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Ineffectiveness of *in vivo* Dialysis in Prolonging Life in X-Irradiated Dogs.* (20437)

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One possible explanation for the lethal effects of ionizing radiation is the accumulation of toxic substances in the body. Experimental evidence both for and against this suggestion has been adequately reviewed by Lawrence, Valentine, and Dowdy(1). Assuming that such a toxic substance did accumulate as a consequence of irradiation and that this substance was readily dialyzable, it might be possible to reduce its concentration to non-toxic levels, by means of an "artificial kidney," and thus decrease or prevent the damaging effects of radiation. The present experimental study was designed to explore this possibility.

Methods and materials. All animals employed in this study were adult mongrel dogs of both sexes ranging in weight from 12.7 to 24.0 kg, and they were fed a regular stock diet of 20% horse meat and 80% commercial dog chow. The "artificial kidney" and the technics employed for the *in vivo* dialysis of the blood have been previously described(2,3). Blood from a femoral artery was pumped at a rate of approximately 200 ml per minute through the dialyzer and back into the animal via the femoral vein. Flowing through the dialyzer in the opposite direction, and separated from the blood by 20,000 sq cm of cellophane membrane, was the dialyzing solution which contained glucose at a concentration of 0.1% and the principal electrolytes at the same concentration as found in the extracellular fluid(2). The dialysis treatment usually lasted for a period of 3-4 hours, during which time approximately 100 liters of dialyzing solution was pumped through the dialyzer. The efficiency of this procedure is shown in Fig. 1 by the rate at which previously injected Na^{24} can be removed from the dog. Sham-

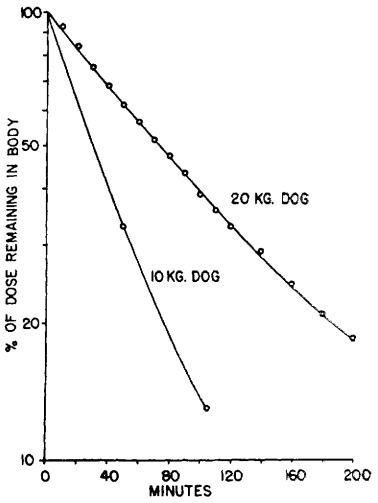

FIG. 1. Effectiveness of "artificial kidney" in removing Na^{24} from dogs.

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dialysis consisted of exactly the same procedure except that no dialyzing solution was put through the dialyzer. The radiation dosages reported in this paper are defined as the number of roentgen units delivered at the top surface of the animal and were measured "in air" at the center of the beam with a Victoreen "r" meter. The x-ray beam in every instance was filtered through 0.5 mm of Cu and 1.0 mm of Al, which corresponds to a HVL of 1.35 mm of Cu. Variations in the radiation procedure were as follows:

Dosage administered		X-Ray machine	
Total r	r/min.	KV	ma.
500	6	220	15
550	6	220	9

Experimental and results. Ten dogs (Group I) were given 550 r whole body x-irradiation but no dialysis treatment. Ten comparable dogs (Group II), which also received 550 r x-irradiation, were treated on the assumption that a toxic factor might be produced during or immediately following x-irradiation. Dialysis was, therefore, begun about 5 minutes before, and was continued for 1½ hours after the irradiation period. The results summarized in Table I show an 80% mortality in both groups at 32 days after irradiation, and the apparent decrease in the average survival time of the treated animals from 17 to 12 days is of questionable significance.

Experimental groups III and IV deal with the effect of the dialysis and sham dialysis procedures respectively when administered 0.5 to 3.0 days after x-irradiation. A total of 20 animals (Group III) were subjected to the dialysis procedure, and of these 10 received 550 r and 10 received 500 r whole-body x-irradiation. To determine whether the irradiated animal might become less able to withstand the dialysis procedure, 13 comparable dogs (Group IV) were sham-dialyzed one-half to 3 days after receiving a whole body x-irradiation dose of either 500 r (8 dogs) or 550 r (5 dogs). Thus, any difference in the survival of the animals in the 2 groups could be attributed to an effect of actually dialyzing the blood. Although every dog in both groups died before the 32nd post-irradiation day, the

TABLE I. Effect of *In Vivo* Dialysis on Survival of X-Irradiated Dogs.

Group	No. of dogs	Time treatment begun	Accumulative deaths during post-irradiation period (in days) 1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	32	% dead at 32 days	Avg survival times (days)
I Control	10	None	0	0	0	0	1	1	2	4	5	5	5	5	7	7	8	8	80	17 ± 6.6*
II Dialyzed	10	Immed. before irrad.	0	1	1	2	4	4	4	4	5	6	7	8	8	8	8	8	80	12 ± 6.6
III Dialyzed	20	.5-3 days after irrad.	2	3	5	7	8	11	14	19	19	20	20	20	20	20	20	20	100	8.9 ± 4.8 (8.8 ± 2.9) †
IV Sham-dialyzed	13	.5-3 days after irrad.	0	0	0	0	4	6	6	10	11	12	12	12	12	12	12	13	100	13 ± 6.4 (10.4 ± 2.8) †

* Stand. dev.
† Includes only animals given 500 r.

dialyzed animals died somewhat earlier than the sham-dialyzed dogs (Table I, groups III and IV). None of the latter survived less than 7 days after irradiation, whereas 7 of the 20 dialyzed dogs died within the same period. The average survival time for the dialyzed animals was only 8.9 ± 4.8 days as compared to 13 ± 6.4 days for the sham-dialyzed dogs. However, if we compare only the results obtained with dogs which were given 500 r, the difference in the survival times for the dialyzed and the sham-dialyzed animals was not so marked (8.8 ± 2.9 vs. 10.4 ± 2.8 days, respectively). Greater significance is attached to these experimental results since the animals were selected with more care to insure that the physical condition of the animals used in the 2 groups was similar at the start of the experiment, and, furthermore, the dialysis and sham-dialysis procedures were both carried out on the same day with the same artificial kidney set-up.

The body weight, rectal temperature, erythrocyte and platelet count, clotting time, and hematocrit readings were comparable in all irradiated dogs regardless of treatment. A comparison of the total leukocyte counts in the irradiated dogs of the different groups showed no important differences after the third day, *i.e.*, a severe leukopenia developed in all dogs regardless of the dialysis treatment. However, a temporary but striking leukocytosis appeared within 24 hours after the animals were dialyzed, and it lasted for about 24-48 hours. As to the mechanism of this leukocytosis, it is not known whether it represents an increased production of cells or simply a release of preformed cells; at any rate, the capacity of the irradiated dogs to respond in this manner disappeared 36 or more hours after irradiation.

Discussion. The success of the *in vivo* dialysis procedure in improving the survival of x-irradiated dogs depends upon the validity of the following assumptions: 1) the lethal effect of radiation is mediated through the action of a toxic substance, 2) the dialysis procedure employed would be effective in reducing the concentration of such a factor(s) to a non-toxic level, and 3) the time for dialysis would be correctly selected and of sufficient duration to be of real therapeutic value. It is evident that the experiments described in this paper provide no evidence as to the presence or absence of toxic factors which are either predominantly intracellular in their distribution or are not readily dialyzable for any reason (*e.g.*, protein binding). However, some conclusions might be drawn as to the role of possible toxic factors that are readily dialyzable and which are located primarily in the extracellular fluids. If the results obtained with Na^{24} typify the effectiveness of the dialysis procedure in removing such factors from the body, it seems doubtful that their presence at the time of irradiation, or immediately after irradiation, was responsible for the subsequent death of the irradiated animals. Furthermore, if there was a gradual accumulation of such substances until toxic levels were reached, a temporary reversal of this process by the dialysis treatment at 1-3 days after irradiation might have been expected to decrease the mortality rate. This was not observed. The effect of more prolonged treatments administered later in the post-irradiation period was not determined.

Summary and conclusions. Dogs given 500-550 r whole body x-irradiation were subjected to an *in vivo* dialysis of their blood during the early post-irradiation period. No improvement in the survival of these animals was noted. When applied 0.5-3.0 days after irradiation, the dialysis procedure caused a slight decrease in the average survival time, as compared to sham-dialyzed controls. The results tend to minimize the importance of readily dialyzable "toxins" in the lethal action of x-irradiation.

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