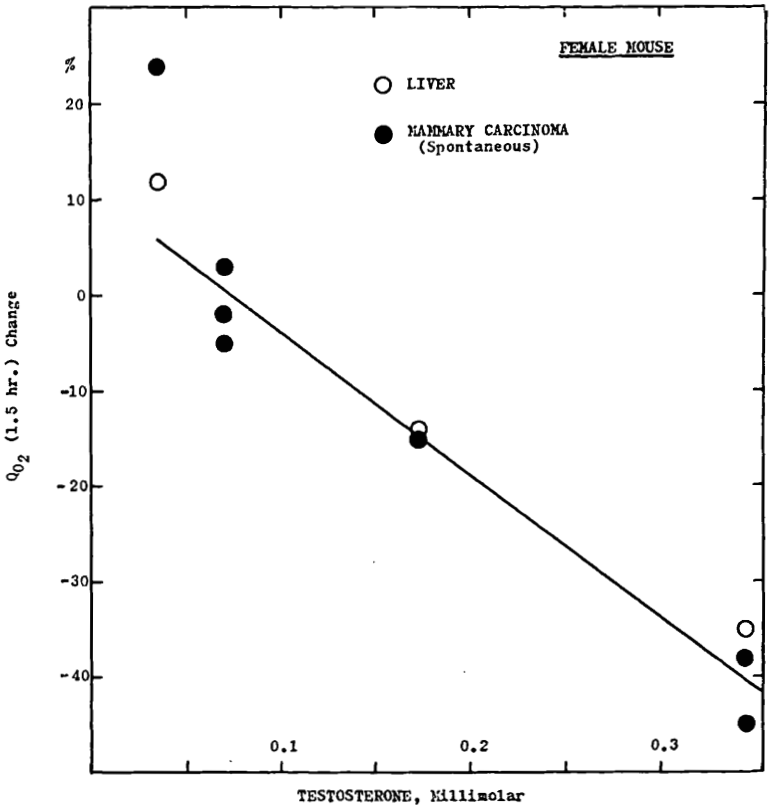

FIG. 1. Effect of testosterone on respiration of liver and spontaneous mammary carcinoma slices from female mice.

muscle(6,7), liver(8,9), and kidney(8,9) preparations. Moreover, the degree of inhibition has been correlated(9) with the quantity of testosterone added.

Summary. The oxygen consumption of liver and spontaneous mammary tumor slices from female mice was initially slightly increased and then progressively decreased by increasing concentrations of added testosterone.

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Distribution of Radioactive Colchicine in Some Organs of Normal and Tumor-bearing Mice.* (18886)

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A small quantity of radioactive colchicine labelled with carbon-14 was first prepared by the use of biosynthesis technics in this laboratory during the past year. The limited quan-

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tities of radioactive colchicine obtained thus far by this method have been employed in experiments on the distribution of this drug in the tissues of normal and tumor-bearing mice. Radioactive colchicine makes it possible to determine with greater precision the presence of a small amount of colchicine in tissues, or in a conglomerate of cells. The results presented herein indicate that the distribution of colchicine in some tissues of tumor-bearing animals is markedly altered from the normal pattern.

Methods. Radioactive colchicine randomly labelled with carbon-14 and containing a specific activity of 40,000 counts/min/mg or 27 microcuries/g was obtained from *Colchicum autumnale* corms which were made radioactive by the biosynthetic procedures developed in this laboratory(1). The alkaloid was extracted and purified by modifications of the available methods devised by one of us (W) to make possible the handling of minute quantities of starting material and of purified material(2). For administration to mice the colchicine was dissolved in distilled water (1 mg/ml) and injected subcutaneously at a dose of 1 ml per mouse. This dose produced diarrhea after 2 to 3 hours and death ensued after 8 to 12 hours. Throughout these experiments C-57 black mice secured from the Bar Harbor Laboratory were used. The animals weighed 20-25 g. No distinction was made as to sex but no pregnant animals were used.

The tumor employed was sarcoma 180, and was implanted in the scapular region. In our laboratory the implant was observable after 5-7 days, and reached its development without necrosis after 10-15 days; at which time the animals were sacrificed. All of the animals used for distribution studies were sacrificed 4 hours after injection. The organs were removed, washed in saline to remove blood, dried between filter paper, weighed and homogenized in a Potter and Elvehjem homogenizer. The homogenates (10%) were then extracted with 70% ethanol and filtered. The filtrate was evaporated to a small volume, diluted with water and extracted with petroleum ether. The aqueous fraction was then extracted with chloroform and this extract was then evaporated to dryness and taken up in chloroform C.P. (0.7% ethyl alcohol). This extract was then allowed to pass through an alumina column. The resulting eluate contained colchicine while other substances were adsorbed on the column. The identification of the colchicine was accomplished by the use of a polarographic method(2). Equal parts of each sample were analyzed using an internal Geiger counter of special construction(3).

The data so obtained are expressed as counts/min per gram of tissue and as percentage of total counts found in the animals.

Results and discussions. Our reasons for performing this study were to (a) determine whether tumor tissue has a tendency to accumulate colchicine and (b) to ascertain whether the presence of tumors in mice brings about changes in the distribution pattern of colchicine.

It was found that labelled colchicine was not present in blood, brain, muscle and heart 4 hours after injection into normal mice. Table I shows the distribution of colchicine in some organs of normal mice C-57. Colchicine was found in the liver in very small quantities. The intestine, kidney and spleen accumulated the drug in considerable amounts. It is known from the papers of Jacobj(4) and more recently Brues(5) that most of the colchicine is excreted in the feces and urine during the first hours after injection. The variability of the percentage of colchicine in the kidney and intestine might be explainable on the basis of differences in excretion.

In the tumor-bearing mice it was also found that colchicine is not present in blood, brain, muscle and heart.

In Table II the uptake of colchicine in some organs of tumor-bearing mice is shown. In the intestine and kidney the uptake of colchicine was no smaller than was observed in

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TABLE I. Distribution of Colchicine in Normal Mice. One column represents the number of counts over background per g of tissues. The other column represents the same values expressed as % of the total counts taken in a mouse.

	Intestine		Kidney		Liver		Spleen	
	cpm/g	%	cpm/g	%	cpm/g	%	cpm/g	%
1.	50	2.22	54.1	30	18.5	10.2	67.2	37
2.	21.1	11.7	92.9	50.6	6.9	3.8	64.2	33.9
3.	64.8	26	78.5	31.4	3.3	1.3	104.4	41.3
4.	74.5	26.6	82.1	29.3	21.1	7.5	103	36.6
5.	67	26.4	53.6	21.4	29.1	10.9	104.2	41.8
6.	23.2	12.8	33.5	18.6	49.4	27.4	74	41.2

TABLE II. Distribution of Colchicine in Tumor Bearing Mice. One column represents the number of counts over background per g of tissue. The other column represents the same values expressed as % of the total counts taken in a mouse.

	Intestine		Kidney		Liver		Tumor		Spleen	
	cpm/mg	%	cpm/mg	%	cpm/mg	%	cpm/mg	%	cpm/mg	%
1.	174	40.4	116	27	76.8	17.9	71.1	17.7	0	
2.	72	55.4	35.6	27.4	13.5	10.3	12.1	6.9	0	
3.	118.2	48.2	74.9	31.2	29.2	12.1	26.2	17.5	0	
4.	79.3	33	58.6	24.4	51.6	21.5	50.1	21.1	0	
5.	57.4	27.7	43.2	21.4	48.9	24.4	53.7	26.5	0	
6.	104.2	40	97.3	37	29.1	11	31.7	12	0	
7.	74.6	31	36.1	18.9	90.4	33.5	40	16.6	0	
8.	98	49	36.1	23.7	20	10	29.7	18.3	0	

normal mice. Liver and tumor contained approximately the same amount of colchicine, which amounted to 10 to 26 percent of the total counts/min/g found in the mice. The colchicine is taken up by sarcoma in an amount sufficient to produce its specific action on that tissue.

It was found that in the spleen of normal animals the accumulation of colchicine was from 33 to 42% of the injected dose. However, in the spleen of tumor-bearing animals no colchicine could be detected. Concentration of colchicine in the spleen of normal mice presupposes intervention of the reticuloendothelial system. To test this hypothesis the reticuloendothelial system in normal mice was blocked by an injection of India ink. The radioactive colchicine was injected 2 or 3 or 4 hours later, and the spleen was removed 4 hours after and analyzed for colchicine. The amount of colchicine found was approximately the same as found in a mouse not injected with India ink.

Summary. 1. Labelled colchicine was detected only in some organs of normal and tumor-bearing mice. 2. The uptake of colchicine in sarcoma 180 is as high as the uptake of liver. 3. Spleen is one of the organs having the highest concentration of colchicine in normal mice. 4. It was found that there was no colchicine in the spleen of tumor-bearing mice.

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