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### Title

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University of California, Berkeley, California

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ABSTRACT

The effect of deuterium oxide ( $D_2O$ ) on the survival of mice inoculated with Ehrlich's mouse ascites tumor has been studied. Mice maintained on 25%- and 30%  $D_2O$  drinking water showed an improved survival time of about 6 days whereas 40%- $D_2O$  drinking water had no effect on survival time. The effect is interpreted in terms of inhibition of tumor cell division and systemic toxicity.

THE EFFECT OF D<sub>2</sub>O ON SURVIVAL OF MICE WITH ASCITES TUMOR\*Ann M. Hughes, Bert M. Tolbert,<sup>†</sup> Karl Lonberg-Holm,<sup>§</sup> and Melvin CalvinRadiation Laboratory and Department of Chemistry  
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The improved availability of mass-produced deuterium at reasonable prices ( \$28 per pound for D<sub>2</sub>O) has made it of interest to renew the study of metabolic effects of deuterium in plants and animals. The older literature on this subject has been ably reviewed by Chance and Allen<sup>1</sup> and Thorn<sup>2</sup> who include several reports on the effects of deuterium on a variety of tumors, Rea and Yuster<sup>3</sup> inoculated rats with a sarcoma, and after the tumor was established, injected 0.11% D<sub>2</sub>O in and around the tumor every other day for ten treatments. They reported no inhibition of tumor growth. Woglom and Weber<sup>4</sup> brought the body water of mice to 0.3% and then implanted sarcoma 180 or carcinoma 63 while continuing D<sub>2</sub>O treatment. They also reported no effect on the tumor.

These results are not surprising in view of other reports which have indicated that greater than 5% D<sub>2</sub>O body-water concentration is needed to produce any gross metabolic changes in animals. Barbour and Allen<sup>5</sup> report a significant inhibition of carcinoma and lymphosarcoma growth in mice maintained on 40%-D<sub>2</sub>O drinking water. This produced a body-water deuterium oxide concentration of about 20%. More recently, Weinberger and Porter<sup>6</sup> and Holm-Hansen, Moses, and Yarberry<sup>7</sup> have demonstrated an inhibition of algal reproduction at deuterium water concentrations over about 30%.

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In this report we wish to describe the effect of  $D_2O$  on the survival of mice with Ehrlich's ascites tumor. At the time of our first report on this work,<sup>8</sup> preliminary results on a similar study were presented by Finkel.<sup>9</sup> More recently, an article by Katz et al has presented these data in a more detailed form.<sup>10</sup>

### EXPERIMENTAL

The body-water concentration of  $D_2O$  in young adult male and female  $C_{57}$ -strain mice was brought up to 20 to 30% in two days as follows: The mice were injected intraperitoneally daily with 1.5 ml of isotonic 99 + %  $D_2O$  water. At the same time different groups were given 25, 30, or 40%  $D_2O$  in the drinking water, and food, ad lib. Controls were similarly injected and treated, but with  $H_2O$  instead of  $D_2O$ . On the third day the  $D_2O$ -treated mice and controls were each inoculated with 0.1 ml of a tumor suspension containing about  $1 \times 10^6$  Ehrlich's mouse-ascites tumor cells.\* Inoculum from the same sample was used for each group and its controls. The  $D_2O$ -treated mice were continued on their 25%, 30% or 40% drinking water. Survival time after tumor inoculation was determined. Each experiment was repeated.

All water  $D_2O$  is expressed as volume percent, which is essentially the same as atom percent.

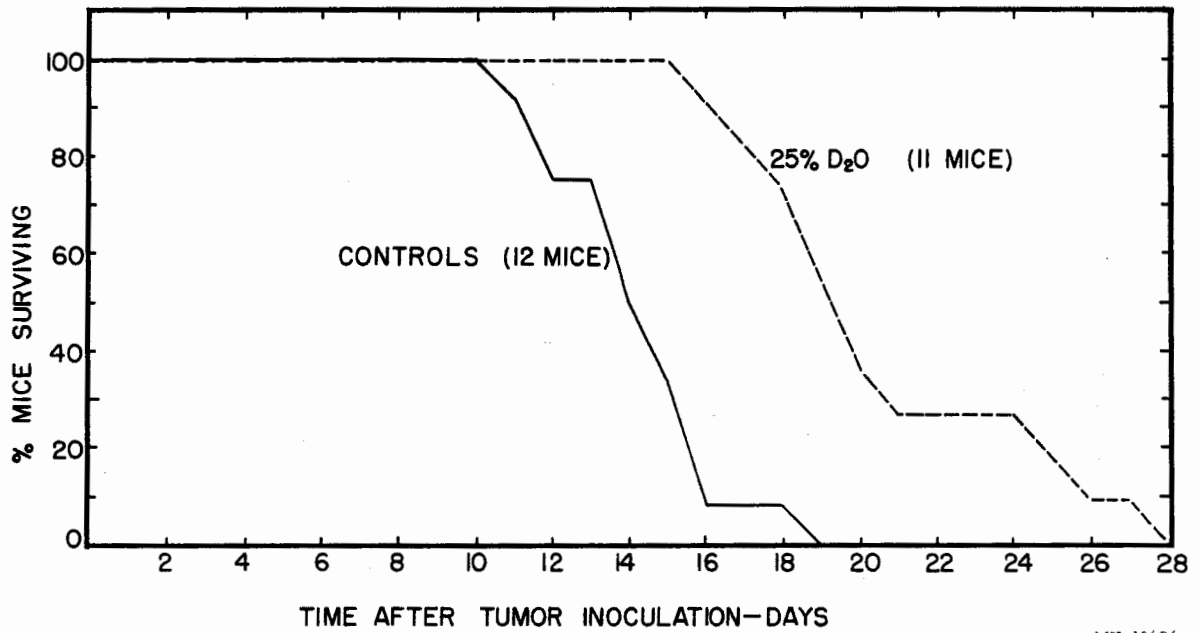
### RESULTS

Preliminary experiments on deuterium toxicity in mice had shown that drinking water of 50%  $D_2O$  was surely fatal, killing the mice in a few days. However, we were able to maintain mice on 40%  $D_2O$  for several months without any deaths. Therefore, 40%  $D_2O$  was the highest concentration of drinking water used in our experiments.

In all of our experiments the tumor cells multiplied, swelling the abdomens of the deuterated as well as the normal mice. We found no evidence of actular tumor regression. The survival-time curves for the mice treated with 25%, 30%, and 40%  $D_2O$  drinking water are given in Figs. 1 to 3. Each group of animals had their own controls, as there is some

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\*This tumor has been maintained in  $C_{57}$  mice in this laboratory for more than one year.



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Fig. 1. Influence of 25%-D<sub>2</sub>O drinking water on the survival of mice after ascites-tumor inoculation. The mean survival time was increased by  $6.3 \pm 1.4$  days, where 1.4 days is the standard error for the difference of the mean.

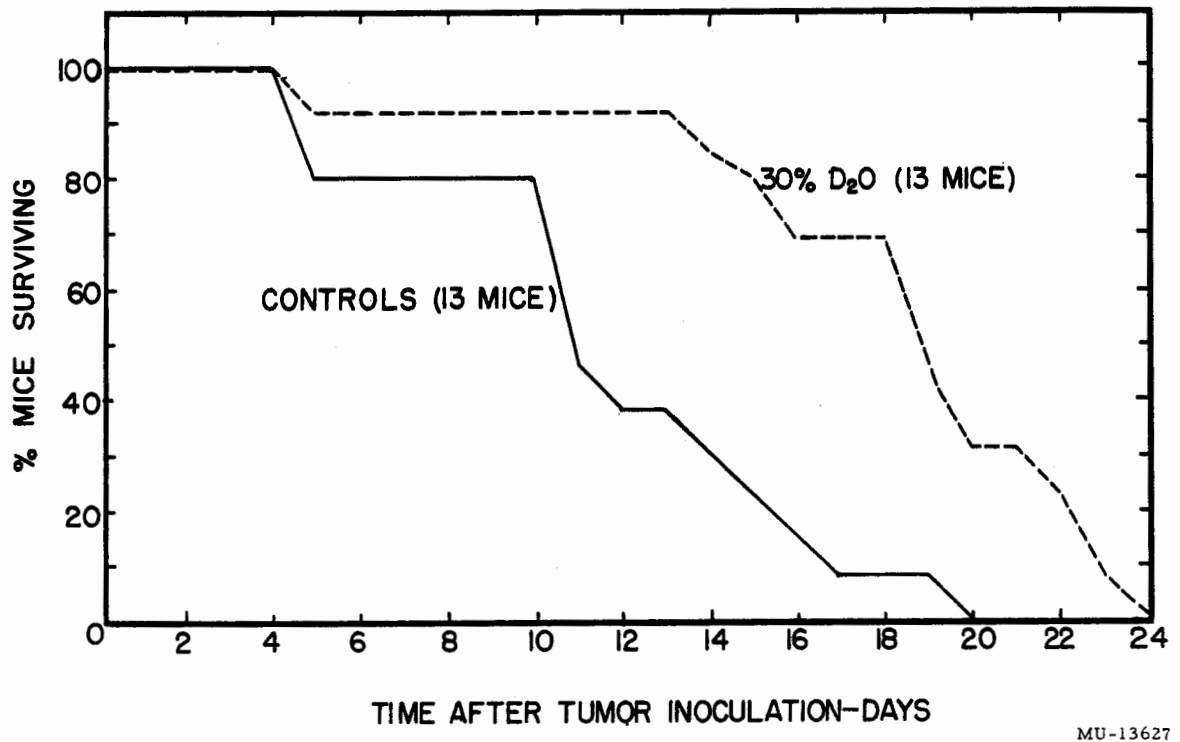
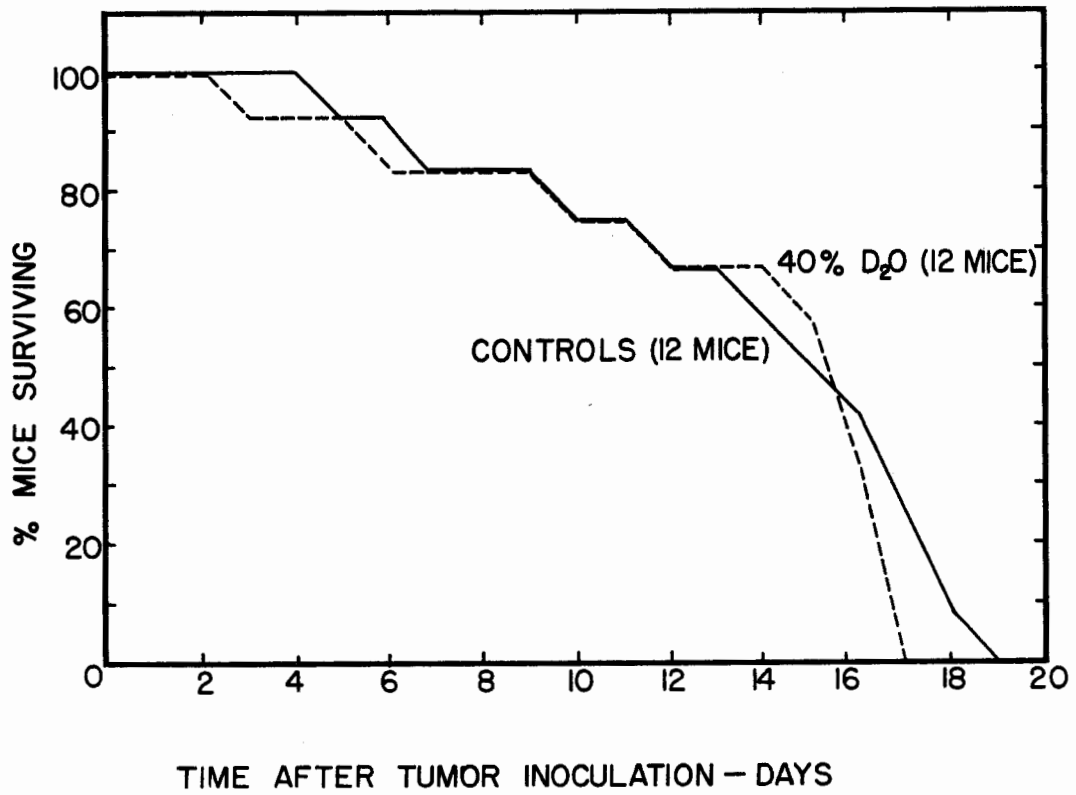


Fig. 2. Influence of 30% drinking water on the survival of mice after ascites-tumor inoculation. The mean survival time was increased by  $6.6 \pm 1.9$  days, where 1.9 days is the standard error for the difference of the mean.





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Fig. 3. Influence of 40% drinking water on the survival of mice after ascites-tumor inoculation. The mean survival time changed from 14.0 days for the controls to 13.5 days for the deuterated mice.

variation in the lethal characteristics of any given sample of the tumor inoculum. As can be seen from Figs. 1 and 2, the mice given 25%- and 30%-D<sub>2</sub>O drinking water had an appreciably longer survival time than their respective controls. In addition, the deuterated mice continued to be bright and lively in spite of the tumor for a longer period than the controls.

The 40%-D<sub>2</sub>O drinking water had no inhibitory effect on the ascites tumor. It would appear that it might even potentiate the lethal effect of the tumor. This substantiates the observation of Barbour and Allen that although 40%-D<sub>2</sub>O in the drinking water inhibited the growth of mouse carcinoma and lymphosarcoma, the survival time of the animals was shortened.<sup>5</sup>

#### DISCUSSION

The data of Holm-Hansen, Moses, and Yarberry<sup>7</sup> on the division of algae cells in D<sub>2</sub>O indicates that moderate deuterium concentrations can inhibit cell division. They found that in unadapted algae, 50% D<sub>2</sub>O in effect stopped cell division although the cells were still alive and, in fact, grew in size. It is possible that this same inhibition of cell division by deuterium occurs in higher biological systems, but the toxicity of the deuterium to these systems is such that it is difficult to raise the deuterium oxide levels high enough to make such inhibition truly effective.

Our experiments indicate that 25%- and 30%-D<sub>2</sub>O drinking water provide a moderate inhibition of the tumor growth and increase animal survival. The 40% D<sub>2</sub>O is already at a rather toxic level and 50% D<sub>2</sub>O cannot be used for this type of experiment. The data of Katz<sup>10</sup> and Finkel<sup>9</sup> help confirm our inference that increased survival time of the mice maintained on 25%- and 30%-D<sub>2</sub>O drinking water is due to a decreased rate of cell division.

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