

# Biochemistry of Metallocenes. I. Distribution of $^{59}\text{Fe}$ or $^{103}\text{Ru}$ -Labeled Metallocene Carboxylic Acid in Mice

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*Metallocene carboxylic acids labeled with  $^{59}\text{Fe}$  or  $^{103}\text{Ru}$  were administered to mice and the organ distributions and amounts of label excreted were determined. Both metallocenes were excreted approximately 90 times faster than the respective inorganic chlorides  $^{59}\text{FeCl}_3$  or  $^{103}\text{RuCl}_3$ . The metallocenes showed an extremely high kidney-to-muscle ratio (up to 1,000).  $^{99\text{m}}\text{Tc}$ -labeled renal agents, tested for comparison, showed lower ratios. Retention of radioactivity in blood and the presence of free iron in urine indicate that the ferrocene derivative is degraded in vivo, but the ruthenocene analog is not.*

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For the development of radiopharmaceuticals it is desirable to select independently the physical characteristics of the radionuclide (e.g., energy and half-life) and the chemical nature of the compound. Since most useful gamma-emitting nuclides are metals, it is difficult to synthesize radiopharmaceuticals with controllable chemical properties. This problem can be overcome by the use of chelating agents, although only to a very limited extent. A more favorable combination of both factors can be achieved with radioactive metallocenes, since in this class of compounds a metal atom is strongly linked to two cyclopentadienyl rings (1). The aromatic character of metallocenes (2) makes possible a considerable number of derivatives.

Another advantage is the simple one-step procedure for labeling metallocene derivatives with radioactive metals (1). The emitters used in this study,  $^{59}\text{Fe}$  and  $^{103}\text{Ru}$ , were selected because they are gamma-emitters with main energies of 1.1 MeV and 0.498 MeV, respectively. Although these gamma energies are not ideal for clinical applications,  $^{103}\text{Ru}$  at least does offer possibilities for preliminary clinical trials. Moreover, the beta emission of  $^{103}\text{Ru}$  (0.21 MeV) is suitable for whole-body autoradiography.

Metallocene carboxylic acids labeled with  $^{59}\text{Fe}$  or  $^{103}\text{Ru}$  were administered to mice to determine the in vivo stability of the compounds, their excretion pattern, and the organ distribution. For comparison, inorganic  $^{59}\text{FeCl}_3$  and  $^{103}\text{RuCl}_3$  were also administered.

## MATERIALS AND METHODS

**Radioactive materials.** We obtained  $^{99\text{m}}\text{Tc}$ -Sn-glucoheptonate, \*  $^{99\text{m}}\text{Tc}$ -Fe-ascorbate, †  $^{99\text{m}}\text{Tc}$ -ascorbate-DTPA, †  $^{67}\text{Ga}$  citrate, ‡  $^{59}\text{FeCl}_3$  (1.5 Ci/mmmole), ¶ and  $^{103}\text{RuCl}_3$  (0.5 Ci/mmmole) ¶ commercially.

**Synthesis of radioactive metallocenes.** The desired carboxylic acids were prepared by heating the radioactive metal chloride ( $^{103}\text{RuCl}_3$  or  $^{59}\text{FeCl}_3$ ) with either ferrocene carboxylic acid or the methylester. The former necessitated additional hydrolysis to the carboxylic acid. Approximately 20 mg of the methylester of the ferrocene carboxylic acid was heated at 180°C for 2 hr in an evacuated vial containing 2 mg (50–500  $\mu\text{Ci}$ ) of  $^{103}\text{RuCl}_3$ . The contents of the vial were dissolved in acetone, and inorganic halides were separated from the radioactive and inactive metallocene by absorption on a column (12 × 1 cm) of basic aluminum oxide. Further separation of the products was achieved by thin-layer chromatography on Kieselgel-Fertigplatten using 8:1 benzene-ethanol. Both metallocene carboxylic acids have a  $R_f$  of 0.33 in this system. Final yields varied between 10% and 50% of the added radioactivity.

The specific activities obtained were 0.5  $\mu\text{Ci}/\mu\text{mole}$  for  $^{59}\text{Fe}$ -ferrocene carboxylic acid and 22

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$\mu\text{Ci}/\mu\text{mole}$  for  $^{103}\text{Ru}$ -ruthenocene carboxylic acid. Since the final products of ruthenocene and ferrocene carboxylic acids could not be separated, a mixture of both compounds with a 1:12 molar ratio (Ru:Fc) was obtained.

The radioactivity on the chromatograms was measured directly by the Dünnschicht scanner§ with an efficiency (3) of 45% for the beta and Auger-electron emissions.

**Animals.** All animals were adult CF-1 mice weighing 23–28 gm. To test the tumor affinity of the injected compounds, each mouse carried a solid Ehrlich carcinoma (diameter, ~10 mm) on the left hind leg. For in vitro experiments, Ehrlich ascites tumors (Stamm Dahlem) were used 8 days after intraperitoneal inoculation.

**Administration of radioactive substances.** All  $^{99\text{m}}\text{Tc}$ -labeled compounds were produced from  $^{99}\text{Mo}$  generators according to the specifications of the supplier. Gallium-67 citrate was dissolved in 0.9% saline solution. For the comparisons,  $^{99\text{m}}\text{Tc}$ -labeled compounds and  $^{67}\text{Ga}$  citrate were administered intraperitoneally.

The radioactive metalocenes were dissolved in 1,2-propylene glycol and 50  $\mu\text{l}$  of the solution was injected intraperitoneally. Comparative experiments have shown that, 6 hr or longer after intravenous or intraperitoneal injection, no differences in the pattern of organ distribution could be detected. The dose of metalocene carboxylic acids administered was 3–12  $\mu\text{mole}/\text{kg}$ . Separate experiments showed that mice can tolerate a dose of up to 50  $\mu\text{mole}/\text{kg}$  of ferrocene carboxylic acid. There is no obvious reason to expect that the ruthenocene derivative would have a different toxicity.

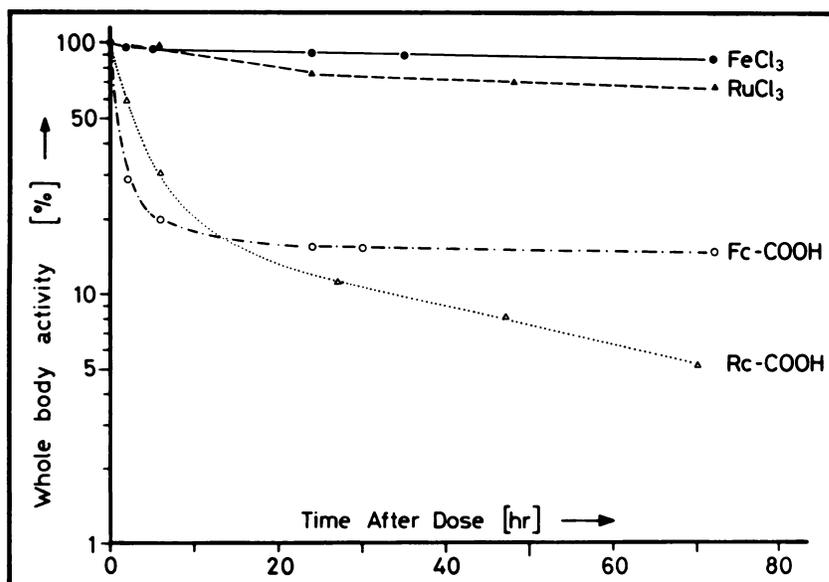
**Organ distribution.** Immediately after injection of a radioactive solution, whole-body radioactivity was measured by placing the mouse in a plastic container which was then inserted into the well of a NaI scintillation counter. Excretion percentages were calculated from the decrease in radioactivity measured for each animal. All animals were killed with chloroform. Muscle samples were taken from the hind leg. Excised organs were blotted dry of blood, weighed, and assayed in an automatic gamma counter with an efficiency of 11% for  $^{59}\text{Fe}$  and 27% for  $^{103}\text{Ru}$ . All measurements were corrected for radioactive decay. For the isolation of Ru ion and of possible metabolites from urine, freshly collected urine samples (50  $\mu\text{l}$ ) were chromatographed on Kieselgel-Fertigplatten using n-butanol–glacial acetic acid–water solution (4:1:1).

## RESULTS

**Clearance of metalocene carboxylic acids.** Administered metalocene carboxylic acid is eliminated faster than trichlorides of either ruthenium or iron (Fig. 1). The biologic half-time in animals was found to be 195 hr for  $^{103}\text{RuCl}_3$  and 2 hr for  $^{103}\text{Ru}$ -ruthenocene carboxylic acid (time interval, 0–10 hr).

After injection of  $^{59}\text{Fe}$ -ferrocene carboxylic acid, radioactivity was excreted only during the first 24 hr, after which no further excretion occurs. In contrast, after injection of the  $^{103}\text{Ru}$ -labeled compound, label was excreted throughout the experimental period (72 hr), mostly in the urine.

Thin-layer chromatography of the urine from animals receiving  $^{103}\text{Ru}$ -ruthenocene carboxylic acid showed that most radioactivity co-chromatographed with ruthenocene carboxylic acid. No inorganic ru-



**FIG. 1.** Excretion of radioactivity in mice after intraperitoneal administration of  $^{59}\text{Fe}$ - or  $^{103}\text{Ru}$ -labeled metalocenes and metal halides. Each group consists of 7 female CF-1 mice. "100%" represents whole-body activity assayed immediately after injection. Doses were 12  $\mu\text{mole}/\text{kg}$  (40  $\mu\text{Ci}/\text{kg}$ ) for metalocene carboxylic acids and 4  $\mu\text{mole}/\text{kg}$  (40  $\mu\text{Ci}/\text{kg}$ ) for metal halides. (Fc) Ferrocene; (Rc) ruthenocene.

TABLE 1. DISTRIBUTION OF  $^{103}\text{Ru}$  IN MICE 24 HR AFTER INTRAPERITONEAL ADMINISTRATION OF LABELED RUTHENOCENE CARBOXYLIC ACID AND  $\text{RuCl}_3$

	Group	Percent dose/gram tissue*							Kidney-to-muscle ratio	
		Muscle	Blood	Heart	Lung	Liver	Kidney	Adrenal		Spleen
$\text{Ru-COOH}$	Male (n = 7)	0.015 $\pm 0.005$	0.042 $\pm 0.02$	0.029 $\pm 0.02$	0.06 $\pm 0.01$	6.92 $\pm 1.6$	16.4 $\pm 2.6$	0.13 $\pm 0.35$	0.13 $\pm 0.07$	1,096
	Female (n = 7)	0.0071 $\pm 0.003$	0.013 $\pm 0.005$	0.018 $\pm 0.01$	0.03 $\pm 0.01$	1.17 $\pm 0.38$	3.2 $\pm 1.1$	0.18 $\pm 0.03$	0.04 $\pm 0.02$	445
$\text{RuCl}_3$	Female (n = 7)	1.58 $\pm 0.2$	6.32 $\pm 0.6$	2.4 $\pm 0.2$	3.8 $\pm 0.3$	6.6 $\pm 0.8$	9.9 $\pm 1.4$	5.7 $\pm 0.6$	5.5 $\pm 1.1$	6.3

Each mouse received 50  $\mu\text{l}$  of a propylene glycol solution of a 1:12 molar mixture of  $^{103}\text{Ru}$ -ruthenocene and  $^{59}\text{Fe}$ -ferrocene derivatives.

Doses: 12  $\mu\text{mole}$  metalocene carboxylic acid/kg (19  $\mu\text{Ci}$   $^{103}\text{Ru}$ /kg);  $\text{RuCl}_3$ : 4  $\mu\text{mole}$ /kg (4  $\mu\text{Ci}$   $^{103}\text{Ru}$ /kg).

\* Each value is mean for 7 mice  $\pm$  s.d.

thenium ion could be detected, whereas ionic iron was detected with  $^{59}\text{Fe}$ -ferrocene carboxylic acid.

**Organ distribution.** The distribution of radioactivity in mice 24 hr after injection of  $^{103}\text{Ru}$ -ruthenocene carboxylic acid and  $^{103}\text{RuCl}_3$  is summarized in Table 1, in which the concentrations are expressed in percent of the injected dose per gram of organ. After administration of  $^{103}\text{RuCl}_3$ , the concentration of radioactivity in the organs tested was rather high and showed no great differences.

With the ruthenocene derivative, however, the radioactive content of all organs tested except liver and kidney was low (Table 1). The highest  $^{103}\text{Ru}$  concentration was found in the kidney, especially in male mice. This result was confirmed by autoradiography (Fig. 2). High uptake in the kidney was also found after injection of  $^{59}\text{Fe}$ -ferrocene carboxylic acid (Table 2). But at 24 or 72 hr after administration, spleen and blood showed an increase in the  $^{59}\text{Fe}$  concentration, which may be due to in vivo degradation of ferrocene-liberating ionic iron.

We compared the renal uptakes of the labeled metalocene carboxylic acids with those of radiopharmaceuticals currently used for renal scanning. Since the literature data (4-7) involved different methods and animal types, a direct comparison of them with our values for metalocene carboxylic acid is not reliable. Accordingly,  $^{99\text{m}}\text{Tc}$ -Sn-heptogluconate and  $^{99\text{m}}\text{Tc}$ -Fe-ascorbate were administered to CF-1 mice under the same conditions as for the labeled metalocenes.

Results from these experiments showed that the percent administered dose per gram of kidney reached the same order of magnitude with  $^{99\text{m}}\text{Tc}$ -Fe-ascorbate as with the metalocene carboxylic acid. The  $^{99\text{m}}\text{Tc}$ -Sn-heptogluconate, however, showed con-

siderably higher kidney concentrations (Table 3). When the results were expressed as kidney-to-muscle concentration ratios, the labeled metalocenes had higher values than either of the  $^{99\text{m}}\text{Tc}$ -labeled renal agents.

**In vivo stability.** Figure 3 shows the  $^{59}\text{Fe}/^{103}\text{Ru}$  radioactivity concentration ratio in different tissues after administration of equimolar amounts of the corresponding metalocene derivatives. The high ratio for the spleen after 24 hr and especially the high ratio for blood (370) after 24 and 70 hr suggest that the ferrocene carboxylic acid is partly degraded to ionic iron. Consistent with this interpretation, the rate of excretion of  $^{59}\text{Fe}$  (beginning 8 hr after injecting  $^{59}\text{Fe}$ -metalocene) shows the same slope as that found after administration of  $^{59}\text{FeCl}_3$  (Fig. 1). This view is further confirmed by the rise in the  $^{59}\text{Fe}$  concentration in the blood after 24 hr, which is then 20-30 times the concentration in muscle (Table 3). These findings (e.g., high spleen and blood concentration) are similar to the organ distribution data

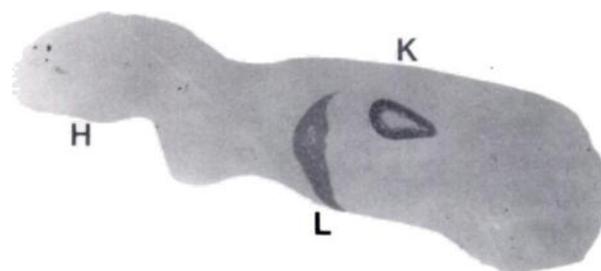


FIG. 2. Autoradiography of whole-body slices of mice after administration of 12  $\mu\text{mole}$ /kg (40  $\mu\text{Ci}$ /kg) of  $^{103}\text{Ru}$ -ruthenocene carboxylic acid. Exposure was 54 days on Kodirex x-ray film. Animals were killed 24 hr after intraperitoneal injection: (H) head; (L) liver; (K) kidney.

**TABLE 2. ORGAN DISTRIBUTION OF <sup>59</sup>Fe IN MICE AFTER INTRAPERITONEAL ADMINISTRATION OF <sup>59</sup>Fe-FERROCENE CARBOXYLIC ACID**

Hours after administration	Percent dose/gram tissue									Kidney-to-muscle ratio
	Muscle	Blood	Heart	Lung	Liver	Kidney	Adrenal	Spleen	Bone	
2	0.076	0.37	0.16	0.33	8.36	12.2	0.62	0.33	0.24	160
24	0.044	0.88	0.25	0.42	11.6	12.2	0.41	2.19	0.42	277
72	0.056	1.83	0.40	0.55	10.5	6.0	0.60	1.07	0.31	107

Dose: 28 μmole of ferrocene carboxylic acid/kg (19 μCi <sup>59</sup>Fe/kg).  
Each value is mean for 7 female mice.

**TABLE 3. ORGAN DISTRIBUTION OF <sup>99m</sup>Tc-LABELED RADIOPHARMACEUTICALS FOR RENAL SCANNING IN MICE**

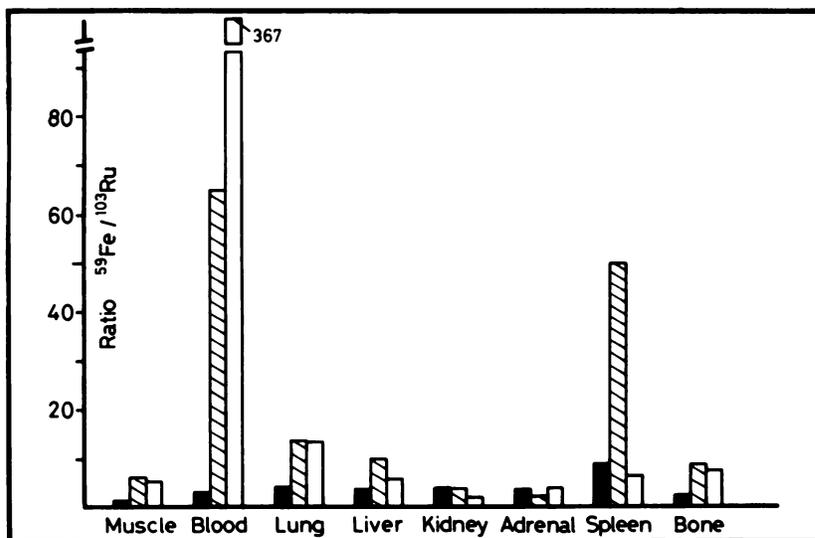
Substance	Hours after injection	Percent dose/gram tissue						Kidney-to-muscle ratio
		Muscle	Blood	Lung	Liver	Kidney	Spleen	
<sup>99m</sup> Tc-Sn-Glucoheptonate (n = 7)	2	0.62	3.7	2.4	6.6	57	1.8	92
	24	0.096	0.35	0.27	0.33	2.5	0.21	27
<sup>99m</sup> Tc-Fe-ascorbate-DTPA (n = 7)	2	0.11	0.33	0.28	0.76	6.9	0.33	72
	24	0.024	0.065	0.074	0.26	1.0	0.14	44
<sup>99m</sup> Tc-Fe-ascorbate (n = 7)	2	0.19	0.38	0.30	1.9	7.8	1.05	41
	24	0.04	0.076	0.43	0.43	1.3	0.54	33

The <sup>99m</sup>Tc-labeled compounds, dissolved in 0.9% NaCl, were injected intraperitoneally into female mice (0.4 mCi/kg). All values are corrected for <sup>99m</sup>Tc decay.

obtained after administration of <sup>59</sup>FeCl<sub>3</sub> (9,10). All these observations support the view that a slow metabolic degradation of a ferrocene derivative to ionic iron occurs, as described for another ferrocene compound by Edwards et al. (8).

For <sup>103</sup>Ru-labeled ruthenocene carboxylic acid no

such indications were found. The organ distribution of <sup>103</sup>Ru after administration of the ruthenocene derivative is completely different from those found after administration of the <sup>103</sup>Ru and <sup>59</sup>Fe as metal chlorides. With <sup>103</sup>RuCl<sub>3</sub> a nearly equal distribution of <sup>103</sup>Ru was found in all organs tested (Table 1),



**FIG. 3.** Ratio of <sup>59</sup>Fe to <sup>103</sup>Ru tissue concentrations after intraperitoneal administration of 12 μmole/kg (40 μCi/kg) of metallocene carboxylic acids to mice. Each column represents values from 7 female CF-1 mice for <sup>59</sup>Fe and 7 mice for <sup>103</sup>Ru. Animals were killed after 2, 24, and 72 hr, and specific activity (cpm/gm) in organs determined. (Solid bars) 2 hr; (hatched bars) 24 hr; (clear bars) 70 hr.

which is in good agreement to the results of Seidel (11) and Furchner et al. (12). The stability of the radioactive ruthenocene moiety in the body therefore appears established.

**Affinity for tumor tissue.** The tumor affinity of the radioactive metallocenes in mice carrying solid Ehrlich carcinomas was also explored. Since the concentrations of  $^{59}\text{Fe}$  or  $^{103}\text{Ru}$  in the tumor tissue were only 2–4 times that in muscle, no further data are presented. The possibility of increasing the tumor uptake of radioactive acids (13,14) was tried in vitro. The pH value of metallocene carboxylic acid was about 6.8 (15). In tumors, the application of large amounts of glucose provides a corresponding lowering of pH due to the high aerobic glycolysis associated with tumor cells (14). This phenomenon should depress the ionization of the metallocene carboxylic acid, thus facilitating the penetration of the uncharged molecule through the cell wall. Consequently, we compared metallocene carboxylic acids with  $^{67}\text{Ga}$  citrate regarding their uptake by Ehrlich ascites tumor cells in vitro at different extracellular pH values. In agreement with earlier calculations (13,14), an increasing penetration of the radioactive acids into the tumor cells was found at the lower pH values (Table 4). Although the differences are statistically significant, they are too small to have practical application.

#### DISCUSSION

The compounds  $^{59}\text{Fe}$ -ferrocene carboxylic acid and  $^{103}\text{Ru}$ -ruthenocene carboxylic acid are examples of the combination of gamma-emitting nuclides with an organic molecule capable of considerable variation. Unlike the radioiodinated pharmaceuticals, in which the radioactive nuclide is often labile (16), the central metal atoms of metallocenes are strongly attached to the molecule, leading to exceptional chemical stability of the aromatic system (2).

In vivo experiments with the metallocenes, however, showed that when  $^{59}\text{Fe}$  was the central atom, partial degradation of the molecule occurred, with the liberation of ionic  $^{59}\text{Fe}$ . With  $^{103}\text{Ru}$  as the central atom, the aromatic ring system was resistant to in vivo degradation. Although some metabolism of the ruthenocene carboxylic acid occurred, and metabolites with the ruthenocene moiety were excreted, no inorganic  $^{103}\text{Ru}$  was detected in the urine of animals treated with  $^{103}\text{Ru}$ -ruthenocene carboxylic acid. The ruthenocene derivatives appear more suitable for use as radiopharmaceuticals because of their greater in vivo stability.

With either  $^{103}\text{Ru}$  or  $^{59}\text{Fe}$ , the distribution in mice of the labeled metallocene carboxylic acid is very different from that of the metal halide. The kidney-

**TABLE 4. INFLUENCE OF pH ON THE PENETRATION OF LABELED ORGANIC ACIDS INTO TUMOR CELLS**

Substance	cpm/mg cells (average $\pm$ s.d.)		
	cpm/mg buffer		
	pH 6.3	pH 7.2	pH 7.6
$^{59}\text{Fe}$ -Fc-COOH (n = 6)	1.46 $\pm$ 0.2	1.24 $\pm$ 0.2	1.14 $\pm$ 0.2
$^{103}\text{Ru}$ -Rc-COOH (n = 10)	1.77 $\pm$ 0.1	1.58 $\pm$ 0.1	1.23 $\pm$ 0.05
$^{67}\text{Ga}$ citrate (n = 6)	2.93 $\pm$ 0.1	1.05 $\pm$ 0.2	1.01 $\pm$ 0.2

Four milliliters of Krebs-Ringer phosphate buffer (with indicated pH), containing 7% of Ehrlich ascites tumor cells, was incubated at 37°C with 0.2  $\mu\text{mole/liter}$  of metallocene carboxylic acid labeled with  $^{59}\text{Fe}$  or  $^{103}\text{Ru}$ . After 20 min cells and medium were separated by centrifugation.

Experiment was duplicated with carrier-free  $^{67}\text{Ga}$  citrate.

to-muscle concentration ratio, especially with the ruthenocene carboxylic acid (Table 1), is high enough to warrant comparison with radiopharmaceuticals commonly used for renal scanning:  $^{131}\text{I}$ -Hippuric acid (16),  $^{197}\text{Hg}$ -neohydrin (4,5), and  $^{99\text{m}}\text{Tc}$ -Fe-ascorbate (6,17).

Mice tolerated 50  $\mu\text{mole/kg}$  doses of the ferrocene carboxylic acid, and our results were obtained with 10–25% of that dose. Further dose reduction may be achieved by using metallocene derivatives of higher specific activities.

The results described here and earlier experiments (18) show the potential of the metallocenes as radiopharmaceuticals. The existence of a simple labeling procedure (1), which converts a ferrocene derivative into the corresponding ruthenocene derivative, suggests that short-lived emitters could be used. For medical applications (studying renal functions) the ruthenocene derivative could thus be labeled with  $^{97}\text{Ru}$  instead of  $^{103}\text{Ru}$ . Ruthenium-97 is a gamma-emitter with its main peak at 215 keV and a half-life of 2.9 days.

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#### FOOTNOTES

\* Squibb Radiopharmacia/von Heyden, Munich, Germany.

† New England Nuclear Corp., Dreieichenhain, Germany.

‡ Karl Thomae GmbH, Biberach, Germany.

§ Isotopen-Dienst West, Spremlingen, Germany.

§ Labor Prof. Berthold, Wildbad, Germany.

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## ANNUAL SPRING SYMPOSIUM

## SIERRA VALLEY NUCLEAR MEDICINE ASSOCIATION

April 30, 1977

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Lake Tahoe, Nevada

The Sierra Valley Nuclear Medicine Association, in conjunction with the Northern California Chapter of the Society of Nuclear Medicine is presenting its Annual Spring Symposium, Saturday, April 30, 1977. This year's program is on "Pediatric Nuclear Medicine."

The speakers will include David L. Gilday, M.D., of Toronto, Hirsch Handmaker, M.D., of San Francisco, Philip Matin, M.D., of Roseville, Calif., and others.

Topics will include technical aspects of imaging, ventilation, skeletal, cardiovascular, renal, and testicular scanning.

A physicians workshop is planned for Friday afternoon, from 3-6PM on "Computers in Nuclear Medicine," with John Verba, M.D., using M.D.S. and A.D.A.C. Varian.

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