Studies on the Cachexia of Tumor-bearing Animals

II. Catalase Activity in the Tissues of Hepatoma-bearing Animals*

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SUMMARY

Several rat and mouse hepatomas and the liver and kidneys of the host animals were assayed for catalase activity. Little or no activity could be demonstrated in the subcutaneously transplanted Novikoff hepatoma, Hepatoma LC18, and Hepatoma 3683 of rats, and in a number of transplanted hepatomas of mice and hamsters. A relatively high activity was found, however, in the transplanted Hepatoma 5123 and the ethionine-induced hepatomas of rats, and in the spontaneous hepatomas of C3H mice, even though a definite depression was observed in the catalase activity of the liver and kidneys of these tumor-bearing animals. In animals bearing transplanted Hepatoma HC the catalase activity of the tumor was exceedingly high, often exceeding the levels observed in the liver and kidneys.

The catalase level of Hepatoma 5123 was not altered under the stress of a protein-free diet which produced a characteristic lowering in the liver catalase of both normal and tumor-bearing animals. Similarly, both sex and age significantly altered the level of the tissue catalase activity of the host but had no apparent effect on the level of the hepatoma catalase. The site of the tumor implantation also did not change the levels of catalase activity of the tumor tissue.

The significance of these data is discussed with reference to *the concept of "toxohormone"* being released by tumors to produce a lowering of the catalase activity in the host tissues.

One of the classical effects of a tumor on its host is the production of a lowered catalase activity in the liver and the kidneys (1, 3, 4, 6–9, 11–13, 15, 17, 19, 20, 22, 23, 25, 29, 31–33, 40, 43, 44, 51, 53). It has been postulated that a substance, often referred to as toxohormone (37, 38), is produced by tumor cells which passes through the circulation to the liver and kidneys causing a reduction in the catalase activity of these organs. If such a substance were produced in tumor cells presumably it would also have a direct effect on the catalase present in these cells. This would be consistent with the previous findings that tumor tissues, in general, have a negligible level of catalase activity (21).

Recent reports (41, 42) have shown that, in Hepatoma 5123, a number of enzymes whose activity had been previously found to be very low or virtually absent in other hepatomas are present in significantly high levels. In view of these reports, a study has been made to ascertain the level of catalase activity in the 5123 tumor and in several other hepatomas.

MATERIALS AND METHODS

Animals and tumors.—The types of tumors and the species and strains of animals used for transplantation are shown in Table 1. All the animals used in these studies were raised in the laboratories at the National Institutes of Health. In most experiments the animals were kept individually

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in the wire cloth-bottom cages in a temperature-controlled room, maintained at 74° F. or 79° F.

Diets.—Hamsters, and rats of the Fischer and the Osborne-Mendel strains were kept on the Purina Laboratory Chow. Other animals were fed the NCI stock diet, the composition of which was given previously (44). Food and water were available at all times.

The protein-free diet, used in some of the studies, which was patterned after that of Rechcigl *et al.* (45, 46), had the following percentage composition: glucose (Cerelose), 15.0; dextrin, 60.8; hydrogenated vegetable fat (Crisco), 14.0; corn oil (Mazola), 2.0; cellulose (Solka-Floc), 2.0; salt mixture (30), 4.0; and vitamins (blended with glucose), 2.2. The following vitamins, expressed in gm., were included per kg. of vitamin mixture: vitamin A concentrate (200,000 units per gm.), 4.5; vitamin D concentrate (400,000 units per gm.), 0.2; α-tocopherol, 5.0; ascorbic acid, 45.0; inositol, 5.0; choline chloride, 75.0; menadione, 2.25; *p*-aminobenzoic acid, 5.0; niacin, 4.5; riboflavin, 1.0; pyridoxine HCl, 1.0; thiamine HCl, 1.0; calcium pantothenate, 3.0; biotin, 0.02; folic acid, 0.09; and vitamin B_{12}, 0.002.

Catalase assay.—The animals were killed by decapitation and exsanguination. The organs or tissues in question were immediately removed and weighed. The entire tissue or organ was homogenized to avoid the selection of a piece which was not representative.

The tissues were homogenized for 2 minutes in a Waring Blendor with 49 volumes of ice-cold distilled water. Catalase was assayed spectrophotometrically on a continuously recording spectrophotometer[1] with a log-absorbance attachment[2] by a modification (18) of the method of Beers and Sizer (5). To carry out these assays 50 μl. aliquots of the homogenates were added to two cuvettes containing 2.9 ml. of 0.02 M phosphate buffer at pH 6.8 and 22° C. The pen of the spectrophotometer was then set at the base line, and 30 μl. of 1.0 M hydrogen peroxide was rapidly added to the experimental cuvette with the "adder-mixer" described by Boyer and Segal (10). Recording was started immediately, and the decrease in optical density at 230 mμ was traced directly onto semi-logarithmic paper.[3] From the slope of the line obtained the first-order rate constant, K_0, for a given determination, was calculated. One unit of catalase is sufficient enzyme to split 63.2 per cent of a given concentration of H_2O_2 in 1 second and is equivalent to 5.85 μg. of purified rat liver catalase (43).

TABLE 1

TUMORS UTILIZED IN CATALASE STUDIES

Host	Strain	Tumor	Carcinogen	Reference
Rat	F 344/N (Fischer 344)	Hepatoma LC18	N-2-Fluorenylacetamide	16
Rat	Sprague-Dawley	Novikoff hepatoma	4-Dimethylaminoazobenzene	39
Rat	ACI/N (Irish)	Hepatoma 3683	N-2-Fluorenyldiacetamide	35
Rat	BUF/N (Buffalo)	Hepatoma 5123	N-2-Fluorenylphthalamic acid	36
Rat	OM/N (Inbred Osborne Mendel)	Ethionine hepatoma	DL-Ethionine	*
Rat	BUF/N (Buffalo)	Ethionine hepatoma	DL-Ethionine	*
Rat	ACI/N (Irish)	Hepatoma H-35	N-2-Fluorenyldiacetamide	50
Rat	OM/N (Inbred Osborne-Mendel)	Hepatoma HC	DL-Ethionine	49
Mouse	C3Hf	Hepatoma 129P	Carbon tetrachloride	2
Mouse	C3Hf	Hepatoma 129S	Carbon tetrachloride	2
Mouse	C3Hf	Hepatoma 134A	Carbon tetrachloride	2
Mouse	C3H	Spontaneous hepatoma	Spontaneous	†
Hamster	Golden (Syrian)	Angiosarcoma	4-Dimethylaminoazobenzene	52‡
Hamster	Golden (Syrian)	Osteogenic sarcoma	N-2-Fluorenylacetamide	14‡

* Received from Dr. H. Sidransky, National Cancer Institute.

† Received from Dr. W. Heston, National Cancer Institute.

‡ Received from Dr. P. Gullino, National Cancer Institute.

RESULTS

Catalase activity of various hepatomas.—Catalase activities of the hepatomas studied are tabulated in Table 2. It may be observed that little or no activity was found in the LC18, Novikoff, and the 3683 rat hepatomas. Similarly, very little catalase

[1] Cary Model 11 MS Recording Spectrophotometer, Applied Physics Corporation, Pasadena, California.

[2] Modified Brown Recorder, Applied Physics Corporation, Pasadena, California.

[3] Chart No. 1092, Applied Physics Corporation, Pasadena, California.

activity was detected in a number of transplanted mouse and hamster hepatomas. On the other hand, a considerable amount of activity was observed in the Hepatoma 5123 and in the primary and the transplanted ethionine-induced rat hepatomas. A high activity was also found in spontaneous hepatomas of mice.

The primary tumors of this series of ethionine-induced hepatomas possessed higher levels of catalase activity than did the corresponding transplanted tumors. In our experiments it is interesting to note that the primary hepatomas of males had greater catalase activity than those of females.

Catalase activity in the tissues of the tumor-bearing host.—The reduction of liver and kidney catalase activity in animals bearing different tumors is shown in Table 3. The depression in the liver and kidney catalase was observed not only in animals bearing the 3683, LC18 and Novikoff hepatomas, where tumors are low in catalase activity, but also in animals bearing Hepatoma 5123, which has a significant level of catalase activity, as seen in Table 2. The data in Table 3 indicate that catalase depression in the liver and kidneys was related to the size of the 5123 tumor.

The relation of the catalase depression to the

TABLE 2

CATALASE ACTIVITY OF VARIOUS HEPATOMAS

Hepatoma	Site and gen. no.	Days after transpl.	Sex	No. observ.	Catalase activity range (U/gm)	(U/gm) Av.
	Rats					
LC 18	S.C.	14–19	F	10	0–2	1
Novikoff	S.C.	10	F	4	1–4	3
3683	S.C.	15	F	6	4–7	5
Ethionine*	liver-primary		M	1		63
"	S.C. 3d	44–64	M	2	24–28	26
"	S.C. 4th	43	M	1		50
"	S.C. 7th	28–29	M	2	35–40	38
"	S.C. 9th	29–49	M	3	22–44	32
"	S.C. 15th	40	M	2	20–30	25
Ethionine†	liver-primary		M	4	55–78	67
"	liver-primary		M	2	30–46	38
"	S.C. 1st	112	M	1		39
"	S.C. 2d	103	M	4	30–75	47
5123	S.C. 18th	65	F	6	23–54	35
H-35	S.C.	64–79	MF	3	32–68	52
	Mice					
Spontaneous	liver-primary		M	7	40–147	74
"	" "		F	4	39–94	71
H 129	S.C.	13–23	M	2	3–4	4
H 134	S.C., ascites	13–23	M	2	0–2	1
	Hamsters					
Angiosarcoma	S.C.	36	M	3	7–15	10
Osteogenic sarcoma	S.C.	36	M	3	3–6	5

* In OM/N rats. † In BUF/N rats.

size of the tumor is further illustrated in Chart 1. In this chart the total catalase activities of host liver and the Hepatoma 5123 were plotted against tumor weight. There was a progressive decrease in total liver catalase activity with increasing tumor size and also a gradual increase in the total tumor catalase activity.

An even more striking example of the liver and kidney catalase depression in the presence of high tumor catalase levels was found in animals bearing the HC ("high catalase") hepatoma, as shown in Table 4. This is one of the two recently developed lines of hepatomas (49), which were derived from the same primary ethionine-induced tumor. The catalase activity of the tumor was at times so high that it greatly exceeded the level observed in the liver and kidneys.

Effect of a protein-free diet on the catalase activity of the Hepatoma 5123.—In view of previous studies (47) on the lowering of the liver catalase of normal animals following the feeding of a protein-free diet, it was of interest to ascertain whether a comparable decrease would occur in the catalase activity of the tumor. The results of such experiments with rats bearing the Hepatoma 5123 are shown in Chart 2. Animals with small tumors were carefully selected for this study to avoid catalase depression in the tissues of the host, which occurs in the presence of large tumors.

A gradual decrease in the catalase activity was noted in normal liver as well as in the liver of the tumor-bearing animals during the first 2 days on a protein-free diet. No further decrease was found during the next 5 days on the protein-free diet.

TABLE 3

LIVER AND KIDNEY CATALASE ACTIVITY OF HEPATOMA-BEARING RATS

Hepatoma	Tumor % body weight	No. observations	Liver catalase		Kidney catalase†	
			U/gm	U/mg N	U/gm	U/mg N
Control		6	164±6*	4.9±0.1	62	2.0
3683	19	6	90±3	3.2±0.2	44	
Control		3	177±9	5.5±0.9	43	
LC 18	15	6	46±5	2.0±0.3	32	1.3
Control		2	163±1	5.4±0.01	50	2.2
Novikoff	14	4	77±12	2.7±0.5	51	1.9
Control		4	206±8	6.7±0.4	57±2	2.1±0.1
5123	3	7	160±10	5.8±0.3	54±1	2.0±0.1
5123	18	13	90±8	2.9±0.3	31±4	1.2±0.05

* Standard error of the mean.

† All kidney samples, with the exception of 5123 group, were pooled.

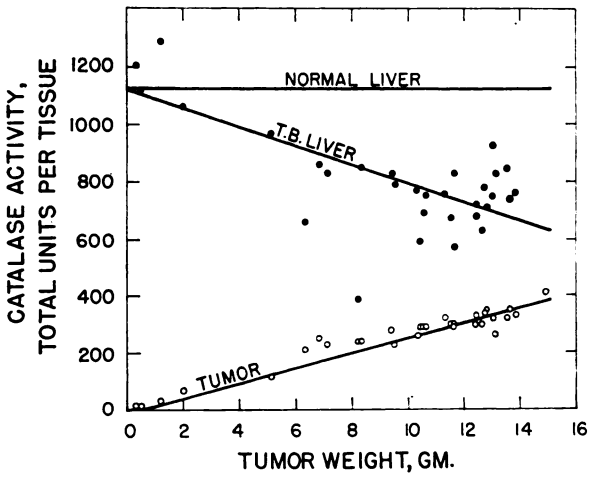

CHART 1.—Tissue catalase activity of female rats bearing the Hepatoma 5123. T. B. liver refers to liver of a tumor-bearing host.

TABLE 4

CATALASE ACTIVITY IN TISSUES OF RATS BEARING THE HC-HEPATOMA

Tumor weight (gm.)	Catalase activity (U/gm)		
	Liver	Kidney	Tumor
9.0	187	60	236
11.9	133	70	330
18.1	156	47	226
36.5	35	23	267
51.5	106	38	213
52.0	74	34	280
138.1	84	55	275

On the other hand, no significant lowering of catalase occurred in the 5123 hepatoma, even though the catalase of the host liver was reduced.

Effect of the host on the tumor catalase activity.— Another study was carried out to determine whether the site of tumor implantation would affect the enzymatic activity of the Hepatoma 5123. As can be seen from Table 5 there was no apparent effect of site of implantation, since the subcutaneous and the intraperitoneal implants grown in the same animal possessed approximately the same levels of catalase activity. Single subcutaneous or intraperitoneal inoculations in different animals gave similar results (Table 6). It can also be seen in Table 6 that the catalase activity of these tumors was not affected by the sex of the host animal.

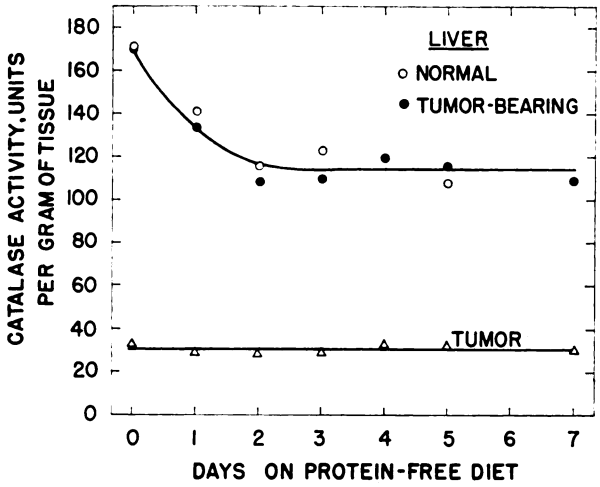

CHART 2.—Tissue catalase activity of normal female rats and rats bearing the Hepatoma 5123 fed protein-free diet.

TABLE 5

CATALASE ACTIVITY OF THE 5123 HEPATOMA TRANSPLANTED IN TWO DIFFERENT SITES OF THE SAME ANIMAL

Rat no.	Tumor weight (gm.)		Catalase activity (U/gm)	
	S.C.*	I.P.†	S.C.	I.P.
1	0.8	2.8	43	57
2	2.2	2.6	58	57
3	3.4	1.2	55	64
4	4.1	9.3	50	51
5	5.3	5.4	50	31
6	6.0	4.0	47	64
Average:	3.6	4.2	51	54

* Subcutaneous. † Intraperitoneal.

A similar stability in the tumor catalase activity was observed in male and female host animals of varying ages (Table 7). On the other hand, both sex and age significantly altered the level of liver catalase activity. In case of the kidney, the catalase activity was affected by the sex of the animal, whereas the age of the animal was without apparent influence.

DISCUSSION

The data obtained in this study demonstrate the presence of significant levels of catalase activity in a number of primary and transplanted hepatomas, spontaneous as well as induced. These findings are not consistent with the previously held view (21) that tumor tissues in general contain no or negligible amounts of catalase.

TABLE 6

EFFECT OF SEX OF THE HOST ANIMAL AND SITE OF TUMOR IMPLANTATION ON THE CATALASE ACTIVITY IN HEPATOMA 5123

Sex	Tumor site	Tumor weight (gm.)	No. observations	Catalase activity (U/gm)	
				Range	Average
Females	S.C.	9.4	3	35–52	46
"	I.P.	15.8	3	22–53	35
Males	S.C.	22.4	3	34–42	37
"	I.P.	22.3	4	28–49	39

Recent studies in our laboratory (49) may furnish a possible explanation as to why Greenstein and other investigators failed to observe significant levels of catalase activity in tumors, particularly the rat hepatomas (24, 26–28, 34). We have succeeded in isolating from a primary ethionine-induced hepatoma, two lines of transplantable hepatomas (carried subcutaneously), one (HC) possessing extremely high catalase activity, sometimes exceeding that of the normal liver, and the second line (LC) with a low enzymatic activity. The tumors of the two lines did not differ histologically, and furthermore no other major enzymatic or chemical difference other than the catalase activity was found. The tumor lines were established in the first transplant generation and have persisted for over fifteen generations without a major change in the levels of catalase activity.

In view of the above results it seems likely that the failure of previous investigators to observe significant amounts of catalase in tumors could have been caused by the loss of either the catalase-producing cells or the catalase-producing mechanisms within the cells during tumor transplanta-

TABLE 7

EFFECT OF SEX AND AGE ON THE CATALASE ACTIVITY OF TISSUES OF RATS BEARING 5123 HEPATOMA*

SEX	AGE (MONTHS)	LIVER CATALASE†		KIDNEY CATALASE		TUMOR CATALASE	
		U/gm	U/mg N	U/gm	U/mg N	U/gm	U/mg N
M	3	137±7	4.5±0.2	47±2	1.6±0.05	42±3	1.6±0.05
M	5	177±6	5.3±0.3	49±2	1.6±0.03	47±6	1.8±0.12
M	9	195±6	5.8±0.4	47±1	1.6±0.04	47±3	1.8±0.10
F	3	116±11	3.8±0.2	32±5	1.2±0.07	40±2	1.5±0.09
F	4	130±3	4.0±0.1	29±2	1.2±0.06	37±2	1.4±0.04
F	11	140±7	4.4±0.3	30±1	1.1±0.04	41±2	1.7±0.03

* Each group represents five animals.

† On the basis of the covariance analysis it was found that the difference in level between the sexes is highly significant (P = 0.01). The slopes, resulting from the plotting of catalase data against age, were significantly different from zero. When the data were expressed as units/gm the slopes were not parallel. After the correction for the variation in the nitrogen concentration (units/mg N) there was not any evidence that two regressions are not equal—i.e., there is parallelism.

tion. The very low or zero levels of catalase activity observed in many tumor tissues are therefore not necessarily typical of but rather appear to be coincidental with the neoplastic process.

The enzymatic assays of the liver and kidney indicate that a depression can be observed in the catalase activity of the tissues of the tumor-bearing host, even in the presence of significant levels of catalase activity in tumor tissues. These observations do not of course disprove the concept of toxohormone. They do, however, point to the need for reexamination of this concept, since it seems unlikely that such a factor released from tumors would depress the enzyme level of the liver and kidneys without markedly affecting the catalase activity of the tumor itself.

There remains a possibility, however, that toxohormone is not released in an active state within the tumor cell and that this might account for its failure to completely depress the catalase activity of certain hepatomas. Another possibility is that there may be two (or more) biologically, if not physically, distinct species of catalase within the liver. It is possible that during carcinogenesis one form of catalase may be retained in some hepatomas but not in others, and that this form may be inaccessible to toxohormone and therefore remain active. This would be consistent with the findings of the present study showing the relative stability of tumor catalase toward the effects of the host (i.e., sex and age of the host, tumor site) and the lack of its response to a protein deficiency.

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