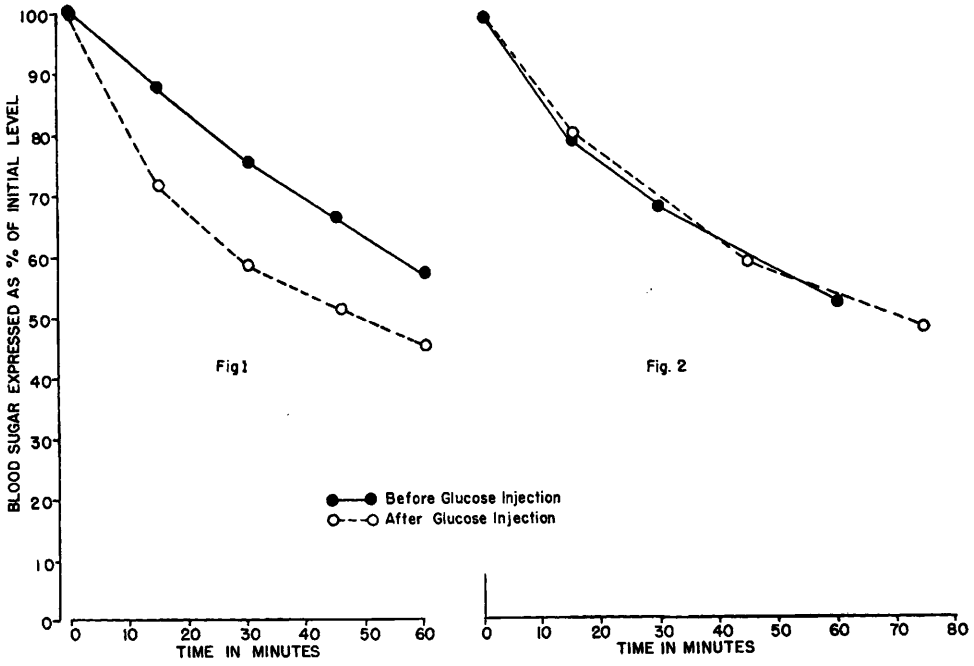

FIG. 1. Averages of blood sugar levels in 4 hepatectomized dogs before and after intravenous administration of glucose.

FIG. 2. Averages of blood sugar levels in 6 eviscerated dogs, before and after intravenous administration of glucose (experiments of Soskin and Mirsky) (1).

appearance of blood-sugar before and after the administration of glucose. The findings suggest that in hepatectomized animals the intravenous injection of glucose stimulates the secretion of insulin which accelerates the rate of removal of sugar from the blood by tissues other than liver.

Received August 23, 1951. P.S.E.B.M., 1951, v78.

Effect of Early Small Exchange Transfusion on the X-Irradiated Dog.* (19029)

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During the course of a series of experiments on the hemolytic action of ionizing radiation, utilizing the technic of differential agglutination of erythrocytes in the dog, 4 dogs were exposed to 450 r whole body X-irradiation. Within ½-hour after completion of irradiation the dogs were rapidly bled of 250 cc and transfused with an equal volume of fresh, normal, compatible and serologically identifiable dog blood(1). The results of the studies on the fate of the transfused erythrocytes will be reported elsewhere. Although the dosage of X-irradiation given these dogs

* This study was aided partially by a contract between The University of Rochester and The Office of Naval Research, Department of the Navy (NR 131-174) and partially under a contract with The United States Atomic Energy Commission at The University of Rochester Atomic Energy Project.

1. Swisher, S. N., Izzo, M. J., and Young, L. E., unpublished observations.

is approximately an LD 70 in this laboratory, none of the 4 animals in the above group died or became ill with the radiation syndrome. The following experiment was designed to determine if this procedure of small exchange transfusion immediately after irradiation had any therapeutic effect on the irradiated dog.

Methods. Twenty healthy dogs of the mixed beagle and mongrel breed weighing approximately 20 lb used in this laboratory for irradiation studies were paired for sex and weight into two groups. The animals had been immunized for distemper and had been given a vermifuge approximately 6 weeks before use. They were kept in separate cages and fed a diet of Purina dog chow with free access to water both before and during the experiment. Control determinations of hematocrit, white blood cell count, and platelet count were made on blood obtained by jugular puncture on each of 3 days of the week prior to irradiation. Standard laboratory methods were used in all of these determinations. The animals to be transfused were typed for presence of the canine "A" factor in their erythrocytes as described by Christian, *et al.*(2) and Young, *et al.*(3). Compatible donors were then chosen from a donor colony of healthy large animals, giving A+ dogs either A+ or A– blood, but only A– blood to A– recipients. Cross matches of donor's cells and recipient's serum, and recipient's cells and donor's serum were carried out in small tubes utilizing fresh plasma, and cells suspended in fresh plasma incubated together for 15 minutes at room temperature followed by centrifugation, as an additional precaution against hemolytic transfusion reactions. The pairs of animals were then exposed to 550 r delivered from a 1000 KVP General Electric Industrial X-ray unit operated at 3 ma using a lead plano-convex filter, ½-inch thick in the center. Radiation was delivered at a rate of 6.4 r/minute as measured by a Victoreen chamber prior to exposure of each pair of animals. Target to skin distance was 38 inches. Animals were exposed in a standing position while confined to the uniform field area in a large mesh wire cage. Within 30 minutes of completion of irradiation, 250 cc of blood were removed during a 5- to 10-minute period from the animal chosen for transfusion, by jugular puncture. Immediately after bleeding, the animal was given 250 cc of whole donor blood by rapid drip into a leg vein during a 10- to 15-minute period. Donor blood was dawn in 250 cc units from 1 to 4 hours before use into 40 cc of cold acid citrate dextrose blood preservative (ACD) solution in standard Baxter vacuum bottles and stored at 4°C until used. A mild shock-like picture after bleeding was seen in 2 of the 10 animals before transfusion was instituted. This was rapidly controlled by transfusion. In 2 of the animals, mild immediate reactions to transfusion occurred. These were characterized by restlessness, hyperpnea, some instability of gait, and vomiting or retching. These findings disappeared within 15 minutes. Post-transfusion serum samples were free of hemolysis, and hemoglobinuria was not seen. In our opinion, these reactions were not hemolytic in nature but were a manifestation of inability of the animal to readjust his cardiovascular system to the rapid changes in blood volume. From other experiments carried out in a similar manner on dogs of this size while transfusing serologically identifiable cells(1), it has been shown that approximately 15 to 20% of the cells in the immediate post-transfusion blood specimens are donor cells. Thus it can be assumed that approximately that fraction of the recipient's blood volume was replaced with donor blood in the present experiment. Controls were untreated. Following irradiation, peripheral blood was obtained from both control and transfused animals either several hours after irradiation or on the day following irradiation and then at 3- or 4-day intervals for the same determinations that were obtained during the pre-irradiation period. Animals in both groups were given only standard kennel care and subsequent transfusions were not administered. Clinical observations were recorded daily on all animals. Animals

2. Christian, R. M., Ervin, D. M., and Young, L. E., *J. Immunol.*, 1951, v66, 37.

3. Young, L. E., O'Brien, W. A., Miller, G., Swisher, S. N., Ervin, D. M., Christian, R. M., and Yuile, C. L., *Trans. N. Y. Acad. Sci.*, 1951, Ser. II, v13, 209.

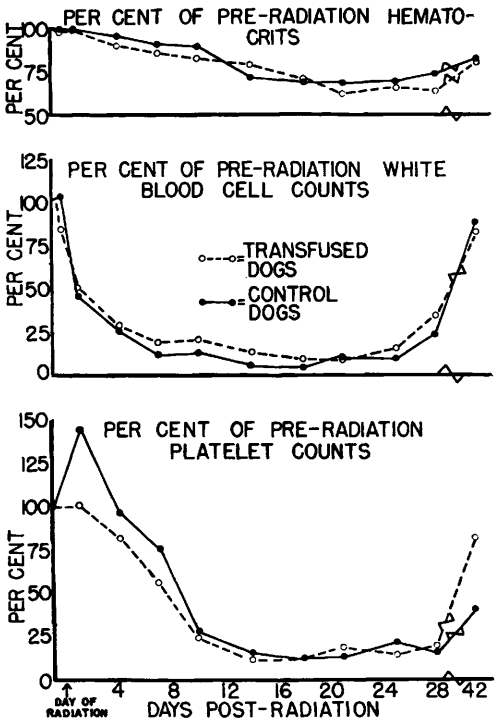

FIG. 1. Graph of average change in hematocrits, white blood cell counts, and platelet counts in control and transfused groups of animals. Three pre-irradiation determinations on each animal were averaged for 100% value for that animal.

that died were autopsied immediately.

Results. Fig. 1 is a graph of the changes in average white cell count, platelet count and hematocrit in the two groups. The 3 pre-irradiation values for each of these determinations were averaged for each animal and were considered as the 100% value for that animal. Subsequent changes were calculated as per cent of this initial value. Fig. 1 shows the average of these percentages for the two groups. It will be seen that there is no significant difference in white cell count or hematocrit between the transfused and control groups. Platelet counts were made on only four pairs of animals on the first post-irradiation day. The difference in platelet counts observed has been tested statistically and a non-significant "t" obtained. Similarly, the difference in platelet counts observed 6 weeks post-irradiation is not significant because of the small number of survivors. Clinical observations revealed no difference between the groups. Survivors in both groups remained clinically well or became only mildly ill except for one surviving transfused animal who developed bilateral retrobulbar hemorrhage and necrosis of the orbits. Although this animal survived, he was sacrificed 45 days post-irradiation because of this lesion. Autopsy revealed no lesion which might be expected to cause death. Animals in both groups who died became clinically ill 3 to 4 days before death.

Fig. 2 shows the cumulative mortality experience, indicating the total number of animals in each group dead on each post-irradiation day. Total mortality in the control group was 70%, and was 40% in the transfused group at the end of 45 days. Calculation of χ^2 indicates that there is a 20% chance that a difference as great as this could be observed if in fact there were no differences in the two groups. This is a rather low level of reliability and the final significance of the observed difference could only be settled by an experiment involving larger numbers of animals. Survivors were randomly distributed among the pairs of animals irradiated together. The marked delay of 7 days in onset of morbidity and mortality in the transfused group would seem to be of much more significance. Six of the seven control dogs who died had succumbed 3 days before the first of the transfused animals died. Previous experience in this laboratory with similar doses of irradiation in similar animals shows that in all groups of control animals the mortality was largely complete by the 21st day, post-irradiation, and in no instance was a delay in onset of mortality to the 21st day post-irradiation encountered. This difference in onset of mortality in the two groups leads

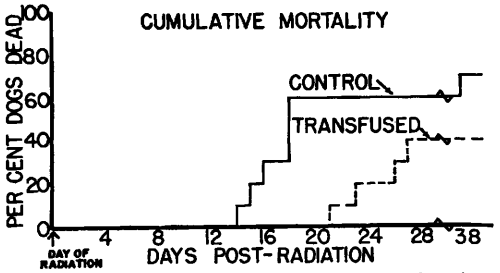

FIG. 2. Chart showing total number of animals dead on each post-irradiation day.

us to feel that the observed difference in ultimate mortality may well be significant.

Autopsy disclosed no significant difference in cause of death between the dead animals of the two groups. All deaths were principally due to widespread hemorrhage into all organs. Similarly, clinical examination of the survivors of the 2 groups at the end of the experiment revealed no differences of note.

Discussion. It has recently been shown that mortality from ionizing radiation exposure can be influenced in a number of ways in various species. Jacobson has shown that shielding of the spleen during irradiation(4) or surgical transfer of normal splenic tissue immediately post-irradiation(5) significantly increases the tolerance of mice to X-irradiation. Allen has observed a similar effect in dogs when the head is shielded during irradiation (6). Salisbury and colleagues demonstrated a reduction in mortality in a small number of irradiated dogs effected by a single massive cross transfusion carried out in the immediate post-irradiation period(7). There was no apparent delay of onset of mortality in their group of cross transfused animals. Brecher and Cronkite have observed a decrease in mortality in rats in whom parabiosis was established after irradiation(8). These observations and the data reported here would seem to be in accord with the hypothesis that early transfer of some cellular or humoral factor from a normal to an irradiated animal by a variety of means or protecting tissue which may contain such a factor during radiation exposure can beneficially influence the subsequent course of the animal's response to radiation injury. Studies thus far reported give little indication of the nature of such a factor or of its mode of action. It may be hypothesized that this factor acts (1) to hasten the onset of repair processes; (2) to inhibit or remove some toxic product produced by radiation; (3) to minimize the ultimate cell damage initiated by irradiation; or (4) to transplant blood forming cells directly from donor to recipient(8). The data of Jacobson showing a rapid return of marrow activity in spleen-protected mice indicate that the effect may be to hasten onset of repair processes. The data reported here suggest that the hypothetical factor concerned may be present in whole blood. The present experiment does not separate the possible beneficial effect of bleeding and subsequent transfusion, or of the effect of ACD solution received by the transfused animals. The lability of such an hypothetical factor during storage of the blood is likewise not considered. Thus, interpretation of the mechanisms by which the observed results occurred must be made with these limitations in mind.

The findings in the present experiment suggest the feasibility of attempting immediately after exposure relatively large exchange transfusion of fresh blood in humans exposed to doses of whole body irradiation in the range of high lethality such as might occur with an accidental laboratory exposure. It is probable, however, that with doses appreciably above the LD 100 level ultimate mortality would not be affected.

Summary. 1. Immediate removal of 250 cc of blood and replacement with an equal volume of normal compatible whole blood in 20 lb dogs given 550 r whole body irradiation (expected LD 80) results in a marked delay in onset of radiation syndrome and mortality. There is a suggestive decrease in ultimate mortality as well. 2. No differences in average leucocyte count, platelet count, or hematocrit were observed in the two groups, nor were there differences in clinical or postmortem anatomical findings. 3. The implications of these results are discussed.

The authors are indebted to Drs. Joe Howland and L. E. Young for advice and facilities provided for these studies, and to Dr. Arthur M. Dutton for statistical aid.

Received August 23, 1951. P.S.E.B.M., 1951, v78.

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6. Allen, J. G., personal communication.

7. Salisbury, P. F., Rekers, P. E., Miller, J. H., and Marti, N. F., *Science*, 1951, v133, 6.

8. Brecher, G., and Cronkite, E. P., PROC. SOC. EXP. BIOL. AND MED., 1951, v77, 292.