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.

References

1. ALLEN, J. GARROTT, and SANDERSON, MARGARET. The cause and correction of abnormal bleeding after 450 r of total body irradiation in dogs. (Metallurgical Laboratory Report, Univ. Chicago, October 12, 1945.)
2. SHOUSE, S. S., WARREN, S. L., and WHIPPLE, G. H. *J. exp. Med.*, 1931, **53**, 421.
3. WARREN, S., and DRAGER, R. H. The pattern of injury produced by the atomic bombs at Hiroshima and Nagasaki. *U. S. nav. Bull.*, **1946, 46, 1349.**

Treatment of Plutonium Poisoning by Metal Displacement[1]

JACK SCHUBERT[2]

Argonne National Laboratory, Chicago, Illinois

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.

[2] Present address: Department of Physiological Chemistry, Medical School, University of Minnesota, Minneapolis 14.

The writer wishes to express his appreciation for the cooperation and technical assistance of members of the Medical and Biology Divisions, Argonne National Laboratory.

level remained about three times greater than that of the controls for several days after the cessation of zirconium therapy.

A small part of the heightened excretion was due to the sodium citrate solvent. However, the amount of plutonium eliminated by the animals treated with sodium citrate alone fell abruptly to pretreatment levels after the sodium citrate injections were discontinued.

None of the treatments significantly altered the quantity of plutonium excreted in the feces.

Tissue analyses revealed that the zirconium-treated rats had only about half as much plutonium in the skeleton and in the liver as the control animals, but the concentration of plutonium in the muscle and kidneys of these animals was greater than that found in the controls. The bone and liver concentrations of plutonium in the rats treated with sodium citrate did not seem to differ appreciably from those in the controls.

Five months after the dog received an intravenous injection of 0.058 mg. of plutonium/kg. treatment with very small doses of zirconium citrate (4–16 mg./kg. of body weight), injected intravenously, was begun. A very definite increase in urinary excretion of plutonium occurred within the first few days following each dose of zirconium. The extent of the rise in the elimination rate in the urine was directly proportional to the amount of zirconium injected. The increased rate of excretion was continued for at least three weeks after the cessation of zirconium treatment. Even with these dosage levels, which were far below the maximal dose by a factor of at least 10, the elimination rate of urinary plutonium was increased more than 150 per cent over the pretreatment level.

The average excretion of plutonium in the feces of the dog, following the zirconium treatment, appeared to increase but slightly.

In rats treated with zirconium about five weeks after the injection of plutonium, a roughly 10-fold increase in the urinary excretion of plutonium was observed. These animals were sacrificed shortly after treatment and were found to have only half as much plutonium in the liver as the controls. The bone content of plutonium was unchanged.

It appears, therefore, that zirconium first acts to displace plutonium from the liver. Later it migrates to the bone and slowly but continuously displaces the deposited plutonium to an extent which depends on the concentration of zirconium relative to the plutonium.

Radioautograph studies (*1*) have shown that plutonium, cerium, yttrium, and zirconium are laid down in the uncalcified organic matrix of the bone and in the endosteum and periosteum. Strontium, on the other hand, is deposited almost exclusively in bone salt, and it might be expected that zirconium treatment would have little effect in cases of radiostrontium poisoning. This was shown experimentally where it was found that zirconium treatment had only a negligible effect on the excretion rate of radiostrontium and on its concentration in the liver and bone of rats. Experiments to test the effect of zirconium treatment in cases of radioyttrium poisoning are in progress.

A study of the toxicity of zirconium and other metals revealed that zirconium was by far the safest for therapeutic use. When zirconium was given in single massive doses of 1.5, 1.75, and 2.0 grams/kg. of body weight, the percentages surviving were 100, 50, and 0, respectively. No harmful chronic effects have as yet been found.

Within 24 hours after the injection of zirconium, 80–90 per cent of the metal was excreted in the urine. Its fecal excretion is, however, very low.

The action of sodium citrate in promoting the excretion of plutonium can be attributed to its ability to increase the diffusibility of plutonium (*2*) and thus facilitate its clearance through the kidney.

Further investigations of metal displacement therapy in cases of chronic poisoning by plutonium and other long-lived radioelements are in progress.

References

1. Copp, D. H., Axelrod, D. J., and Hamilton, J. G. The deposition of radioactive metals in bone as a potential health hazard. (To be published.)
2. Schubert, J. Unpublished work completed in June 1946.

Effect of Temperature on the Growth and Sterility of Maize

Donald F. Jones
Connecticut Agricultural Experiment Station, New Haven, Connecticut

Varieties of corn grown in the Northeast and in the Middlewest at the same latitude are noticeably taller in the East. Several environmental conditions, principally light intensity and temperature, are involved in this growth difference. Plants of many species, including maize, grown under tobacco shade cloth are significantly taller and broader in leaf than plants from the same lot of seed grown in full sunlight. Under the cloth shade the temperature is the same as outside, but the humidity is higher and the light intensity is lower. The same effect is noticed in the field, where short-stalked varieties of corn are grown in single rows between taller varieties. Where there is a wide alley between ranges, the plants at the ends of the rows are shorter than those in the center of the rows, the plants graduating in height. Here humidity and temperature are the same, but light intensity varies.

Some corn seedlings started in the greenhouse and set outdoors were shorter at maturity than plants from the same seed started outdoors. This indicated that temperature in the early stages of growth had an effect. To test this, seeds of a uniform, vigorous, first-generation hybrid ($WF_9 \times$ P8) were germinated in an incubator at about 30° C. until the shoots and roots were from $\frac{1}{4}$ to $\frac{1}{2}$ inch long. Three different lots of these sprouted seedlings were held at 40, 50, and 60° C. for one hour, after which they were planted in pots and left in the greenhouse until it was certain the plants would grow. They were then set in the field alongside plants from the same lot of seed sown in the open ground at the same time the treated seedlings were started in the incubator. Some of the heat-treated seedlings died, but enough were started in each lot and later thinned to give an even stand of plants in the field.

All three lots of heat-treated seedlings were shorter in height, less vigorous in growth throughout the season, and later in flowering than the untreated plants. All lots grew to full maturity and were measured after growth had ceased. The results in inches of height were: control, 101; 40° C., 87; 50° C., 89; and 60° C., 93, *i.e.* an average of 90 inches in