oil, was administered s.c. once weekly starting on the day after tumor implantation. Animals were sacrificed on Day 21 after transplantation of the neoplasm. Tumors and mammary tissues were removed, trimmed of fat and hemorrhagic tissue, weighed, and quick-frozen in an acetone-Dry Ice freezing mixture. Samples were stored at —20°C until assayed for enzymes, nucleic acids, and lipids. The uteri and ovaries of these animals were also removed and weighed.

Enzymes were essayed on the supernatant of tissue homogenates, obtained by centrifugation at 20,000 × g for 20 min, deionized water being used as the homogenizing medium. All of the enzyme measurements were conducted under similar conditions and involved the measurement of absorbancy changes at 340 m/i due to the reduction or oxidation of the appropriate nicotinamide adenine dinucleotides.

The enzyme activities, expressed as μmoles of reduced NAD phosphate (NADPH) produced /min/100 mg (in the case of glycerophosphate dehydrogenase, the activity was expressed as μmoles of NADH oxidized/min/100/mg), are directly comparable. The following procedures were employed: glucose-6-phosphate dehydrogenase (n-glucose-6-phosphate:NAD oxidoreductase, EC 1.1.1.49) by Glock and McLean (7); malate dehydrogenase (decarboxylating) (1-malate:NAD oxidoreductase, decarboxylating, EC 1.1.1.40) Ochoa et al. (18); isocitrate dehydrogenase (isocitrate:NAD oxidoreductase, decarboxylating, EC 1.1.1.42) Ochoa method (17); glycerolphosphate dehydrogenase (n-glucose-3-phosphate:NAD oxidoreductase, EC 1.1.1.8), Beisenherz et al. (2), modified by using dihydroxyacetone phosphate as the substrate and measuring the oxidation of NADH.

Nucleic acids were analyzed by the extraction method of Schneider (23), RNA being estimated by the orcinol reaction according to Cerriotti (4) and DNA being estimated by the diphenylamine reaction according to Dische (5). The lipid components investigated, cholesterol, free fatty acids, and triglycerides, were extracted and separated by thin layer chromatography on silica gel by means of procedures detailed earlier (Hilf, R., Michel, I., Gibbs, C. C., and Bell, C., NADP-Linked Enzymes and Lipogenesis in Normal and Neoplastic Mammary Tissue: Effect of Estrogen and Dietary Glucose, submitted for publication). Following elution of the separated lipids from the gel, colorimetric analyses were performed. Cholesterol was determined by a modified Lieberman-Burchard reaction, free fatty acids were determined by the procedure of Duncombe (6), and triglycerides were measured by the procedure of Van Handel and Zilversmit (26).

Data are presented as the mean ± S.E. Significance was determined by the Student "t" test; a probability (P) value equal to or less than 0.05 was considered to be significant.

Results

Effect of Estrogen on Tumor and Organ Weights

Table 1 contains a summary of the results pertaining to the effect of several doses of estradiol valerate on the rate of growth of the R3230AC mammary carcinoma. A significant reduction of tumor growth was observed at a dose of 0.1 mg/kg/week (P = 0.05) and higher doses of estrogen reduced tumor growth even further. The ratio of treated/control tumor weights (T/C) is presented in the last column. The anticipated dose-response of the uterus to estrogen treatment was obtained. Table 1 also contains the data concerning the effect of estrogen on the weight of the ovaries, which was decreased at the intermediate...
Responses of Mammary Tumor and Tissue to Estrogen

The Effect of Various Doses of Estradiol Valerate on Enzyme Activities and Nucleic Acid Contents of the R3230AC Mammary Tumor

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control</th>
<th>Dose Administered (mg/kg/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>Glucose 6-phosphate dehydrogenase</td>
<td>0.67 ± 0.054</td>
<td>0.616 ± 0.052</td>
</tr>
<tr>
<td>Malate dehydrogenase (decarboxylating)</td>
<td>0.467 ± 0.034</td>
<td>0.469 ± 0.033</td>
</tr>
<tr>
<td>Isocitrate dehydrogenase</td>
<td>0.440 ± 0.017</td>
<td>0.401 ± 0.022</td>
</tr>
<tr>
<td>Glucosephosphate isomerase</td>
<td>5.90 ± 0.09</td>
<td>5.73 ± 0.10</td>
</tr>
<tr>
<td>Phosphoglucomutase</td>
<td>0.057 ± 0.007</td>
<td>0.046 ± 0.006</td>
</tr>
<tr>
<td>Glycerocephosphate dehydrogenase</td>
<td>0.074 ± 0.003</td>
<td>0.073 ± 0.006</td>
</tr>
<tr>
<td>DNA*</td>
<td>4.897 ± 0.159</td>
<td>4.168 ± 0.120</td>
</tr>
<tr>
<td>RNA*</td>
<td>7.217 ± 0.176</td>
<td>7.209 ± 0.208</td>
</tr>
<tr>
<td>RNA/DNA ratio</td>
<td>1.452 ± 0.043</td>
<td>1.732 ± 0.069</td>
</tr>
<tr>
<td>Cholesterol*</td>
<td>1.036 ± 0.109</td>
<td>1.817 ± 0.059</td>
</tr>
<tr>
<td>Free fatty acids*</td>
<td>9.59 ± 0.70</td>
<td>13.78 ± 2.73</td>
</tr>
<tr>
<td>Triglycerides*</td>
<td>25.2 ± 6.5</td>
<td>32.2 ± 5.7</td>
</tr>
</tbody>
</table>

* All results are expressed as mean ± S.E.
† Activity expressed as μmoles reduced nicotinamide adenine dinucleotide phosphate (NADPH) produced/min/100 mg tissue weight.
‡ Differs significantly from control values, P < 0.05.
§ Activity expressed as μmoles NADH oxidized/min/100 mg tissue weight.
4 Concentration measured as μg/mg tissue weight.

Doses of estradiol valerate and increased at the highest dose of estrogen. The hormonal treatment had no effect on the growth of the tumor-bearing animals as reflected by the data of carcass weight (carcass weight = total weight - tumor weight).

Effect of Estrogen on Enzyme Activities, Nucleic Acids, and Lipids in the R3230AC Carcinoma

Earlier reports showed that glucose-6-phosphate dehydrogenase, malate dehydrogenase (decarboxylating), and phosphoglucomutase activities increased in the neoplasms of animals receiving 10 mg/kg/day of either diethylstilbestrol or estradiol valerate (12, 13). It was of interest, therefore, to determine whether the enzyme responses were related to the dose of hormone. A summary of the data from experiments employing several doses of estradiol valerate, ranging from 0.001 mg/kg/week to 10 mg/kg/week, is presented in Table 2. Glucose-6-phosphate dehydrogenase and malate dehydrogenase (decarboxylating) activities rose in a dose-related fashion, an increase in activity occurring with as little as 0.01 mg/kg/week of estradiol valerate. Phosphoglucomutase activity decreased at the lower levels of estrogen treatment and increased at the highest dose. The activities of isocitrate dehydrogenase and glucosephosphate isomerase decreased as the dose of estrogen was increased. Glycerocephosphate dehydrogenase activity decreased markedly in the neoplasms and this decrease was dose-related.

Analyses for nucleic acids revealed that DNA concentration was initially decreased by estrogen and gradually returned to the control levels as the dose of estradiol valerate increased (Table 2). In these studies no level of estrogen increased DNA concentration. A somewhat similar pattern of changes occurred with RNA concentration, a decrease in RNA/mg tissue being obtained at the lower doses of estrogen. As the dose of the hormone was increased, RNA returned to control levels and was significantly elevated at the 10 mg/kg/week dose of estradiol valerate. The resulting RNA/DNA ratios rose above the control ratio at all of the estrogen doses employed, the greatest elevations occurring at the highest doses of the hormone.

In view of these changes in DNA concentration, expression of enzyme activities relative to the amount of DNA rather than as absolute activities could alter the picture concerning the relationship of enzyme activity to the dose level of estrogen. Obviously, the enzyme activities which were elevated significantly by hormone treatment would appear to be higher since DNA concentration decreased. Regarding isocitrate dehydrogenase and glucosephosphate isomerase activities/mg DNA, a decrease in the activity of the former occurred only at the 2 highest doses of estradiol valerate, whereas the activity of the latter enzyme was not significantly decreased at any of the estrogen dose levels. Since the decrease in activity of glycerocephosphate dehydrogenase was so marked, the changes in DNA concentration did not significantly alter the pattern of decreased enzyme activity resulting from estrogen treatment.

Table 2 also contains the data pertaining to the analyses of cholesterol, free fatty acids, and triglycerides in the carcinoma. The concentration of cholesterol was not altered by any of the doses of estradiol valerate used in these studies. However, the levels of both the free fatty acids and triglycerides were markedly elevated in the neoplasms and this elevation appeared to be related directly to the dose of estrogen administered to the test animals. As little as 0.01 mg/kg/week of estradiol valerate in-
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Effects of Various Doses of Estradiol Valerate on Enzyme Activities in the Mammary Gland in Fisher Rats

Table 3: The Effect of Various Doses of Estradiol Valerate on Enzyme Activities and Nucleic Acid Contents of the Mammary Gland in Fischer Rats

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control</th>
<th>Dose administered (mg/kg/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Glucose-6-phosphate dehydrogenase*</td>
<td>0.030 ± 0.004</td>
<td>0.023 ± 0.002</td>
</tr>
<tr>
<td>Malate dehydrogenase (decarboxylating)*</td>
<td>0.057 ± 0.007</td>
<td>0.039 ± 0.004</td>
</tr>
<tr>
<td>NADP - isocitrate dehydrogenase*</td>
<td>0.060 ± 0.008</td>
<td>0.051 ± 0.004</td>
</tr>
<tr>
<td>Glucosolphosphate isomerase*</td>
<td>0.83 ± 0.08</td>
<td>0.77 ± 0.04</td>
</tr>
<tr>
<td>Phosphoglucomutase*</td>
<td>0.004 ± 0.001</td>
<td>0.004 ± 0.001</td>
</tr>
<tr>
<td>Glycerolphosphate dehydrogenase*</td>
<td>0.469 ± 0.053</td>
<td>0.408 ± 0.047</td>
</tr>
<tr>
<td>DNA*</td>
<td>1.02 ± 0.19</td>
<td>0.95 ± 0.09</td>
</tr>
<tr>
<td>RNA*</td>
<td>0.65 ± 0.11</td>
<td>0.66 ± 0.07</td>
</tr>
<tr>
<td>RNA/DNA ratio*</td>
<td>0.66 ± 0.03</td>
<td>0.69 ± 0.02</td>
</tr>
<tr>
<td>Cholesterol*</td>
<td>0.709 ± 0.084</td>
<td>0.948 ± 0.111</td>
</tr>
<tr>
<td>Free fatty acids*</td>
<td>13.06 ± 3.39</td>
<td>11.91 ± 3.74</td>
</tr>
<tr>
<td>Triglycerides*</td>
<td>286.1 ± 25.3</td>
<td>323.3 ± 13.7</td>
</tr>
</tbody>
</table>

* All results are expressed as mean ± S.E.
* Activity expressed as µmoles reduced nicotinamide adenine dinucleotide phosphate (NADPH) produced/min/100 mg tissue weight.
* Differs significantly from control values, P < 0.05.
* Activity expressed as µmoles NADH oxidized/min/100 mg tissue weight.
* Concentration measured as µg/mg tissue weight.

The same biochemical parameters measured in the tumor were also determined in mammary tissue obtained from the tumor-bearing animals. The results are recorded in Table 3. Compared to the enzyme activities in the neoplasms of the control animals (diluent-treated), the activities of all of the enzymes in the mammary gland were considerably lower, with the exception of the activity of glycerolphosphate dehydrogenase. The enzyme activities in the normal tissue were approximately 1/4 to 1/2 of the activity obtained in the tumor. On the other hand, glycerolphosphate dehydrogenase activity was approximately 7 times higher in the mammary glands than in the carcinoma.

Although all of the enzyme activities studied were elevated by the highest doses of estrogen used, some differences in the dose-related responses were noted. Glucose-6-phosphate dehydrogenase activity increased significantly with as little as 0.1 mg/kg/week of estrogen, whereas glycerolphosphate dehydrogenase activity increased only at the highest dose of estradiol valerate (10 mg/kg/week). Malate dehydrogenase (decarboxylating), isocitrate dehydrogenase, glucosephosphate isomerase, and phosphoglucomutase activities all increased at both the 0.1 mg/kg/week and 10 mg/kg/week doses of the estrogen. It was of interest to note that malate dehydrogenase (decarboxylating) activity decreased initially (at both the 0.001 mg/kg/week and the 0.01 mg/kg/week doses) at the lower doses prior to increasing at the higher dose levels.

Under the influence of continued estrogen treatment, the mammary glands were stimulated to grow, this growth being reflected by an increase in both DNA and RNA concentrations and accompanied by a slight but significant elevation of the RNA/DNA ratio at the 2 highest doses of estradiol valerate. In view of these changes in DNA, it was appropriate to also consider expressing enzyme activity in terms of the content of DNA of the tissue. Recalculation of the enzyme data in this manner, e.g., activity/mg DNA, brought out a change in the dose-response pattern. Glucosephosphate isomerase activity, rather than showing an elevation at the higher doses of estrogen treatment, decreased in terms of activity/mg DNA. The same was true for glycerolphosphate dehydrogenase. Also, elevations in both phosphoglucomutase and isocitrate dehydrogenase activities decreased and were no longer significantly higher than the control levels. However, the patterns of changes in glucose-6-phosphate dehydrogenase and malate dehydrogenase (decarboxylating) activities remained elevated regardless of the manner of expressing enzyme activity.

Table 3 also contains data of the analyses of mammary tissue for cholesterol, free fatty acids, and triglycerides as influenced by the dose of estrogen administered to the animals. In terms of concentration per unit of weight, cholesterol content increased as the dose of hormone was increased. Free fatty acid levels were not significantly altered at any of the dose levels of estradiol valerate, whereas the triglyceride content decreased at the 10 mg/kg/week dose level. It was also important to consider the concentration of these lipid components in terms of cell number or DNA. When these substances were expressed as µg lipid/mg.
DNA it was evident that the cholesterol levels remained constant regardless of the dose of estrogen used, and both free fatty acid and triglyceride levels decreased as the dose of hormone increased.

Discussion

The data presented here confirm the effects of estrogen on several enzyme activities in the R3230AC mammary carcinoma (12, 13) and extend them by demonstrating that these responses are related to the dose of estrogen administered to the animals. The elevations in glucose-6-phosphate dehydrogenase, malate dehydrogenase (decarboxylating), and phosphoglucomutase activities, expressed either in terms of wet weight of tumor or DNA concentration, suggest that these enzymes play a role in the hormonally induced secretory (lactational) changes which occur in the neoplasm following estrogen treatment. Elevations in the activities of both glucose-6-phosphate dehydrogenase and malate dehydrogenase (decarboxylating) have been reported as occurring in the mammary gland during lactation (8, 21). The elevation in malate dehydrogenase (decarboxylating) activity may be a reflection of the proposed role of this enzyme in lipogenesis (19, 29). The responses of this tumor to estrogen, and the ability to actinomycin D to prevent these responses (13), are quite similar to the pattern of responses reported in other hormone target organs (15). An important difference, however, is that the rate of growth of the tumor is inhibited by estrogen treatment, whereas the normal estrogen target organs, e.g., uterus, mammary glands, are stimulated to grow by hormonal treatment. This difference in response to estrogen suggests that the results of hormone-stimulated metabolism in the neoplasia may be the production of proteins other than cell proteins, i.e., milk proteins.

In contrast to the tumor, the same hormonal treatment induces growth of the mammary glands, as reflected by the marked elevations in DNA and RNA. Accompanying this growth were increases in the activities of all of the enzymes measured. After accounting for changes in cell numbers by expressing the enzyme activities in terms of DNA, there was still an increase in the activities of both glucose-6-phosphate dehydrogenase and malate dehydrogenase (decarboxylating), further supporting the suggestion of a role of these enzymes in hormone-induced secretory changes.

To help elucidate the relationships of the enzyme responses to lipid metabolism, measurements of cholesterol, free fatty acids, and triglycerides were made. In conjunction with these lipid measurements, glycerolphosphate dehydrogenase activity was also determined. This enzyme was selected for study because of its role in triglyceride synthesis, since this NAD-linked dehydrogenase mediates the conversion of dihydroxyacetone phosphate to glycerolphosphate. Thus, in the mammary gland, sustained estrogen treatment resulted in a decreased glycerolphosphate dehydrogenase activity and this was accompanied by decreased levels of free fatty acids/mg DNA and triglycerides/mg DNA. This parallel behavior of enzyme activity and lipid contents did not occur in the neoplasm in which, although there was a marked decrease in the activity of glycerolphosphate dehydrogenase, there was a striking dose-related increase in the levels of free fatty acids and triglycerides. This discrepancy cannot be resolved at present. It has been suggested by several workers (16, 25) that the rate of breakdown of triglycerides to fatty acids acts as one of the control mechanisms for the synthesis of triglycerides. If triglycerides accumulate, as they would in the mammary gland during lactation and suckling, it is conceivable that this would act to inhibit the formation of more glycerolphosphate, the substrate for triglyceride formation. It should be noted that the mammary gland is comprised to a large extent of adipose tissue as indicated by the high levels of free fatty acids and triglycerides in the control glands. The tumor, on the other hand, has much lower levels of these lipids and a considerably lower level of glycerolphosphate dehydrogenase activity, an observation which has been shown by Boxer and Shonk (3) to be a common occurrence in a number of animal tumors. Further work is indicated to determine whether a causal relationship exists between these parameters.

Finally, a problem exists in selecting a normal tissue counterpart to mammary neoplasms. This question was recently discussed by Abraham and Chaikoff (1) in their studies on the metabolism of a mouse mammary adenocarcinoma. The data presented here dealt primarily with the pattern of responses following treatment of the same animal with a specific dose of a hormone. Since the R3230AC tumor has shown morphologic and biochemical changes similar to those observed in the lactating mammary gland, the use of this neoplasm as a model seems justified.

References

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