The Distribution of Doses of Radioactive Phosphorus in Leukemic Patients*†

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The therapeutic value of radioactive phosphorus (P^{32}), first utilized by Lawrence for the treatment of leukemia, is being rapidly established (3, 5, 7, 8, 12). In general it may be said that this radioactive isotope affords a reasonably efficacious means of radiation of leukemic cells without producing radiation sickness.

While numerous tracer studies (6) have been carried out with the aid of radioactive phosphorus, the possibility must be considered that there may be some alterations in the absorption and retention of the isotope, when given in larger amounts, due to the biological effect of the β radiation such as, for instance, a change in cell permeability. The alteration of cell permeability by radiation has been clearly established. Undoubtedly there are considerable variations in the amount of radioactive material absorbed in the different tissues because of variations in the amount of blood contained, in the degree of leukemic infiltration, in the extent of necrosis of leukemic cells, and in the extent of necrosis of normal but highly radiosensitive cells, entirely apart from the selective absorption of the tissue elements themselves.

Radioactive phosphorus[1] has been administered as Na_2HPO_4, usually in doses of 1 to 3 mc. given in approximately 300 cc. of 5 per cent glucose and 0.85 per cent saline intravenously. The amounts of total phosphorus ($P^{31} + P^{32}$) administered with each dose vary according to the specific activity of the lot used; the range is from 2 to 20 mgm. of phosphorus. The half life of P^{32} is 14.3 days. It disintegrates to sulfur, giving off β radiation that is capable of penetrating 2 to 4 mm. of tissue. As a rough comparison with more familiar types of radiation, 1 μc. retained in 1 gm. of tissue for 24 hours delivers 43 roentgen equivalents to that tissue (10).

Owing to the relatively low penetrating power of these β radiations, the effect of radiation on any given tissue depends largely upon the amount of radioactive phosphorus absorbed and retained by that tissue. Therefore it is important to know the amounts present in various tissues and fluids of the body at various times after administration of this radioactive material.

This study is based on autopsies in 10 leukemic patients performed 1 to 35 days after the last dose of radioactive phosphorus was administered. In most of the autopsies reported here the radioactive phosphorus had a high specific activity—from 0.5 to 0.14 mc. per mgm. of phosphorus. Measurements of radioactivity were carried out with the aid of a Lauritsen type electroscope or a modified Geiger counter, accurate within 10 per cent to as low as 0.001 μc. All measurements were calculated back to the date of the last injection given.

The material was obtained at autopsy by removing aliquot samples of tissue ranging from one entire organ in the case of the adrenals to 20 or 30 gm. in the case of the liver. Most of these samples were dried and ashed at 400° C. before measurement. Wet ashing was carried out on some samples and no significant variation from the dry ash method was encountered.

For convenience in discussing the data the cases have been divided into three groups: acute leukemia in adults (3 cases), acute leukemia in children (5 cases), and chronic leukemia in adults (2 cases). The deposition of P^{32} was virtually the same in all three.

Table I presents the essential data. The results are expressed in microcuries per gram of tissue and per cubic centimeter of body fluids. Our results are of much the same order of magnitude as those of Lawrence (8) and Erf (1).

Evidence that the amount of tumor may be a dominant factor in the distribution of the radioactive material is seen in our case 40 (Table I), where involved liver and lymph node gave comparable results, 0.112 and 0.112 respectively; in case 44 (Table I), where tumor tissue involving spleen, liver, and

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[1] The radioactive phosphorus was obtained through the cooperation of Professor Robley D. Evans, Massachusetts Institute of Technology; Dr. E. O. Lawrence, Crocker Radiation Laboratory; and the Harvard Cyclotron Committee.

TABLE I: RADIOACTIVITY OF TISSUES AND FLUIDS

Case No.	Days *	μc./kg.	Total dose, μc.	Microcuries per gram: Heart	Lung	Spleen	Pancreas	Liver	Intestine	Adrenal	Kidney	Uterus	Lymph nodes	Aorta	Thyroid	Muscle	Fat	Cartilage	Bone	Cortical bone	Bone marrow	Brain	Microcuries per cubic centimeter: Blood	Urine	Pericardial fluid	Spinal fluid	Bile	Pleural fluid
ACUTE LEUKEMIA IN ADULTS																												
18	5	23.6	2,965	.0465		.107		.0846			.0317			.0408					.0427										
	1	28.2																										
40	13	20.4	4,710	.079	.074	.053	.077	.112		.059	.0845	.0322	.112	.0338	.0156	.0384	.0079			.0648‡	.96‡	.0125	.0278				.052	
	6	27.7																										
51	27	46.8	6,275	.051	.076	.076	.059	.097		.065	.073		.039	.021		.041	.014	.012	.027			.009	.010			.0014	.079	
	19	49.1																										
	6	14.2																										
ACUTE LEUKEMIA IN CHILDREN																												
49	123	30.0	3,880	.03	.033	.058	.04	.058		.03	.04		.04			.02		.009	.027†		.027	.011‖	.008**			.0012	.005	.004
	107	40.0																					.008††					
	82	20.0																										
	69	50.2																										
	24	14.0																										
	22	17.5																										
	11	0.5																										
	2	2.0																										
44	38	65.0	3,680		.077	.122		.125	.0785		.1		.148			.057		.029		.086	.069		.037	.06	.0211		.0735	
	26	27.3																										
	8	27.3																										
	2	47.7																										
	24	38.1						.076			.0266		.0575	.0136		.0396		.0049	.0975†	.0324	.053	.0058	.0096			.0015	.0605	
	6	68.1																										
36	50	28.4	3,387	.0445	.053	.0705																						
	37	26.6																										
22	31	39.0	1,630			.028		.025			.031									.043	.076							
	21	6.0																										
	13	36.5																										
23	158	55.3	1,690	.0162	.027	.0535	.0229	.0365		.0056	.0382		.0493	.0124		.0256			.214‡			.00046	.0224			.00455	.0525	
	151	14.7																	.373†									
	140	50.0																	.142§									
	103	45.6																										
	35	39.8																										
CHRONIC LEUKEMIA IN ADULTS																												
8	1	35.9	2,680	.061	.0705	.082	.0366	.135			.0956		.0500	.0358	.0347				.0332†		.0987		(.142‡‡)					
																					.0332†							
9	9	33.6	2,250	.0313	.0635	.0586	.0313	.059		.0492	.0395		.0389	.0179		.022		.00856		.0356‡	.0678‡		.0116				.042	

* Number of days each administration precedes death. † Ribs. ‡ Vertebra. § Femur. ‖ Meninges. ** Right heart. †† Left heart. ‡‡ Leukocytes.

lymph nodes gave closely parallel readings, 0.122, 0.125, and 0.148 respectively; and in case 9 (Table I), spleen 0.059, liver 0.059, tumor from soft parts (intestinal nodule) 0.058, and tumor from bone marrow 0.068 mc. per gm. The time interval after administration of the last dose of radioactive material in these cases varied from 2 to 9 days.

As the time interval increased, the bone contained a relatively larger amount of radioactive phosphorus. Thus the ribs of case 23, 14 days after the administration of 901 mc., held over 10 times as much P^{32} as case 49 one day after the administration of 1,060 mc. In the short time most of our patients lived following the last dose even this was influenced by the degree of leukemic infiltration, as shown by case 23, where the amount of P^{32} retained in the tissues was highest in the rib involved in the leukemic process, less in a vertebra, which also was less involved, and least in the femur, which showed the smallest amount of leukemic infiltration. These readings were obtained 14 days after the last dose was given.

As evidence that the hepatic cells themselves as well as the leukemic cells present in the liver take up P^{32} actively, the amount present in the bile may be cited. Thus in cases 40 and 51 the amount per cubic centimeter of bile equals that per gram of spleen. However, in case 49 the bile contained relatively little. In this case there was other evidence of hepatic dysfunction.

Some tissues took up but little P^{32}, chiefly owing to the small amount of nuclear material and protoplasm in relation to total mass. Thus in case 40, fat showed one-fourteenth the concentration found in the liver and in case 51, one-eighth.

In these short term observations cortical bone did, however, show a fairly high concentration of P^{32}, as would be expected from its chemical composition.

Striking is the slight amount of radioactive material found in the brain in spite of the importance of phosphorus in its substance. This was uniformly lower than in any of the other tissues. This result may be expected in view of the low rate of metabolism of the brain. The amount in the spinal fluid was much lower than in the blood, owing to the absence of any number of cells in the spinal fluid.

Within a few hours after injection but little P^{32} remains in the blood plasma, and that circulating is practically all in the blood cells (2). Soon after injection of P^{32} the liver, spleen, lungs, kidneys, and bone contain the largest amounts of the material. These earlier results have been checked by a later series, as yet unpublished, which gives comparable results. Thus P^{32} administered to normal rodents (4, 9, 13) as well as to leukemic human subjects shows the same tendency to be deposited, at least at first, in some of those organs where leukemic infiltration is apt to occur. This localization, combined with the differential absorption by the rapidly growing leukemic cells (11), gives P^{32} a differential deposition clearly favorable to the selective irradiation of leukemic cells.

SUMMARY

The deposition of radioactive phosphorus, as determined in the tissues of 10 patients dead of leukemia, was greatest in those tissues that usually show a heavy infiltration of leukemic cells. The liver, spleen, kidneys, and bone marrow contained relatively large amounts. Slowly metabolizing tissues, as brain, fat, and cartilage, contained but little. The concentration in the bile was sometimes fairly high.

The distribution of P^{32} in human tissue is generally comparable with that obtained in rodents experimentally.

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