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**PREPARATION OF GALLIUM-68 RADIOPHARMACEUTICALS
FOR POSITRON TOMOGRAPHY**

Progress Report

for period

November 1, 1977 to October 31, 1980

Michael J. Welch, Ph.D.

**The Edward Mallinckrodt Institute of Radiology
Washington University School of Medicine
510 South Kingshighway
St. Louis, Missouri 63110**

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ABSTRACT

Although the germanium-68—gallium-68 generator is probably the only source of positron-emitting radionuclides that could enable the widespread application of positron tomography, the commercially available $^{68}\text{Ga}/^{68}\text{Ge}$ generator system suffers from several major disadvantages. The most important of these is that the generator is eluted with EDTA, which forms a very strong chelate with gallium. In order to produce radiopharmaceuticals other than ^{68}Ga -EDTA, it is first necessary to break the stable EDTA complex and remove all traces of EDTA. This procedure adds several steps and a significant amount of time to procedures for preparing ^{68}Ga -radiopharmaceuticals. We have developed a new generator using a solvent extraction system which will produce ^{68}Ga -oxine (8-hydroxyquinoline), a weak chelate. Using this agent we have synthesized several ^{68}Ga -radiopharmaceuticals and tested them in vitro and in vivo. We have also carried out some preliminary studies to compare generator systems which produce ^{68}Ga in an ionic form. Attempts have been made using polarographic and chromatographic techniques, and in vivo distribution data, to investigate the stability of radiogallium complexes with a series potentially lipophilic complexing agents.

PREFACE

The following progress report is a cumulative report covering the past three years (November 1, 1977 through October 31, 1980). The following portions of the work which is described were completed during the last one year period (November 1, 1979 - October 31, 1980):

1. Testing of new $^{68}\text{Ge}/^{68}\text{Ga}$ generator systems for the production of ionic gallium-68;
 2. Completion of clinical trials of the liver agent, ^{68}Ga -ferric hydroxide colloid, in patients with proven (or highly suspected) metastatic or primary hepatic neoplasms;
 3. Preparation and chromatographic analysis of ^{68}Ga EDTMP, and preliminary in vivo uptake studies in a rat model for myocardial infarction;
 4. Approaches to the production of lipophilic ^{68}Ga -labeled compounds.
- In cases where literature publications of the work described are available, these are included as appendices which are referred to in the text.

The particular points which are requested to be included in a comprehensive progress report (as per letter from Donald W. Cole, Jr., October 17, 1979) are summarized below.

I. The main research accomplishments, with special reference to originally stated objectives.

We have developed a $^{68}\text{Ge}/^{68}\text{Ga}$ solvent extraction generator, which is one of several new systems to produce the positron-emitter ^{68}Ga that have been described to date. According to reports in the literature, our 10 mCi

$^{68}\text{Ge}/^{68}\text{Ga}$ solvent extraction generator has been made with considerably larger amounts of activity than the more recently proposed chromatographic systems which yield ionic ^{68}Ga . Due to radiolysis effects, scale-up of generator systems is often accompanied by serious problems. We intend to continue our investigations on $^{68}\text{Ge}/^{68}\text{Ga}$ generator systems -- both solvent extraction systems to produce ^{68}Ga -oxine, and chromatographic systems to produce ionic ^{68}Ga -- in an effort to find the best system for use as a source for large amounts of ^{68}Ga (~10-15 mCi) in a form which can readily be converted to useful ^{68}Ga -radiopharmaceuticals.

We have developed rapid methods to prepare several ^{68}Ga -radiopharmaceuticals using the ^{68}Ga -oxine eluted from our solvent extraction generator. These include ^{68}Ga -ferric hydroxide colloid, ^{68}Ga -proteins, ^{68}Ga -human albumin microspheres, ^{68}Ga -EDTMP, and ^{68}Ga -platelets. We have also investigated a series of ligands with high stability constants with structures that are based on that of enterobactin. Although these ligands have not yielded the desired highly lipophilic ^{68}Ga -radiopharmaceuticals. Our studies with these complexes have provided a great deal of information concerning the structure-activity relationships of a series of radiogallium chelates based on enterobactin.

II. Plans for the continuation of present objectives and possible new objectives in consideration of past results.

As mentioned above, we plan to continue our search for an ideal large scale $^{68}\text{Ge}/^{68}\text{Ga}$ generator system, and plan to use the ^{68}Ga obtained from this system to synthesize, characterize, and study the in vivo behavior of a

variety of ^{68}Ga -labeled radiopharmaceuticals. Based on our results to date, it appears that we have designed a ligand for ^{68}Ga which will have a high stability constant, and be highly lipophilic. As such, our major emphasis in the continuation of this project will be the synthesis of this ligand, and investigations on the behavior of the chelate formed between this ligand and ^{68}Ga .

III. Graduate students trained, degrees granted, and post-doctoral tenures completed.

Gary J. Ehrhardt, Ph.D. - completed post-doctoral tenure from November 1, 1977 - February 28, 1979; he is now Senior Research Chemist at the Research Reactor, University of Missouri, Columbia, MO.

Sivarajan Pandian, Ph.D. - was a post-doctoral associate working on this project from July 1979 through April 1980; he is currently completing his post-doctoral tenure working on a different project in our research group.

Stephen M. Moerlein - graduate student; Ph.D. expected 1980.

Marcy North - graduate student; M.S. expected 1981.

IV. Bibliography, with titles of publications associated with this contract.

A new germanium-68/gallium-68 generator. Ehrhardt GJ, Welch MJ, J Nucl Med 19:925-929, 1978.

Gallium-68 labeling of albumin and albumin microspheres. Wagner SJ, Welch MJ, J Nucl Med 20:428-433, 1979.

Applications of gallium-68 produced by the gallium-68-oxine generator.

Ehrhardt GJ, Wagner SJ, Welch MJ, Second International Symposium on Radiopharmaceutical Chemistry, Oxford, England, 1978. J Labelled Compounds and Radiopharm 16:111, 1979.

Radiopharmaceuticals for neurological studies, in Radiopharmaceuticals II: Proceedings of Second International Symposium on Radiopharmaceuticals. Welch MJ, Tewson TJ, Society of Nuclear Medicine, New York, 1979, pp 201-217.

The design and testing of an automated $^{68}\text{Ge}/^{68}\text{Ga}$ solvent extraction generator. Ehrhardt GJ, Hood R, Djordjevic L, Welch MJ, 26th Annual Meeting of the Society of Nuclear Medicine, Atlanta, GA, 1979, J Nucl Med 20:682, 1979.

Radiolabeled compounds of biomedical interest containing nuclides of gallium and indium, in ACS Symposium on Inorganic Chemistry in Biology and Medicine, Welch MJ, Moerlein S, American Chemical Society, Martell AE (ed), Washington, D.C., 1979, in press.

Tricatecholamide analogs of enterobactin as Ga and In radiopharmaceuticals. Moerlein SM, Welch MJ, Raymond KN, Weigl FL, Proceedings of Third International Symposium on Radiopharmaceutical Chemistry, St. Louis, MO, 1980, to be published in J Lab Comp Radiopharm.

Chemistry of gallium and related elements. Welch MJ, to be presented at the International Conference on Gallium and Related Elements, Banff, Alberta, Canada, September 1980, to be published by Academic Press.

Positron tomographic imaging of the liver with Ga-68 iron hydroxide colloid. Kumar B, Miller TR, Siegel BA, Mathias CJ, Markham J, Ehrhardt GJ, Welch MJ, submitted to Am J Roentgenol.

V. Opinion on the present state of knowledge in this area of research, its significance in the field of nuclear medicine, and needed future investigations.

Gallium-68 is one of a very limited number of positron-emitting, generator-produced radionuclides. Investigations with ^{68}Ga have led to a series of ^{68}Ga -labeled radiopharmaceuticals. One of these radiopharmaceuticals, ^{68}Ga -ferric hydroxide colloid, has been investigated in a limited clinical trial in this project, and others are being investigated here and at several other institutions. If our work on this project can lead to the development of a highly lipophilic ^{68}Ga ligand, the result will be a broad spectrum of ^{68}Ga -radiopharmaceuticals for use with positron emission transaxial tomography in institutions which do not have access to a cyclotron.

VI. Present division of Federal support for Principal Investigator.

<u>Grant</u>	<u>Source</u>	<u>Title</u>	<u>Amount</u>	<u>% Effort</u>
HL 13851	NIH	Cyclotron-Produced Isotopes	43,926	60
HL 14147	NIH	SCOR in Thrombosis	87,696	10
NS 06833	NIH	Interdisciplinary Stroke	102,730	10
DE-AS02-77EV04318	DOE	^{68}Ga Positron Emission	74,712	10

OBJECTIVES

The aims of this project are to:

1. Develop a germanium-68/gallium-68 generator that does not produce gallium-68 as gallium-EDTA;

2. To use the product of this generator to produce a series of gallium-68 radiopharmaceuticals.
3. To devise a lipophilic gallium radiopharmaceutical.

WORK IN PROGRESS

Work carried out on this project over the past three years has centered on the following areas:

1. Development of an improved germanium-gallium generator;
2. Preparation of radiopharmaceuticals using the ^{68}Ga -oxine from a solvent extraction generator system;
3. Development of a general method for preparing gallium-68 labeled proteins;
4. Approaches to the production of lipophilic gallium-68 labeled compounds.

1. GALLIUM-68 GENERATORS

We have developed a solvent extraction germanium-68/gallium-68 generator which yields gallium-68 in the form of ^{68}Ga -oxine. The details of this generator system have been discussed by Ehrhardt and Welch (1) (See Appendix A). An automated solvent extraction generator was fabricated in the Washington University Cyclotron machine shop during the period June 1977 to October 1978 (2); the use of such a system greatly reduces the problems of high radiation exposure to the operator which are associated with solvent extraction generator systems (See Appendix B).

We have encountered problems in producing some ^{68}Ga -radiopharmaceuticals, specifically labeled platelets, utilizing ^{68}Ga -oxine from a large scale (~ 10 mCi ^{68}Ge) generator. It was initially thought that these problems were attributable to the extensive radiation damage to the siliconized glass separatory funnels and test tubes, causing the release of contaminating metal ions. Subsequent investigations using both clear teflon and quartz vessels were unsuccessful in eliminating these problems. Thus, the $^{68}\text{Ge}/^{68}\text{Ga}$ solvent extraction generator which has been developed provides a good yield of ^{68}Ga , with a minimum of ^{68}Ge parent breakthrough, in a weakly complexed form which is useful for preparing a variety of ^{68}Ga -radiopharmaceuticals. However, there are difficulties associated with using the ^{68}Ga -oxine eluted from this generator to label some radiopharmaceuticals, specifically platelets. Also, inherent in the use of a solvent extraction system are difficulties in automating the organic-aqueous phase separation and increased risks of irradiation and contamination.

For these reasons, we have begun preliminary investigations of some alternative generators which provide ^{68}Ga in a convenient ionic form. Several new generator systems have been described which provide ^{68}Ga in ionic form. However, these generators have either been prepared only on very small prototype scales (~ 5 - 10 μCi), or the amounts of ^{68}Ge loaded onto the generators is not reported. Thus, we have begun comparative studies of several $^{68}\text{Ge}/^{68}\text{Ga}$ generator systems using ~ 2 mCi ^{68}Ge per generator.

Comar and co-workers (3) recently described a $^{68}\text{Ge}/^{68}\text{Ga}$ generator consisting of 10 μCi ^{68}Ge adsorbed onto a 3.5 gram SnO_2 column; their

generator is eluted with 1 M HCl to give a good yield of ^{68}Ga , with low ^{68}Ge breakthrough and metal contamination. We have attempted to prepare a tin dioxide/1 M HCl generator containing 2 mCi ^{68}Ge ; however, to date we have only been successful in loading ~ 0.9 mCi onto a 5 gram SnO_2 (Carlo-Erba, Milano, Italy) column. The elution profile of the generator is good, with $\sim 70\%$ ^{68}Ga elution yield using 5 ml 1 M HCl. However, the ^{68}Ge breakthrough ($1.38 \pm 0.19\%$) is unacceptably high.

An inorganic generator system eluted with aqueous alkaline solutions for the generation of ionic Ga-68 has recently been proposed (4,5). The ^{68}Ga is obtained as the gallate ion (GaO_2^-), which is readily convertible to various ^{68}Ga -radiopharmaceuticals. The preliminary reports of such a generator system using alumina columns eluted with dilute NaOH do not mention the amount of ^{68}Ga which was used. Since the amounts were likely very small, and generator properties can vary significantly when larger amounts of radioactivity are used, we have prepared a 2 mCi generator for preliminary investigations by adsorbing ^{68}Ge onto a 1 x 5 cm column of neutral alumina (BioRad AG-7). Elution of the generator with 5 ml 0.1 M NaOH gives a 50-60% yield of ^{68}Ga . However, the ^{68}Ge breakthrough values which we have obtained are unacceptably high. The ^{68}Ge breakthrough has steadily risen from initial values in the range 0.006 - 0.9, to an average of 3.9 ± 0.5 after 60 elutions. The Al^{3+} level determined colorimetrically by complexation with aluminon reagent has decreased to < 5 mg/ml.

Thus, our preliminary studies on the comparison of solvent extraction and chromatographic $^{68}\text{Ge}/^{68}\text{Ga}$ generators are not promising with respect to the

usefulness of large scale chromatographic generators for the production of ionic gallium-68. However, further studies on modified chromatographic generator systems must be carried out before a final conclusion can be drawn as to the ideal generator system to provide large amounts of pure and usable ^{68}Ga for radiopharmaceutical preparation.

2. RADIOPHARMACEUTICAL PREPARATION

The ^{68}Ga -oxine eluted from both a 2-3 mCi ^{68}Ge prototype solvent extraction generator and a 10 mCi ^{68}Ge solvent extraction generator has been used to prepare various ^{68}Ga -labeled radiopharmaceuticals. A few preliminary studies have also been carried out on the preparation of ^{68}Ga -radiopharmaceuticals from ionic ^{68}Ga eluted from the column chromatographic generators described above.

^{68}Ga -Ferric Hydroxide Colloid

We have prepared a liver radiopharmaceutical, ^{68}Ga -ferric hydroxide colloid. The manuscript presented in Appendix C summarizes the preparation of this ^{68}Ga -labeled liver radiopharmaceutical, animal distribution studies on the agent, and clinical trials using the ^{68}Ga -radiopharmaceutical in conjunction with positron emission tomography (PETT IV).

^{68}Ga -Labeled Platelets

Previous studies have shown that endothelial injury (6), deep vein thrombosis (7), and atherosclerotic lesions (8) can be scintigraphically detected using indium-111-labeled platelets. The use of ^{68}Ga as the label for

platelets adds the advantage of detection of such disorders with a positron imaging device (9).

The procedure used for preparing ^{68}Ga -labeled platelets is as follows. Platelets are separated from 43 ml of whole blood collected in 7 ml modified ACD solution (E.R. Squibb and Sons, Inc., Princeton, NJ). The whole blood is centrifuged at 180g for 15 minutes; the platelet rich plasma is transferred to a plastic conical tube and spun at 2000g for 10 minutes. The platelets are washed with a 1:7 solution of ACD and 0.9% NaCl (pH 6.5) and resuspended in the labeling solution, which consists of ^{68}Ga -oxine (reconstituted in 50 μl of ethanol and 150 μl 0.9% NaCl) and 4 ml 1:7 ACD/0.9% NaCl solution. The cells are incubated at room temperature for 20 minutes, then washed with plasma retained from the initial cell separation. The final ^{68}Ga -platelet preparation is resuspended in plasma separated from 20 ml whole blood drawn into 2 ml 3.8% sodium citrate.

Using ^{68}Ga -oxine eluted from a 3 mCi $^{68}\text{Ge}/^{68}\text{Ga}$ solvent extraction generator, a mean labeling efficiency of $48 \pm 21\%$ was obtained for eight cases. As shown in Table I, the ^{68}Ga -label remains stably attached to the platelets; this is analogous to what is observed with other platelet labels. ^{68}Ga -platelets which have been washed with plasma and resuspended in plasma containing 50 μg oxine release approximately 30% of the radiolabel over 4 hours. In other words, the ^{68}Ga slowly exchanges from its binding site in the platelet to oxine. Labeled platelets which are resuspended in citrated plasma were evaluated in vitro by their ability to aggregate in response to certain stimuli (collagen and ADP). In seven of the eight cases, the ^{68}Ga -platelets

responded to both ADP and collagen.

While our initial studies on ^{68}Ga -labeled platelets prepared using 2-3 mCi ^{68}Ga eluted from the prototype solvent extraction generator gave labeling efficiencies around 50%, attempts to label platelets with gallium-68 eluted from our 10 mCi solvent extraction generator resulted in much lower labeling yields (10-20%). This drop in platelet labeling yields using ^{68}Ga from the larger generator is presumably due to the presence of impurities released from the vessel containing the ^{68}Ga as a result of radiolysis damage.

In order to more critically evaluate the viability of ^{68}Ga -platelets, an in vivo model with a known site of injury must be utilized. Thrombi and pulmonary emboli can be localized scintigraphically using ^{111}In -platelets; similarly, ^{68}Ga -platelets have been used to detect fresh emboli via positron tomography. More animal studies should be carried out, using larger amounts of ^{68}Ga , to establish the in vivo distribution of ^{68}Ga -platelets in cases of carotid artery intimal damage, pulmonary emboli, mural thrombi, and deep vein thrombosis. PETT imaging with ^{68}Ga -platelets may prove to be a good method to demonstrate coronary artery thrombosis, initially induced in an animal model via an electrical current technique (10).

^{68}Ga -EDTMP

^{68}Ga -ethylenediaminetetramethylene phosphonate (^{68}Ga -EDTMP) is a useful skeletal imaging agent (11), and ^{113}mIn -EDTMP has been shown to localize in injured myocardium in rats (12). We have prepared ^{68}Ga -EDTMP in high yields, and have carried out animal distribution studies using a rat model for damaged

myocardium to investigate the potential of this radiopharmaceutical as a myocardial infarct imaging agent.

^{68}Ga -EDTMP was prepared by adding ^{68}Ga -oxine in 0.25 ml 1 M HCl to 0.25 ml of an EDTMP stock solution (100 mg/ml, neutralized to pH 6.5). ^{67}Ga -EDTMP was prepared in an analogous manner, using ^{67}Ga -citrate in 1 M HCl. After incubation for 3 minutes, the labeling mixture was neutralized to pH 6.5 with 1 M NaOH. The resulting solution was analyzed via paper chromatography using two solvent systems: A = pyr:EtOH:H₂O, 1:2:4; B = isopropanol (275 ml), H₂O (125 ml), TCA (15 g) and concentrated NH₃ (1 ml) (13). Typical radiochromatograms for ^{67}Ga -citrate, ^{68}Ga -oxine, and $^{67,68}\text{Ga}$ -EDTMP in these two solvent systems are shown in Figures 1-6. These radiochromatograms were obtained using a new radiochromatogram scanner which was designed for use with both positron and γ -emitting radiopharmaceuticals developed by us in the first period of this contract.

The affinity of ^{68}Ga -EDTMP for damaged myocardium was investigated using a rat model for infarcted myocardium -- skeletal muscle injury by liq. N₂ freezing of the quadriceps femoris (14); $^{99\text{m}}\text{Tc}$ -pyrophosphate ($^{99\text{m}}\text{Tc}$ pyp) was used as a standard for comparison. ^{68}Ga -EDTMP and $^{99\text{m}}\text{Tc}$ -pyp were injected 24 hours following the injury, and the rats were sacrificed one hour post injection. Samples of blood, damaged muscle, normal muscle, and tibia were removed and counted for both $^{99\text{m}}\text{Tc}$ and ^{68}Ga .

Table II shows the % injected dose per gram of tissue for both ^{68}Ga -EDTMP and $^{99\text{m}}\text{Tc}$ -pyp. The results are expressed as the mean $\pm$ standard deviation for eight rats. Studies were also carried out to examine the effect of the amount

of chelating agent (EDTMP or pyp) injected on the affinity of the radiopharmaceuticals for damaged muscle. As shown in Table III, the amount of chelating agent has a marked effect on the affinities of both ^{68}Ga -EDTMP and $^{99\text{m}}\text{Tc}$ -pyp. Each number is the mean $\pm$ standard deviation for three rats.

^{68}Ga -EDTMP has also been prepared using ionic ^{68}Ga eluted from both the $\text{SnO}_2/1\text{ M HCl}$ and $\text{Al}_2\text{O}_3/0.1\text{ M NaOH}$ 2 mCi prototype $^{68}\text{Ge}/^{68}\text{Ga}$ generators. In both cases, the volume of eluted ^{68}Ga (in either 0.1 M NaOH or 1 M HCl) was reduced by rotary evaporation, and 10-25 mg EDTMP was added. After 3 minutes incubation, the solutions were neutralized to pH 6.5 and analyzed via paper chromatography as described above. In both cases, all of the ^{68}Ga activity present was attached to EDTMP.

Further animal studies must be carried out on a larger animal model for myocardial infarction in dogs, and imaging of damaged myocardium upon injection of ^{68}Ga -EDTMP in conjunction with positron tomography must be carried out. However, preliminary data suggests that the affinity of ^{68}Ga -EDTMP for damaged myocardium is close enough to that of $^{99\text{m}}\text{Tc}$ -pyp to make it a useful myocardial infarct imaging agent when the advantages of positron tomography are considered.

3. DEVELOPMENT OF A GENERAL METHOD FOR THE LABELING OF ^{68}Ga -PROTEINS

A method of attaching ^{68}Ga to proteins via the bifunctional chelating agent DTPA has been developed. The preparation and characterization of proteins labeled with ^{68}Ga in this manner, as well as in vivo clearance data and PETT images of dog's lungs after injection of ^{68}Ga -DTPA-HSA microspheres

have been described (15) (see Appendix D).

4. APPROACHES TO THE PRODUCTION OF LIPOPHILIC ^{68}Ga -LABELED COMPOUNDS

Initial attempts in this direction utilized cryptates as potential agents for use with ^{68}Ga . However, studies carried out using U.V. spectroscopy, HPLC and polarography have led us to believe that such complexes are either unstable or it is difficult to form the complex.

Enteric bacteria such as Escherichia coli and Salmonella typhimurium are known to synthesize low molecular-weight iron-chelating agents called siderophores to satisfy their nutritional demands for iron (16,17). Enterobactin is a siderophore which is the most powerful ferric iron chelating agent known (18,19). Although its high log K of 52 is able to solubilize ferric iron and facilitate the transport of the metal into cells, enterobactin is a cyclic ester which readily hydrolyzes at physiological pH, and hence is not useful as a metal-complexing drug. Development of 2,3-dihydroxybenzoylamide analogs of enterobactin has led to iron-binding ligands which are characterized by both high stability constants and resistance to solution hydrolysis (20,21). These synthetic tricatecholate ligands have been shown to be kinetically and thermodynamically capable of removing iron from transferrin under physiological conditions (22). Because gallium is a Group IIIB element with charge, ionic radius, and complexation characteristics similar to ferric ion (23,24), the applicability of synthetic catecholamide ligands as gallium-binding radiopharmaceuticals was investigated.

Initially, the three ligands TiP-MECAMS, 3,4DiP-LICAMS, and 3,4DiP-LICAM

(Figure 7) were studied. Because of the short half-life of gallium-68, which imposes severe limitations on the length of any experiment, preliminary in vitro and in vivo studies of these agents were carried out using ^{67}Ga . Each ligand, synthesized according to published techniques (25,26), was kindly supplied to us by Prof. K. Raymond (Department of Chemistry, University of California, Berkeley, CA). The stability constants of the gallium complexes were determined using ^{67}Ga and competitive exchange between the ligand and EDTA. ^{67}Ga -citrate was added to a 0.1 M citrate buffer containing tri-catecholate ligand and EDTA in varying ratios. After 24 hours at room temperature, the ^{67}Ga -catecholamide and ^{67}Ga -EDTA which formed were separated by gel permeation chromatography on Sephadex G10 (1 x 145 cm) eluted with 0.05 M Tris-acetate buffer (pH 7.0). Fractions were collected and counted in a NaI(Tl) well counter, and the relative concentrations of ^{67}Ga EDTA and ^{67}Ga -catecholamide were determined based on the elution volumes for each complex. At the equilibrium concentrations ratio of EDTA to catecholate (that concentration which gave equal yields of ^{67}Ga -EDTA and ^{67}Ga -catecholamide), the log stability constant of the latter was calculated according to

$$\log K_{\text{Ga-ligand}} = \frac{[\text{EDTA}]}{[\text{catecholamide}]} \quad (21.1)$$

where [EDTA] and [catecholamide] are the total concentrations of EDTA and ligand, respectively, and 21.1 is the log K, for Ga-EDTA as determined electrochemically (27). The results of these experiments are shown in Table IV, which indicates that gallium is strongly bound by these ligands. These results suggest that sulfonation of the aromatic ring increases the stability

constant of the complex, probably by increasing the acidity of the parent catecholamide compound (21).

As an adjunct study of the usefulness of these ligands in nuclear medicine, the complexation between In and the tricatechols was studied. Indium is a Group IIIB metal which has chemical properties very similar to gallium (23), and has found widespread use in the nuclear medicine field as the In-111 and In-113m nuclides (28). The stability constants of these complexes were determined by Sephadex separation after competitive equilibration with EDTA, as was done with the ^{67}Ga complexes. The decay characteristics of ^{111}In (Figure 8) allow the use of an alternative technique to study complexation of this metal. The angular correlation between the direction of emission of the cascading 173 keV and 247 keV γ -rays (emitted within 8.5×10^{-8} sec of each other) are studied as a function of their chemical environment in the so-called PAC (perturbed angular correlation) experiment (29,30). The coincidence counting rate as a function of the angle of emission of the two cascading gamma rays is given by

$$W(\theta, t) = \frac{1}{\tau_n} \exp(-t/\tau_n) \left[1 + A_{22}G_{22}(t)P_2\cos\theta \right]$$

where t is the time interval between the emission of the two cascading γ rays, τ_n is 122 nsec (mean lifetime of the intermediate state), A_{22} is a characteristic constant of the nuclear decay scheme (0.18), and $P_2\cos\theta = (3\cos^2\theta - 1)/2$ (a simplification of the Legendre polynomial expansion for the

characteristic directional distribution for each transition). $G_{22}(t)$ is the differential angular perturbation factor which describes the interaction between the nuclear decay process and extranuclear fields. For a coincidence unit in which the time resolution is larger than the intermediate level life, the integral angular perturbation factor is studied, given by

$$\langle \overline{G_{22}(\infty)} \rangle = (1/\tau_n) \int_0^{\infty} G_{22}(t) \exp(-t/\tau_n) dt$$

Experimentally, the integral angular perturbation factor is calculated according to

$$\langle \overline{G_{22}(\infty)} \rangle = \frac{2\bar{A}}{-A_{22}(3-\bar{A})}$$

WHERE

$$\bar{A} = 1 - \frac{\overline{W(\pi, \infty)}}{\overline{W(\pi/2, \infty)}}$$

$\overline{W(\pi, \infty)}$ IS THE TOTAL NUMBER OF COINCIDENCES AT 180°

$\overline{W(\pi/2, \infty)}$ IS THE TOTAL NUMBER OF COINCIDENCES AT 90°

This method was applied to the determination of the stability constants of ^{111}In -TIP-MECAMS, ^{111}In -3,4DIP-LICAMS, and ^{111}In -3,4DIP-LICAM by adding the metal to 0.1 M citrate (pH 7.0) solutions containing varying ratios of EDTA to catecholamide. By studying the change of the integral angular perturbation factor of the solution, the exchange of ^{111}In from catecholamide to EDTA was seen as $\langle \overline{G_{22}(\infty)} \rangle$ decreased from 0.44 to 0.18. The relative EDTA to catecholate concentration ratio was thereby determined for the point of

mid-exchange, i.e. for $\langle \overline{G_{22}(-)} \rangle = 0.36$ taking the $\log K_i$ for In-EDTA = 25.3 (31), the relative K log stability constants were calculated, as in the gel permeation experiments. These results are also listed in Table IV, and show reasonable agreement with the data obtained from gel permeation studies.

Biological distribution data for the three gallium complexes was determined using 150 g rats injected with 10-20 μ Ci of the respective ^{67}Ga complex. The animals were sacrificed at several times post injection (1,3,5,18, and 24 hours) and the various organs were removed, counted and the percent injected dose/gram of tissue calculated.

The results for ^{67}Ga -3,4DiP-LICAMS, ^{67}Ga -TiP-MECAMS and ^{67}Ga -3,4DiP-LICAM are shown in Tables V, VI, VII, as well as the biodistribution for ^{67}Ga -citrate as a control (Table VIII). Each value represents the mean for at least three rats. As shown in these tables, the distributions for all three complexes differ from the citrate control. All show significant decreases in blood, liver, and bone activity at 24 hours, and the sulfonated derivatives show substantial kidney localization. Exchange of the ^{67}Ga -complexes to form ^{67}Ga -transferrin does not seem to be occurring.

To further investigate the pharmacokinetics of these complexes in rats, the clearance data shown in Figures 9-13 were determined. In these experiments, the percent injected dose per organ was determined shortly after injections (10,20,30,60, and 120 minutes) for the liver, kidneys, intestines, and bladder (urine) to find correlations with the decrease in blood radioactivity. The points represent means of data obtained from three or more animals and indicate results for the three catecholamide complexes as well as

^{67}Ga -citrate and ^{67}Ga -EDTA. As Figure 9 shows, the blood levels drop faster for the LICAM and LICAMS analogs than for the MECAMS derivative. However, all complexes leave the blood pool at a slower rate than ^{67}Ga -EDTA.

Figures 10 and 11 show the effect of renal uptake and excretion.

^{67}Ga -EDTA shows the expected rapid drop in renal activity as the complex is excreted into the bladder, which shows a cumulative activity of about 45% of the injected dose at 2 hrs. The two sulfonated complexes, ^{67}Ga -3,4DiP-LICAMS and ^{67}Ga -TiP-MECAMS show high renal activity, with relatively slow urine accumulation. Apparently, these ligands are undergoing tubular reabsorption after being filtered/secreted into the renal tubules, so that the net renal clearance is slower. This may be a function of the isopropyl groups on the amide nitrogens, since it would be expected that without these groups the amide would deprotonate and show increased aqueous solubility. ^{67}Ga -3,4DiP-LICAM, on the other hand, shows little renal absorption or clearance.

Figures 12 and 13 show how ^{67}Ga -3,4DiP-LICAM is cleared via the liver into the intestines; the initial high liver uptake of the complex falls at about the same rate as the rapid increase in intestinal activity. ^{67}Ga -TiP-MECAMS also shows increased liver uptake with time, but the steady fall of intestinal activity suggests that this complex is merely being trapped by some type of hepatic trapping mechanism.

In conclusion, 3,4DiP-LICAMS and TiP-MECAMS complexes with gallium clear from the blood pool primarily via the kidneys, while the less polar ^{67}Ga -3,4DiP-LICAM is excreted via hepatic pathways. Since no specific organ

localization was found for these ligands, as a side-application, the usefulness of these catecholamide in decreasing the blood background of ^{67}Ga -citrate in tumor or abcess imaging procedures was investigated. Figures 14 and 15 show the 4 and 24 hour ^{67}Ga citrate distribution, in a normal 1.5 kg rabbit administered 300 μCi of activity, as well as the scans at 4 and 24 hours of a 1.5 kg rabbit administered 300 μCi ^{67}Ga citrate at time zero followed by a 60 μg dose of TiP-MECAMS two hours later. It is apparent from these images that TiP-MECAMS is able to complex in vivo with plasma-bound ^{67}Ga and to decrease blood background activity. This is a similar effect to that observed by Oster et al using deferoxamine (32); it should, however, be noted that deferoxamine binds both divalent and trivalent metals whereas the tricatechol ligands are specific for trivalent metals.

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TABLE I

% OF ^{68}Ga ACTIVITY ASSOCIATED WITH
PLATELETS RESUSPENDED IN

<u>TIME</u>	<u>WHOLE BLOOD</u>	<u>PLASMA</u>	<u>PLASMA WITH OXINE</u>
0 min	86.5	86.5	87.8
15	89.2	89.1	83.6
30	86.8	84.1	80.3
60	88.0	88.6	79.0
2 hr	87.6	84.0	72.9
3	86.0	80.0	69.5
4	83.4	81.0	69.0
5	86.1	84.6	----

TABLE II
COMPARISON OF TISSUE DISTRIBUTION OF ^{68}Ga -EDTMP
AND $^{99\text{m}}\text{Tc}$ -PYP IN RATS

	% I.D. per gram	
	^{68}Ga -EDTMP	$^{99\text{m}}\text{Tc}$ -pyp
blood	1.14 ± 0.07	0.41 ± 0.01
damaged muscle	2.22 ± 0.14	2.36 ± 0.38
normal muscle	0.26 ± 0.16	0.18 ± 0.16
bone	3.35 ± 0.66	3.32 ± 1.08

TABLE III

THE EFFECT OF THE AMOUNT OF CHELATING AGENT ON
THE AFFINITY OF ^{68}Ga -EDTMP AND $^{99\text{m}}\text{Tc}$ -PYP
FOR DAMAGED MUSCLE IN RATS

AMOUNT OF CHELATING AGENT	<u>cts per gram of damaged muscle</u> <u>cts per gram of normal muscle</u>	
	^{68}Ga -EDTMP	$^{99\text{m}}\text{Tc}$ -pyp
0.1 mg	1.63 ± 0.28	3.75 ± 1.24
0.5 mg	3.07 ± 0.91	6.40 ± 2.27
2.0 mg	6.09 ± 1.79	11.3 ± 4.9

TABLE IV

LOG STABILITY CONSTANTS^{*}
(in 0.1 M citrate, pH 7.0)

LIGAND	IPAC	Sephadex G-10 Separation	
	^{111}In	^{111}In	^{67}Ga
TiP-MECAMS	23.1±0.5	22.0±0.5	26.0±0.5
3,4DiP-LICAMS	25.4±0.5	24.8±0.5	26.0±0.5
3,4DiP-LICAM	22.8±0.5	21.8±0.5	22.5±0.5

^{*}Based on $\log K_1 = 25.3$ for In-EDTA

$\log K_1 = 21.1$ for Ga-EDTA

(G. Anderegg, Helv. Chim. Acta, 50:2333, 1967)

TABLE IV

BIODISTRIBUTION OF ^{67}Ga -3,4DiP-LICAMS
(in 150 gram Sprague-Dawley rats)

% I.D. PER GRAM	TIME POST INJECTION				
	1 hr	3 hrs	5 hrs	18 hrs	24 hrs
BLOOD	0.30 ± 0.05	0.27 ± 0.07	0.24 ± 0.08	0.02 ± 0.01	0.01 ± 0.01
HEART	0.17 ± 0.02	0.13 ± 0.01	0.13 ± 0.02	0.03 ± 0.01	0.04 ± 0.01
LUNGS	0.27 ± 0.01	0.21 ± 0.04	0.18 ± 0.05	0.04 ± 0.02	0.06 ± 0.01
LIVER	0.28 ± 0.03	0.42 ± 0.08	0.37 ± 0.06	0.18 ± 0.06	0.24 ± 0.04
SPLEEN	0.11 ± 0.02	0.16 ± 0.05	0.19 ± 0.04	0.05 ± 0.01	0.06 ± 0.01
KIDNEYS	17.56 ± 2.88	22.16 ± 4.88	13.91 ± 0.96	8.74 ± 2.36	11.14 ± 4.67
MUSCLE	0.08 ± 0.04	0.08 ± 0.01	0.07 ± 0.01	0.02 ± 0.01	0.03 ± 0.01
BONE	0.15 ± 0.02	0.22 ± 0.07	0.25 ± 0.03	0.01 ± 0.01	0.05 ± 0.00
BRAIN	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.00	0.01 ± 0.01

TABLE V

BIODISTRIBUTION OF ^{67}Ga -3,4DiP-LICAMS
(in 150 gram Sprague-Dawley rats)

% I.D. PER GRAM	TIME POST INJECTION				
	1 hr	3 hrs	5 hrs	18 hrs	24 hrs
BLOOD	0.30±0.05	0.27±0.07	0.24±0.08	0.02±0.01	0.01±0.01
HEART	0.17±0.02	0.13±0.01	0.13±0.02	0.03±0.01	0.04±0.01
LUNGS	0.27±0.01	0.21±0.04	0.18±0.05	0.04±0.02	0.06±0.01
LIVER	0.28±0.03	0.42±0.08	0.37±0.06	0.18±0.06	0.24±0.04
SPLEEN	0.11±0.02	0.16±0.05	0.19±0.04	0.05±0.01	0.06±0.01
KIDNEYS	17.56±2.88	22.16±4.88	13.91±0.96	8.74±2.36	18.32±3.08
MUSCLE	0.08±0.04	0.08±0.01	0.07±0.01	0.02±0.01	0.03±0.01
BONE	0.15±0.02	0.22±0.07	0.25±0.03	0.01±0.01	0.05±0.00
BRAIN	0.01±0.01	0.01±0.01	0.01±0.01	0.00	0.01±0.01

TABLE VI

BIODISTRIBUTION OF ^{67}Ga -TIP-MECAMS
(in 150 gram Sprague-Dawley rats)

% I.D. PER GRAM	TIME POST INJECTION				
	1 hr	3 hrs	5 hrs	18 hrs	24 hrs
BLOOD	0.77±0.12	0.18±0.03	0.08±0.03	0.02±0.02	0.03±0.03
HEART	0.34±0.04	0.18±0.06	0.10±0.02	0.12±0.03	0.10±0.03
LUNGS	0.47±0.05	0.23±0.08	0.14±0.02	0.17±0.08	0.13±0.02
LIVER	1.43±0.18	1.64±0.60	1.34±0.18	1.09±0.42	0.94±0.24
SPLEEN	0.35±0.01	0.39±0.11	0.39±0.27	0.41±0.17	0.35±0.07
KIDNEYS	19.52±1.47	28.95±10.73	28.93±10.11	32.47±14.84	25.42±3.63
MUSCLE	0.16±0.02	0.13±0.07	0.11±0.08	0.08±0.03	0.06±0.01
BONE	0.29±0.06	0.24±0.06	0.09±0.06	0.15±0.05	0.14±0.03
BRAIN	0.03±0.01	0.01±0.01	0.01±0.01	0.01±0.01	0.01±0.01

TABLE VII

BIODISTRIBUTION OF ^{67}Ga -3,4DiP-LICAM
(in 150 gram Sprague-Dawley rats)

% I.D. PER GRAM	TIME POST INJECTION				
	1 hr	3 hrs	5 hrs	18 hrs	24 hrs
BLOOD	0.28±0.04	0.17±0.06	0.11±0.02	0.02±0.01	0.02±0.01
HEART	0.13±0.02	0.07±0.01	0.06±0.01	0.02±0.01	0.02±0.01
LUNGS	0.22±0.05	0.11±0.02	0.08±0.01	0.02±0.01	0.05±0.02
LIVER	0.71±0.19	0.34±0.21	0.34±0.02	0.13±0.08	0.19±0.02
SPLEEN	0.08±0.02	0.08±0.01	0.10±0.05	0.10±0.03	0.11±0.02
KIDNEYS	4.14±1.28	5.61±3.89	4.93±1.23	2.84±0.72	3.60±0.79
MUSCLE	0.08±0.02	0.04±0.01	0.04±0.01	0.01±0.01	0.01±0.01
BONE	0.11±0.01	0.10±0.01	0.09±0.04	0.14±0.05	0.15±0.03
BRAIN	0.01±0.01	0.01±0.01	0.01±0.01	0.00	0.00

TABLE VIII

BIODISTRIBUTION OF ^{67}Ga -CITRATE
(in 150 gram Sprague-Dawley rats)

% I.D. PER GRAM	TIME POST INJECTION				
	1 hr	3 hrs	5 hrs	18 hrs	24 hrs
BLOOD	2.23±0.38	1.42±0.15	1.27±0.16	0.30±0.02	0.21±0.02
HEART	0.80±0.05	0.73±0.06	0.57±0.08	0.26±0.02	0.26±0.05
LUNGS	0.98±0.15	0.86±0.09	0.76±0.31	0.36±0.05	0.30±0.03
LIVER	0.75±0.31	1.08±0.12	1.54±0.56	1.32±0.20	1.90±0.09
SPLEEN	0.58±0.06	0.98±0.08	1.16±0.36	1.75±0.58	1.88±0.95
KIDNEYS	0.83±0.09	0.83±0.02	0.87±0.23	0.84±0.04	0.82±0.03
MUSCLE	0.23±0.10	0.34±0.06	0.23±0.02	0.10±0.01	0.08±0.03
BONE	0.95±0.45	1.35±0.12	1.42±0.46	2.44±0.26	2.65±0.30
BRAIN	0.10±0.03	0.08±0.02	0.06±0.03	0.04±0.01	0.04±0.01

FIGURE LEGENDS

FIGURE 1: Radiochromatogram (Whatman No. 1 paper) of ^{67}Ga -citrate in solvent A. Solvent A = pyr:EtOH:H₂O, 1:2:4.

FIGURE 2: Radiochromatograph (Whatman No. 1 paper) of ^{67}Ga -citrate in solvent B. Solvent B = isopropanol (275 ml), H₂O (125 ml), TCA (15 g), and conc. NH₃ (1 ml).

FIGURE 3: Radiochromatogram (Whatman No. 1 paper) of ^{68}Ga -oxine (pH 6.5 - 7.0) in Solvent A.

FIGURE 4: Radiochromatogram (Whatman No. 1 paper) of ^{68}Ga -oxine (pH 6.5 - 7.0) in solvent B.

FIGURE 5: Radiochromatogram (Whatman No. 1 paper) of ^{68}Ga -EDTMP (pH 6.5 - 7.0) in solvent A.

FIGURE 6: Radiochromatogram (Whatman No. 1 paper) of ^{68}Ga -EDTMP (pH 6.5 - 7.0) in solvent B.

FIGURE 7: Chemical structures of the catecholamide ligands: 3,4DiP-LICAM, 3,4DiP-LICAMS, and TiP-NECAMS.

FIGURE 8: Decay scheme of indium-111.

FIGURE 9: Blood clearance of several radiogallium chelates in rats.

FIGURE 10: Renal clearance of several radiogallium chelates in rats.

FIGURE 11: Cumulative bladder activity of several radiogallium chelates in rats.

FIGURE 12: Liver clearance of several radiogallium chelates in rats.

FIGURE 13: Intestinal clearance of several radiogallium chelates in rats.

FIGURE 14: Images of rabbits 4 hrs post injection of ^{67}Ga -citrate and ^{67}Ga -citrate followed by 60 mg TiP-MECAMS.

FIGURE 15: Images of rabbit 24 hrs post injection of ^{67}Ga -citrate and ^{67}Ga -citrate followed by administration of 60 mg TiP-MECAMS.

^{67}Ga -citrate/HCl
solvent A

$R_f = 0.97$

FIGURE 1

^{67}Ga -citrate/HCl
solvent B

$R_f = 0.97$

FIGURE 2

^{68}Ga -oxine, pH 6.5-7.0
solvent A

$R_f = 0.97$

FIGURE 3

^{68}Ga -oxine, pH 6.5-7.0

solvent B

$R_f = 1.0$

FIGURE 4

FIGURE 5

^{68}Ga -EDTMP
solvent B

$R_f = 0.49$

FIGURE 6

$\text{X}=\text{H}$: 3,4 DiP-LICAM

$\text{X}=\text{SO}_3\text{H}$: 3,4 DiP-LICAMS

TiP-MECAMS

FIGURE 7

PARTIAL DECAY SCHEME OF ^{111}In

FIGURE 8

FIGURE 9

FIGURE 10

FIGURE 11

FIGURE 12

FIGURE 13

4-HOURS POST-INJECTION

POSTERIOR

R

L

0.3 mCi/kg ^{67}Ga -Citrate

R

L

0.3 mCi/kg ^{67}Ga -Citrate

+40 $\mu\text{mole/kg}$ TIP-MECAMS after 2 hrs

FIGURE 14

24-HOURS POST-INJECTION

POSTERIOR

R

L

0.3 mCi/kg ^{67}Ga -Citrate

R

L

0.3 mCi/kg ^{67}Ga -Citrate

+ 40 $\mu\text{mole/kg}$ TiP-MECAMS after 2 hrs

FIGURE 15

TIME ALLOTMENT OF PROFESSIONAL STAFF

	<u>Current % Effort</u>	<u>% Effort for Rest of Period</u>
Michael J. Welch, Ph.D.	10%	10%
Barry A. Siegel, M.D.	10%	10%
Michel M. Ter-Pogossian, Ph.D.	5%	5%
B. Kumar, M.D.	5%	5%
Karen D. McElvany, Ph.D.	5%	5%
S. Pandian, Ph.D.*	--	--
Stephen M. Moerlein, M.A.	20%	20%
Marcy North	50%	50%

*Dr. Pandian was involved on the ⁶⁸Ga-radiopharmaceutical project from July 1979 to September 1979 at 50% effort. He is now working on another project in this laboratory.

EQUIPMENT PURCHASED (November 1979 - October 1980)

LKB Multiperex peristaltic pump - Value \$1715.00

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