The Effect of Tumor Growth on Liver Catalase Concentration

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Brahn (3) observed very low liver catalase activity in human beings who had died as the result of malignant growths. Later work showed that of all the individual liver enzymes studied in cancerous rats and mice the activity of catalase was by far the most affected. Greenstein and co-workers (6, 7) have reported that with the progressive growth of the tumor there is a decrease in liver catalase activity—the activity may be as low as 1/10 to 1/20 of the original value; that the effect of the tumor growth is reversible, since on removal of the tumor the liver catalase activity returns to the original level; and that this effect is produced in general by all fast-growing tumors. Greenstein (6) and Appleman and co-workers (2) have observed that large individual variations in liver catalase occur in animals at apparently the same stage of tumor development. Both have reported that kidney and erythrocyte catalase are affected but slightly, if at all, by the presence of a tumor.

The present paper reports the results obtained in a study of the effects of the growth of transplanted and spontaneous tumors on the liver catalase concentration of mice, and the effect of the growth of mouse and rat tumor tissue cultivated in the yolk sac on the liver catalase activity of the supporting chick embryo.

The yolk sac cultivation of tumor tissue in embryonated eggs was developed in this laboratory and has been used continuously for more than 8 years (11). Tumor tissue implanted in this manner into eggs grows vigorously and uniformly. Since nontumorous rat and mouse tissue cannot be transplanted serially in eggs, the yolk sac tumor represents a pure culture of tumor cells.

It was considered that the reaction of the liver catalase concentration of chick embryos supporting the growth of rat and mouse tumor tissue could furnish data of special value in helping to resolve the problem of tumor-catalase relationship.

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MATERIALS AND METHODS

Six different tumors were used in this study: a spontaneous DBA mammary carcinoma and transplants of a DBA mammary carcinoma, DBA spindle-cell sarcoma, DBA lymphosarcoma, CSH mammary carcinoma, and rat sarcoma.

The DBA mammary carcinoma originated spontaneously in stock mice in 1941 and has been maintained by serial transplantation in embryonated eggs and mice. It has been designated as DBA mammary carcinoma 1. Transplants of this tumor in mice attain a size of 5–7 gm. in about 23 days, at which time the death of the mouse occurs. This tumor has been carried continuously by yolk sac cultivation for more than 8 years. It often has an adverse effect on the supporting embryo because of a transferred toxic effect described in a previous report (10).

The spindle-cell sarcoma designated as DBA Sarcoma 131 originated by stromal malignancy (9) from transplants of egg-cultivated DBA mammary carcinoma 1. It has been carried in mice for 122 transplant generations. This tumor grows rapidly and uniformly after transplantation, attaining a size of about 8 gm. by the eighteenth day. It has a low vascularization factor and depresses the hemoglobin concentration of the host mouse much less than does DBA mammary carcinoma 1.

The lymphosarcoma designated as Lipoid III also originated by stromal malignancy from transplants into the mouse of egg-cultivated DBA mammary carcinoma 1 (9). This tumor has a high vascularization factor and affects the hemoglobin concentrations of the host much more than does DBA mammary carcinoma 1. Transplants of this tumor in mice grow rapidly and are highly malignant to the host, which rarely survives beyond the thirteenth or fourteenth day. The tumor is difficult to weigh, as it invades the surrounding tissue, penetrating into the muscles of the body wall. It
has been carried in mice for 165 transplant generations.

The C3H mammary carcinoma originated spontaneously in stock mice and has been carried by egg and mouse transplantation for 3 years. The reaction of this tumor to egg cultivation has been described (11).

The rat sarcoma originated spontaneously in the mesenteric tissues of the visceral cavity of a stock rat. It grows more vigorously in egg cultures than in its normal host. The chick embryo appears to be little affected by this tumor, even when it attains several grams in weight.

Mice of the DBA strain received implants of DBA mammary carcinoma 1, Sarcoma 131, and Lipoid III. Spontaneous tumors were provided by exbreeder DBA females. Control mice were of the same sex and age as the corresponding experimental group.

Embryonated eggs were inoculated with tumor tissue in the yolk sacs by a technic reported in detail (11). The DBA mammary carcinoma 1, the C3H mammary carcinoma, and the rat sarcoma were cultivated in this manner.

Mice were anesthetized with ether, decapitated, the tumors and livers removed, washed with saline to remove the blood, and weighed. The livers were homogenized, and a weighed amount of the homogenate was diluted with distilled water. Chick livers and tumors were treated in a similar manner.

Catalase determinations were made by the sodium perborate method of Feinstein (5). All determinations were made on the same day that the animals were killed.

Enzyme activity was expressed in milliequivalents of sodium perborate destroyed per milligram of liver.

RESULTS

The data obtained on the effect of tumor growth on the liver concentration in mice are summarized in Tables 1 and 3. The comparable results obtained with tumor-bearing embryonated eggs are shown in Table 2.

These experimental data show that when catalase activity is calculated on the basis of units per milligram of liver, or concentration, DBA mammary carcinoma 1 induces no reduction; DBA Sarcoma 131 and spontaneous tumors, slight reductions; and Lipoid III (lymphosarcoma), a reduction of 45 per cent of the control level in mice. In the embryonic chicks a reduction in concentration is noted for all tumors. When, however, catalase activity is calculated on the basis of the whole liver, or total liver catalase per mouse or chick, values were obtained which equal or exceed those of the controls. The DBA mammary carcinoma 1 and the DBA 131 in mice are associated with total liver catalase values well above those of the controls, 130 per cent and 125 per cent, respectively. The spontaneous tumors in mice are associated with total liver catalase values that are slightly higher than those of the controls. In chick embryos bearing the C3H mammary carcinoma, the liver catalase concentration was reduced to 73 per cent of the control value, while the total liver catalase was increased to 181 per cent of the controls. Exceptions to this are the mice bearing the Lipoid III and the embryonic chicks bearing the DBA mammary carcinoma 1, in which both the concentration and the total liver catalase values were reduced. The exceptions will be discussed later.

Liver size was increased in all experimental groups, varying from 114 per cent of control, in embryonic chicks bearing the rat sarcoma, to 189 per cent of control in mice with spontaneous tumors. Even the livers of the mice bearing the DBA mammary carcinoma 1 in which no reduction in liver catalase was observed either in concentration or in total liver catalase showed an increase in weight up to 135 per cent of the controls.

DISCUSSION

The low values for liver catalase of tumor-bearing animals reported by Greenstein and co-workers and by Weil-Malherbe and Schade (12) have not been found by other investigators. Appleman and co-workers and Dounce and Shanewise (4) reported less drastic reductions in their work with rats. It was suggested by Appleman that this discrepancy may be due to differences among strains of rats, the type of tumor used, the diet and experimental technic employed. In the present experiments, by using mice of the same strain fed the same diet and eggs from the same flock of chickens, two different but equally uniform hosts were employed in which to study the effects of various tumors. Since the same experimental technic was used for all experiments, the only variable with respect to each host was the tumor.

There was a marked increase in liver size of tumor-bearing animals in all experimental groups whether or not catalase concentration was affected. Appleman et al. and Dounce and Shanewise reported enlargement of the livers of tumor-bearing rats with reduced catalase activities, but Greenstein and Weil-Malherbe and Schade gave no figures on liver size. Kynette et al. (8) in their study on the effects of egg-grown tumors on the chick embryo reported enlarged livers. Histologically, these affected chick livers were characterized...
by a proliferation of cells bordering the sinusoids, hepatic cells tending to separate into small aggregates, and, in severe case, areas of necrosis and depositions of erythrocytes. There is little doubt that liver damage is a phenomenon concomitant with cancer. A study on eight hepatic functions in patients with gastrointestinal cancer by Abels et al. (1) revealed a high incidence of insufficiencies in these functions.

Large variations in liver catalase concentrations were observed in animals at apparently the same stage of tumor development. This is in agreement with other investigators. Large individual variations were found, however, for total catalase values as well as for catalase concentration in both tumorous and nontumorous animals of the same age.

Table 1
THE EFFECT OF TUMOR GROWTH ON THE LIVER CATALASE CONCENTRATION OF DBA MICE
(5 mice each in control and experimental groups)

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<tbody>
<tr>
<td>Transplanted mammary carcinoma (DBA 1)</td>
<td>3.8</td>
<td>1.30 1.62</td>
<td>0.122±0.014</td>
<td>0.127±0.015</td>
<td>158.3±18.9</td>
<td>205.5±22.8</td>
<td>104.1 130.0</td>
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<td>Transplanted spindle-cell sarcoma (DBA 131)</td>
<td>5.6 1.18 1.62</td>
<td>0.125±0.014</td>
<td>0.115±0.010</td>
<td>149.0±24.9</td>
<td>188.2±46.2</td>
<td>92.0 126.0</td>
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<td>Spontaneous mammary carcinoma</td>
<td>2.9 1.63 2.09</td>
<td>0.166±0.018</td>
<td>0.146±0.018</td>
<td>271.8±58.9</td>
<td>299.8±41.8</td>
<td>88.0 110.3</td>
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<tr>
<td>Transplanted lymphosarcoma (Lip III)</td>
<td>1.18 1.80</td>
<td>0.155±0.011</td>
<td>0.070±0.011</td>
<td>181.9±9.5</td>
<td>126.1±20.9</td>
<td>45.2 69.5</td>
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* Milliequivalents of NaBO₃.

Table 2
THE EFFECT OF TUMOR GROWTH ON THE LIVER CATALASE CONCENTRATION OF EMBRYONATED EGGS
(5 to 10 eggs in control and experimental groups)

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<tr>
<td>C57H mammary carcinoma</td>
<td>0.83 10</td>
<td>0.104 0.196</td>
<td>0.094</td>
<td></td>
<td>0.069</td>
<td></td>
<td>9.7</td>
<td></td>
<td>12.8</td>
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<td>73.4 131.0</td>
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<tr>
<td>DBA mammary carcinoma</td>
<td>0.9 11</td>
<td>0.175 0.213</td>
<td>0.124±0.025</td>
<td>0.077±0.009</td>
<td>21.1±5.8</td>
<td>17.2±3.0</td>
<td>62.1 81.5</td>
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<td>Rat sarcoma</td>
<td>2.3 12</td>
<td>0.238 0.270</td>
<td>0.114±0.014</td>
<td>0.091±0.011</td>
<td>26.7±0.5</td>
<td>24.1±1.8</td>
<td>78.8 90.3</td>
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* Milliequivalents of NaBO₃.
† Whole livers were not weighed separately.

Table 3
THE EFFECT OF THE GROWTH OF A TRANSPLANTED LYMPHOSARCOMA ON THE LIVER CATALASE CONCENTRATION OF MICE
(5 mice each in control and experimental groups)

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<tr>
<td>3</td>
<td>1.19 1.54</td>
<td>0.166±0.010</td>
<td>0.160±0.013</td>
<td>196.2±10.4</td>
<td>215.3±18.3</td>
<td>96.4 100.7</td>
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<td>9</td>
<td>1.17 1.40</td>
<td>0.165±0.011</td>
<td>0.165±0.017</td>
<td>193.3±25.6</td>
<td>227.8±11.6</td>
<td>100.0 117.8</td>
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<tr>
<td>15</td>
<td>1.26 2.00</td>
<td>0.168±0.022</td>
<td>0.062±0.014</td>
<td>208.1±50.5</td>
<td>182.7±12.1</td>
<td>38.3 60.9</td>
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* Milliequivalents of NaBO₃.
III was the only one that was associated with a reduction of total liver catalase. This highly malignant lymphosarcoma is more invasive than are other transplanted tumors, and it stimulates unusual vascularization of the neoplastic area, whereby it robs the host of a large amount of blood. Cachexia appears on about the seventh day after tumor inoculation. From the data given in Table 3 it will be noted that total liver catalase was not reduced until the twelfth day, or shortly before the death of the animal. Decreased liver catalase could not have been a causative factor in the cachexia, since it was not found until after the animal had been severely affected.

Of the egg-grown tumors, the DBA mammary carcinoma was associated with a reduction in total liver catalase. The general toxic effects of this tumor on the chick embryo have been described by Taylor and Carmichael (10). The slightly lower total catalase values for the chicks associated with the rat sarcoma can be attributed to a reduction in size of the tumor-bearing embryo. It has been shown that increasing tumor size is associated with a decrease in the weight of the host chick (8) which would result in a corresponding reduction in the size of the liver. This is not regarded as a reduction in total liver catalase.

The liver catalase concentration may not have been directly affected by the presence of a tumor in the host. It seems more probable that the changes observed in liver catalase activity in association with tumor growth were mediated by the fact that the liver of tumor-bearing animals increases in size without a corresponding increase in liver tissue (8). Consequently, a milligram of liver from a tumor-bearing animal has less active liver tissue in it than a milligram of control liver. The result was that the liver catalase activity per milligram tended to be lower in association with tumor growth. On the other hand, the experimental livers were enough larger than the controls to compensate for this factor and to bring the total liver catalase activity up to or above that of the livers from the nontumorous animals. This may explain the results of other investigators, who found a reduction in liver catalase concentration in tumor-bearing animals but only slight or no reduction in kidney and erythrocyte catalase activity from the same animal. The kidneys enlarge only slightly in association with tumor growth.

SUMMARY

A study was made of the effect of tumor growth on the concentration of liver catalase in mice and in chick embryos supporting the growth of yolk sac tumors.

A total of 80 DBA mice was used, the experimental groups of which bore transplants of a mammary carcinoma, a sarcoma, a lymphosarcoma, and a spontaneous mammary carcinoma.

Tests were completed on the livers of 44 chick embryos. The tumor-bearing eggs had been inoculated in the yolk sac with a DBA mammary carcinoma, a C3H mammary carcinoma, and a rat sarcoma.

There was a reduction in liver catalase activity in association with tumor growth in both the embryo and mouse series of experiments when the enzyme activity was based on unit weight of liver for experimental and control group.

The total liver catalase of the tumor-bearing mice and of the embryos supporting tumors tended to be unaffected or slightly higher than that of the corresponding controls.

It is suggested that, since the presence of a tumor in an animal is associated with changes in the liver which result in an increase in weight without a corresponding increase in active liver tissue, the effect is to dilute the per milligram catalase concentration. The increase in liver size compensates for the dilution effect, so that the total liver catalase activity is relatively unaffected.

REFERENCES

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