CHEMICAL & PHARMACEUTICAL BULLETIN

Vol. 27, No. 2

February 1979

Regular Articles

[Chem. Pharm. Bull.
27(2) 279-286 (1979)]

UDC 615.31'466.011.5.033.074 : 543.52.061

Distribution of Some Disulfhydryl-Containing Chelating Agents labeled with Indium-113m and Gallium-67 in Mice

NORIKO MOTOHASHI, MINEKO TERAOKA, ITSUHIKO MORI,^{1a)} YUKIO SUGIURA,
NAKAO KOJIMA, and HISASHI TANAKA^{1b)}

*Kobe Women's College of Pharmacy^{1a)} and Faculty of Pharmaceutical
Sciences, Kyoto University^{1b)}*

(Received March 3, 1978)

The organ distribution of new disulfhydryl-compounds, 2,3-dimercaptopropionylglycine (DMPG) and 2-mercaptopropionyl-L-cysteine (MPC), labeled with $^{113m}\text{In}(\text{III})$ and $^{67}\text{Ga}(\text{III})$ were examined in mice, and the results were compared with those of dimercaptosuccinic acid complex and metal ion without those ligands to evaluate their applicabilities as diagnostic agent in nuclear medicine. The DMPG complex was found to be localized in liver, whereas the MPC complex in kidney. The addition of metal ion carrier varies the distribution patterns of the complex species, on account of the formation of the polymerized products. In the case of indium complexes, the behavior of the ligand was reflected to their distribution patterns more clearly than in the case of gallium complexes. The complex species formed in the labeling reactions were characterized by the electrophoretic and gel-filtration techniques.

Keywords—radiopharmaceutical; organ distribution; ^{113m}In -labeling; ^{67}Ga -labeling; disulfhydryl-compound; carrier effect

The labeled compounds of ^{111}In (or ^{113m}In) and ^{67}Ga have attracted keen interest as diagnostic agent in nuclear medicine, on account of the favorable physical properties of these radioisotopes. However, only a few labeled compounds, such as ^{111}In -transferrin, ^{111}In -bleomycin, ^{67}Ga -citrate, and ^{67}Ga -DTPA, have been evaluated in clinical use.²⁾ The extremely high hydrolyzability of these metal ions has prevented further study to find adequate ligands, which should be labeled with these radioisotopes, and the development of new radiopharmaceuticals by the use of these radioisotopes has not been achieved. The search for the ligands, which are capable to prevent the hydrolysis of metal ions by the complexation is an essentiality to expand the application of these radioisotopes in nuclear medicine. Our preliminary survey on the reactivity of indium and gallium ions with some ligands which involve various coordination groups indicated the high complex-forming ability in some sulfhydryl-containing ligands, such as penicillamine³⁾ and cysteine.⁴⁾ In particular, new disulfhydryl-containing ligands, namely 2,3-dimercaptopropionylglycine (DMPG) and 2-mercaptopropionyl-L-cysteine

- 1) Location: a) Motoyamakita-machi, Higashinada-ku, Kobe; b) Yoshida, Shimoadachi-cho, Sakyo-ku, Kyoto.
- 2) M.L. Thakur, *Int. J. Appl. Radiat. Isot.*, **28**, 183 (1977).
- 3) N. Kojima, Y. Sugiura, and H. Tanaka, *Bull. Chem. Soc. Jpn.*, **49**, 1294 (1976).
- 4) N. Kojima, Y. Sugiura, and H. Tanaka, *Bull. Chem. Soc. Jpn.*, **49**, 3023 (1976).

(MPC), prevented the hydrolysis of indium and gallium ions effectively,⁵⁾ by the complexation, and hence further investigation on these ligands seemed to be worthy for a purpose to develop new diagnostic agent. This paper deals with the organ distributions of DMPG and MPC labeled with ^{113m}In and ^{67}Ga . The result was compared with those in the metal complexes of dimercaptosuccinic acid (DMS) which has already been used as a ligand for the diagnosis. The effect of these ligands was evaluated by the comparison of the distributions of the complexes with those of these metal ions themselves. In addition, the influence of the presence of the non-radioactive carrier towards the distribution was examined.

Experimental

DMPG and MPC were prepared by the method⁵⁾ reported previously. DMS was purchased from Dojin Co. ^{113m}In was eluted from ^{113}Sn – ^{113m}In generator (5 mCi: Radiochemical Centre) with 0.04 N HCl, and ^{67}Ga was obtained in the form of $^{67}\text{GaCl}_3$ and it was dissolved in 0.01 N HCl. Indium sulfate and gallium hydrochloride prepared from gallium metal (99.99%, Nakarai Chemicals, Ltd.) with concentrated hydrochloric acid, were used as the carrier of these metal ions. All other reagents used were of commercial reagent grade. Each ligand was dissolved in 0.1 M acetate buffer (pH 5.6) and added to the solution of ^{113m}In or ^{67}Ga (4–6 $\mu\text{Ci/ml}$) with or without the carrier. The pH of the solution was adjusted to be 7.0 with 0.1 N NaOH solution. The final concentration of the ligand and the carrier was 1×10^{-2} and 3×10^{-3} M, respectively. In this paper, ^{113m}In or ^{67}Ga represents the state of the carrier free, and ^{113m}In –In or ^{67}Ga –Ga represents the presence of the carrier.

Labeled products were checked by means of electrophoresis by the use of a precoated cellulose plate, Avicel SF (Funakoshi Pharmaceutical Co.) in 0.1 M phosphate buffer of pH 7.0. Labeled sample solutions (0.2 ml, 0.8–1.2 μCi) were injected intravenously into ddy-male mice, weighing 20–25 g (5 weeks old). At 0.5, 1, 3 and 5 (or 6) hrs after the injection, they were sacrificed and γ -activities in various organs were measured with a Dinabot well-type scintillation counter, Auto-Logic 111 by the comparison with a standard. The results were expressed in terms of % dose/gr tissue (or % dose/blood ml). The weights of blood, muscle, and bone were estimated respectively as 7, 40, and 10% of the weight of a mouse, for the calculation of the distribution.

The molecular weight of the polymerized labeled product was estimated by gel-filtration technique, by the use of Sephadex G-25, superfine (on a 2×30 cm column), in comparison with the behavior of three markers, namely insulin B (M.W. 3464), insulin A (M.W. 2340) and vitamin B₁₂ (M.W. 1355.4).

Results and Discussion

Electrophoretic Study

As shown in Figs. 1 and 2, the disulfhydryl-containing ligands, DMPG, MPC, and DMS, were detected where the radioactivity of ^{113m}In or ^{67}Ga was observed. This results indicate the formation of the labeled complex species. No difference was observed between the electrophoretic patterns with and without the carrier, and the formations of some negative charged complexes were indicated in both cases. Our previous potentiometric and PMR data revealed that 2:1 DMPG or MPC -indium or -gallium complex has total charge of 3-.⁵⁾ The electrophoretic patterns of indium ions are different from those of its complexes and their radioactivities predominantly remain near the original point (see Fig. 1B). The species, such as $\text{In}(\text{H}_2\text{O})_6^{3+}$, $\text{In}(\text{OH})_2^{2+}$, and $\text{In}(\text{OH})_2^+$ are expected to be present at acidic pH region, whereas some polymeric hydrolyzed species of indium is considered to be formed at neutral pH region. Fig. 2B shows the electrophoretic patterns of gallium ions. The spots observed in the positive side and at the original point may be attributed to a hydrolyzed species, $\text{Ga}(\text{OH})_4^-$ and polymer complex species, respectively.

Gel-filtration Study

As seen in Fig. 3, the molecular weights of the indium complex species formed are different from each other between the cases with the presence and the absence of the carrier.

5) Y. Sugiura, N. Kojima, and H. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **25**, 2263 (1977); N. Kojima, Y. Sugiura, and H. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **26**, 440 (1978).

Fig. 1. Electrophoretograms of In(III) Complexes and In(III) Ions

A: (a) ^{113m}In -DMPG, ^{113m}In -In-DMPG, (b) ^{113m}In -MPC, ^{113m}In -In-MPC, (c) ^{113m}In -DMS, ^{113m}In -In-DMS.
 B: (a) ^{113m}In (pH 1.5), (b) ^{113m}In (pH 7.0), (c) ^{113m}In -In (pH 1.6), (d) ^{113m}In -In (pH 7.0).
 Conditions of electrophoresis: precoated cellulose, 2×10 cm, 30 V/cm, 20 min, 0.1 M phosphate buffer (pH 7.0).
 The ligands were detected by the color development with Co^{2+} in ammonia alkaline solution.

Fig. 2. Electrophoretograms of Ga(III) Complexes and Ga(III) Ions

A: (a) ^{67}Ga -DMPG, ^{67}Ga -Ga-DMPG, (b) ^{67}Ga -MPC, ^{67}Ga -Ga-MPC, (c) ^{67}Ga -DMS, ^{67}Ga -Ga-DMS.
 B: (a) ^{67}Ga (pH 2.2), (b) ^{67}Ga (pH 7.0), (c) ^{67}Ga -Ga (pH 2.8), (d) ^{67}Ga -Ga (pH 7.0).
 Conditions of electrophoresis: precoated cellulose, 2×10 cm, 30 V/cm, 20 min, 0.1 M phosphate buffer (pH 7.0).
 The ligands were detected by the color development with Co^{2+} in ammonia alkaline solution.

Fig. 3. Elution Patterns of In Complexes with a Sephadex Column

column: Sephadex G-25 (superfine), 2 × 30 cm,
elution solvent: 0.15 M NaCl solution,
flow rate: 15 ml/hr, fraction volume: 1.0 ml.

○—○ ^{113m}In -DMPG, ●—● ^{113m}In -In-DMPG,
□—□ ^{113m}In -MPC, ■—■ ^{113m}In -In-MPC,
△—△ ^{113m}In -DMS, ▲—▲ ^{113m}In -In-DMS.

The three markers of insulin B (M.W. 3464), insulin A (M.W. 2340) and vitamin B₁₂ (M.W. 1355.4) were eluted in 26–27, 33 and 41–42 ml, respectively.

Fig. 4. Elution Patterns of Ga Complexes with a Sephadex Column

column: Sephadex G-25 (superfine), 2 × 30 cm,
elution solvent: 0.15 M NaCl solution,
flow rate: 15 ml/hr, fraction volume: 1.0 ml.

○—○ ^{67}Ga -DMPG, ●—● ^{67}Ga -Ga-DMPG,
□—□ ^{67}Ga -MPC, ■—■ ^{67}Ga -Ga-MPC,
△—△ ^{67}Ga -DMS, ▲—▲ ^{67}Ga -Ga-DMS.

The three markers of insulin B (M.W. 3464), insulin A (M.W. 2340) and vitamin B₁₂ (M.W. 1355.4) were eluted in 26–27, 33 and 41–42 ml, respectively.

These complexes were impossible to be characterized by the electrophoretic study. The readiness to form polymerized species in three kinds of ligand decreases in the order, DMS > MPC > DMPG. In the case of gallium complexes, the peaks of ^{67}Ga -DMPG and ^{67}Ga -Ga-DMPG were superimposed well, indicating the formation of the complex species of comparable molecular weight, regardless of the presence or absence of the carrier. On the contrary, in the case of ^{67}Ga -Ga-DMS complex, the molecular weight of the complex was higher in the presence of the carrier than that in the absence of the carrier, as seen in Fig. 4. The formation of some oligomeric indium and gallium complexes with molecular weight of about 1500–2500 are presumed, except for the case of DMPG. The result in PMR study in the complex of indium also suggested that the molecular weight of the complex formed is higher in the case of DMPG than that estimated to be about 2000–3000 in the case of MPC.⁵⁾

Fig. 5. Organ Distribution of ^{113m}In Complexes

(a) ^{113m}In -DMPG, (b) ^{113m}In -MPC, (c) ^{113m}In -DMS.
●—● liver, ○—○ blood, ×—× kidney,
▲—▲ bone, △—△ muscle, ■—■ spleen.

Interaction of Transferrin with Indium and Gallium Complexes

The gel-filtration was performed at pH 7.4 on the systems containing transferrin and the ^{67}Ga and $^{113\text{m}}\text{In}$ complexes of DMPG, MPC, and DMS. Sephadex G-25 was equilibrated with Tris buffer (pH 7.4) and a 1×10 cm column was prepared. Ga^{3+} or In^{3+} was labeled with ^{67}Ga or $^{113\text{m}}\text{In}$ and added to the ligand solution dissolved in the Tris buffer. The complex solution was incubated with transferrin for 20 min. The concentration of the ligands, metal ions, and protein were 0.2, 0.05, and 0.05 mM, respectively. The chromatographic results showed clearly that the metal complexes were stable and metal ions were not deprived from these ligands by the reaction with transferrin, except for the case of MPC-indium (III) complex.

Distribution Study

Figure 5 shows the organ distribution of $^{113\text{m}}\text{In}$ complexes. The higher localizations were observed in liver in the case of $^{113\text{m}}\text{In}$ -labeled DMPG and in kidney in the case of

TABLE I. Organ Distribution of $^{113\text{m}}\text{In}$ -In- and ^{67}Ga -Ga-Complexes in Mice

Compound	Time hr	Percent dose per gr tissue ^{a)}					
		Blood	Liver	Kidney	Spleen	Muscle	Bone
$^{113\text{m}}\text{In}$ -In-DMPG	1	2.56 ± 0.33	6.59 ± 0.98	18.05 ± 0.47	0.69 ± 0.03	1.35 ± 0.26	15.21 ± 0.22
	5	1.01 ± 0.05	6.04 ± 0.33	24.59 ± 1.65	0.77 ± 0.09	0.53 ± 0.23	19.64 ± 2.99
$^{113\text{m}}\text{In}$ -In-MPC	1	3.25 ± 0.46	19.86 ± 0.80	19.89 ± 2.47	8.82 ± 2.11	0.71 ± 0	11.78 ± 3.02
	5	1.54 ± 0.52	17.07 ± 0.77	20.69 ± 1.39	12.08 ± 1.71	0.82 ± 0.27	12.43 ± 1.93
$^{113\text{m}}\text{In}$ -In-DMS	1	5.47 ± 0.20	7.91 ± 0.53	58.57 ± 3.43	17.50 ± 3.86	0.78 ± 0.13	23.30 ± 0.87
	5	1.43 ± 0.02	9.16 ± 0.47	54.85 ± 1.62	14.52 ± 1.79	0.87 ± 0.17	33.99 ± 7.31
^{67}Ga -Ga-DMPG	1	1.84 ± 0.06	7.39 ± 0.36	4.18 ± 0.41	0.66 ± 0.03	1.09 ± 0.02	17.69 ± 2.84
	5	1.13 ± 0.11	3.64 ± 0.19	2.56 ± 0.40	0.66 ± 0.10	0.27 ± 0	21.32 ± 5.25
^{67}Ga -Ga-MPC	1	1.38 ± 0.18	8.43 ± 0.52	5.43 ± 1.30	16.45 ± 4.98	0.41 ± 0.05	27.14 ± 0.51
	5	1.29 ± 0.12	8.47 ± 0.62	2.56 ± 0.10	13.06 ± 1.23	0.37 ± 0.05	27.30 ± 4.93
^{67}Ga -Ga-DMS	1	2.38 ± 0.28	4.98 ± 0.42	4.09 ± 0.01	10.00 ± 0.18	0.76 ± 0.50	21.53 ± 0.37
	5	2.09 ± 0.21	6.14 ± 0.54	3.69 ± 0.23	6.54 ± 1.58	0.53 ± 0.28	28.18 ± 2.99

a) The values are the mean value $\pm$ SE of the percent dose per gram of wet tissue for a 3-animal group.

Fig. 6. Organ Distribution of In Metal Ions

(a) $^{113\text{m}}\text{In}$ (pH 1.5), (b) $^{113\text{m}}\text{In}$ (pH 7.0),
 (c) $^{113\text{m}}\text{In}$ -In (pH 1.6), (d) $^{113\text{m}}\text{In}$ -In (pH 7.0).
 ●, liver, ○, blood, ×, kidney,
 ▲, bone, △, muscle, ■, spleen.

$^{113\text{m}}\text{In}$ -labeled MPC, respectively. The higher localization in kidney and much lower localization in liver were observed in $^{113\text{m}}\text{In}$ -labeled DMS than in other two complexes. DMS has been applied to the diagnosis of kidney disease as $^{99\text{m}}\text{Tc-Sn-DMS}$.⁶⁾ In the complexes of indium, the presence of the carrier gave remarkable influence on the localization. The localization in kidney and bone was higher when the carrier was present than the case of the carrier free (Table I). In addition, $^{113\text{m}}\text{In-In-MPC}$ and $^{113\text{m}}\text{In-In-DMS}$ revealed considerably high localization in spleen and liver, in which the carrier free complexes were scarcely localized. Figure 6 shows the organ distribution of indium (III) ion without the ligands. In the case of the

indium solution prepared in the acidic region, where the complex species such as $\text{In}(\text{H}_2\text{O})_6^{3+}$, $\text{In}(\text{OH})_2^{2+}$, and $\text{In}(\text{OH})_2^+$ are formed,⁷⁾ $^{113\text{m}}\text{In}$ -radioactivity was predominantly observed in kidney and bone. On the contrary, polymeric indium hydrolyzed species prepared at neutral pH region was localized highly in liver as well as in spleen. The organ distribution patterns of $^{113\text{m}}\text{In}$ and $^{113\text{m}}\text{In-In}$ were found to be similar, when the solutions were prepared in the same pH region, but their excretion rates from body differ clearly from each other. In conclusion, the present results seem to reveal that the organ distribution of the carrier free $^{113\text{m}}\text{In}$ complexes of DMPG, MPC, and DMS is

Fig. 7. Organ Distribution of ^{67}Ga Complexes

(a) ^{67}Ga -DMPG, (b) ^{67}Ga -MPC, (c) ^{67}Ga -DMS.
 ●—●, liver, ○—○, blood, x—x, kidney,
 ▲—▲, bone, △—△, muscle, ■—■, spleen.

Fig. 8. Organ Distribution of Ga Metal Ions

(a) ^{67}Ga (pH 2.2), (b) ^{67}Ga (pH 7.0),
 (c) $^{67}\text{Ga-Ga}$ (pH 2.3), (d) $^{67}\text{Ga-Ga}$ (pH 7.0)
 ●—●, liver, ○—○, blood, x—x, kidney,
 ▲—▲, bone, △—△, muscle, ■—■, spleen.

6) D. Enlander, P.M. Weber, and L.V. Remeclions, *J. Nucl. Med.*, **15**, 743 (1974); H. Handmarker, B.W. Young, and J.M. Lowenstein, *J. Nucl. Med.*, **16**, 28 (1975).

7) M.J. Welch and T.J. Welch, "Radiopharmaceuticals," ed. by G. Subramanian, B.A. Rodes, J.F. Cooper, and V.J. Soddy, The Society of Nuclear Medicine, Inc., New York, 1975, pp. 73—79.

controlled mainly by the biological properties of these ligands, and that the presence of excess ligand contributes to the rapid excretion of radioactive indium. On the other hand, the high localization in kidney and bone, and the delay in the excretion are the characteristic behavior of $^{113\text{m}}\text{In}$ -labeled complexes with the carrier. The distribution of $^{113\text{m}}\text{In}$ -In-MPC and $^{113\text{m}}\text{In}$ -In-DMS to spleen and liver suggests that these complexes are the highly polymerized product.

Figure 7 shows the organ distribution of ^{67}Ga complexes. The complexes labeled with ^{67}Ga were localized in bone similarly to the cases of indium complexes. Among three kinds of complex, ^{67}Ga -MPC showed the highest localization to bone. As seen in Table II, the localization to bone was higher in the presence of carrier than in its absence. The localization of ^{67}Ga -Ga-MPC and ^{67}Ga -Ga-DMS in spleen and liver was high as in the case of $^{113\text{m}}\text{In}$ -In complexes. Figure 8 shows the organ distribution of gallium (III) ion without the ligand. In the case of the solution prepared in the acidic region, where the complex species such as $\text{Ga}(\text{OH})_3$ and $\text{Ga}(\text{OH})_4^-$ are formed,⁸⁾ the localization of gallium in liver and spleen was found to be predominant. The behavior is probably due to the polymer formation. The influence of the formation of the polymer seems to appear more remarkably, and the behavior which depends upon the properties of the ligands was less clearly observable, on the organ distribution of these dithiol-gallium-complexes, than in the case of indium complexes.

TABLE II. Organ Affinities of Metal Ions and their Complexes with Disulfhydryl-containing Compounds

Metal		None	Ligand			
			$\begin{array}{c} \text{SH} \text{ SH} \\ \text{CH}_2\text{CHCONHCH}_2\text{-} \\ \text{COOH} \end{array}$ DMPG	$\begin{array}{c} \text{SH} \\ \text{CH}_2\text{CHCONHCH-} \\ \text{COOH} \end{array}$ MPC	$\begin{array}{c} \text{SH} \\ \text{CH}_2 \\ \text{CH} \end{array}$ DMS	
$^{113\text{m}}\text{In}$	$^{113\text{m}}\text{In}$	Acidic pH	Kidney	(Liver)	(Kidney)	Kidney, Bone
		Neutral pH	Kidney, Liver			
	$^{113\text{m}}\text{In-In}$	Acidic pH	Kidney >> Bone	Kidney, Bone	Kidney, Liver, Bone	Kidney >> Bone, Spleen
^{67}Ga	^{67}Ga	Acidic pH	Bone	(Bone)	(Bone)	(Bone)
		Neutral pH	Bone			
	$^{67}\text{Ga-Ga}$	Acidic pH	Bone	Bone	Bone > Spleen, Liver	Bone, Spleen
$^{99\text{m}}\text{Tc}$	$^{99\text{m}}\text{TcO}_4^-$	Stomach, Seminal vesicle	Liver	Kidney	Kidney, ^{a)} Bone	
	$^{99\text{m}}\text{Tc-Sn}$	Liver, Spleen				
^{57}Co		(Kidney, Liver)	(Kidney, Liver)	Kidney	Bone	

(): Organ affinity is not specified.

^{a)} I. Ikeda, O. Inoue, and K. Kurata, *Int. J. Appl. Radiat. Isotop.*, **27**, 681 (1976).

Table II summarizes the organ affinity of $^{113\text{m}}\text{In}$ and ^{67}Ga complexes together with that of the corresponding $^{99\text{m}}\text{Tc}$ and ^{57}Co complexes. Indium has affinity primarily with kidney and secondarily with bone, whereas gallium predominantly with bone. On the other hand, the biological behavior of the ligands can possibly be presumed through that of ^{57}Co -labeled ligands, because ^{57}Co has no specific affinity with any organs. MPC which bears cysteine residue was localized in kidney, similarly to $^{99\text{m}}\text{Tc}$ -cysteine.⁹⁾ DMS was localized mainly in bone and kidney, whereas DMPG did not show any organ specificity. $^{99\text{m}}\text{Tc}$ -DMS complex has been suggested to be present as a polymerized form.¹⁰⁾ The analogous ligand, 2-mercapto-

8) S. Kulprathipanja and D.J. Hnatowich, *Int. J. Appl. Radiat. Isot.*, **28**, 229 (1977).

9) D.M. Vanlic-Razremenic and D.A. Gorkic, *Eur. J. Nucl. Med.*, **1**, 235 (1976); I. Ikeda, O. Inoue, and K. Kurata, *Int. J. Appl. Radiat. Isot.*, **27**, 681 (1976); *idem*, *Int. J. Nucl. Med. Biol.*, **4**, 56 (1977).

10) B.M. Browen, D.R. Henderson, J.E. Kellam, and D.E. Wood, *Amer. J. Hosp. Pharm.*, **29**, 502 (1972).

propionyl-glycine is known to be excreted very rapidly.¹¹⁾ The size of the colloid and their readiness in the incorporation to the organ have been related respectively in the following way¹²⁾; namely when the size of the colloid is $3\text{m}\mu$, $3\text{--}5\text{m}\mu$, $50\text{--}100\text{m}\mu$, and $3\text{--}6\mu$, it is incorporated to bone marrow, incorporated and excreted through kidney, accumulated in kidney, and accumulated in spleen. Contrary to the expectation from these relationships, $^{113\text{m}}\text{In}\text{--In}\text{--MPC}$, $^{113\text{m}}\text{In}\text{--In}\text{--DMS}$, $^{67}\text{Ga}\text{--Ga}\text{--MPC}$, and $^{67}\text{Ga}\text{--Ga}\text{--DMS}$ whose molecular weights were estimated be 1500—2500, showed relatively high affinity with spleen and liver. The discrepancy may be explained in terms of the polymerization of the metal ion released from the complexes of the metal carrier to yield the colloid of large size. The indium (III) and gallium (III) complexes of DMPG is stable *in vivo*, as is judged from its pattern of the distribution. Although the indium (III) and gallium (III) complexes with high formation constant were found to form *in vitro* with DMPG, MPC, and DMS,⁵⁾ the complexes were not stable *in vivo*, except for the case of DMPG.

11) T. Chiba, H. Kitoo, and N. Toshioka, *Yakugaku Zasshi*, **93**, 112 (1973).

12) W.B. Nelp, "Radiopharmaceuticals," ed. by G. Subramanian, B.A. Rodes, J.F. Cooper, and V.J. Sodd, The Society of Nuclear Medicine, Inc., New York, 1975, pp. 349—355.