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Response of Mouse Breast Tumors to L-Triiodothyronine and Irradiation. (25810)

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In 1951 it was shown that mice made hyperthyroid by oral administration of thyroxine showed increased mortality when given total body irradiation(1). A year later L-triiodothyronine (T3) was isolated from human plasma(2). T3 by various assays was several times as active as thyroxine, and it was postulated that thyroxine is deiodinated to T3 in peripheral tissues before exerting its effect(3). In animals peak physiologic activity with increased oxygen consumption was exhibited by fourth day of T3 administration(4). L-triiodothyronine was strongly accumulated by Ehrlich mouse ascites carcinoma cells(5). Increased glycolysis without increased mitotic rate of growing tumor cells in tissue culture was observed after treatment with T3(6). Stein and Griem studied the effect of combined T3 and x-ray therapy on myeloid chloroleukemic rat tumor, mouse neuroblastoma, and human bronchogenic carcinoma(7). They noted more marked tumor regression after combined therapy so that a lower x-ray dose would accomplish the same therapeutic result. The skin reaction was accelerated. The purpose of this study was to evaluate the effect of x-radiation on transplanted mouse breast adenocarcinoma when animals had been made hyperthyroid by administration of L-triiodothyronine.

Method. Randomly selected ZxC57 black F_1 male and female hybrid mice, aged 3 to 6 months, were kept in cages in air-conditioned room maintained at 72°F. An ample supply of tap water and Purina fox chow was always available. Twenty-five mg of T3 were dissolved in 25 cc of propylene glycol and 25 cc of sterile water and kept in freezing compartment. The same material was used throughout preliminary toxicity studies as well as actual experiment. Five groups of 5 mice each were injected intraperitoneally with .25, .50, .75, 1, and 2 mg/kg respectively, for 4 consecutive days. Weights were recorded daily and animals observed for signs of hyperthyroidism. The first 3 groups developed moderate diarrhea and a transient weight loss, most marked on third day. Weights were back to normal by 6th day. In groups receiving 1 mg/kg weight fluctuation was less marked but signs of hyperthyroidism were evident. The animals had diarrhea, loss of coat sheen, marked increase in activity, increased water and food consumption without increase in weight. The group receiving 2 mg/kg showed polydipsia, transient weight loss, bulimia, increased respiratory rate, and loss of coat sheen. By 5th day these animals showed extreme lassitude. Dose of 1 mg/kg was optimum and this was in the dose range employed by Stein and Griem(7). Spontaneous adenocarcinoma of the breast originating in a Z female mouse and transferred by serial transplantation for 2 generations was processed

TABLE I. Animal Survival.

Group	T3 (mg/kg)	X-ray (r)	No. of animals	Avg survival (days)*
1	1	0	25	19.4 ± 1.6[1]
2	0	4500	"	42.2 ± 3.2[1,2,3]
3	1	4500	"	47.1 ± 3.2[1,2]
4	0	0	15	28.8 ± 2.2

* Includes stand. error.

[1] Highly significant difference from Group 4 (P = .001).

[2] Highly significant difference from Group 1 (P = .001).

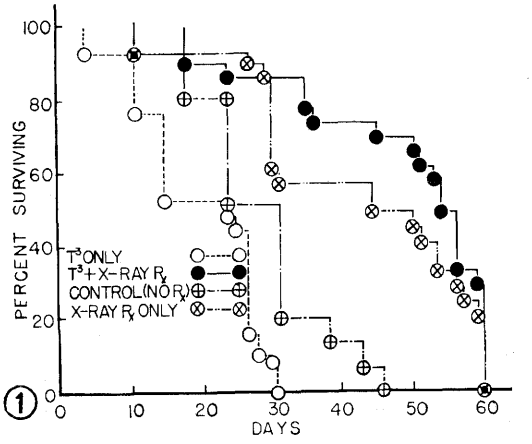
[3] Insignificant difference from Group 3 (P = .28).

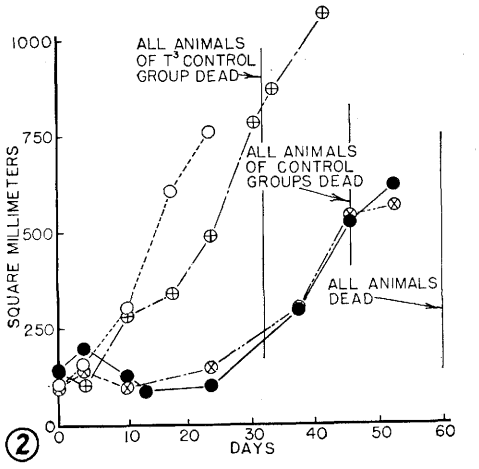
with a tissue press. A suspension of fresh tumor cells in sterile physiologic saline was injected subcutaneously in ventral aspect of hind leg of 90 ZxC57 black F_1 hybrid mice. At end of 25 days the tumors averaged 11 mm in diameter and the animals were randomly divided into 4 separate groups. The first group of 15 animals received no therapy and was maintained as control. Two groups of 25 animals were treated with T3, 1 mg/kg intraperitoneally, for 4 days and on the morning of fifth day one of the T3 treated groups as well as a control group of 25 animals were treated with 4500 r in air (140 KV, HVL 3 mm Al, FSD 13 cm, dose rate 200 r/min). Radiation was delivered to the tumor-bearing leg while the rest of body was shielded with lead (Table I).

Results. The following parameters were observed: Life span, tumor size, and body weights, presented in Fig. 1, 2 and 3.

A statistically significant increase in life span was noted in groups receiving x-ray therapy as compared to controls. There was also a significant decrease in longevity of the T3 control group compared to the group which received no therapy. No significant difference in life span was noted between the group receiving T3 in addition to x-ray treatment compared to group receiving x-ray alone (Fig. 1, Table I).

Tumor growth rates were studied by measuring breadth and length of tumor with a Vernier caliper. These values were multiplied and the products averaged for graphing. In group receiving T3, tumor growth rate was accelerated to a significant degree compared to controls which received no therapy. In





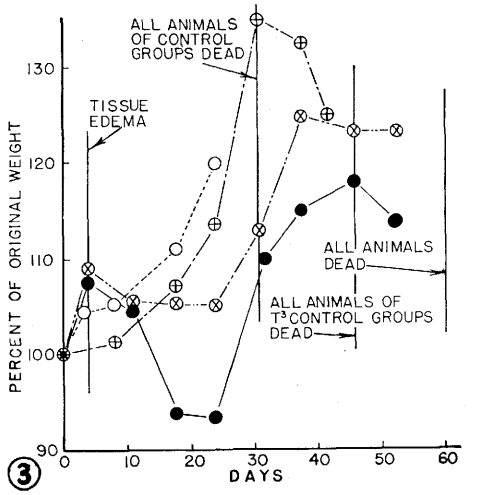


FIG. 1. Life span.

FIG. 2. Tumor size. On day 24 a significant difference between tumor size of control groups was demonstrated (P = .001).

FIG. 3. Animal wt.

groups receiving x-ray treatment an initial increase is tumor size, attributed to tissue edema, was noted. This was followed by regression and ultimate tumor regrowth. At time of death all animals in each group exhibited huge tumors. These tumors contributed to approximately one-third of animals' total body mass (Fig. 2).

Control groups gained weight more rapidly than the group receiving x-ray treatment. In groups receiving irradiation, initial slight weight gain might be attributed to tissue edema. This was followed by weight loss which paralleled tumor regression. Weight gain accompanied tumor growth in all groups but several days prior to death weight loss was observed. The group receiving T3 plus x-ray averaged 5 g less in weight than the other groups (Fig. 3).

Two weeks following irradiation maximum tumor regression and skin reaction were noted. In the group receiving T3 plus x-ray, moist epidermitis and superficial ulceration were observed, while in the group which received x-ray alone epilation and a brisk erythema were most commonly seen. In several animals receiving both T3 and x-ray limb amputation occurred subsequent to irradiation.

Conclusions. 1. Growth rate of transplanted mammary tumor in ZxC57 black F_1 hybrid mice treated with L-triiodothyronine was increased. 2. Average life span of tumor-bearing mice receiving L-triiodothyronine was significantly shortened. 3. In mice receiving L-triiodothyronine and x-ray, increased skin reaction was noted. 4. There was no significant difference between average life span of tumor-bearing groups receiving combined irradiation plus triiodothyronine and the group which received local irradiation only.

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Effect of Single Dose of DL-Serine on Lipide Phosphorylation in Kidney of Rats.* (25811)

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Interference of plasma lipide metabolism in degenerative kidney lesions has been reported (1). The present study is, to our knowledge, the first to investigate metabolism and distribution by column chromatography of phospholipides in experimental renal necrosis produced by administration of a single dose of DL-Serine.

Methods. Experimental necrosis was produced by administration of a single dose of DL-Serine by the method of Fishman and Artom(2). Male albino rats of Sprague-Dawley strain weighing 80-100 g were fed 10% casein diet(3) for 10 days supplemented daily with a B vitamin solution(4) not containing pyridoxine. Control animals received a similar diet daily supplemented with Vit. B solution containing pyridoxine. After being on the diet for 10 days, the rats were stomach-tubed with single dose of 100 mg of DL-Serine; control animals received water. Forty-

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