effect of this temperature on the rate of their excretion in the urine.

Many years ago Brunton (*1*) found that warming reduced the incidence of death in animals poisoned with chloral hydrate, a depressant which is largely detoxified by conjugation in the liver, and recommended that victims of acute chloral poisoning be kept warm. The data presented here also provide a rational basis for the application of warmth in cases of acute barbiturate poisoning involving short-acting barbiturates which are inactivated by the tissues.

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Hyperheparinemia: Cause of the Hemorrhagic Syndrome Associated With Total Body Exposure to Ionizing Radiation[1]

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Hemorrhage is one of the most striking features of the syndrome which follows acute whole-body exposure to ionizing radiations in the midlethal range. This irradiation-induced bleeding phenomenon occurs in man as well as in many experimental animals. In our experience the dog proved more suitable for study than the rabbit, guinea pig, rat, mouse, or goat, and the picture displayed by the dog later proved to be very similar to that seen in man following the bombing of Hiroshima and Nagasaki (*3*).

The hemorrhagic disease of irradiation is accompanied by a thrombocytopenia. Both bleeding and clotting times are prolonged, and clot retraction is impaired. At death, both animal and man show extensive hemorrhages which may occur in all organs of the body but which are first seen in the organs of motions, such as the intestines, heart, lungs, skeletal musculature, and urinary bladder.

This disease has been thought to result from the associated thrombocytopenia (*2*). However, in a study carried out on dogs during the past three years we have concluded that the thrombocytopenia plays only a secondary role in producing hemorrhage (*1*). Of greatest significance in this disease is the presence in the blood of an increased amount of free heparin. These conclusions are based on the following observations:

(1) The clotting time in both man and dog may be greatly prolonged or the blood rendered entirely incoagulable after acute exposure to ionizing radiations such as X-rays delivered over the entire body. If the clotting time is sufficiently prolonged, the blood of an irradiated dog will delay the clotting time of normal blood, thus demonstrating the presence of an active anticoagulant not normally present in blood.

(2) Evidence that this anticoagulant is heparin is based on the fact that specific antiheparin substances, such as toluidine blue and other members of the thionine series, and protamine

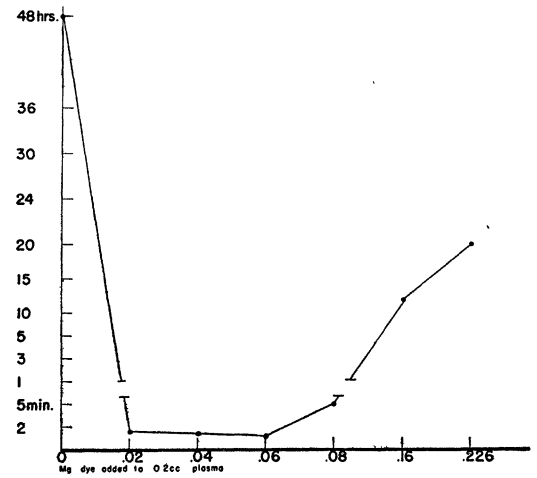

Fig. 1. The antiheparin and the anticoagulant effect of toluidine blue on the clotting time of plasma in an irradiated dog (Dog 108).

will return the clotting time to normal both *in vivo* and *in vitro*. These substances will prevent or stop hemorrhage even though the platelet count may be less than 50,000. The effect of toluidine blue on the *in vitro* clotting time of an irradiated dog is shown in Fig. 1. It will be noted that the dye is both coagulant and anticoagulant, and that its effective antiheparin range gives way to its anticoagulant property as the concentration of the dye increases. The clotting time of the blood of

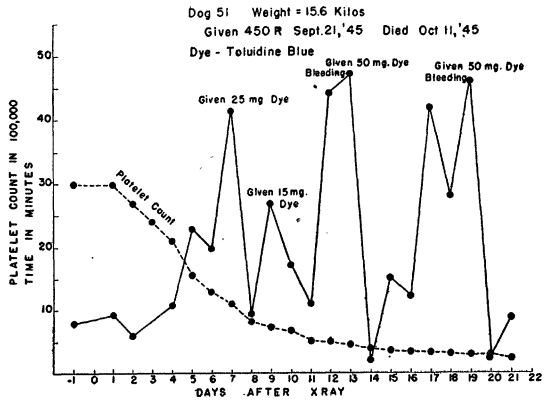

Fig. 2. The effect of repeated injections of toluidine blue on the whole-blood clotting time of an irradiated dog.

this animal was greater than 48 hours, but after the intravenous injection of 24 mg. of toluidine blue the clotting time returned to normal within 20 minutes after dye administration.

(3) An anticoagulant which was indistinguishable from heparin, was isolated from the blood of irradiated dogs, and on the basis of the number of units of potency per milligram of

[1] This paper is based on work performed under Contract No. W-7401-eng-37 with the Manhattan Project for the University of Chicago. It will appear in Volume 22B of the *Manhattan Project Technical Series* as a part of the contribution from the University of Chicago Project.

weight the isolated material proved to be as active as our standard (Abbott) sodium acid salt of heparin. Our material was inactivated by both toluidine blue and protamine and was heat stable.

(4) Thrombocytopenia *per se* did not appear to play an important role in the development of hemorrhage because, while hemorrhage and thrombocytopenia always occurred in the same animal, the time of onset of each varied considerably and did not always coincide (Fig. 2). Moreover, when the dye was given, bleeding was controlled, but the platelet count, if reduced, was not raised.

(5) The administration of vitamin K, ascorbic acid, calcium salts, and fresh whole blood transfusions did not prevent the onset of hemorrhage or stop bleeding once it occurred.

These observations have led us to study the effect of toluidine blue on the course of the hemorrhagic manifestations associated with such diseases as ideopathic thrombocytopenia and acute leukemias. The preliminary results indicate that significant temporary alleviations of the hemorrhagic manifestations may be thus induced.

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Treatment of Plutonium Poisoning by Metal Displacement[1]

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The great increase in availability and use of radioactive elements since the advent of the chain-reacting pile has intensified the need for effective treatment of radioelement poisoning. Radium poisoning has been a recognized danger since 1925. At present we are concerned primarily with plutonium (Pu^{239}), which emits 140,000,000 alpha particles/mg./minute and has a half-life of about 24,000 years. Many of the long-lived radioelements, including plutonium, which find their way into the body are deposited mainly in the skeleton. An appreciable amount of plutonium is also found in the liver and spleen. The dangers of plutonium far exceed those of radium poisoning because of the relatively large quantities of plutonium available and because of the number of individuals exposed.

From a consideration of ion exchange principles it may be predicted that the excretion of plutonium from "plutonized" animals would be increased by treatment with large amounts of the soluble salts of certain metals. The metals considered were those possessing a high valence and a metabolism similar to plutonium, so that their concentration relative to plutonium in a given site could be preponderant. An ideal metal would combine maximum displacing properties with minimum toxicity. The treatment, called metal displacement therapy, utilizes an innocuous metal, zirconium, to hasten the removal of plutonium from the body. Although this is still in very early and preliminary experimental stages, the results obtained so far are encouraging.

TABLE 1

EFFECT OF ZIRCONIUM AND SODIUM CITRATE TREATMENT ON THE URINARY EXCRETION OF PLUTONIUM IN RATS*

(Data expressed as average per cent of injected dose of plutonium excreted each day)

Days elapsed following Pu injection	Pu control	Treatment			
		Zirconium (100 mg. on 2nd hr. and 3rd day after Pu injection)	Zirconium (50 mg. on 2nd and 24th hr. after Pu injection)	Sodium citrate (4 ml. of 10% sol. on 2nd hr. and 3rd day after Pu injection)	Sodium citrate (2 ml. of 10% solution on 2nd and 24th hr. after Pu injection)
0–1	0.75	8.2	5.1	3.2	3.1
1–2	.051	.12	.66	.07	.68
2–3	.027	.032	.060	.037	.041
3–4	.041	.60	.078	.19	.041
4–5	.045	.022	.060	.016	.023
5–7	.022	.07	.058	.011	.018
7–10	.021	.064	.083	.020	.017
10–12	.024	.060	.059	.021	.010
12–14	.016	.064	.053	.026	.022
Total Pu excreted in urine for 14-day period.....	1.1	9.6	6.5	3.7	4.0

* The rats (200-gram females) received 1.1 mg. of Pu/kg.

From a series of preliminary experiments dealing with the excretion of plutonium by rats after intravenous injections of aqueous solutions of lanthanum, cerium, and zirconium salts, it was concluded that, of those tested, zirconium was the most promising metal on which to concentrate effort.

The injection solution used contained from 20 to 25 mg. of zirconium dissolved in 10 per cent sodium citrate.

Young adult (200 grams) albino female rats and a young mongrel dog were used. The time at which zirconium treatment was begun, following the intravenous injections of plutonium, varied from two hours to five months, in the case of the dog. The rats received intraperitoneal and the dog intravenous injections of the zirconium citrate solution.

The effect of zirconium treatment on the urinary excretion of plutonium is shown in Table 1. The administration of zirconium in those rats treated shortly after the injection of plutonium was followed by as much as a 15-fold increase in the amount of plutonium excreted in the urine over a 24-hour period. When the output of plutonium had dropped, a reinjection of zirconium was followed by a second rise in the elimination rate. Actually, the reinjected rats excreted nearly as much plutonium on the fourth day following plutonium administration as the control rats eliminated during the first 24 hours. Finally, the sustained therapeutic action was shown by the observation that the excretion

[1] This report is based on work begun early in 1945 and performed under Manhattan District Contract No. W-31-109-eng-38 at the Metallurgical Laboratory of the University of Chicago and the Argonne National Laboratory, Chicago.

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