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Nuclear Medicine Program Progress Report for Quarter Ending June 30, 1990

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Contract No. DE-AC05-84OR21400

Health and Safety Research Division

NUCLEAR MEDICINE PROGRAM PROGRESS REPORT FOR QUARTER ENDING JUNE 30, 1990

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Work sponsored by
DOE Office of Health and
Environmental Research

Date Published - August 1990

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SUMMARY

In this report a novel electrochemical method is described for the separation of copper-64 and copper-67 following the irradiation of zinc targets. This method is based on the spontaneous electrodeposition of copper on a platinum electrode immersed in the zinc target solution (1 M H_2SO_4/1 M $ZnSO_4$) without requiring an external electromotive force (EMF). The other components of the cell consist of a zinc electrode immersed in a saturated $ZnSO_4$ solution in 1 M H_2SO_4 separated from the target solution by a glass frit. The distinct advantages of this method in comparison to solvent extraction method currently used include simplicity, time, and lower radiation exposure. The apparatus can easily be adapted for in-cell use.

No-carrier-added N-[2-(3-[^{125}I]iodo-4-hydroxyphenyl)ethyl]-maleimide has been prepared by direct iodination of N-[2-(4-hydroxyphenyl)ethyl]maleimide with (Na[^{125}I]-chloramine-T. The precursor was prepared by condensation of tyramine with maleic anhydride followed by ring annulation. Studies in rats (n=5; 15 min, 1, 4, and 24 h) showed low thyroid uptake of radioactivity which reached a plateau after 4 h, indicating *in vivo* stability. This new radioiodinated maleimide analogue, like other N-phenyl-substituted maleimides, reacts with bovine serum albumin (BSA) under mild conditions and has been used for labeling a lung-endothelial-cell-specific antibody (411-201B). The [^{125}I]-labeled antibodies are currently being evaluated for immunoreactivity and tumor specificity.

During this period several agents were also supplied to Medical Cooperative investigators, including iodine-123-labeled and iodine-131-labeled fatty acid analogues for studies at the Brookhaven National Laboratory, the Cardiology Department at the Free University of Amsterdam, and the University of Bonn, West Germany. A tungsten-188/rhenium-188 generator was supplied to the University of Massachusetts, and osmium-191 was supplied for fabrication of generators for patient studies in Finland.

SPONTANEOUS ELECTROCHEMICAL DEPOSITION – A NOVEL METHOD FOR SEPARATION OF CARRIER-FREE COPPER-67 AND COPPER-64 FROM ZINC TARGETS

Spontaneous electrochemical deposition is an alternative technique for the separation of carrier-free radioisotopes of copper from highly radioactive zinc targets. This technique was envisioned as being particularly useful for the separation of carrier-free copper-67 (Cu-67) produced by neutron irradiation of milligram amounts of natural zinc or enriched zinc-67 (Zn-67) by the (n,p) Zn-67 reaction. There is considerable interest in exploring the potential use of Cu-67 ($t_{1/2}$=62 h) for therapeutic applications, and copper-64 (Cu-64) ($t_{1/2}$=12.7 h) for diagnostic applications using positron emission tomography (PET). Currently Cu-67 is produced routinely at two DOE sites via high-energy proton irradiation of natural zinc. The separation procedures we currently employ for separation of reactor-produced Cu-67 involves a solvent extraction technique, which is time consuming and labor intensive, and thus complex and expensive. The spontaneous electrochemical technique for separation of radioisotopes of copper from zinc targets overcomes these problems.

In this process, radioisotopes of copper are separated from a proton- or neutron-irradiated zinc target by means of spontaneous electrodeposition without an external electromotive force (EMF). The electrolysis apparatus is shown in Figure 1 and consists of a U-shaped electrolysis cell (right and left half cells), a Zn electrode (1.5 mm O.D. rod) immersed in a saturated solution of $ZnSO_4$ in 1 M H_2SO_4 (left half cell) and a Pt electrode (1.5 mm O.D. Pt rod spot welded to a ~2 cm^2 Pt mesh) immersed in a 1 M solution of $ZnSO_4$ and 1 M in H_2SO_4 containing Cu-67 in the dissolved target (right half cell). In this mixture, tracer levels of Cu-67 were added to zinc solutions and represent a typical target solution. The two solutions are separated by a porous barrier (10-20 micron fritted glass disc, ~2 cm^2 surface area), which allows electrical contact but prevents excessive mixing of the solutions by interdiffusion. Within 30 min after connecting the two half cells, the Cu-67 is quantitatively electro deposited on the Pt electrode. Connection of the two half cells is simply achieved by connecting the Pt and Zn electrodes with a suitable conductor.

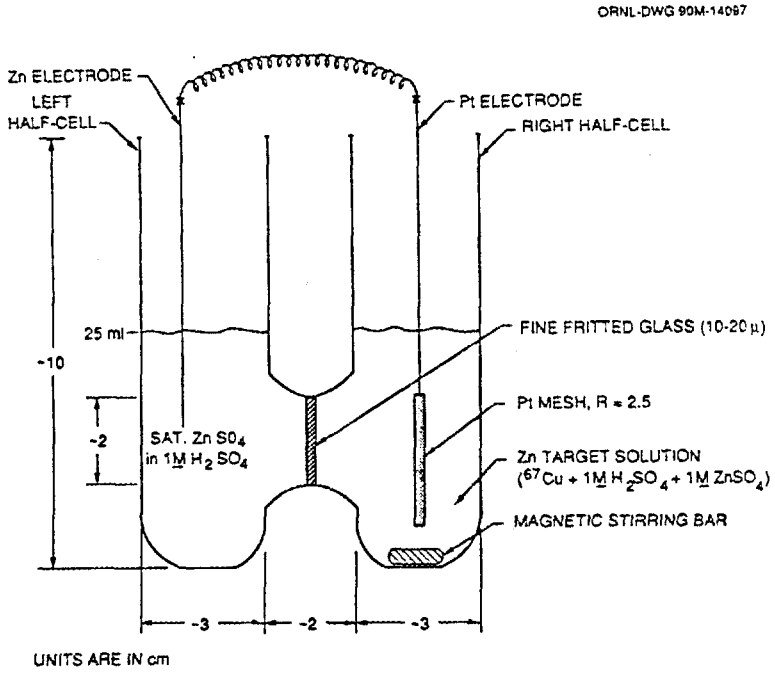


Figure 1. Apparatus for spontaneous electro deposition of carrier-free Cu-67.

Subsequently, the Pt electrode is removed from the electrolysis apparatus and the deposited carrier-free Cu-67 is dissolved by immersing the Pt electrode in concentrated HNO_3 for 1-2 min. The effect of duration of electrolysis is shown in Figure 2, which illustrates that the fraction of electroplated Cu-67 increases exponentially with time and reaches ~95% within 30 min. The process is independent of copper ion concentration, ranging from $\leq 1 \times 10^{-8}$ M to 1×10^{-3} M (Table 1). The effect of concentration of zinc ion is shown in Table 2, and quantitative plating can be achieved within 30 min when the concentration of zinc was <1.0 M. When the concentration of zinc is ≥1 M, quantitative plating is achieved by extending the duration of electrolysis to 60 min. No significant variation is observed in the plating efficiency when the concentration of H_2SO_4 decreases three orders of magnitudes, from 1 M to 1.0×10^{-3} M (Table 3). When the left half cell is replaced with other half cells (Table 4), quantitative plating of carrier-free Cu-67 is achieved within 30 min in all cases with exception to the $PbO_2/PbSO_4/H^+$ half cell, where no copper was plated. Since the standard half cell potential (E^0) of $PbO_2/PbSO_4/H^+$ (Table 4, 2nd column) is more positive than Cu^{+2}/Cu by ~1.3 volts, plating of copper would not be expected.

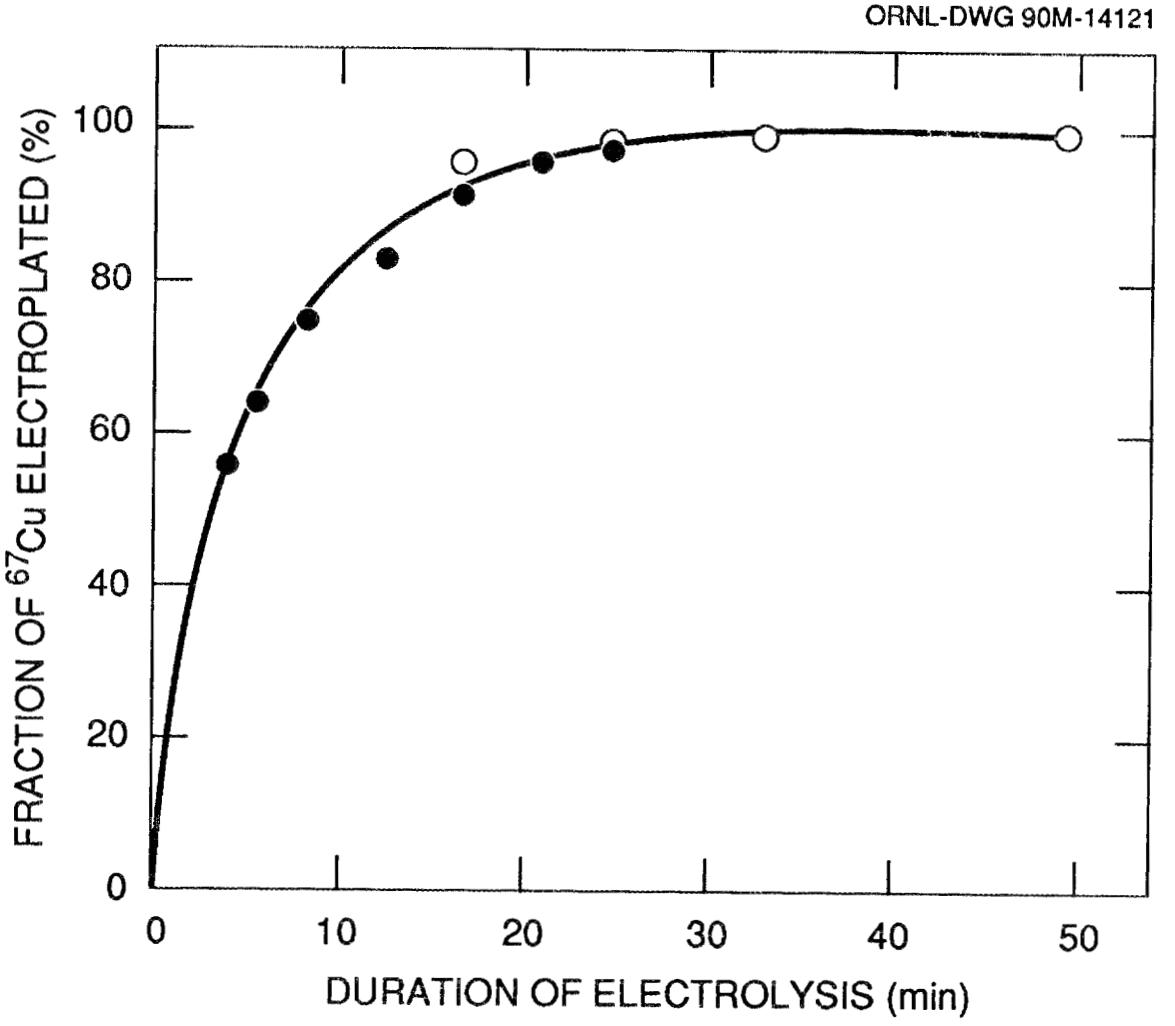


Figure 2. Effect of the duration of electrolysis on electroplating of Cu-67. Composition of electrolyte = left 1/2 cell: saturate solution of $ZnSO_4$ in 1 M H_2SO_4 (Zn electrode). Right 1/2 cell: 1 M H_2SO_4; $\leq 1 \times 10^{-3}$ (o) or 1 M (•) and carrier-free Cu-67 (Pt electrode, $A \approx 2.5$ cm^2); temperature = 25°C.

Table 1. Effect of concentration of copper sulfate[a-c]

Concentration of $CuSO_4$, M	Fraction of Cu-67 electroplated, %
$\leq 1x10^{-8}$	98.6
$5.21x10^{-6}$	100.0
$5.73x10^{-5}$	99.3
$3.12x10^{-4}$	100.0
$7.82x10^{-4}$	99.8

[a)]Composition of Electrolyte: Left 1/2 cell: saturate solution of $ZnSO_4$ in 1 M H_2SO_4 (Zn electrode); Right 1/2 cell: 1 M H_2SO_4 and various amount of [$CuSO_4$] (Pt electrode).

[b)]Duration of electrolysis = 30 min

[c)]Temperature = 25°C

Table 2. Effect of concentration of zinc sulfate[a-c]

	Fraction of Cu-67 Electroplated, %	
	Duration of electrolysis, minutes	
Concentration of $ZnSO_4$, M	30	60
$\leq 1x10^{-3}$	97.0	98.6
$1.0x10^{-2}$	99.2	99.6
$1.0x10^{-1}$	98.6	99.2
1.0	88.5	100
Sat. soln.	83.8	97.7

[a)]Composition of Electrolyte: Left 1/2 cell: saturate solution of $ZnSO_4$ in 1 M H_2SO_4 (Zn electrode); Right 1/2 cell: 1 M H_2SO_4, various amount of $ZnSO_4$ and carrier-free ^{67}Cu (Pt electrode).

[b)]Temperature = 25°C

Table 3. Effect of concentration of H_2SO_4[a,b]

	Fraction of Cu-67 Electroplated, %	
	Duration of electrolysis, minutes	
Concentration of H_2SO_4, M	30	60
1.0×10^{-3}	97.5	99.9
1.0×10^{-2}	99.9	-
1.0×10^{-1}	99.9	-
1.0	99.8	-

[a)]Composition of Electrolyte: Left 1/2 cell: saturate solution of $ZnSO_4$ in 1 M H_2SO_4 (Zn electrode); Right 1/2 cell: various amount of H_2SO_4, $\leq 1 \times 10^{-3}$ $ZnSO_4$ and carrier-free Cu-67 (Pt electrode).

[b)]Temperature = 25°C

Table 4. Effect of various half cells on deposition of Cu-67[a-c]

Left Half cell	Standard half cell potential (E^0), V	Fraction of Cu-67 electroplated, %
Zn^{+2}/Zn	-0.763	99.9
Fe^{+2}/Fe	-0.443	99.5
Co^{+2}/Co	?	99.9
Ni^{+2}/Ni	-0.250	99.9
Fe^{+3}/Fe	-0.036	-
Sn^{+2}/Sn	-0.136	100
Sn^{+4}/Sn	-0.008	-
H^+/H_2	0.000	-
Cu^{+2}/Cu	+0.337	0.0
$PbO_2/PbSO_4/H^+$	1.685	0.0

[a)]Composition of Electrolyte: Left 1/2 cell: various half cells; Right 1/2 cell: 1 M H_2SO_4 and carrier-free Cu-67.

[b)]Duration of electrolysis = 30 min

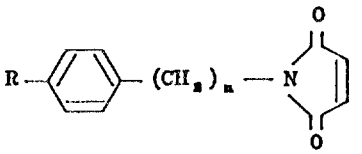
[c)]Temperature = 25°C

The electrodeposition of metal ions at trace concentrations from aqueous solution onto electrodes of a less noble metal is well known. However, our unique application of this technique for the separation of the deposited metal from electrode material has not, to our knowledge, yet been reported. This is also the first report describing the application of spontaneous electrochemical technique in the preparation of carrier-free Cu-67 or Cu-64. The first application of electrolytic separation of Cu-64 under an external EMF was reported by Steigman[1] and later the application of this technique for the production of no-carrier-added Cu-67 was reported by other workers.[2] Other techniques which have been used for the separation of copper at trace concentrations from other metal ions include extraction,[2] ion exchange,[3] and dry distillation.[3]

Separation factors which have been achieved from macro amounts (grams) of Zn ($\geq 5 \times 10^6$), trace amounts of Fe, Co and Ga ($\geq 1 \times 10^5$), and Ni and V ($\geq 5 \times 10^4$), exceed those reported for other processes. Considering only the half cell potentials, the spontaneous electrochemical process in principal can be used for separation of other electropositive metal ions such as Po-210, carrier-free Bi-210 from Pb-210 (produced through the natural decay of U-238) and Po-206/Bi-206 from proton-irradiated bismuth targets. Our current studies now focus on applying this technique to reactor-irradiated enriched zinc targets to assess this approach for the routine reactor-production of Cu-67.

EVALUATION OF RADIOLABELING OF ANTIBODIES OF COLON CARCINOMA (CO-17-1A) AND LUNG ENDOTHELIAL CELLS (411-201B) WITH RADIOISOTOPES OF IODINE AND COPPER

Radioactive iodine is often incorporated into antigen-specific antibodies either by direct iodination or by immunoconjugation. Direct radioiodination requires exposure of the antibody to electrophilic conditions and allows ready incorporation of iodine into the phenyl moiety of tyrosine residues. The antibodies, thus radiolabeled, can suffer *in vivo* deiodination probably by the action of deiodinases of thyroid hormones, since the radioiodinated products are structurally similar to radioiodinated tyrosine residues of the antibody. Our radioiodination approach for immunoconjugation is designed to synthesize *in vivo* stable radioiodinated reagents which can be readily attached to an antibody with retention of immunoreactivity. We have developed a radioiodinated iodophenylmaleimide for labeling immunoproteins potentially useful in diagnosis and therapy of cancer. The agent was designed primarily to overcome *in vivo* deiodination, a problem generally experienced with proteins which have been directly radioiodinated with radioactive iodine. Indeed, this problem has been overcome using iodophenylmaleimide (Figure 3, 1) and the data describing our results have recently been published in a research report.[4] In this study the maleimide agent was used for labeling a tumor-specific monoclonal antibody B72.3.



(1) R=I, n=0
(2) R=OH, n=2

Figure 3.

We have further evaluated the versatility of the maleimide class of compounds by radioiodination of two antibodies, which include a lung-endothelial-cell-specific monoclonal antibody (273-34A) which was radiolabeled using [iodine-125]hydroxyphenylethylmalemide (2) (ORNL/TM-11427), an analogue of iodophenylmaleimide, and separated from cross-linked antibodies using a Sephadex column. These studies were performed with

Dr. Steve Kennel at the Biology Division of Oak Ridge National Laboratory. Since 273-34A antibody is not tumor-specific, the radiolabeled antibody was not studied in laboratory animals. Nevertheless, the study indicates utility of the maleimide class of compounds for labeling proteins potentially useful for radioimmunoassay or for in vivo tracer studies. Radioiodinated iodophenylmaleimide has also been used for labeling 17-1A tumor-specific monoclonal antibody. Similar to B72.3, the maleimide radiolabeled 17-1A antibody has also been found to show in vivo stability in nude mice bearing LS1748 human colon cancer. These studies were performed in collaboration with Dr. D.-J. Buchsbaum at the University of Michigan, Ann Arbor, Michigan.

Since these two well characterized antibodies were readily available, we also pursued the attachment of radioisotopes of copper. Radiolabeling was performed with high specific activity Cu-64 produced at the Missouri University Research Reactor (MURR). The 411-201B antibodies (antilung endothelial, S. Kennel, ORNL) and CO-17-1A antibodies (anticolon carcinoma, Drs. Crook and Washburn, ORAU) were first radiolabeled by the attachment of the bifunctional chelate on the antibody by the phosphoryl method. The development of this bis-thiosemicarbazone (TSC) bifunctional chelate for copper has been described earlier (ORNL/TM-11014). Fifty μmol of triethylamine and 51.0 μmol of diphenylphosphoryl azide were added to a solution containing 24.3 μmol of chelate in 0.5 mL DMF at 0°C. After stirring at 0°C for 1.5 h, 10 μL of this solution was then added to 1 mL solutions (0.05M borate buffer, pH=9.0) containing 1.35 mg of 411-201B or 2.0 mg of CO-17-1A. The solutions were stirred at 0°C for 1 h and then each passed through a column of Sephadex-G25 with borate buffer as the eluent. The fractions corresponding to the solvent front were collected and dialyzed against normal saline for 24 h. The solutions containing the antibodies were then lyophilized and stored in the freezer until radiolabeling with Cu-64. A sample of the TSC-chelated CO-17-1A antibody was supplied (Dr. L. C. Washburn and co-workers) for immunoreactivity testing. The results of these studies indicated that the antibody retained its immunoreactivity (>80%) post complexation with the chelate and prior to radiolabeling.

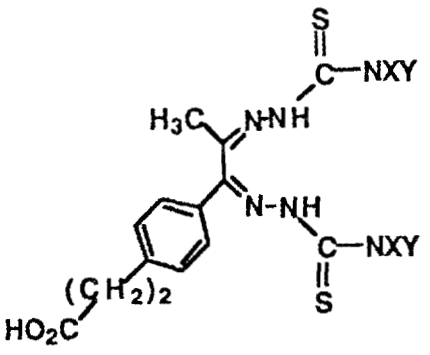
The antibodies were radiolabeled with copper-64 by combining solutions of 0.68 mg of 411-201B and 1.5 mg of CO-17-1A in 0.5 mL of a 0.1 M acetate buffer (pH=6) with 0.2 mL (474 μCi) and 0.22 mL (521 μCi) of a copper-64 cupric chloride solution, respectively. The solutions were gently stirred at room temperature for 30 min. Blue dextran was then added to the solution as a marker and each solution was passed through a column of AcA resin and eluted with phosphate buffered saline containing 5% BSA. The fractions containing the radiolabeled antibody were analyzed: 411-201B, 221 μCi (46.1% radiochemical yield; 329 μCi/mg); CO-17-1A, 233 μCi (44.7% radiochemical yield, 154 μCi/mg).

Tissue distribution studies with the Cu-64-labeled Co-17-1A antibody in rats (Table 5) indicated that after 18 h the Cu-64 had been released from the antibody and the tissue distribution was similar to that of the injection of free cupric ion. Studies with the radiolabeled 411-201B indicated that the copper-64 labeled antibody retained between 10-18% of the immunoreactivity compared with the reported immunoreactivity value of the I-125-labeled antibody. These results indicate that the antibody lost its immunoreactivity during the radiolabeling procedure.

Table 5. Tissue distribution of Cu-64-labeled CO-17-1A in rats.

Tissue	Average % dose/gram
Liver	13.5
Kidney	8.2
Bone marrow	6.9
Lung	6.7
Large intestine	4.6
Tumor	4.5
Small intestine	4.5
Spleen	2.4
Blood	1.6
Femur	0.86
Muscle	0.60

We are now evaluating modifications of the bifunctional chelate to overcome the problem of the rapid loss of the copper label *in vivo*. We have prepared a series of bifunctional chelates in which the alkyl groups of the terminal nitrogen on the thiosemicabazone ligand have been modified (Figure 4). We have subsequently labeled IgG as has been previously reported using the activated ester method and studied the exchange of copper with free EDTA ligand in solution. The results of this study are shown in Figure 5. The data show that compound **4**, in which a phenyl group is placed on the terminal nitrogen, shows less ligand exchange as compared to the other ligands. The stability of the copper-IgG complex in aqueous solution with no EDTA present was also studied and no loss of copper from the protein was observed over 24 h. We are currently studying the stability of these ligands in the presence of serum and 6M urea.



Compound	X	Y
1	H	CH_3
2	H	H
3	CH_3	CH_3
4	H	Phenyl

Figure 4. Substituted bifunctional ligands.

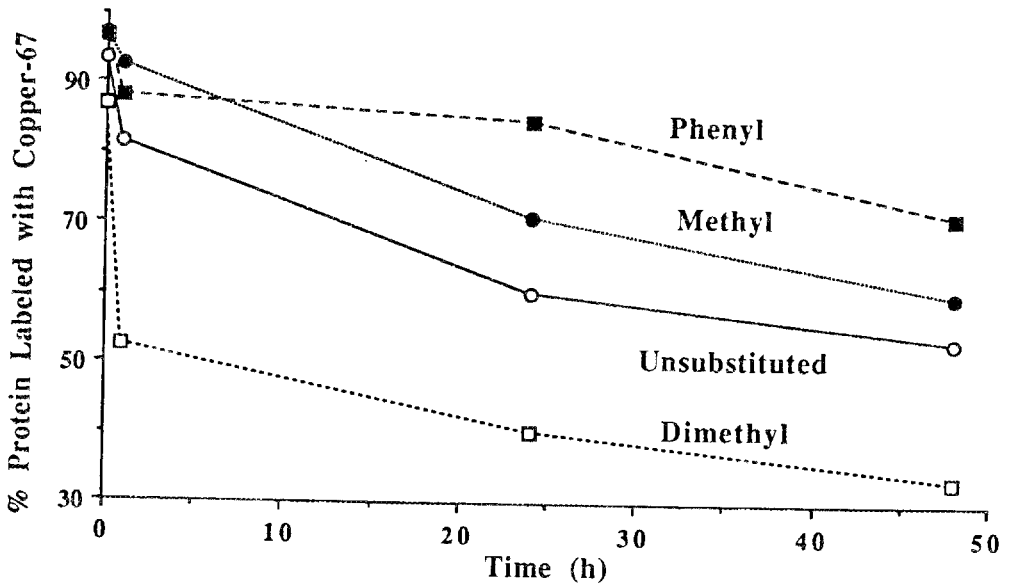


Figure 5. The stability of copper-protein complex with excess EDTA. (See Figure 4 for structures).

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2. Brown, L. C., and Callahan, A. P., Int. J. Appl. Radiat. Isot., 23:535 (1972).
3. Mirzadeh, S., Mausner, L. F., and Srivastava, Suresh C., Appl. Radiat. Isot., 37:29 (1986), and references therein.
4. Srivastava, P. C., Buchsbaum, D. J., Allred, J. F., Brubaker, P. G., Hanna, D. E., and Spicker, J. K., Biotechniques, 8:536 (1990).

AGENTS FOR MEDICAL COOPERATIVES

Three samples of iodine-125-labeled BMIPP and one sample of iodine-131-labeled IPPA were supplied to the Cardiology Department, Free University, Amsterdam, The Netherlands (F. Visser, M.D.), for collaborative studies with an open-chest canine model. Four shipments of iodine-123-BMIPP were made to Brookhaven National Laboratory, Upton, New York (P. Som, D.V.M.) for SPECT studies of the effects of cocaine intoxication on fatty acid metabolism in dogs. One shipment of iodine-125-BMIPP was made to the University of Bonn, Bonn, West Germany (Dr. J. Kropp). The University of Michigan (Dr. Buchsbaum) received one shipment of iodine-125.

Two shipments of reactor-produced osmium-191 for fabrication of osmium-191/-iridium-191m generators for Phase I patient studies with iridium-191m were made to the VTT Reactor Laboratory, in Espoo, Finland (J. Hiltunen). A tungsten-199/rhenium-188 generator was supplied to collaborators at the University of Massachusetts, Worcester, Massachusetts (A. B. Brill, M.D., Ph.D.) to evaluate direct radiolabeling of antibodies with rhenium-188.

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Presentations

Dan McPherson participated in the Visiting Industrial Scientist and Engineer Program sponsored by the Industrial Research Institute at Berea College on April 9, 1990. In addition to presenting a seminar entitled "Chemistry and Nuclear Medicine," he also met with students and faculty to discuss opportunities for chemistry graduates in industry and postgraduate education.

Members of the Nuclear Medicine Group co-authored a paper presented at the Annual Meeting of the European Association of Nuclear Medicine (EANM) held in Amsterdam, the Netherlands on May 20-24, 1990.

Kropp, J., Knapp, F. F., Jr., Ambrose, K. R., Assman, T., Urmetz, S., Nissen, H. P. and Biersack, H.-J., "Metabolites of IPPA, BMIPP and DMIPP Fatty Acids in Rat Hearts. A Quantitative HPLC Study."

Members of the Nuclear Medicine Program also authored several papers presented at the recent meeting of the Society of Nuclear Medicine held in Washington, D.C., on June 18-25, 1990:

Kropp, J., Knapp, F. F., Ambrose, K. R., Visser, F., Biersack, H.-J., and Blystone, S. L. "Release of an Unexpected Myocardial Metabolite of Radioiodinated 15-(p-Iodophenyl)-3-R,S-Methylpentadecanoic Acid (BMIPP) from Isolated Rat Hearts and Canine Hearts *In Vivo*."

Srivastava, P. C., Allred, J. F., Lambert, C. R., and Kennel, S. J. "No-Carrier-Added Preparation of a New Radioiodinated Maleimide as a Potentially Attractive Radioimmunoconjugator with Low *In Vivo* Deiodination."

Srivastava, P. C., Lambert, C. R., Allred, J. F., Kennel, S. J., and Hasan, A. "I-125-Labeled Azomycin Acyclonucleoside: Design and Synthesis of an Attractive Misonidazole Analogue for Imaging Hypoxia."

In addition, several papers were authored by members of the Nuclear Medicine Program at the recent International Radiopharmaceutical Symposium held in Princeton, New Jersey, on June 25-29, 1990:

Clem, R., Lambercht, R. M., Pippin, C. G., Roselli, M., Mirzadeh, S., Gansow, O. A., and Cholcher, D. "Radiochemistry of Lead-203 for Radiolabeling Antibody Conjugates."

Lee, T. W., McPherson, D. W., Callahan, A. P., Rice, D. E., Ting, G., and Knapp, F. F., Jr. "A Simple Colorimetric Method for Determination of the Specific Activity of Spallation-Produced Copper-67 (Cu-67) Using the Bis-(N^4-Methyl)Thio-semicabazone (TSC) of Phenylglyoxal."

Mirzadeh, S., Brechbiel, M. W., and Gansow, O. A. "Radiometal Labeling of Immunoproteins: A Study of the Covalent Attachment of SCN-Bzl-DTPA Ligands to Immunoglobulin."

Pippin, C. G., Kumar, K., Mirzadeh, S., and Gansow, O. A. "Kinetics of Isotope Exchange Between Copper(II) and Copper(II) 1,4,7-Triazacyclononane-N,N',N" Triacetate."

Srivastava, P. C., and Hasan, A. "Iodoazomycin Acyclonucleoside: A Potential SPECT Imaging Agent with High Tumor Uptake."

Publications

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