adapted for use with a series of different plants, but is only illustrated here with the bean. The results with this technique are not directly interpretable to conditions other than those actually tested. However, this procedure allows a rapid laboratory screening technique to test for both stimulatory or inhibitory effects of chemicals.

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Excretion of Gallium by the Rat and by Man[1]

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Dudley (*1–3*), working with rats, dogs, rabbits, and goats, found the principal route of excretion of gallium to be the kidney. Confirmation of this has been noted in previous reports (*4, 5*). The purpose of this report is to detail the comparative excretion of gallium in the rat following intravenous administration of (1) $GaCl_3$, a rapidly ionizing salt, prepared by dissolving irradiated $Ga(NO_3)_3$ in HCl and then neutralizing with NaOH to a pH of 2.2; (2) the slowly ionizing complex, gallium citrate, which was prepared in an ion exchange column and stabilized at pH 7.0 with sodium citrate (*6*). A second comparison is made between the excretion by the rat and by man of tracer and larger intravenous doses of gallium citrate prepared according to a method described by Dudley (*7*).

Procedures. The rats, young adult Wistar-strain males weighing 275 ± 25 g, were injected via the tail vein. One of the human subjects had multiple myeloma, one had osteogenic sarcoma, and one had Hodgkin's disease, but all three were considered essentially normal from the standpoint of excretory mechanisms. Other details, such as care of the animals, collection techniques, tissue sampling, and counting procedures, have been described previously (*5*). In performing the $GaCl_3$ studies, 5 rats were sacrificed at 6, 12, 48, and 96 hr and 4 at 24 hr following injection. For the citrate study, 4 rats were sacrificed at 12, 24, 48, 72, and 96 hr after injection. Depending upon the time of sacrifice, the rats received between 200 and 300 μc of Ga^{72} in 1.5–2 mg of stable gallium. The patients received the mc doses noted in Table 1 of the gallium citrate preparations, which had a specific activity of about 1 mc/5 mg of gallium. In all instances, the urine and feces were collected with negligible or no cross-contamination (*8*).

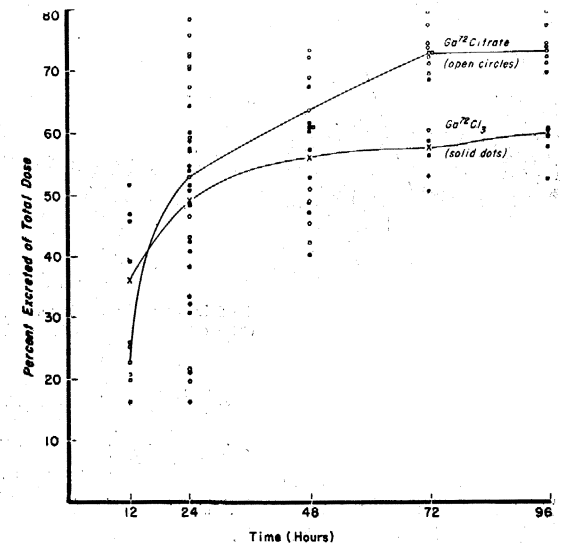

FIG. 1. Urinary excretion by the rat of intravenously injected Ga^{72}, expressed in terms of percentage of total dose excreted as a function of time in hours.

The data have been corrected for radioactive decay to the time of injection.

Results. Fig. 1 indicates the variation from animal to animal of the fraction of the administered dose recovered from the urine. However, the arithmetical

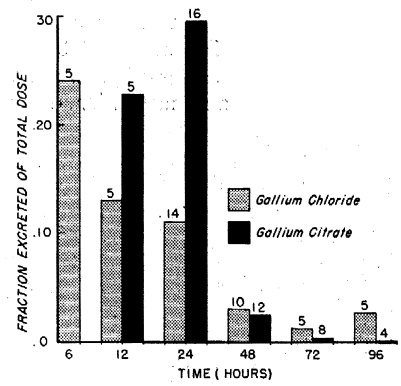

FIG. 2. Daily urinary excretion rate of gallium; average of the fractions of total recovered dose during the periods indicated. The numbers above each bar indicate the number of samples.

average and the median values check each other closely, so that the lines, as drawn, picture a reasonable central tendency. Thus, about 73% of the gallium administered as the citrate was excreted by the fourth day compared with 59% for the chloride salt. In Fig. 2 the excretion is drawn on a nonaccumulative basis to show that during the first 6 hr gallium as the chloride is excreted more rapidly, and also to demonstrate the fact that its subsequent excretion rate is lower than that of the citrate. Essentially all the gal-

[1] Gallium used in the study was furnished by Comdr. H. C. Dudley (MSC), USN, of NMRI, Bethesda, Md.

[2] Comdr. (MC) USN. The opinions or conclusions contained in this report are those of the authors. They are not to be construed as necessarily reflecting the views or endorsement of the Navy Department.

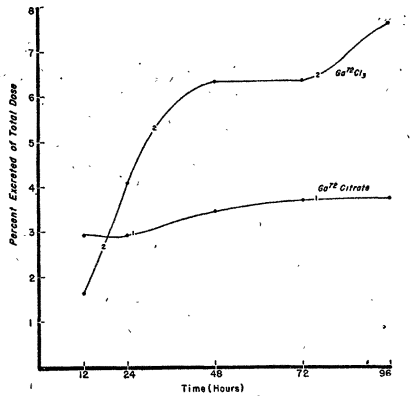

FIG. 3. Fecal excretion by the rat of intravenously injected Ga^{72}, expressed in terms of percentage of total dose excreted as a function of time in hours.

lium as gallium citrate was excreted during the first 3 days.

In contrast, the fecal excretion (Fig. 3) of the $GaCl_3$ was about twice that of the citrate salt. At 96 hr the urine/feces ratio was about 8 for the chloride salt and 19.3 for the citrate complex.

The curves of decrease of gallium radioactivity in the rats (Fig. 4) were constructed by subtracting the cumulative urinary and fecal excretion from the total recovered activity and normalizing these to 100%. By chance both curves intersect the 50% excretion level at about 20 hr, which time is termed the biological half-life. The physical half-life of Ga^{72} is 14.3 hr and is plotted to the same scale for comparison.

In man the chief route of excretion is also the urinary tract. In Table 1, which shows the 96-hr cumulative excretion in the urine of 3 patients, it appears that the excretion of gallium was affected by the size of dose of the stable metal. The shape of the curves of excretion is roughly exponential, as in Figs. 1 and 4. The fecal excretion in these human cases was less than 1% of the total dose administered. A biological half-life similar to that in Fig. 4 can be given only provisionally as about 100 hr. This uncertainty arises because the number of subjects is limited, and variations probably exist in the rate of excretion relative to the dose of the metal. This point is under intensive investigation.

The biological and physical half-life values, because they are used in isotope radiation tissue dose formulas, are of particular importance for all isotope studies. Generally they are combined into a factor termed the "effective half-life," defined as the ratio of the product of the physical and biological half-lives to their sum (*9*). This "effective half-life" relates to the over-all decline and has no bearing on changes in concentration in specific tissues. The latter can vary independently of the total effective half-life and is the significant factor in computing therapeutic tissue doses. In the rat studies, the effective half-life at that dose level was 8.33 hr (Fig. 4). This value for the larger doses in man was calculated to be about 12.5 hr; the slower rate of excretion of the tracer doses

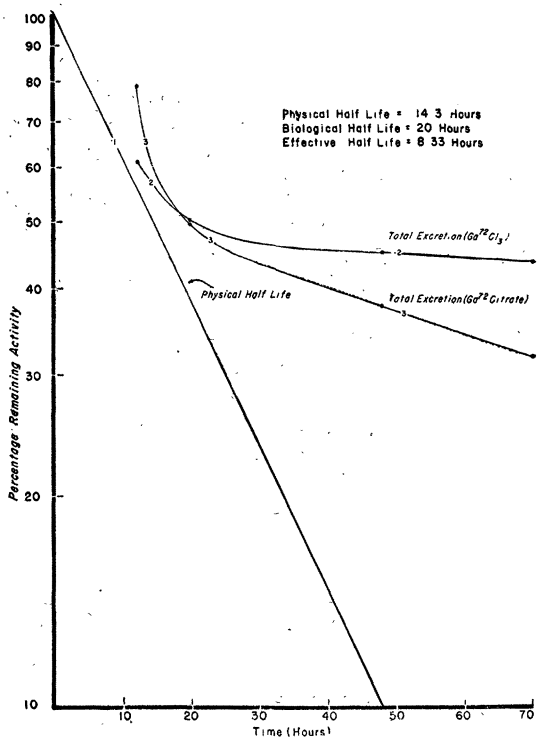

FIG. 4. Curves showing amount of intravenously injected $Ga^{72}Cl_3$ and gallium 72 citrate remaining in the rat compared with the curve of the physical half-life of this Ga^{72}.

would lengthen the effective half-life insignificantly because of the short physical half-life.

The difference between the excretion patterns in rat urine of the two forms of gallium is probably real. The chloride has a pH of 2.2, ionizes readily, precipitates proteins, including plasma protein, and forms colloidal aggregates at pH 7.4. The citrate

TABLE 1

URINARY EXCRETION OF GALLIUM BY THE HUMAN

Patient No.	Diagnosis	Isotope dose		Metal dose		Percentage of initial dose excreted in 96 hr
		mc	mc/kg	mg	mg/kg	
		1.00	—	5	—	26
1	Osteogenic sarcoma	22.5	0.86	90	2.81	47
		52.0	1.62	185	5.75	40
		46.3	1.45	180	5.60	46
		49.0	1.53	166	5.19	40
		1.00	—	5	—	6
2	Multiple myeloma	8.00	0.14	105	1.90	18
		49.90	0.92	166	3.07	22
		1.00	—	5	—	37
3	Hodgkin's disease	20.00	0.34	107	1.78	37
		51.50	0.83	200	3.33	48

complex, on the other hand, is stable at pH 7.0 and does not precipitate proteins, but probably exists as a fine colloid or aggregate. Under these circumstances it would be unusual if these two forms were handled by the body in the same manner and/or at the same rate.

A distinct species difference is present relative to this metal. The rat, for example, tolerates some 10 times more gallium citrate than the dog, according to studies in progress. Man probably fits somewhere between these two species.

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Inhibitory Action of Adrenalin on Growth of Rat Sarcoma[1]

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In an earlier study (*1*) it was found that tumor tissue, when minced with adrenal gland prior to implantation into susceptible rats, failed to grow because of some substance present in the gland. The inhibition of the growth of tumor grafts took place regardless of whether the adrenals were obtained from normal, tumor-bearing, or tumor-immune rats. The present study is concerned with the action of one of the hormones of the adrenal gland—namely, adrenalin—on the growth of tumor tissue.

The adrenalin used was in the form of a sterile solution containing 1 mg of epinephrine in 1 ml of sterile physiological salt solution to which 0.1% sodium bisulfite and 0.5% chloretone[3] were added as preservatives.

Rats of the Lewis and King A inbred albino strains, and native tumors that were 100% transplantable in rats of their own strain, were used.

Four types of experimental procedure were utilized: Implantation of minced viable tumor tissue to which solutions of adrenalin had been added; intratumoral injections of solutions of adrenalin; injections of adrenalin around small tumors growing in susceptible rats; and injections of adrenalin into the subcutaneous tissue 2–3 hr, 3 days, 7 days, and 10 days prior to implantations of tumor grafts into the same site.

Control experiments were carried out using additions of physiological salt solution, of 0.1% sodium bisulfite, and of 0.5% chloretone in place of adrenalin with the minced tumor tissue implanted into susceptible rats.

The results showed that additions of adrenalin (½ ml to 2–3 ml saline) to equal parts of minced tumor tissue inhibited its growth in 13 of the 25 rats that survived an injection of 2 ml of the suspensions. In some instances the grafts grew to some extent, but this initial growth soon regressed. The addition of physiological salt solution or of 0.1% sodium bisulfite in saline to minced tumor tissue did not inhibit the growth of the tumor tissue, but the addition of solutions containing 0.5% chloretone prevented the growth of the tumor cells.

All the rats in which tumors were injected with adrenalin diluted with salt solution died within 24 hr. When aqueous solutions were injected intratumorally the majority of the treated rats survived. Thirty-four rats in which tumor grafts had grown for 6 days were given 8–12 intratumoral injections, at 3-day intervals, of ½–1 ml of adrenalin diluted in 1 ml sterile distilled water. They exhibited the type of damage that takes place when growing tumors are treated with extracts prepared from tumor by means of 95% alcohol, and that results in oncolysis and development of tumor-immunity in 100% of the treated rats (*2, 3*). The treatment with adrenalin, however, resulted in absorption of tumors in only 20 of the treated rats; of the other 14 rats, 9 died from adrenalin; in 5 rats, the tumors continued to grow.

Injections of adrenalin around growing tumors resulted in death of the majority of the treated rats. Atrophy and absorption of tumors, however, did take place in 7 of the 22 treated rats that survived.

The results brought about by injections of adrenalin into the subcutaneous tissue of a given region prior to implantation of tumor grafts depended upon the interval of time allowed to elapse between the injection of adrenalin and the implantation of the grafts. The grafts failed to grow in 21 of the 34 rats that were engrafted 2–3 hours after the injections of adrenalin; on the other hand, they grew in 5 of the 13 rats following a lapse of 3 days; in 6 of the 9 rats after a lapse of 7 days, and in every one of the 11 rats engrafted 10 days after the subcutaneous injections of adrenalin.

All the rats in which tumors were absorbed, as well as those in which tumor grafts failed to grow, were implanted 3 weeks later with grafts of viable native tumor tissue (challenge grafts) at a distance (left side) from the area previously treated (right side) to test their susceptibility to tumor growth. The challenge grafts failed to grow in 11 of the 13 rats in which suspensions of minced tumor and adrenalin had not grown; in 13 of the 20 rats in which treated tumors had been absorbed following intratumoral injections with adrenalin; in the 7 rats in which tumors atrophied following damage to their circulation by injec-

[1] Aided by a grant in aid from the National Institutes of Health, USPHS, Bethesda, Md.

[2] With the technical assistance of Peter Demchur.

[3] Commercial product of Parke, Davis & Company.