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PREPARATION OF RADIOPHARMACEUTICALS LABELED WITH GALLIUM AND INDIUM

PROGRESS REPORT

FOR PERIOD

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NOTICE

Comprehensive Report

A. Major Research Accomplishments

The goals of the project 3 years ago were:

1. to carry out routine production of Ga-68 labeled radiopharmaceuticals for use, particularly in pulmonary studies;
2. to continue work on the development of Ga-68 labeled radiopharmaceuticals that could be used with positron emission tomography;
3. to evaluate indium-111 and possibly gallium-68 labeled antibodies in animal models;
4. continue development of new chelates and bifunctional chelates for use as radiopharmaceuticals;
5. new approaches to the delivery of radiopharmaceuticals to the brain.

We have made major advances in all of these areas. In area one, we have shown that gallium-68 radiopharmaceuticals can be produced routinely under robotic control for patient studies. This has resulted in several publications by us and by our collaborators in the Pulmonary Division at Washington University.

In the second area, we have continued to study gallium-68 labeled radiopharmaceuticals and have carried out the work to allow gallium-68 labeled macroaggregated albumin to be administered to patients. This was necessary due to the fact that our previous gallium-68 particulate tracer, gallium-68 labeled microspheres could not be prepared due to the fact that the microsphere kit from 3M was removed from the market. In the area of labeled antibodies we have studied indium-111 labeled antibodies in two animal models and compared gallium-68 labeled antibodies with indium and iodine antibodies in one of these models. It appears that gallium-68 labeled antibody fragments may have promise as radiopharmaceuticals.

In the area of new chelates, we have studied several chelates, particularly ones where the gallium and indium are chelated through 3-amino and 3-thiol groups. These chelates appear to be stable in vivo and have potential as new radiopharmaceuticals.

In the area of the preparation of new blood flow tracers, we have investigated not only gallium compounds but copper-62 compounds. A new copper-62 labeled radiopharmaceutical appears to have great potential for the use as a blood flow agent in the brain, heart and kidney. The agent has a greater extraction in the brain than any other metal complex studied and quantitative images provide values of blood flow in good agreement with those obtained with ^{15}O labeled water by a well validated technique.

B. Our plans for the continuation of the present objective are to continue along the five major lines outlined in the previous proposal. We have begun to investigate the use of gallium-68 labeled antibodies and proteins and this will be a major area of study. As discussed in the comprehensive progress report, gallium-68 labeled VLDL has potential for quantitating LDL receptors in the liver and we will plan to continue to evaluate ways of attaching gallium-68 to proteins and evaluating them in this model. In a similar way we will evaluate the gallium-68 labeling techniques with gallium-68 labeled antibodies.

Two types of totally new chelates will be studied. Some of these will be based upon the thiol structure described in the progress report and the other

work will be to prepare derivatives of N,N,N',N'-tetrakis[2-hydroxy-3,5-dimethylbenyl]ethylenediamine which we have shown to have some brain uptake. This is the first gallium or indium complex investigated by us to have any uptake in the brain and we hope to build upon this initial observation. Techniques will also be developed to attach the thiol type ligands to antibodies and work will continue in the evaluation of copper-PTSM as a general PET blood flow tracer.

C. Over the past funding period Susan Madsen and Carol Wiegers are working towards their Ph.D., although no Ph.D.'s have been granted with support from this grant in the last 3 year time period. Drs. Phyllis Otsuka and Dennis Moore have finished their postdoctoral tenures during the past time period. Over the total funding period, several graduate students and postdoctoral fellows have obtained positions in the field of particular note are Dr. Gary Ehrhart who is currently associated with the University of Missouri Radioisotope production facility and Dr. Mark Green who is now an Assistant Professor in the School of Pharmacy at Purdue University.

D. Publications.

1. WG Cance, SA Wells, WG Dilley, JM Welch, FL Otsuka, JM Davie. Human parathyroid antigen: characterization and localization with monoclonal antibodies. Proc Natl Acad Sci USA 83:6112, 1986.
2. FL Otsuka, JB Fleischman, MJ Welch. Comparative studies using ^{125}I and ^{111}In-labeled monoclonal antibodies. Int J Nucl Med Biol 13:325, 1986.
3. FL Otsuka, MJ Welch. Methods to label monoclonal antibodies for use in tumor imaging. Nucl Med Biol 14:243, 1987.
4. MA Mintun, DR Dennis, MJ Welch, CJ Mathias, DP Schuster. Measurements of pulmonary vascular permeability with positron emission tomography and Ga-68 transferrin. J Nucl Med 28:1704, 1987.
5. WG Cance, FL Otsuka, WG Dilley, RW Scott, JM Davie, MJ Welch, SA Wells, Jr. A potential new radiopharmaceutical for parathyroid imaging: radiolabeled parathyroid-specific monoclonal antibodies. Part 1. Evaluation of ^{125}I-labeled antibody in a nude mouse model system. Nucl Med Biol 15:299, 1988.
6. FL Otsuka, WG Cance, WG Dilley, RW Scott, JM Davie, SA Wells, Jr., MJ Welch. A potential new radiopharmaceutical for parathyroid imaging: radiolabeled parathyroid-specific monoclonal antibody. Part 2. Comparison of ^{125}I- and ^{111}In-labeled antibodies. Nucl Med Biol 15:305, 1988.
7. CJ Mathias, Y Sun, MJ Welch, MA Green JA Thomas, KR Wade, AE Martell. Targeting radiopharmaceuticals: comparative biodistribution studies of gallium and indium complexes of multidentate ligands. Nucl Med Biol 15:69, 1988.
8. MJ Welch, MR Kilbourn. Potential labeling of monoclonal antibodies with positron emitters. In Radiolabeled Monoclonal Antibodies for Imaging and Therapy, S.C. Srivastava, ed., Plenum Press, New York, 1988, pp 261.
9. FL Otsuka, MJ Welch. Use of an animal model system for evaluating labeled monoclonal antibodies. In Radiolabeled Monoclonal Antibodies for Imaging and Therapy, S.C. Srivastava, ed., Plenum Press, New York, 1988, pp 343.
10. CJ Mathias, MJ Welch, DB Schwartz, SM Spaethe, P Needleman. Differentiation in vivo of the sequential blood cell invasion following ureter

obstruction of the rabbit kidney. Nucl Med Biol 16:25, 1989.
11. DA Moore, PE Fanwick, MJ Welch. Synthesis, characterization and solid-state structure of a new hexachelating ligand and its complex with gallium (III). Inorganic Chemistry 28:1504, 1989.
12. ME Shelton, MA Green, CJ Mathias, MJ Welch, SR Bergmann. Kinetics of copper-PTSM in isolated hearts: a novel tracer for measuring blood flow with positron emission tomography. J Nucl Med, in press.
13. DA Moore, PE Fanwick, MJ Welch. A novel hexachelating amino-thiol ligand and its complex with gallium (III). Inorganic Chemistry, submitted.
14. CJ Mathias, Y Sun, MJ Welch, JM Connett, GW Philpott, AE Martell. A new bifunctional chelate, $BrMe_2HBED$; an effective conjugate for radiometals and antibodies. Inorganic Chemistry, submitted.
15. JW Brodack, SL Kaiser, MJ Welch. Laboratory robotics for the remote synthesis of generator-based positron-emitting radiopharmaceuticals. Laboratory Robotics and Automation, in press.
16. CJ Mathias, MJ Welch, MR Raichle, LL Lich, A McGuire, KR Zinn, E John, MA Green, MA Mintun. Evaluation of a potential generator - produced PET tracer for cerebral perfusion imaging: single pass cerebral extraction measurements and imaging with copper-labeled-PTSM. J Nucl Med, submitted.

Abstracts

1. FL Otsuka, WG Cance, MJ Welch, SA Wells, WG Dilley, JM Davie. The evaluation of radiolabeled anti-human parathyroid monoclonal antibodies using a nude mouse model system. J Nucl Med 27:958, 1986.
2. PA Jerabek, D Mellenberg, JK Donahue, JM Thomas, FL Otsuka, CJ Mathias, MJ Welch. Application of perturbed angular correlation measurements to the study of In-111 labeled proteins. J Lab Cmpd Radiopharm 23:1226, 1986.
3. CJ Mathias, MJ Welch, MA Green, JA Thomas, AE Martell, Y Sun. New chelates for the preparation of indium and gallium radiopharmaceuticals. J Lab Cmpd Radiopharm 23:1221, 1986.
4. CJ Mathias, MJ Welch. Studies on the entrapment of indium-111 in the liver following administration of proteins labeled using bifunctional chelates. J Nucl Med 28:657, 1987.
5. MJ Welch, CJ Mathias, Y Sun, WG Dilley, H Seesko, SA Wells, Jr., GW Philpott, JM Connett, AE Martell. N-(2-hydroxy-3,5-methylbenzyl)-N'-(2-hydroxy-5-bromoacetamidobenzyl)-ethylene-diamine-N,N'-diacetic acid: a new bifunctional chelate for radiolabeling antibodies. J Lab Cmpd Radiopharm, 26:305, 1989.
6. SM Moerlein, MJ Welch. Parameters affecting the labeling of ^{68}Ga-DTPA-LDL: a potential radiopharmaceutical for in-vivo imaging of tissue low-density lipoprotein receptor activity with PET. J Lab Cmpd Radiopharm, 26:285, 1989.
7. JW Brodack, MJ Welch. Automated synthesis of positron-emitting radiopharmaceuticals based on generator-produced radionuclides. J Lab Cmpd Radiopharm, 26:488, 1989.
8. DA Moore, MJ Welch, KR Wade, AE Martell, RJ Motekaitis. Neutral complexes of In-111 containing triamine based hexachelating ligands. J Lab Cmpd Radiopharm, 26:362, 1989.
9. SM Moerlein, A Daugherty, MJ Welch. Ga-68 DTPA-VLDL: A potential

radiopharmaceutical for PET quantification of tissue low-density lipoprotein receptor activity. J Nucl Med 30:763, 1989.

10. CJ Mathias, Y. Sun, MJ Welch, JM Connett, GW Philpott, AE Martell. BrφHBED: An improved bifunctional chelate for radiolabeling antibodies. J Nucl Med 30:763, 1989.
11. SL Madsen, MJ Welch, CJ Bannochie, AE Martell, MW Brown. In-vitro/-in-vivo behavior of EHPG complexes with metal ions. J Nucl Med 30:848, 1989.
12. ME Shelton, MA Green, CJ Mathias, MJ Welch, SR Bergmann. Microsphere-like retention in isolated hearts of copper-PTSM: a potential generator produced tracer for measuring blood flow with PET. J Nucl Med 30:768, 1989.
13. ME Shelton, MA Green, CJ Mathias, CJ Weinheimer, HL James, MJ Welch, SR Bergmann. Measurement of regional blood flow using copper-PTSM and positron emission tomography (PET). J Nucl Med 30:807, 1989.
14. CJ Mathias, MJ Welch, MA Green, AH McGuire, DJ Perry, ME Raichle, LL Lich, KR Zinn. PET cerebral blood flow imaging with copper-labeled-PTSM. J Nucl Med 30:791, 1989.
15. DA Moore, RJ Motekaitis, AE Martell, MJ Welch. A new amino-thiol ligand for radiopharmaceutical use with indium and gallium. J Nucl Med 30:922, 1989.

All publications are included in the Progress Report as Appendices. Abstracts which have subsequently been published (or submitted) as full papers are grouped in Appendix W.

E. With the widespread use of sophisticated positron imaging devices, there is an increase in demand for positron emitting radiopharmaceuticals. Generator produced radiopharmaceuticals add an extra dimension to the in house cyclotron produced radiopharmaceuticals. Generators for use of radiopharmaceuticals compliment accelerator produced compounds and mean that hospital accelerators could be of simpler design than those currently utilized. It is interesting to note that several companies, particularly IBA (Belgium) Science Research Laboratories (Sommerville, MA) and S.A.I.C. (San Diego) are selling or evaluating small simple accelerators. These simple accelerators together with fluorine-18 labeled compounds from a regional distribution center (a prototype of which is being set up in Los Angeles) and generator produced radiopharmaceuticals would allow a comprehensive PET center to operate without the large chemical staff and laboratory necessary at present. There are only a limited number of generators producing a positron emitting daughter. These include the strontium-82/rubidium-82 generator, the zinc-62/copper-62 generator, the xenon-122/iodine-122 generator as well as the germanium-68/gallium generator. Of these generators, the strontium/rubidium generator produces rubidium-82 which has a half-life of 75 seconds, possibly too short for conversion into any compound except Rb^+. The xenon-122/iodine-122 generator has the parent in a gaseous form which means the system is somewhat complex and liable to failure. The most promising two positron generators are the germanium-68/gallium-68 and the zinc-62/copper-62 generator and over the past funding periods major advances have been made in the development of compounds labeled with these agents. This will allow the use of PET technology in centers other than major medical centers and so be particularly significant in the field of human health and assessment matters.

PROGRESS REPORT

Work carried out on this project over the past contract period have centered on the areas outlined in the initial application. These were:

1. to evaluate the possibility of routine production of gallium-68 radiopharmaceuticals for clinical studies;
2. continued work on the development of gallium-68 radiopharmaceuticals that could be used with positron emission tomography;
3. to evaluate indium-111 and gallium-68 labeled antibodies and proteins in animal models;
4. to continue developments of new chelates and bifunctional chelates for use as radiopharmaceuticals and
5. to investigate new approaches for the delivery of radiopharmaceuticals to the brain.

1. Evaluation of routine production of germanium of gallium radiopharmaceuticals.

Over the past funding period gallium-68 labeled albumin microspheres and gallium-68 microaggregated albumin have been prepared routinely. The need for the development of microaggregated albumin was caused by the removal from the market of the 3M kit utilized in the preparation of labeled microspheres. We investigated parameters necessary for the labeling of microaggregated albumin with gallium and have developed a robotic preparation of this agent. (Appendix O) These gallium radiopharmaceuticals have resulted in a series of papers from our pulmonary colleagues (Appendix X) all of which have relied upon gallium-68 radiopharmaceutical produced by this grant. The conclusion of this phase of the work is that gallium-68 labeled radiopharmaceuticals do play an important role in the battery of radiopharmaceuticals utilized in a PET center.

2. To continue work on the development of gallium-68 labeled radiopharmaceuticals.

A major area in this area has been on the development of new radiopharmaceuticals in which 1,4,7-triazacyclononane is functionalized with three chelating groups. (Appendices K,M,V) We have shown that the hexachelating ligand, N,N',N''-(3,5-dimethyl-2-hydroxybenzyl)-1,4,7-triazacyclononane whose coordination sphere consists of an $N_3O_3^{3-}$ core, forms a stable complex with gallium(III). We have extended this class of compounds to the study of a new hexachelating ligand, N,N',N''-tris(2-mercaptoethyl)-,4,7-triazacyclononane which will allow coordination with an $N_3S_3^{3-}$ core producing a relatively small complex. The in vivo distribution of indium and gallium labeled complex have been studied in rats (Table 1) and it is seen that the radioactivity does clear through the liver. Preliminary stability studies on this complex suggested that at pH 7.4 the pM value (pM = minus log free metal in equilibrium with 10% excess ligand) for gallium and indium are 25.2 and 26.9 respectively. These compare favorably with the pM values for gallium labeled SHBED and PLED and are least 6 or 7 magnitude greater than the corresponding indium chelates. This preliminary data leads us to believe that more lipophilic substitute versions of the TS-TACN complex may have potential as radiopharmaceuticals and this will be a major goal in our upcoming proposal.

3. Evaluation of indium and gallium antibodies and proteins.

We have available to us two animal models for the evaluation of radiolabeled antibodies. One of these is the human transplanted parathyroid model described in appendices A, E and F. The other is the 1A3 antibody which is studied in adult male golden Syrian Hamsters which are transplanted with GW39 cancer cells. We have utilized this latter model (Appendices N-S) to study two new bifunctinal chelates. These bifunctional chelates are based upon the structure of HBED. These bifunctional chelates lead to antibodies with improved immunoreactivity when compared to indium-111 DTPA labeled antibody.

Preliminary work utilizing radiolabeled $F(ab')_2$ fragment of BB5, the human parathyroid antibody (Tables 2-4) suggests that target uptake of fragments occurs in a time frame when 68-minute half-lived gallium-68 can be used. For these studies ^{111}In and ^{68}Ga labeling was carried out using the DTPA anhydride labeled antibody, while for iodine iodogen labeling was used and for fluorine-18 the fluorophenacyl bromide technique (Appendix H) was used. Good target to nontarget values are obtained with the positron labeled antibodies two and four hours after administration. Two different batches of antibody were used in this work one produced at Washington University (Batch I) and one at InVitron Inc. (Batch II). Very different kidney clearance was observed with the two batches and the reason for this is not known. One of the concerns on positron emitting antibodies for diagnosis is the radiation dose, the critical organ. In the case of whole antibodies, this is likely to be the liver whereas in the case of fragments, the kidney. In order to investigate the behaviour of various labeled compounds which clear through the liver we have labeled neogalactosyl glycoalbumin (NGA) with 4 radionuclides. The clearance data in rats is shown in figure 1. It is interesting to note that indium and gallium are trapped whereas iodine and fluorine are cleared. This is relevant both to the intracellular behavior of the labels as well as the radiation dose to the clearance organs following administration.

To extend the possible applications of gallium-68 labeled proteins, we have also investigated the use of gallium-68 labeled low density lipoproteins as agents for studying LDL receptors. (Appendices R, T) Extension of this work will be a major goal over the next three years of the project.

4. The development of new chelates and bifunctional chelates for use as radiopharmaceuticals.

In this area our work has been on preparing bifunctional ligands related to the HPED structure (Figure 2). These agents have been investigated (Appendices N-S) in animal models. We have studied the behavior of EHPG complexes in vivo and in vitro in detail (Appendix U) to study the effect of stereochemistry on the in vivo biodistribution of complexes.

5. Delivery of radiopharmaceutical to the brain.

To date we have been unsuccessful in preparing an agent to deliver gallium-68 to the brain. We have compared and contrasted various metal chelates that have been suggested as agent to measure cerebral blood flow using the single probe model previously described by our group. This model is described in appendix P. Utilizing this model, the permeability surface area product of a whole series of technetium complexes have been evaluated. The permeability surface area products as well as a graphical representation of the underestimation of flow using these agents which are shown in Table 5 and Figure 3. The table includes the true PS as well as a PS SPECT value which

is the value observed with a slow imaging instrument. F' is determined using this retention PS value. Also we have studied copper labeled compounds as copper-62 has potential as a positron emitting generator produced radionuclide. (Appendices L,P,W) It is seen that copper nuclide labeled PTSM has the highest extraction of any metal labeled studies to date. (Appendix P) The copper complex can also be used to quantitate myocardial blood flow in the myocardium and kidney. The comparison of Cu-64 PTSM and $H_2{}^{15}O$ PET blood flow images in the myocardium are shown in Figure 4 (PTSM on right) and the distribution of renal blood flow (Figure 5) has also been measured with Cu-PTSM. Preliminary data utilizing hamsters using the GW39 transplanted tumor model where the uptake of Cu-PTSM is compared to that of with iodinated antipyrene suggests that this agent may also be useful for measuring tumor blood flow. PET images of two of the hamsters showing blood flow distribution are shown in Figure 6. The tumors are in the lower right of each animal.

Table 1:

Biodistribution of Complexes with
TS-TACN (% I.D./gram)

	^{111}In			^{68}Ga		
	1 min.	5 min.	1 hr.	1 min.	5 min.	1 hr.
blood	1.76 ± 0.01	1.12 ± 0.07	0.19 ± 0.02	4.34 ± 1.23	1.98 ± 0.48	0.68 ± 0.28
liver	2.08 ± 0.17	2.61 ± 0.22	0.77 ± 0.16	1.60 ± 0.21	2.44 ± 0.24	1.14 ± 0.15
spleen	0.60 ± 0.06	0.64 ± 0.07	0.23 ± 0.06	0.60 ± 0.15	0.49 ± 0.07	0.26 ± 0.05
kidney	5.23 ± 1.16	6.86 ± 0.55	1.48 ± 0.18	5.95 ± 1.77	9.73 ± 2.18	3.19 ± 0.62
muscle	0.25 ± 0.02	0.26 ± 0.03	0.24 ± 0.04	0.40 ± 0.07	0.38 ± 0.04	0.22 ± 0.03
heart	0.77 ± 0.09	0.60 ± 0.09	0.24 ± 0.02	1.38 ± 0.28	0.79 ± 0.06	0.30 ± 0.07
brain	0.07 ± 0.02	0.04 ± 0.01	0.01 ± 0.03	0.11 ± 0.04	0.07 ± 0.01	0.02 ± 0.01

Table 2:

Biodistribution of Radiolabeled BB$-F(ab')$_2$ Fragments (%ID/gm)

TISSUE

	pT	Blood	Kidney	Muscle
2 Hours				
I-125	6.44 ± 3.25	28.81 ± 4.49	32.70 ± 8.62	1.04 ± 0.24 (n=7)
In-111	6.89 ± 3.78	22.05 ± 2.79	20.38 ± 2.33	1.16 ± 0.12 (n=3)
F-18	n.d.	n.d.	n.d.	n.d.
Ga-68	3.65 ± 1.14	15.72 ± 3.50	28.56 ± 2.68	1.54 ± 0.55 (n=4)
4 Hours				
I-125	6.67 ± 1.87	22.51 ± 2.24	23.89 ± 1.78	1.31 ± 0.56 (n=4)
In-111	n.d.	n.d.	n.d.	n.d.
F-18	6.55 ± 2.08	22.56 ± 4.04	6.86 ± 1.04	0.63 ± 0.36 (n=4)
Ga-68	3.72 ± 0.71	12.30 ± 1.85	30.88 ± 1.31	1.71 ± 0.96 (n=4)

Data are presented as Mean ± S.D.

Table 3:

BB5-F(ab')$_2$ (Batch 1)

2 hr	pT*	Muscle*	pT/muscle
I-125	6.65 ± 3.72	0.93 ± 0.13	7.24 ± 3.96
F-18	9.81 ± 1.29	0.72 ± 0.07	13.86 ± 2.54
In-111	8.94 ± 3.41	0.99 ± 0.26	10.42 ± 6.32
Ga-68	10.96 ± 1.88	1.17 ± 0.27	9.86 ± 3.41
4 hr	**pT***	**Muscle***	**pT/muscle**
I-125	6.67 ± 1.87	1.31 ± 0.56	5.62 ± 2.37
F-18	6.53 ± 2.08	0.63 ± 0.36	12.91 ± 7.83
In-111	13.79 ± 1.41	1.16 ± 0.56	13.64 ± 5.63
Ga-68	14.64 ± 1.47	1.44 ± 0.55	11.32 ± 4.65

* %ID/gm
** Data are presented as the mean ± S.D. for 3 - 7 animals

Table 4:

BB5-F(ab')$_2$ (Batch 1)

Kidney (% ID/gm)*

2 hr	
I-125	40.35 ± 7.91
F-18	68.44 ± 11.24
In-111	29.81 ± 11.43
Ga-68	28.46 ± 4.45
4 hr	
I-125	23.89 ± 1.78
F-18	6.86 ± 1.04
In-111	56.93 ± 1.06
Ga-68	35.20 ± 2.50

* Data are presented as the mean ± S.D. for 3-7 animals

Table 5: PS values of compounds studied

Compound	PS	PS_{spect}	F_{spect}*
$H_2{}^{15}O$	112.8		
d,l-HMPAO	68.9	36.4	27.3
meso-HMPAO	67.5	13.0	11.7
SQ32097	30.3	16.7	14.6
SQ30217	23.8	12.9	11.6
SQ32014	11.6	4.1	4.06
ECD	48.8	29.8	23.5

*True Flow = 60ml/100g/minute

Table 5 (continued)

Compound	PS	PS_{spect}	F_{spect}^{*}
$H_2{}^{15}O$	112.8		
PTSM	87.5	51.9	34.7
$PTSM_2$	79.1	42.6	30.5
IMP	116.9	99.9	48.6
HIPDM	100.9	51.4	34.5
IP	87.6	55.6	36.2

*True Flow = 60ml/100g/minute

1264 85

Figure 1: Liver clearance of NGA labeled with four different radionuclides.

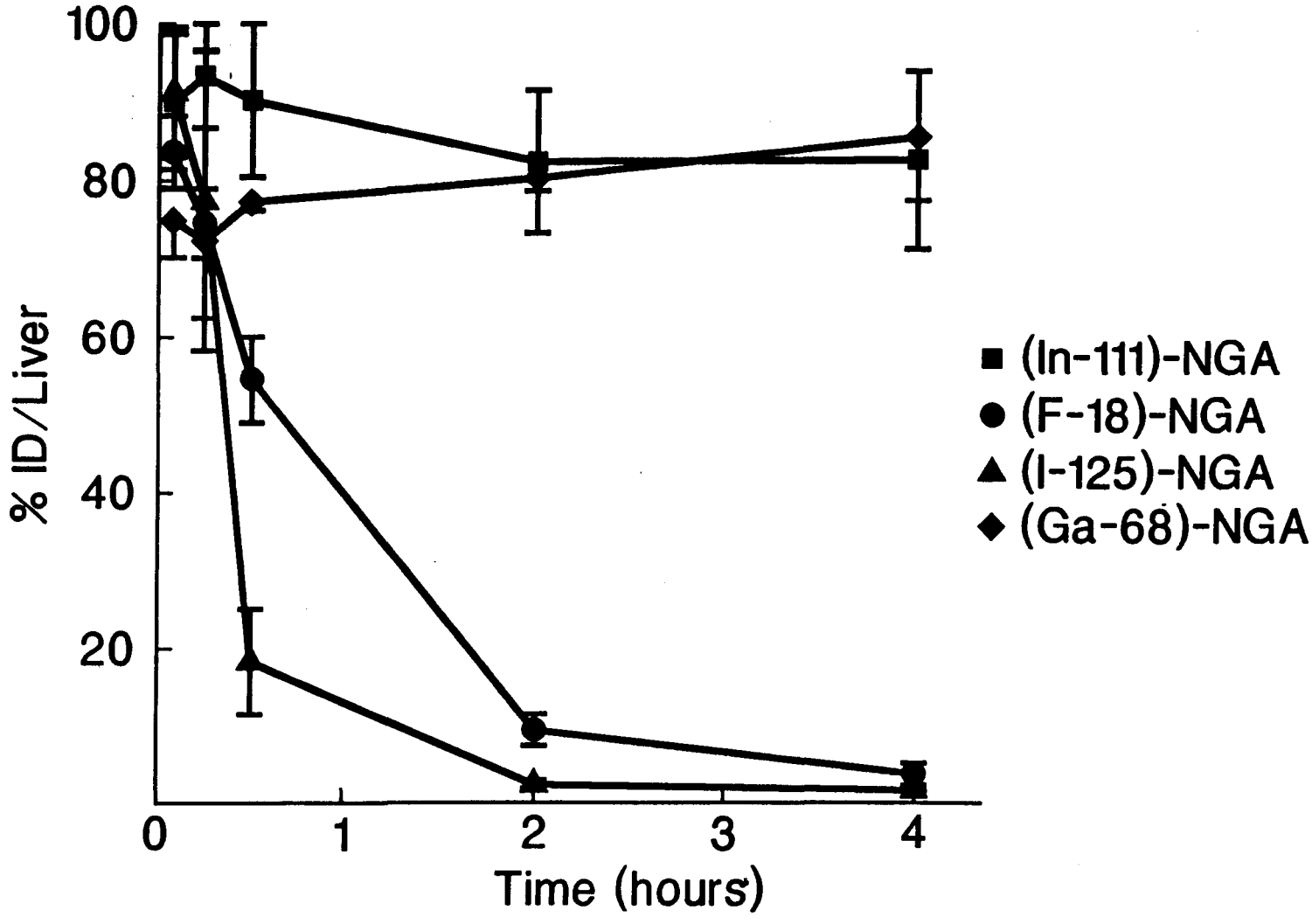
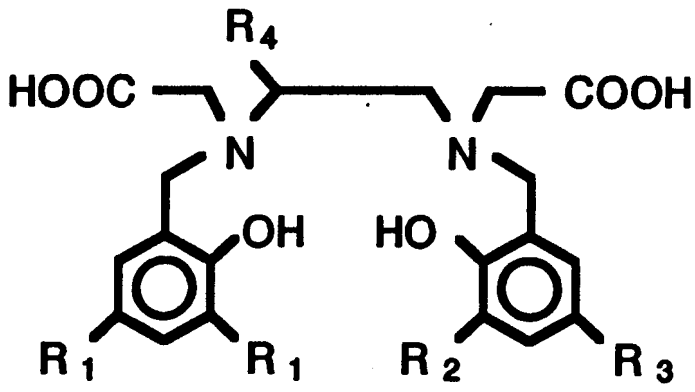


Figure 2: New bifunctional chelates studied.



	R_1	R_2	R_3	R_4
HBED	H	H	H	
Me_4HBED	CH_3	CH_3	CH_3	
BrMe_2HBED	CH_3	H	$NHCOCH_2Br$	
BrΦHBED	H	H	H	$CH_2ΦNHCOCH_2Br$
BrMe_4ΦHBED	CH_3	CH_3	CH_3	$CH_2ΦNHCOCH_2Br$

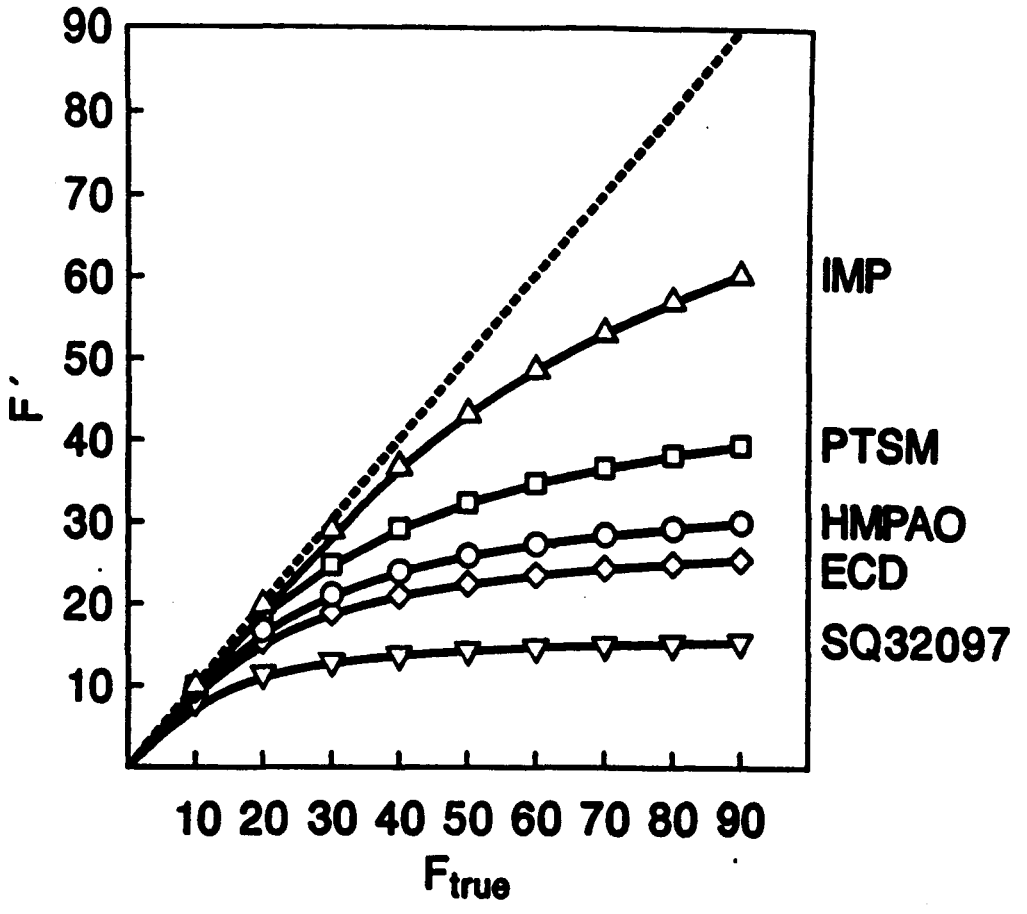


Figure 3: Measured flow F' at increasing true flow for a series of agents with potential brain blood flow radiopharmaceuticals.

Figure 4: Myocardial blood flow images in a dog measured with ^{64}Cu-PTSM (right) and $H_2{}^{15}O$ (left).

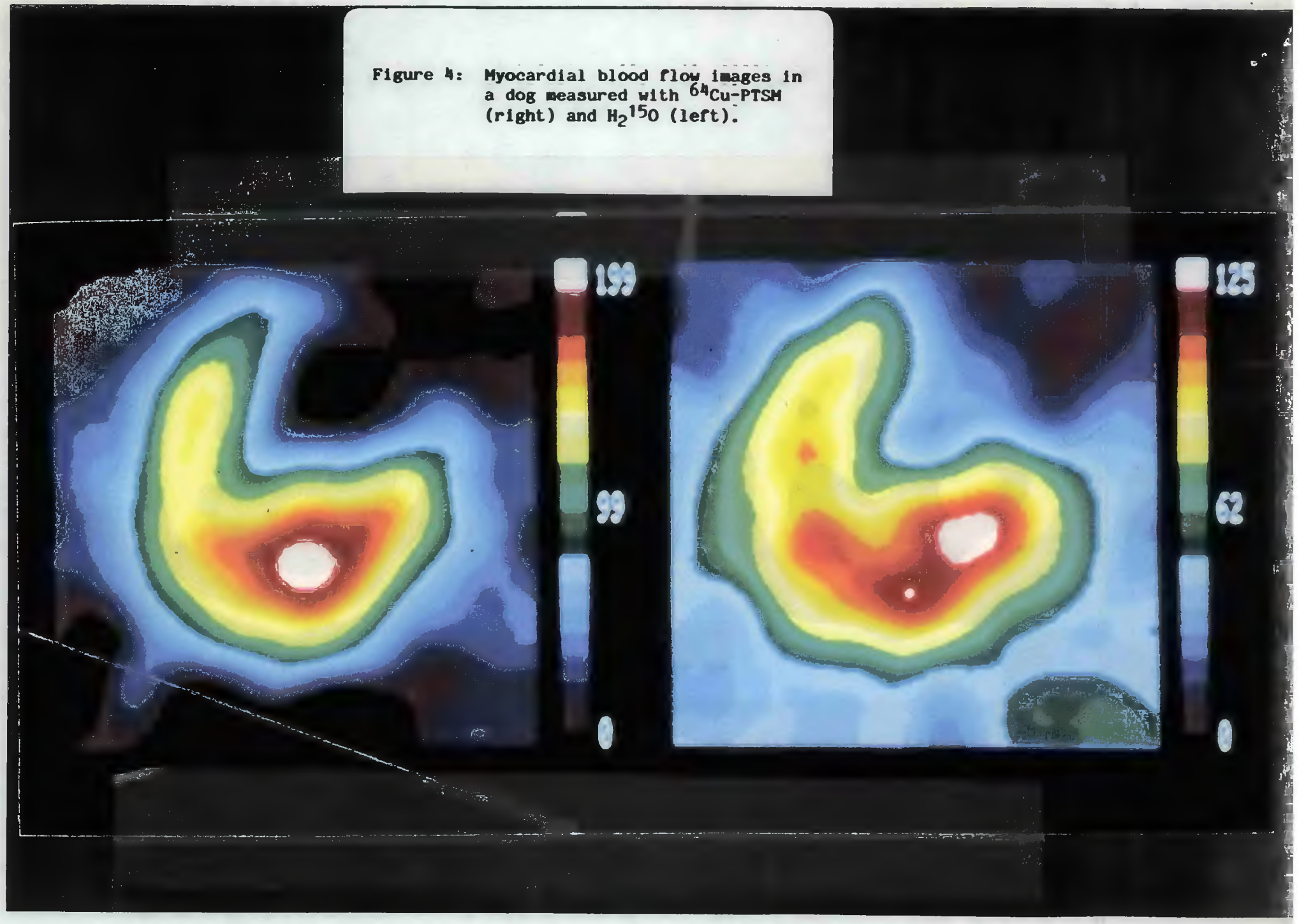
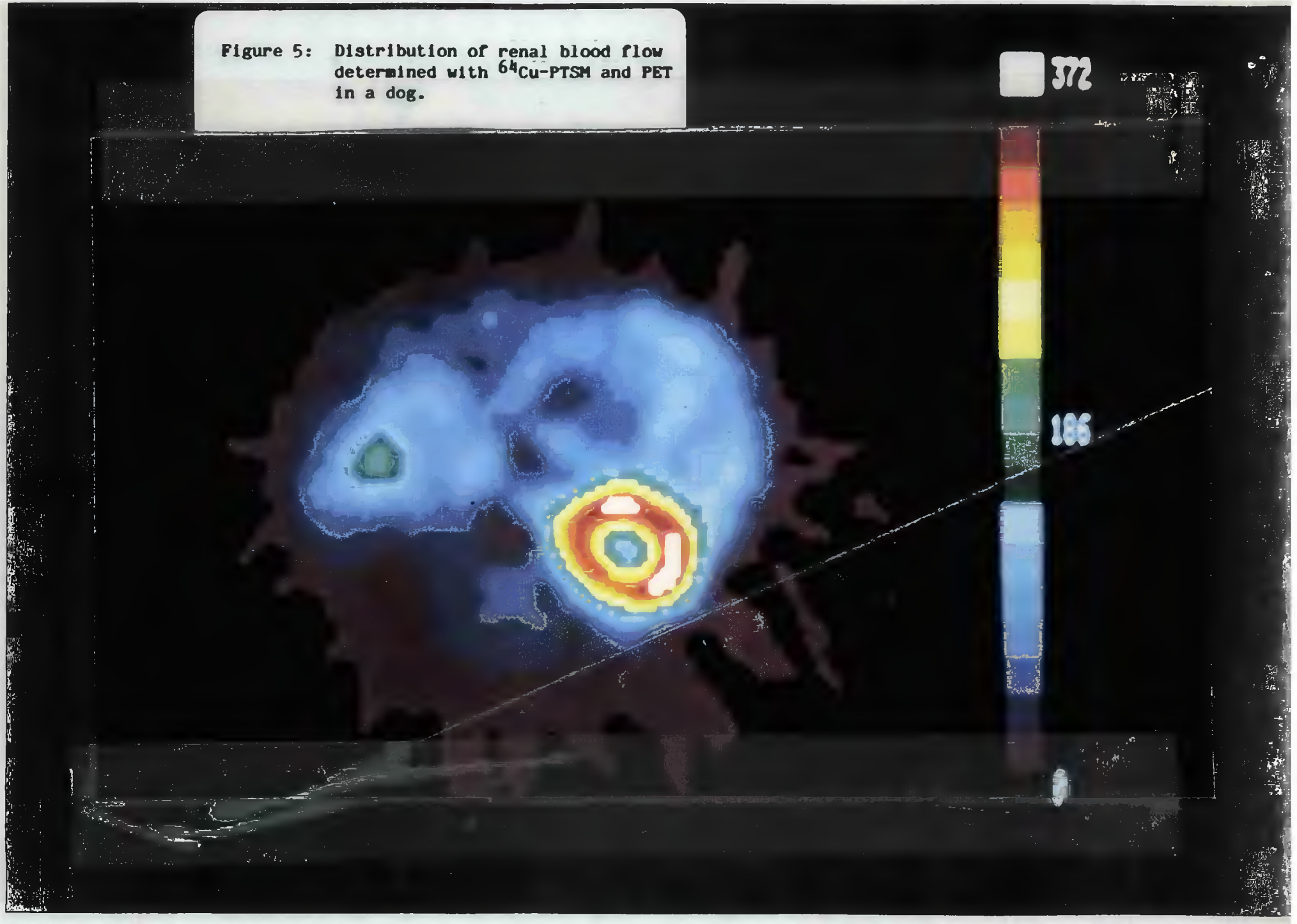


Figure 5: Distribution of renal blood flow determined with ^{64}Cu-PTSM and PET in a dog.



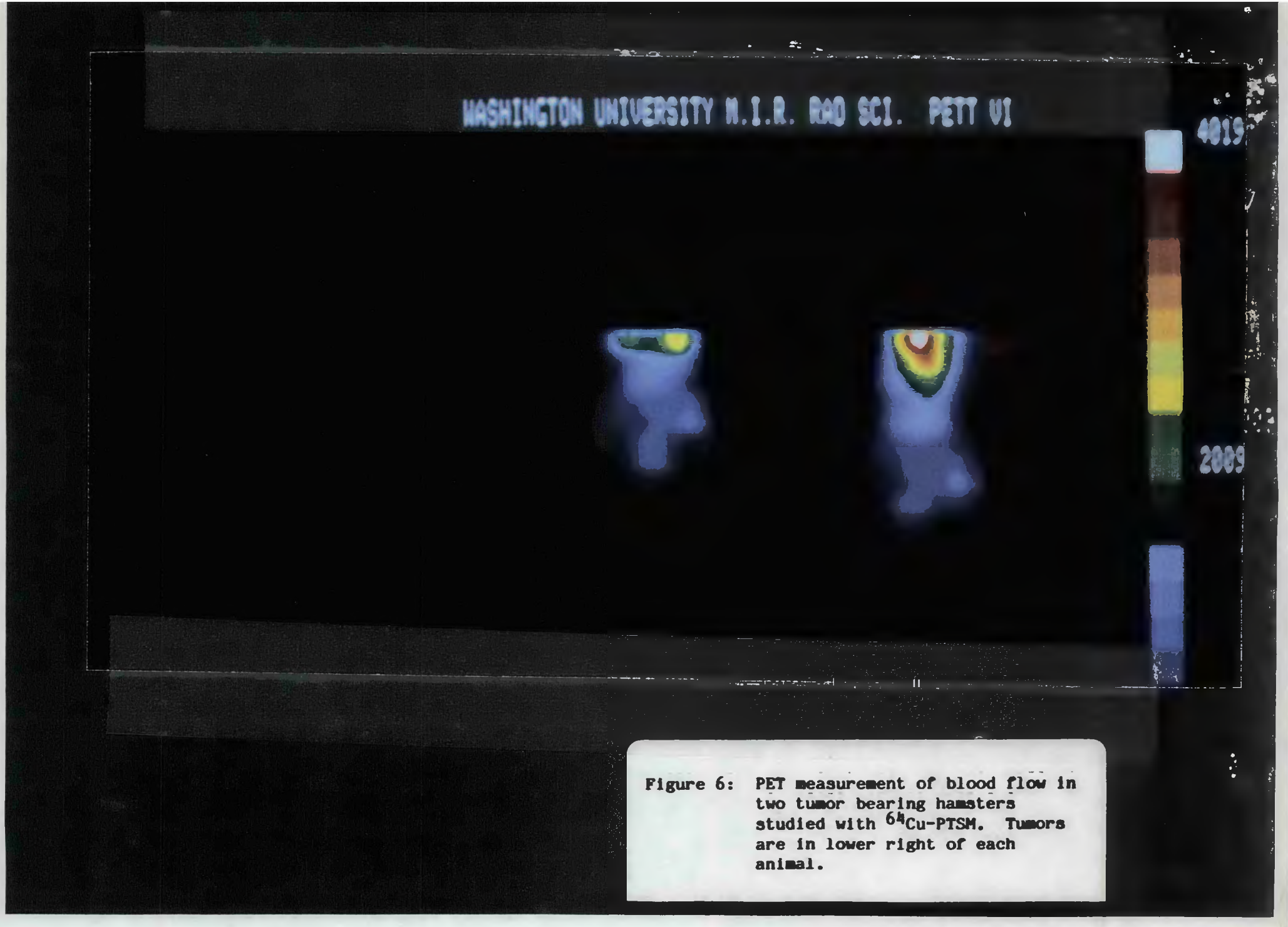


Figure 6: PET measurement of blood flow in two tumor bearing hamsters studied with ^{64}Cu-PTSM. Tumors are in lower right of each animal.

Appendix A

WG Cance, SA Wells, WG Dilley, JM Welch, FL Otsuka, JM Davie. Human parathyroid antigen: characterization and localization with monoclonal antibodies. Proc Natl Acad Sci USA 83:6112, 1986.

All appendices removed and copied separately — JTS