

Comparative Study of Serum Lactic Dehydrogenase Activity in Mice with Transplanted and Induced Tumors*

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We have previously reported an elevation in serum lactic dehydrogenase (LDH) in mice with transplanted tumors (1). The question is whether there is a similar increase in induced tumors.

Since regression of transplanted tumors is accompanied by a decline in serum LDH activity to its normal level, the further question arises whether the serum LDH activity of animals with benign papillomas and malignant tumors undergoes similar modification. In human beings there is an increase in serum LDH level during pregnancy (2). Experiments were designed to answer these questions, and our results are summarized in this report.

MATERIALS AND METHODS

Four experiments with pregnant mice and those bearing different tumors were carried out:

Experiment 1: Induced tumors.—Two groups of mice were used for developing induced tumors. The first group were female CAF mice painted with cigar tar 3 times weekly for 20 months. These were kindly supplied by Miss A. Croninger. Each painting delivered about 40 mg. of cigar tar. Carcinomas appeared 17 months after these regular paintings. Blood samples for LDH analyses were taken when the animals were about 22 months old.

The second group consisted of female Swiss mice 3–6 months of age. They were painted with 0.6 per cent methylcholanthrene in benzene 3 times a week. Mice of the same age painted with benzene only but in the same way served as controls. Blood samples were taken before squamous-cell carcinomas appeared as well as at selected stages in their development.

Experiment 2: Transplanted tumors.—Rhabdomyosarcoma was transplanted subcutaneously in male C3H mice about 1½ months old. This tumor was originally induced in 1945 by intramuscular injection of 0.5 mg. methylcholanthrene in lard. Blood samples were taken between 3 and 30 days after transplantation.

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Experiment 3: Spontaneous tumor.—Seven- to 12-month-old female Swiss mice with spontaneous mammary gland tumors were used. Blood samples were taken when tumors appeared.

Experiment 4: Pregnancy.—Pregnant female Swiss mice about 2–3 months old were used in this experiment. Blood samples were taken at middle and late stages of pregnancy. A group of non-pregnant female Swiss mice of the same age was used as control.

In all the experiments the blood samples were obtained by heart puncture, and serum LDH determinations were made according to the previously reported procedure (1).

RESULTS

Table 1 provides a general summary. The serum LDH activity was generally higher in mice bearing tumors, regardless of the nature of the tumors, except in the case of papillomas in which there was no difference in LDH activity from that in the controls. In pregnancy the LDH values did not appear to be significantly altered.

As in the case of mice with papillomas, the serum LDH of mice whose epidermis was merely rendered hyperplastic was about the same as that of the control animals (Table 2). However, 1 month after the first blood samples were taken, a distinct elevation of serum LDH activity was observed, ranging roughly from 40–400 per cent. Two months after taking the second blood samples a still higher serum LDH activity was observed, as shown in Table 2. Mice with papillomas exhibited no such changes.

Chart 1 shows the serum LDH activity during the period of development of rhabdomyosarcoma transplants. Each point on the curve represents an average of three to four animals; controls, an average of two mice. A similar curve for induced tumors is shown in Chart 2, in which each point represents one to nine determinations. Evidently, both are of the same shape: an early sharp rise in LDH activity followed by a slightly declining plateau and a final marked increase.

In mice with induced tumors, the early rise in

TABLE 1
SERUM LACTIC DEHYDROGENASE ACTIVITY (LDH) OF INDUCED, TRANSPLANTED, AND SPONTANEOUS TUMORS IN MICE

CASE	LDH ACTIVITY (MM LACTATE OXIDIZED/LITER SERUM/HOUR)			
	Experimental		Control	
	Range	Mean	Range	Mean
Cigar tar-induced tumor	139.2	139.2 (1)*	22.4	22.4 (1)
0.6 Per cent methylcholanthrene-induced tumor	130.4-436.4	207.2 (23)	25.4-138.2	72.0 (30)
Rhabdomyosarcoma transplant 3 days after transplantation	80.8-112.0	98.2 (4)	24.8-29.6	27.2 (2)
Mammary gland tumor	69.2-139.6	94.2 (4)	25.4-30.6	36.4 (5)
Papilloma induced by 0.6 per cent methylcholanthrene	31.4-52.2	42.0 (4)	29.8-58.8	42.6 (6)
Pregnancy	31.4-57.4	42.8 (5)	30.8-40.4	36.6 (3)

* Figures in parentheses indicate number of determinations.

TABLE 2
SERUM LACTIC DEHYDROGENASE ACTIVITY (LDH) OF MICE WITH 0.6 PER CENT METHYLCHOLANTHRENE-INDUCED TUMORS AT VARIOUS DEVELOPMENTAL STAGES

SERUM LDH ACTIVITY (MM LACTATE OXIDIZED/LITER SERUM/HOUR)			
Grossly hyperplastic epidermis	Early stage carcinoma and some well developed carcinoma	Late stage carcinoma	Control
	CARCINOMA		
41.4 (50)*	134.8 (71)*		42.4 (6)†
41.0 (52)	61.4 (71)		
41.8 (52)	71.0 (96)		
33.2 (57)	138.2 (92)		28.0 (2)
	156.6 (104)	436.4 (142)*	
	143.6 (107)	270.2 (142)	
	140.0 (92)	410.6 (146)	82.4 (3)
	182.8 (155)	239.2 (211)	128.0 (1)
	PAPILLOMA		
31.4 (78)			42.4 (6)
51.0 (55)			
39.2 (50)	52.2 (71)		
33.2 (57)	38.4 (92)		

* Days after the first painting; each horizontal line represents a single mouse studied at different times.

† Number of determinations.

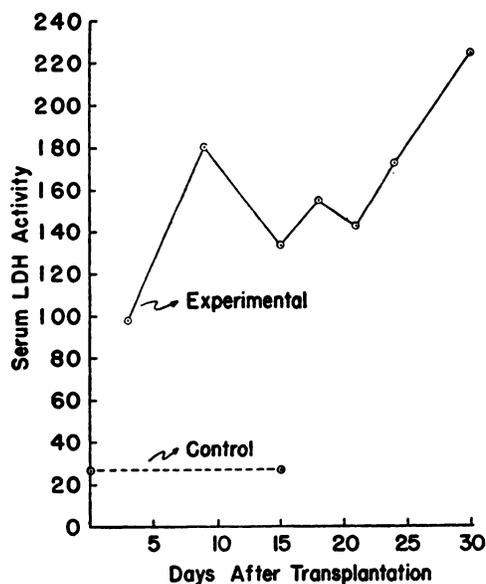


CHART 1.—Serum LDH activity of C3H mice with transplanted rhabdomyosarcoma.

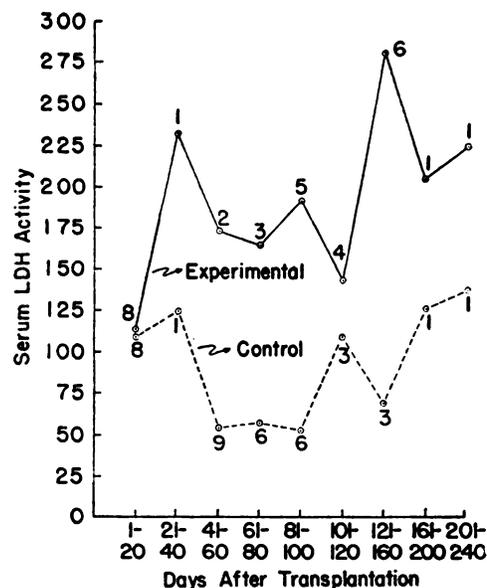


CHART 2.—Serum LDH activity of female Swiss mice with induced tumor.

serum LDH occurred at between 40 and 60 days after the first painting, whereas in mice with transplants it took place about 9 days after transplantation. The duration of the plateau period was 3 months for the induced tumors and only 12 days for the transplanted tumors.

DISCUSSION

First, the LDH increase in serum was only manifested in carcinomatous animals, whether induced or transplanted. Papillomas did not change the enzyme concentration; only when they became malignant did the serum LDH rise. The effect of pregnancy was inconspicuous under the conditions of our experiments, though considerable in the observations of Hill and Levi (2).

The magnitude of the serum LDH response to the presence of tumors varied according to the kind of tumors, apparently depending on the susceptibility of the mice toward the transplanted and induced tumors. That this change in serum enzyme concentration is related to tumor growth seems probable, for it was not observed in control animals without tumors whose epidermis has merely been made hyperplastic by applications of methylcholanthrene in benzene.

Secondly, the serum LDH change associated with tumor growth showed a fixed pattern roughly divisible into three stages: an early rise, a weak

recess, and, lastly, a sharp increase. The duration and magnitude of each period may vary, as indeed they did, but the trend is the same. Some fluctuation may be partially ascribed to the animals' individual susceptibility to the tumors. This fixed behavior of serum LDH seems to reflect certain biochemical changes the mechanism of which remains to be discovered. The explanation for the final decline of LDH shown in Chart 2 eludes us.

SUMMARY

Lactic dehydrogenase (LDH) of mouse serum has been determined in animals with induced and transplanted tumors as well as in pregnant ones. It was found that only with malignant tumors, whether transplanted or induced, did serum LDH increase. Mice with papillomas or in stages of epidermal hyperplasia resulting from the application of methylcholanthrene gave normal serum LDH values. Pregnancy seemed to have no significant effect on serum LDH.

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