BNL-24614

CONF-780948--2

RUTHENIUM-97 LABELED COMPOUNDS --* A NEW CLASS OF RADIOPHARMACEUTICALS

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S. C. Srivastava, P. Som, G. Meinken,
A. Sewatkar and T. H. Ku

Medical Department, Brookhaven National Laboratory,
Upton, N. Y. 11973, U.S.A.

*This work was done under Contract No. EY-76-C-02-0016 with the United States Department of Energy
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ABSTRACT

The excellent physical properties of 2.9 day ruthenium-97 (216 KeV γ, 86%) combined with its chemical reactivity have been exploited for the design of versatile new radiopharmaceuticals. Several compounds were successfully labeled with ruthenium tracer and characterized by in-vitro techniques. Imaging studies were done in rats, rabbits, and dogs. Blood clearance data were obtained in dogs, and organ distribution in mice and rats. Complexes of ruthenium (III and IV) with citrate, DTPA, MDP, EHDP, PYP, ethylenediaminetetramethylene phosphonate (EDTMP), and oxine 7-carboxylic acid acetate, and of ruthenium (II) with 1,10-phenanthroline and 3,4,7,8-tetramethyl 1,10-phenanthroline were prepared and studied. Preparation of a ruthenium-sulfur colloid (nanometer size particles) was achieved and its application in lymphangiography was demonstrated. Ruthenium chloride (pH2) clears from the blood slowly; at 24 hr, the activity remains diffused all over the body including muscle, and excretion is only partial. Ru-DTPA and Ru-citrate both are eliminated rapidly via the kidneys. Ru-EHDP and Ru-EDTMP clear fast from the blood and localize in bone. The bone to blood (B/B) and bone to muscle (B/M) ratios were comparable to or higher than commonly used Tc-99m bone agents for similar time periods. At 24 hrs, ratios (in mice) reached 35 (B/B) and 92 (B/M) for EHDP, and 72 (B/B) and 85 (B/M) for EDTMP. The oxine complex showed excellent promise as a hepatobiliary agent; excretion via the kidneys was negligible. Several complexes of Ru (II) and ammine-Ru (III), especially with nitrogen heterocycles such as pyridines, phenanthrolines, and purine bases are under evaluation in animal tumor models. Uptake of ruthenium phosphate compounds in experimental myocardial infarcts shows promise. BLIP production of Ru-97 has been achieved using the Rh-103 (p, 2p5n) Ru-97 reaction (>100 mCi/day).

These results reinforce our optimism regarding the potential of ruthenium-97 in nuclear medicine, in particular when periodic or delayed scans are either necessary or desirable in order to diagnose or monitor the progress of disease.

INTRODUCTION

Even though short-lived radionuclides, in particular Tc-99m, have found extensive application in nuclear medicine, intermediate half-life nuclides may be extremely valuable for diagnostic studies at longer time intervals. Many nuclear medicine procedures indeed require delayed scanning or frequent imaging over a long time period in order to obtain diagnostically important information. Ruthenium-97 is an ideal nuclide for such applications; its potential in nuclear medicine was first suggested by Subramanian et al in 1970 (1). The 2.9 day half-life and an essentially monoenergetic gamma emission (216 KeV, 86%), in conjunction with the chemical reactiveness of ruthenium provide an extremely useful combination. In many ways, its physical characteristics are superior to Ga-67 and In-111. We have carried out a systematic study on the chemistry of ruthenium and its applications to development of versatile new radiopharmaceuticals. Several agents of interest in nuclear medicine have successfully been labeled with ruthenium tracer and evaluated in animals for many diverse applications. These include ruthenium chloride, and complexes of ruthenium (III and IV) with the following ligands: citrate, diethylenetriaminepentaacetic acid (DTPA), methylene diphosphonate (MDP), ethylidene-hydroxydisodium phosphonate (EHDP), pyrophosphate (PYP), ethylevediamminetetramethylene phosphonate (EDTMP), 8-hydroxyquinoline 7-carboxylic acid (oxine 7-CA), and oxine 7-CA acetate. Ruthenium (II) complexes of 1,10-phenanthroline and 3,4,7,8-tetramethyl 1,10-phenanthroline were also synthesized and studied. A ruthenium-sulfur colloid of nanometer size particles was prepared and its superiority over existing agents for lymphangiography has been demonstrated.

MATERIALS AND METHODS

Most initial investigations were done using ruthenium-103 ($T_{1/2}$ 39.4 d) for the sake of convenience. Ruthenium-103 chloride was obtained as a carrier-free solution in 3.5 N hydrochloric acid from the Oak Ridge National Laboratory. All

chemicals used were high purity reagent grade. Imaging studies were carried out in rats, rabbits and dogs and organ distribution in mice. Blood clearance data were obtained in dogs. For imaging with Ru-103, either a high energy or a tungsten pinhole collimator was used. The complex forming reactions were optimized with regard to different variables - total ligand, time of incubation, pH, temperature, etc. In general, due to slow initial kinetics, a heating period of 10 to 30 minutes at 90° was included in all preparations as a last step. In-vitro analysis of all agents was performed using paper and thin layer chromatography, gel filtration, and cellulose acetate electrophoresis.

Carrier-free Ru-97 was prepared as needed, at the Brookhaven Linac Isotope Producer (BLIP) from proton spallation of high purity (99.9%) rhodium foil (2). The target was bombarded with 200 MeV protons from the Linac. After the bombardment, the target was transferred to a processing hot cell and dissolved by a.c. electrolysis in 6N hydrochloric acid ($0.3A/cm^2$, ~15 hr). After evaporating the solution to near dryness, radiochemical separation of Ru-97 was achieved by distillation of RuO_4 from a sulfuric acid medium, in the presence of an oxidizing agent (permanganate). The distillate was collected in ice-cold 6N HCl saturated with SO_2. The solution was subsequently heated to expel SO_2 and reduce the volume. Recovery of Ru-97 from the target was almost quantitative.

Subcutaneous catecholamine injections were used to produce diffuse myocardial injury in rats (3). These animals were used for the evaluation of ruthenium phosphonate compounds as possible myocardial-infarct agents. In order to evaluate the tumor-specificity of ruthenium agents two tumor models were used: Balb C mice with an implanted KHJJ, EMT-6-sarcoma, and Fisher CDF female rats with squamous cell carcinoma.

Various ruthenium complexes were prepared using either ^{103}Ru, or ^{97}Ru, both available in 3.5 N hydrochloric acid solutions. A suitable quantity of the tracer was neutralized to pH2, an appropriate amount of the ligand was added, and following

an incubation period of 5-20 minutes, the pH was raised to between 5 and 7.5. The resulting solution was heated on a boiling water bath for 10-30 minutes. In some preparations, 1-200 μg ruthenium carrier was added to study the effect of the carrier on biological distribution. The complexes with 1,10-phenanthroline and 3,4,7,8-tetramethyl 1,10-phenanthroline were prepared by reducing the ruthenium solution (carrier-free and with added carrier) with hydroxylammonium chloride in the presence of the ligand, and subsequent heating for 30 minutes after pH adjustment. Oxine 7-carboxylic acid acetate was crystallized from a solution of 8-hydroxyquinoline 7-carboxylic acid in acetic acid. Technetium-99m-antimony sulfide colloid was prepared from a commercial kit. The ruthenium-sulfur colloid was prepared as follows. To a neutralized solution of ruthenium chloride, 40 mg sodium carbonate and 30 mg of gelatin were added. Hydrogen sulfide was bubbled into the mixed solution for 5 minutes. The solution was degassed at 50° by bubbling nitrogen into it, and then the pH was adjusted to 7 with hydrochloric acid. Intermittent degassing was also necessary during the pH adjustment step. The colloidal solutions were sized using polycarbonate membranes (Nucleopore). Chloropentammine ruthenium (III) dichloride labeled with ruthenium tracer was prepared using literature procedures (4,5), modified for incorporation of the activity. The complexes of tripositive Ru $(NH_3)_5$ ion with purine compounds (inosine, adenine, guanosine, etc.) were synthesized employing established methods (6-8).

RESULTS

For most ruthenium complexes, cellulose acetate electrophoresis in a borate /NaOH/KCl buffer of pH8 was found to be the analytical method of choice. Paper and thin layer chromatography were also useful, especially for the Ru-sulfur colloid. Gel filtration generally did not give good separations.

The blood clearance data obtained in dogs, are shown in Fig. 1. Ruthenium

chloride (pH 2, a mixture of 3 and 4 oxidation states) clears from the blood slowly and at 30 minutes after i.v. injection, ∿40% of the activity remains in circulation. At later time periods, most of the activity remains diffused over various parts of the body and the muscle uptake is quite high (∿20% in mice) (Table 1). Upon injection of ruthenium citrate or ruthenium-DTPA, kidneys are visualized immediately. Blood clearance is very rapid, and within 10 minutes after injection, most of the compound leaves the blood via the kidneys and the bladder. Soft tissue uptake was not evident. Ruthenium phosphate compounds, in particular the EHDP and EDTMP derivatives clear fast from the blood and localize in bone. Excretion of >50% of the activity in the urine is observed. Results on Ru-PYP and Ru-MDP were somewhat ambiguous. Significant activity localized in the liver with both these agents and a portion seemed to persist in the circulation in the case of Ru-PYP at later time periods. It appears that either the complex forming reactions for these agents are not yet optimized or that due to poor stability the complexes break down in vivo producing hydrolyzed ruthenium. Efforts to further optimize the preparation of these agents are presently underway.

Organ distribution data in mice for several representative compounds are shown in Table 1. Excretion of Ru chloride and Ru-phenanthroline compounds is slow, even though initially the blood levels fall relatively quickly. Hepatobiliary clearance of the oxine compound and the phenanthroline derivative is noteworthy. Table 2 describes the bone to organ ratios of several Ru-phosphate compounds in mice. It may be seen that except for MDP, soft-tissue uptake of these agents does not occur. Ratios of bone to liver, spleen and kidneys are much higher than the commonly used Tc-99m agents. Some preliminary data on the tumor uptake of ruthenium complexes with citrate and tetramethylphenanthroline are shown in Table 3. Localization of activity in the tumor is seen; however, the background in various organs remains high. Data on several other compounds is presently being obtained. Fig. 2 shows a typical bone image obtained in rabbits with Ru-97-EDTMP. Good images are obtained

TABLE 1

Tissue Distribution of Several Ru Compounds in Mice at Different Time Intervals (Percent injected dose per gram; n=5 for each compound)

ORGAN	Ru-DTPA			Ru-CITRATE			Ru-CHLORIDE, pH2			Ru-1, 10-PHEN.			Ru-OXINE 7-COOH ACETATE		
	0.5 hr	1 hr	2 hr	0.5 hr	4 hr	24 hr	0.5 hr	4 hr	24 hr	0.5 hr	4 hr	24 hr	10 min	30 min	60 min
Blood	1.01± 0.05	0.48± 0.07	0.28± 0.03	0.63± 0.18	0.23± 0.02	0.12± 0.01	9.46± 0.61	6.14± 0.80	3.67± 0.59	0.71± 0.07	0.31± 0.05	0.15± 0.03	7.22± 0.77	4.30± 0.71	2.82± 0.47
Liver	1.09± 0.02	0.96± 0.04	0.86± 0.08	0.57± 0.43	0.31± 0.02	0.30± 0.04	3.54± 0.33	3.20± 0.73	3.21± 0.28	15.00± 1.05	16.20± 1.04	10.30± 0.54	22.00± 3.36	18.40± 2.32	12.80± 2.42
Kidneys	3.28± 0.98	2.42± 2.21	1.44± 0.39	1.9± 1.2	0.61± 0.12	0.50± 0.08	5.85± 2.00	6.73± 1.38	6.34± 1.57	44.20± 1.95	32.60± 5.16	31.2± 2.67	5.36± 0.78	4.42± 0.49	3.42± 0.19
Heart	0.59± 0.06	0.34± 0.06	0.25± 0.05	0.34± 0.15	0.16± 0.02	0.11± 0.03	7.38± 2.35	4.86± 2.05	3.93± 1.16	0.64± 0.07	0.34± 0.04	0.25± 0.03	-	-	-
Lungs	2.25± 0.09	1.34± 0.27	1.13± 0.21	0.59± 0.24	0.29± 0.16	0.28± 0.04	10.6± 1.91	9.23± 2.25	6.81± 0.47	1.86± 0.21	0.91± 0.05	0.49± 0.08	-	-	-
Spleen	0.59± 0.11	0.37± 0.04	0.39± 0.12	0.20± 0.04	0.11± 0.02	0.12± 0.05	1.88± 0.59	1.68± 0.30	2.02± 0.44	0.67± 0.01	0.54± 0.04	0.35± 0.02	1.32± 0.23	0.96± 0.27	0.65± 0.08
Muscle	0.39± 0.02	0.21± 0.03	0.15± 0.03	0.20± 0.09	0.10± 0.02	0.08± 0.02	2.03± 0.63	2.15± 0.40	1.83± 0.08	0.34± 0.06	0.12± 0.02	0.09± 0.02	0.99± 0.18	0.76± 0.12	0.62± 0.12
Bone	0.76± 0.06	0.59± 0.13	0.52± 0.09	0.88± 0.54	0.49± 0.05	0.45± 0.10	3.28± 1.29	2.99± 0.31	2.92± 0.40	0.90± 0.11	0.37± 0.04	0.36± 0.02	0.99± 0.14	0.79± 0.13	0.72± 0.11
Gut & Feces	-	-	-	-	-	-	-	-	-	-	-	-	4.00± 0.42	7.42± 1.70	9.18± 0.83
Total unaccounted*	66.7	74.4	82.4	87.9	93.2	95.8	28.7	34.7	39.9	14.7	29.0	60.5	9.1	10.1	13.2

*Percent of total administered dose excreted or present in other organs (mostly excreted)

TABLE 2

Bone to Blood and Bone to Organ Ratios per gram Tissue in Mice (n=5)

Ratio, Bone to:	Ru-EDTMP			Ru-EHDP			Ru-MDP			^{99m}Tc-MDP			^{99m}Tc-PYP	
	1 hr	5 hr	24 hr	2 hr	5 hr	24 hr	0.5 hr	4 hr	24 hr	0.5 hr	4 hr	24 hr	1 hr	2 hr
Blood	37.9	39.7	72.3	16.4	19.8	34.6	3.7	5.9	9.8	12.2	38.4	88.9	14.0	15.5
Muscle	77.8	80.4	85.0	53.1	60.8	91.9	10.1	14.6	18.0	27.6	91.3	115.7	47.1	52.4
Liver	42.4	37.0	35.6	35.7	31.6	39.0	0.3	1.0	1.3	1.2	3.2	7.0	3.2	3.2
Kidney	8.8	8.9	8.5	2.6	4.9	7.9	1.0	1.7	1.7	2.9	5.2	9.3	4.4	4.2
Lungs	19.5	19.4	20.4	10.4	10.8	13.9	1.8	1.5	2.1	6.1	9.8	16.9	14.0	18.8
Spleen	160.9	105.2	81.7	29.7	47.3	46.0	1.6	0.9	0.5	12.9	4.0	3.1	11.2	11.3

TABLE 3

Initial Data on Tumor Uptake of some Ruthenium-103 Compounds (Balb C Mice, KHJJ-EMT-6-Sarcoma)

Ratio, Tumor to:	Ru (III + IV) Citrate			Ru (II)-tris(3,4,7,8 tetramethylphenanthroline)Cl_2		
	1 hr	6 hr	24 hr	1 hr	6 hr	24 hr
Blood	0.70	1.04	1.74	1.87	3.20	4.10
Liver	0.38	0.36	0.44	0.01	0.01	0.00
Muscle	2.68	3.71	5.40	0.58	0.58	0.48

1 hr to 3 days after injection. The liver activity is due to a colloidal impurity in the Ru-97 sample; this has since been eliminated. Fig. 3 demonstrates the rapid extraction of Ru-oxine 7 CA acetate by the liver and passage of the tracer through the biliary tract into the gut. Urinary excretion of this agent was insignificant in rabbits and dogs. Results on lymph node scanning using a small Tc-99m-antimony sulfide colloid are shown in Fig. 4. A large portion of the activity does not move from the injection site, and the movement to the pelvic area and beyond is quite slow. Images using the Ru-sulfur colloid (Fig. 5) are much better, and the movement of the colloid up the lymphatic system is relatively rapid. Good quality images are obtained up to several days after injection. Synthesis of several purine complexes of Ru-$(NH_3)_5$ ion has been completed. Biological evaluation of these compounds is in progress. Initial results on the localization of phosphonate complexes of Ru-97 in experimental myocardial infarcts in rats have been promising.

DISCUSSION

Ruthenium (Z=44) is a member of the 2nd triad of the group VIII transition metals. It is a highly reactive element and its chemistry is quite complicated. It displays as many as ten oxidation states in its compounds, the common ones being Ru (III), Ru (IV), and Ru (II). The high reactiveness of ruthenium and the desirable physical characteristics of Ru-97, a pure gamma emitter, provide a valuable combination for application to nuclear medicine. This work demonstrates the potential of Ru-97 as a scanning agent as well as an agent for the study of the physiological parameters of various organs. Efficient and economical production of Ru-97 at the BLIP (Brookhaven Linac Isotope Producer) has been found to be feasible (2), and this should make widespread use of this nuclide possible subsequent to the development of suitable radiopharmaceuticals. The 2.9 day half-life would make many studies and procedures possible, not otherwise practical with Tc-99m. The chemistry of ruthenium can be manipulated much as desired to obtain useful compounds for specific applications. Formed elements of blood, proteins, and other biological molecules of interest

could be conveniently labeled with Ru-97. Several applications of the Ru-97 labeled compounds prepared during this work become obvious. Muscle uptake of Ru chloride could be interesting for myocardial studies. Ru-citrate and Ru-DTPA would be useful for kidney function studies. The citrate and phenanthroline complexes of ruthenium and the purine complexes of $(Ru(NH_3)_5)^{3+}$ may be useful as tumor agents, and the DTPA complex for cisternography. The phosphate complexes show promise as myocardial-infarct agents and for the study of bone disease and physiology. Complexes with oxine derivatives should prove useful as hepatobiliary agents and because of their lipophilicity could also be utilized in labeling cellular materials.

Because of the relatively high yield of ruthenium nuclides among the fission products, various studies of biological interest have been reported in the literature (9-21); application to nuclear medicine has been suggested by some authors (13-15; 19-21). The potential of ruthenium compounds in cancer chemotherapy has also been pointed out (8, 16-18, 22, 23).

In the present research, attempts have been made to exploit and systematize the available knowledge on the chemistry of ruthenium and apply it to the development of potential new radiopharmaceuticals based on ruthenium-97.

ACKNOWLEDGMENTS

Thanks are due to P. Richards, and H.L. Atkins for their encouragement and active interest in this work. The technical help of Don Sacker, David Pier, and Kennan Marsh during various stages of this research is gratefully acknowledged. Evaluation of several ruthenium compounds in tumor bearing mice was carried out by S. Larson and his associates at the VA Hospital, Seattle, Washington.

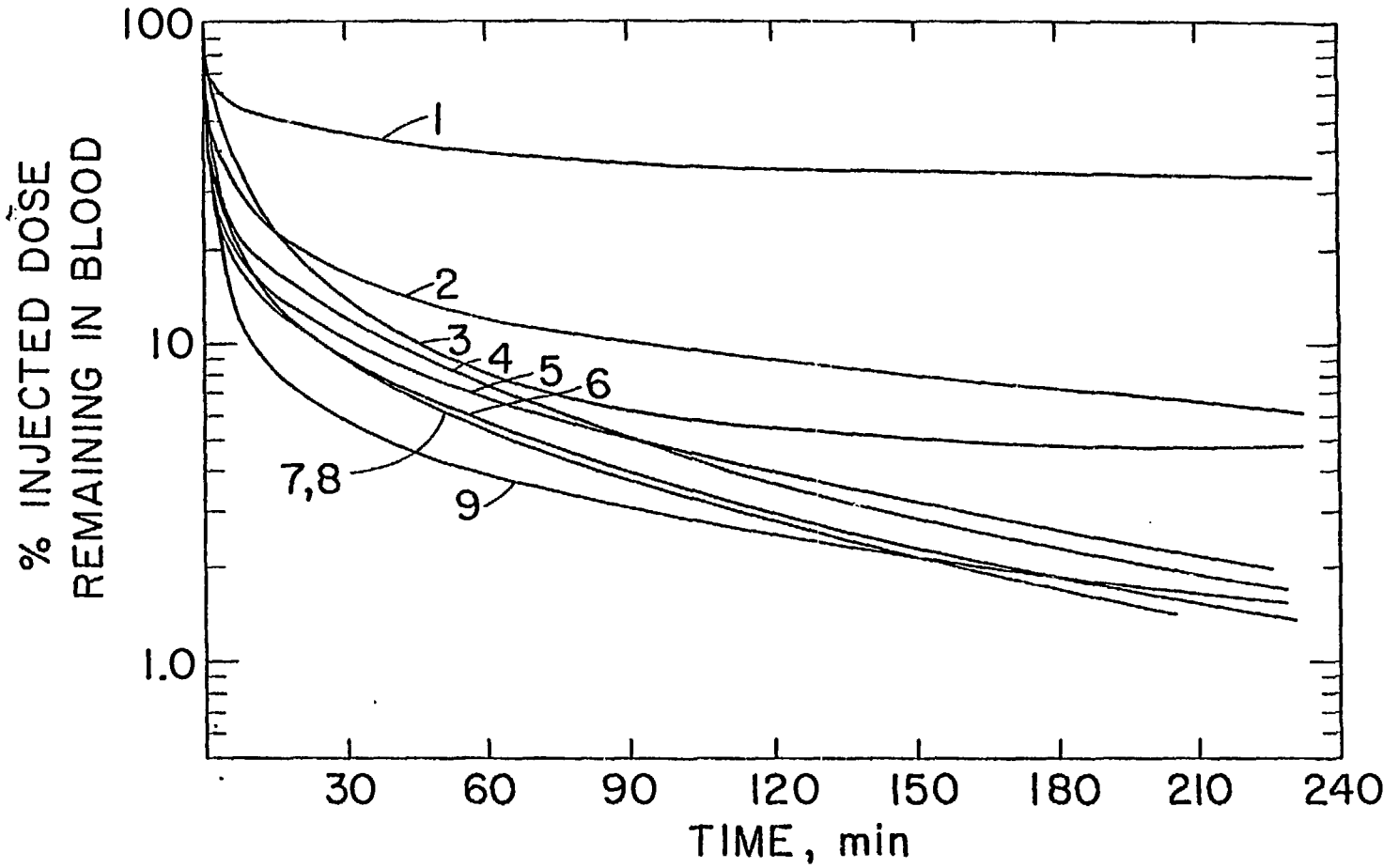


Figure 1: Blood clearance of several ruthenium complexes in dogs. Tc-99m-DTPA and Tc-99m-MDP are included for comparison. 1, ruthenium chloride,pH2; 2, Ru-EHDP; 3, Ru(II)tris-(3,4,7,8-tetramethyl 1,10-phenanthroline) dichloride; 4, Tc-99m-DTPA; 5, Ru-citrate; 6, Ru-EDTMP; 7, Ru-MDP; 8, Tc-99m-MDP; 9, Ru-DTPA.

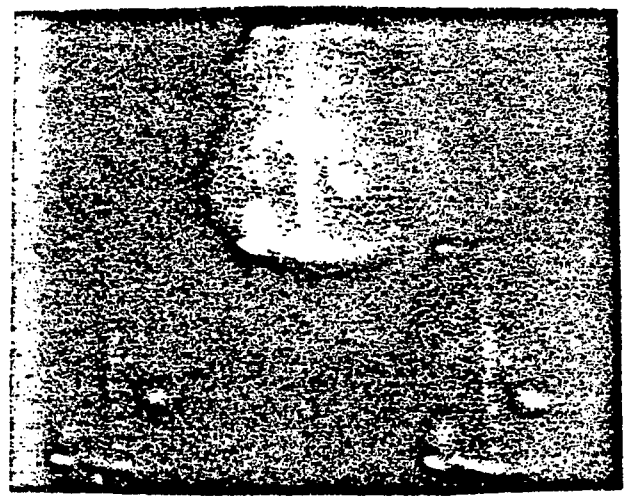
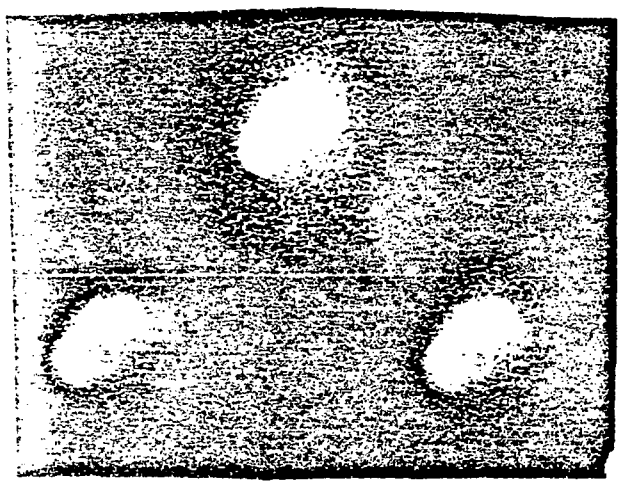


Figure 2: Bone image obtained in rabbit with ruthenium-97-EDTMP, 2 hr post injection



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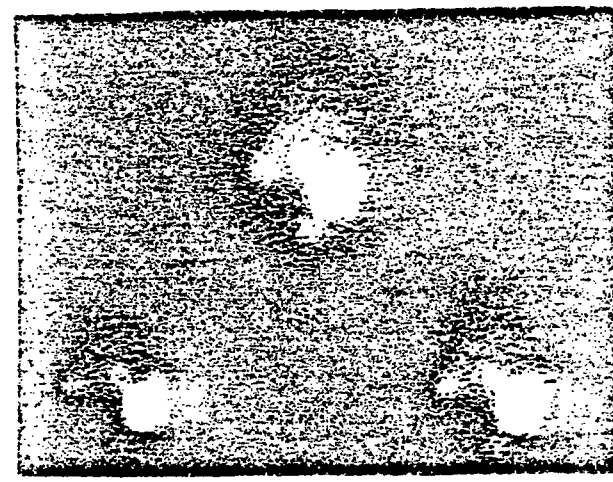
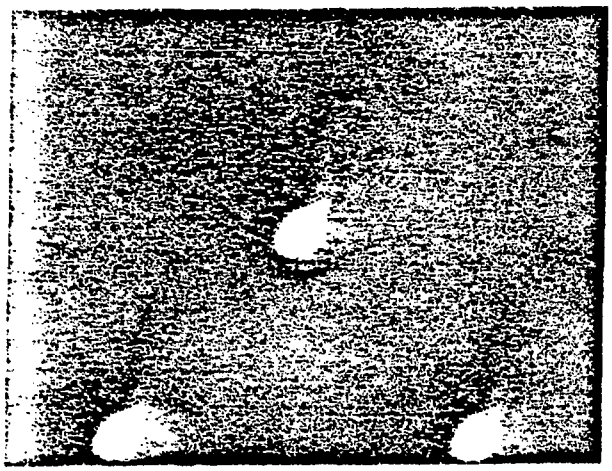


B

Figure 3: Hepatobiliary clearance of ruthenium-97-oxine 7-carboxylic acid acetate in rabbit. A: 5 min post injection; B: 60 min post injection.



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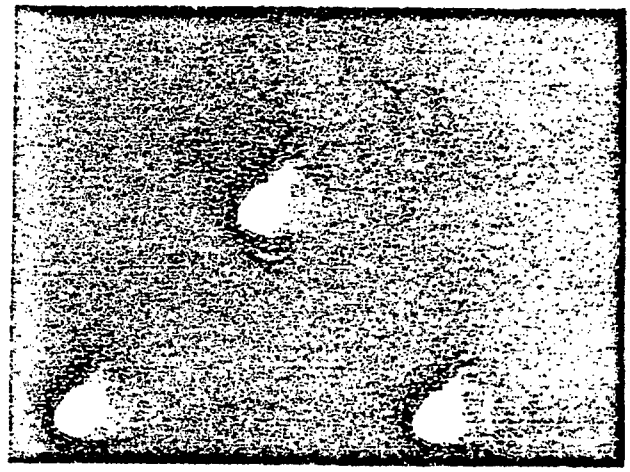

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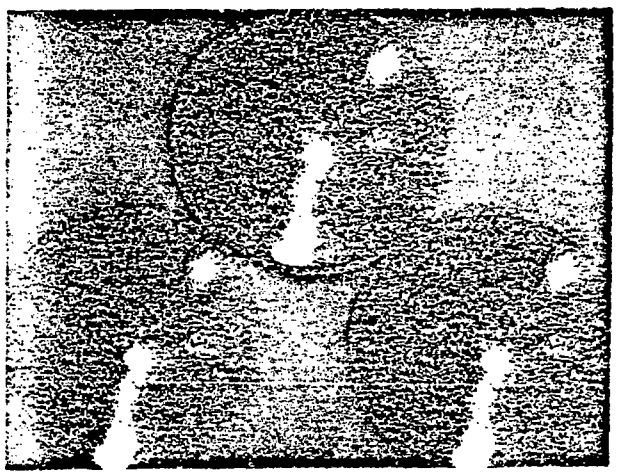

C

Figure 4: Typical images obtained with commercial ^{99m}Tc-antimony sulfide colloid (10±2 nm particles) in rabbit: s.c. injection in right foot pad. A: 25 min post injection; B: 60 min post injection; C: 2.5 hr post injection.

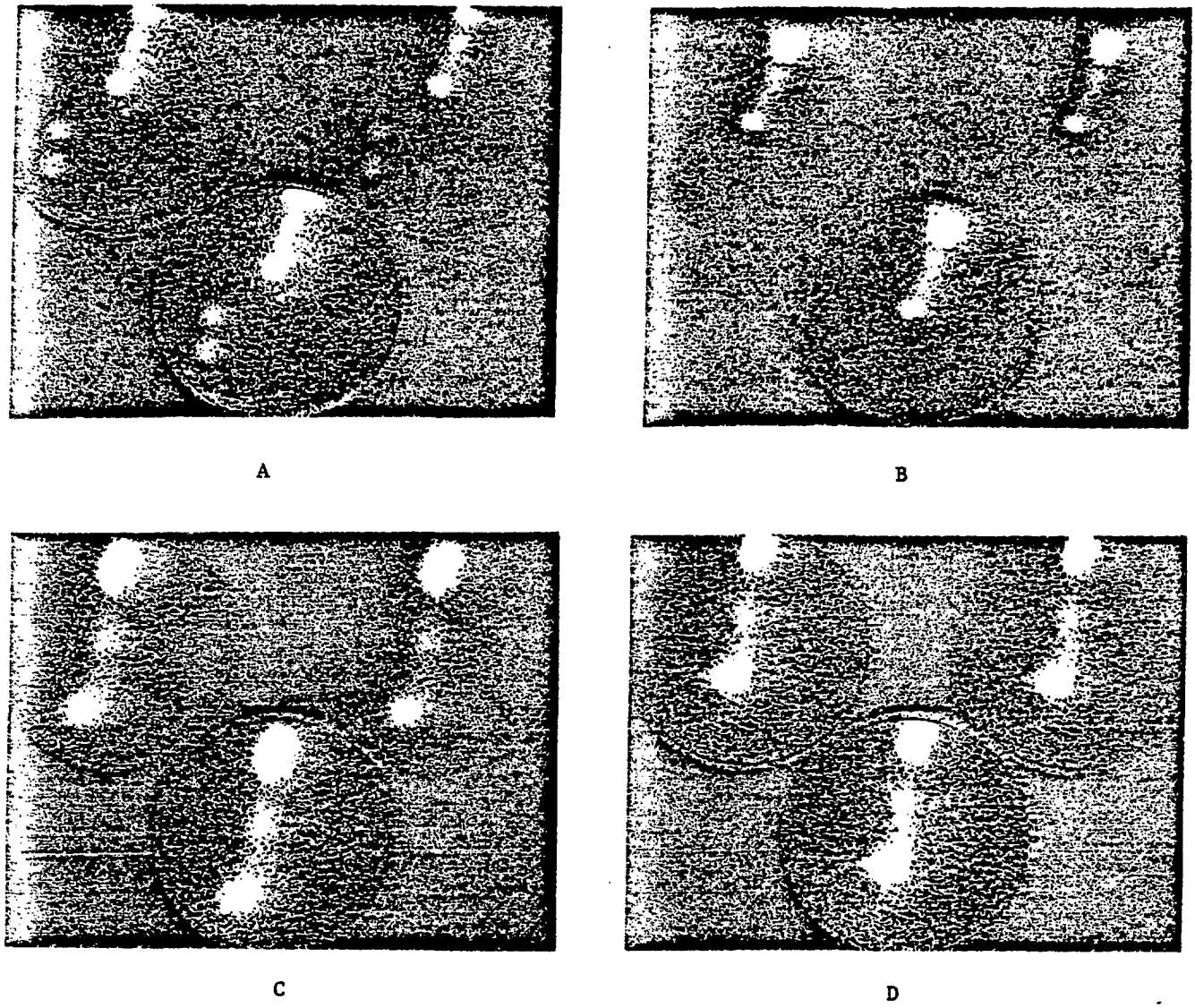

Figure 5: Typical images obtained with ^{103}Ru-sulfur colloid (<30 nm particles) in rabbit; s.c. injection in right foot pad. A: 15 min post injection; B: 40 min post injection; C: 44 hr post injection; D: 5 days post injection.

REFERENCES

1. G. Subramanian, J.G. McAfee, and J.K. Poggenburg, ^{97}Ru: Preliminary evaluation of a new radionuclide for use in nuclear medicine. J. Nucl. Med. 11:365 (1970) (Abstract).

2. T.H. Ku, P. Richards, S.C. Srivastava, T. Prach and L.G. Stang, Jr., Production of ruthenium-97 for medical applications. World Federation of Nuclear Medicine and Biology, 2nd Intl. Congress, Washington, D.C., Sept. 18-21, 1978.

3. D.G. Miller, R.F. Gilmour, Z.D. Grossman, S. Mallov, B.W. Wistow, and R.F. Rohner, Myocardial uptake of Tc-99m skeletal agents in the rat after experimental induction of microscopic foci of injury. J. Nucl. Med. 18:1005 (1977).

4. F.M. Lever, and A.R. Powell, Ammine complexes of ruthenium, J. Chem. Soc. (A), 1477 (1969).

5. L.H. Vogt, Jr., J.L. Katz and S.E. Wiberley, The crystal and molecular structure of Ru-SO_2 coordination compounds. I. Chlorotetrammine (SO_2) ruthenium (II) chloride, Inorg. Chem. 4:1157 (1965).

6. P. Ford, De F.P. Rudd, R. Gaunder, and H. Taube, Synthesis and properties of pentamminepyridine-ruthenium (II) and related pentammineruthenium complexes of aromatic nitrogen heterocycles, J. Amer. Chem. Soc. 90:1187 (1968).

7. M.J. Clarke, Linkage isomers of pentammineruthenium-hypoxanthine complexes, Inorg. Chem. 16:738 (1977).

8. A.D. Kellman, M.J. Clarke, S.D. Edmonds, and H.J. Peresie, Biological activity of ruthenium purine complexes, Proc. 3rd Intl. Symp. Pt Coord. Complexes in Cancer Chemotherapy, Dallas, Texas, Oct. 18-20, 1976.

9. A. Nelson, S. Ullberg, H. Kristoffersson, and C. Rönnbäck, Distribution of radioruthenium in mice. Acta. Radiol. 58:353 (1962).

10. J.E. Furchner, C.R. Richmond, and G.A. Drake, Comparative metabolism of radionuclides in mammals. VII. Retention of ^{106}Ru in the mouse, rat, monkey and dog. Health Phys. 21:355 (1971).

11. R.S. Bruce and S. Jackson, Studies in the metabolism of carrier-free radioruthenium. The preparation and metabolism of nitrosylruthenium nitro complexes. Phys. Med. Biol. 7:463 (1973).

12. D. Seidel, A. Catsch and K. Schweer, DeKorporation von radionukliden, Untersuchungen an radioruthenium. Strahlentherapie 122:595 (1963).

13. L.J. Anghileri, In-vivo distribution of ^{103}Ru ruthenium red. J. Nucl. Biol. Med. 18:155 (1974).

14. T.N. Tan, R.H. Weston and J. P. Hogan, Use of ^{103}Ru-labeled tris (1,10-phenanthroline) ruthenium (II) dichloride as a marker in digestion studies with sheep. Intern. J. Appl. Radiat. Isotopes 22:301 (1971).

15. L.J. Anghileri, Radioactive ruthenium red accumulation by tumors: a potential scanning agent. Strahlentherapie 149:173 (1975).

16. F.P. Dwyer, E. Mayhew, E.M.F. Roe and A. Shulman, Inhibition of Landschütz ascites tumor growth by metal chelates derived from 3,4,7,8-tetra methyl-phenanthroline. Brit. J. Cancer 19:195 (1965).

17. D.O. White, A.W. Harris, F.P. Dwyer and A. Shulman, Actions of metal chelates of substituted 1,10-phenanthrolines on viruses and cells. I. Inactivation of viruses. Austr. J. Exp. Biol. 41:517 (1963).

18. D.O. White, A.W. Harris and A. Shulman, Actions of metal chelates of substituted 1,10-phenanthrolines on viruses and cells. II. Inhibition of viral multiplication. Austr. J. Exp. Biol. 41:527 (1963).

19. M. Wenzel, N. Subramanian, and E. Nipper, Nebennieren-Affinität des γ-emitters ^{103}Ru als Acetyl-Ruthenocen. Naturwiss. 63:341 (1976).

20. M. Wenzel, E. Nipper and W. Klose, Biochemistry of metalocenes. I. Distribution of ^{59}Fe or ^{103}Ru-labeled metalocene carboxylic acid in mice. J. Nucl. Med. 18:367 (1977).

21. M. Wenzel and W. Klose, Thymus-Affinität von ^{103}Ru-cinnamoyl-ruthenocen. Klin. Wochenschrift 55:559 (1977).

22. M.J. Cleare, Transition metal complexes in cancer chemotherapy. Coord. Chem. Rev. 12:349 (1974).

23. J.P. Durig, J. Danneman, W.D. Behnke and E.E. Mercer, The induction of filamentous growth in E. coli by ruthenium and palladium complexes. Chem. Biol. Interactions 13:287 (1976).