28
12-27-78
25 cy. to NTIS

UC-48

ORNL/TM-6638

MASTER

Nuclear Medicine Technology Progress Report for Quarter Ending June 30, 1978

F. F. Knapp, Jr.

HEALTH AND SAFETY RESEARCH DIVISION
OAK RIDGE NATIONAL LABORATORY

OAK RIDGE NATIONAL LABORATORY
OPERATED BY UNION CARBIDE CORPORATION · FOR THE DEPARTMENT OF ENERGY

DISCLAIMER

Printed in the United States of America. Available from
National Technical Information Service
U.S. Department of Commerce
5285 Port Royal Road, Springfield, Virginia 22161
Price: Printed Copy $4.50; Microfiche $3.00

ORNL/TM-6638

Contract No. W-7405-enq-26

HEALTH AND SAFETY RESEARCH DIVISION

NUCLEAR MEDICINE TECHNOLOGY PROGRESS REPORT FOR QUARTER ENDING June 30, 1978

F. F. Knapp, Jr.

Work sponsored by
DOE Division of Biomedical and
Environmental Research

Date Published - December 1978

NOTICE This document contains information of a preliminary nature. It is subject to revision or correction and therefore does not represent a final report.

OAK RIDGE NATIONAL LABORATORY
Oak Ridge, Tennessee 37830
Operated by
UNION CARBIDE CORPORATION
for the
DEPARTMENT OF ENERGY

Previous reports in this series:

ORNL/TM-5809

ORNL/TM-5936

ORNL/TM-6044

ORNL/TM-6181

ORNL/TM-6371

ORNL/TM-6410

CONTENTS

NUCLEAR MEDICINE TECHNOLOGY PROGRESS REPORT FOR QUARTER ENDING JUNE 30, 1978

SUMMARY

Progress is reported for the applications of ^{11}C, ^{195m}Pt, ^{75}Se and ^{123m}Te. Additional human clinical trials with ^{11}C-DL-tryptophan and ^{11}C-1-aminocyclobutane carboxylic acid have been completed. The modified Bücherer-Strecker amino acid synthesis has been used to prepare ^{11}C-DL-phenylglycine and ^{11}C-DL-phenylalanine. These two new ^{11}C-labeled amino acids will be studied as potential tumor localizing agents. Preliminary studies concerning the comparative organ and subcellular distribution of ^{195m}Pt-labeled *cis*- and *trans*- dichlorodiammineplatinum(II) have been completed. The results of *in vivo* studies have shown the *cis* isomer to bind to nuclear DNA to a significantly greater extent than the *trans* isomer. A series of ^{123m}Te-labeled long-chain fatty acid analogs have been prepared as "isosteres" of unsaturated fatty acids. Several of these compounds show pronounced heart uptake in rats and may represent a new class of potential myocardial imaging agents.

CARBON-11

T. A. Butler

Two production runs of ^{11}C-labeled amino acids were made in support of the collaborative program with Oak Ridge Associated Universities (ORAU). Patients were administered ^{11}C-DL-tryptophan for pancreatic uptake studies and ^{11}C-1-aminocyclobutanecarboxylic acid for general tumor localization.

Scans were performed by positron emission tomography.

The modified Bücherer-Strecker amino acid synthesis method used in all of our earlier ^{11}C-labeled compound preparations was applied to the synthesis of ^{11}C-carboxyl-labeled DL-phenylglycine and DL-phenylalanine. Carbon-11 activity levels of 150 mCi and 375 mCi, respectively, were achieved in the final products. The compounds were used in preclinical animal studies to determine tissue distributions in rodents in support of a University of Kentucky collaborative effort with ORAU.

A series of malfunctions in the Oak Ridge National Laboratory (ORNL) 86-inch cyclotron over the past few months appear to have been corrected, and we anticipate obtaining additional proton-beam time in order to accelerate the ^{11}C-collaborative program.

PLATINUM-195m

J. D. Hoeschele and T. A. Butler

As part of the continuing cooperative program to study antitumor compounds, one shipment of ^{195m}Pt-labeled Na_2PtCl_6 and one shipment of ^{195m}Pt-labeled *cis*-$[Pt(NH_3)_2Cl_2]$ (*cis*-DDP) were made to the University of Southern California. Three shipments of ^{195m}Pt-labeled *cis*-DDP were made to the University of Arizona, and three shipments of ^{195m}Pt-labeled Na_2PtCl_6 were made to the University of Kentucky.

Comparative Tissue and Subcellular Distribution Studies and Polynucleotide Binding Experiments with ^{195m}Pt-Labeled *cis*- and *trans*-Dichlorodiammineplatinum(II)

An important but still unexplained aspect of the biological properties of platinum compounds is why *cis*-DDP exhibits antitumor activity while *trans*-DDP is inactive. In collaboration with N. P. Johnson and R. O. Rahn (Biology Division, ORNL) and D. H. Brown (ORAU), we have initiated a systematic study of the differential *in vitro* and *in vivo* binding/distribution properties of these isomers to assess whether different uptake, distribution, or DNA binding might be responsible for the difference in antitumor activities. A knowledge of why these compounds differ in their antitumor activity is vital to the understanding of the mechanism of action of antitumor platinum drugs. The basic objectives of this research are to define the *in vitro* binding properties with DNA, to determine the organ and subcellular distribution in normal and a model tumor system, and to determine the number of platinum atoms bound per DNA base nucleotide (R_b values).

Gross organ distribution

The *in vivo* studies used the American Cross Irish (ACI) rat bearing the Reuber H-35 hepatoma. This particular system was chosen because subcellular fractionation techniques appeared to be well-defined. The distribution of ^{195m}Pt radioactivity in selected organs and the hepatoma 2-24 hr after injection of ^{195m}Pt-labeled *cis*- and *trans*-DDP indicates that organ levels (percent dose/gram of wet tissue) are, in general, higher for *trans*- than *cis*-DDP. The order of increasing levels for *cis*-DDP injected animals is blood < spleen < liver < tumor which is exactly the reverse of that found for the *trans* isomer. The level in the kidney is substantially higher for *trans*- than *cis*-DDP. The 24 hr distribution data, summarized in Table 1, show that the ratio of *trans*-DDP/*cis*-DDP in the blood is approximately 4, a factor which directly

Table 1. The distribution of radioactivity in tissues of ACI rats 24 hr after intravenous administration of Pt-195m-labeled *cis*- and *trans*-DDP

Organ	Percent dose per gram tissue	
	Cis	*Trans*[a]
Blood T	0.25	0.94
N	0.22	(1.14)
Liver T	0.39	0.37
N	0.36	(0.41)
Spleen T	0.23	0.41
N	0.27	(0.75)
Kidney T	1.67	2.73
N	1.73	(3.59)
Tumor T	0.59	0.33

T = tumor (H-35 hepatoma).

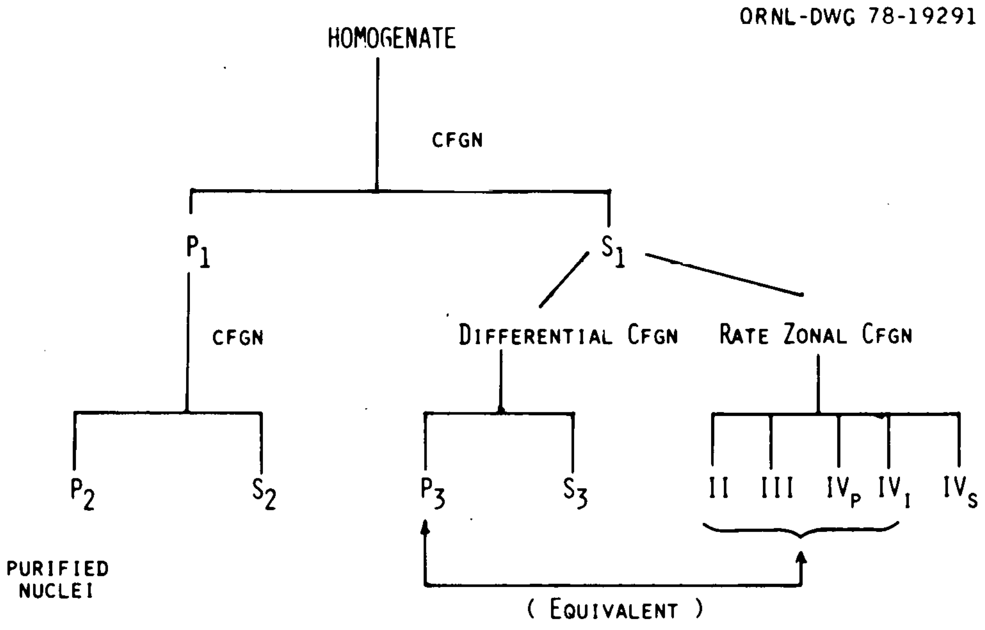
N = normal (control).

[a] N data = from Fischer 344.

parallels the relative chemical reactivity of these isomers. The percent dose/gram of tissue for *trans*-DDP in the livers of tumored (L_T) and normal (L_N) rats and in the tumor (T) are essentially the same. However, the distribution of *cis*-DDP in the tumor (hepatoma) is approximately two fold higher than that for the L_T and L_N.

Subcellular distribution studies

Pt-195m-labeled *cis*- and *trans*-DDP were administered intravenously in physiological saline at doses of 7.5 and 3.0 mg/kg, respectively. Rats were sacrificed over a 2-24 hr post-injection interval and selected organs were excised. Portions of the livers from L_T and L_N animals were used immediately in the standard subcellular fractionation studies. Differential and rate zonal centrifugation techniques were employed in the isolation of subcellular components. The protocol used in isolating the various subcellular components is depicted in Fig. 1. Nuclear DNA was isolated from "purified" nuclei by means of standard techniques and the amount of Pt bound to DNA then determined radiometrically. The most significant difference in the relative subcellular distribution of *cis*- and *trans*-DDP is found for the "purified" nuclei. At 24 hr (Table 2), the level for *cis*-DDP is approximately three times higher in the tumor



Fraction Identification

P_1	Whole Cells	II	Mitochondria
P_2	Purified Nuclei	III	Lysosomes
P_3	II-IV	IV_P	Microsomes
		IV_I	Polysomes (L)
		IV_S	Ribosomes, Polysomes (S)

Fig. 1. Fractionation scheme for the purification of subcellular components from tumor and normal liver cells from rats following administration of Pt-195m-labeled *cis*-DDP.

Table 2. The subcellular distribution of radioactivity 24 hr after intravenous administration of Pt-195m-labeled *cis*- and *trans*-DDP

	Relative Percent			
	Tumor		Liver (normal)	
	Trans	*Cis*	*Trans*	*Cis*
Nuclear Pellet				
S_2	91	81	93	85
P_2	9	19	7	15
Nuclei P_2[a]	1	3	0.8	1.2
Cytoplasm				
Particulate, P_3	53	20	39	19
Soluble, S_3	47	80	61	81

[a] Percent of activity in tissue homogenate.

nuclei compared to either the level of *cis*-DDP in the L_N nuclei or *trans*-DDP in the T and L_N nuclei.

These data parallel the gross organ distribution data at 24 hr. As indicated in Table 3, the most pronounced differences in levels for *cis*-DDP occur in the mitochondrial and soluble fractions. These values are 9 vs 15 (mitochondria) and 31 vs 23 (solubles) for the tumor and normal liver, respectively. Unfortunately, the detailed cytoplasmic distribution data for *trans*-DDP are not available at this time. Distribution data show that *trans*-DDP is approximately equally distributed between the particulate and soluble components, whereas *cis*-DDP is

Table 3. Subcellular distribution of radioactivity 24 hr after intravenous administration of Pt-195m-labeled *cis*-DDP

	Percent in whole cell at 24 hr	
Organ	Tumor	Normal Liver
Cytoplasm	71	68
Nuclear pellet	29	32
Nuclei (purified)[a]	3	1.2
Mitochondria	9	15
Lysosomes	16	19
Microsomes	10	8
Polysomes	5	6
Solubles	31	23

[a] Percent recovery is unknown.

distributed in the soluble components approximately 4 times greater than in the particulates.

In vivo binding of Pt-195m-labeled *cis*- and *trans*-DDP to nuclear DNA

The amount of platinum bound to the isolated DNA was conveniently determined by the use of ^{195m}Pt-labeled complexes. These data presumably represent an index of the degree of binding of *cis*- and *trans*-DDP to the DNA. The results of these studies have shown that both the rate and equilibrium amounts of *cis*- and *trans*-DDP bound to DNA (single- and double-stranded) are approximately the same for the pH range 4-7.

These values are, however, affected by the nature of the buffer employed. The *in vitro* studies of the competitive binding of *cis*-DDP with DNA and poly (rA) indicate irreversible binding (i. e., the amount of Pt bound to a given polymer is unchanged on addition of the second polymer). Finally, the Pt-DNA bond is non-labile (inert) under the alkaline conditions that completely hydrolyze RNA.

The Ratio of Platinum Atoms Bound per DNA Base Nucleotide *In Vivo*

The most striking feature of the *in vivo* distribution/binding of these *cis* and *trans* isomers is in regard to their binding to nuclear DNA. Determinations of the ratio of Pt atoms bound/DNA base nucleotide (R_b) after 2-24 hr post-injection indicate that saturation binding is achieved within 2 hr for both isomers and that the average R_b value for *cis*-DDP for liver and tumor DNA is $5.3 \pm 2.0 \times 10^{-5}$ whereas that for *trans*-DDP is $4 \pm 3 \times 10^{-6}$. This means that approximately 2 to 28 times more *cis*-DDP than *trans*-DDP is bound per DNA base nucleotide. We conclude from these preliminary data that *cis*-DDP binds more effectively to DNA *in vivo* than does *trans*-DDP. These data further suggest that the relative drug effectiveness of *cis*- and *trans*-DDP might be related to the amount of Pt bound to DNA. Consequently, we propose the following qualitative multi-term expression which directly relates the relative drug effectiveness to the major parameters which could influence the amount of DDP bound to DNA.

$$\text{Effectiveness (DNA)} \propto T \cdot C \cdot B \cdot E \cdot G \cdot R$$

Each term in this expression refers to important parameters such as transport properties (T), the Pt/DNA concentration ratio in the nucleus

(C), intrinsic binding properties (from *in vitro* studies) (B), biological effect/per lesion (E), genetic expression of the lesion (G), and repair processes (R). Each term is a ratio of the values which *cis*-DDP (numerator) and *trans*-DDP (denominator) would have for a given parameter. In formulating this expression it was assumed that DNA is the target site and that drug effectiveness increases with the amount of DDP bound to DNA. Numerical evaluation (approximation) of these various factors will come from *in vitro* and *in vivo* studies which are presently in progress and from an analysis of studies reported in the literature. Future work will focus on the further refinement of nuclei purification procedures, particularly for the tumor nuclei. The effect of the variation of dose on the subcellular distribution and Pt/DNA ratios for tumor and liver tissues of ^{195m}Pt-labeled *cis*- and *trans*-DDP will also be further investigated

SELENIUM-75

D. V. Woo, K. R. Ambrose, T. A. Butler, and F. F. Knapp, Jr.

Continuing studies with ^{75}Se-β-aminoethyl selenosulfate have provided additional information concerning its tissue distribution after administration to rats. Preliminary studies were directed at an attempt to isolate the intact non-metabolized ^{75}Se-labeled compound after administration to female rats. Two hours after injection the animals were sacrificed; and the heart, lungs, and liver were removed, homogenized, and the protein precipitated. After centrifugation the tissue homogenates were extracted with chloroform-methanol; and the remaining aqueous portion was lyophilized, resuspended in water, and passed through a cation exchange column. The eluates were then subjected to thin layer chromatographic analysis. The major product detected by these studies was endogenous taurine. There was no chromatographic evidence of any free ^{75}Se-β-aminoethyl selenosulfate in any of the organ extracts examined. Approximately 98% of the total activity in each organ was found to be in the initial protein precipitate. These results suggest that this compound is possibly bound or associated with protein macromolecules or is present in another form that is not directly isolated by these techniques. Further investigations will be conducted to determine if the ^{75}Se-β-aminoethyl selenosulfate is actually incorporated into protein. A previous report (ORNL/TM-6410) describing studies of the tissue distribution of ^{75}Se-β-aminoethyl selenosulfate indicated favorable concentrations in the heart and lung. However, these studies were conducted using ^{75}Se-β-aminoethyl selenosulfate having a specific activity of 20-40 mCi/mmole. To determine what effect specific activities may have on the tissue uptake and distribution kinetics, high specific activity (200 mCi/mmole) ^{75}Se-β-aminoethyl selenosulfate was synthesized and administered to female Fischer strain rats. The tissue distribution of ^{75}Se was not significantly different than that observed in earlier studies using the lower specific activity substrate. However, in these more recent experiments the pancreas was found to contain the highest concentration (mean 8% dose/g) of ^{75}Se 30 min after injection. The second highest organ of uptake at 30 min was the liver (near 2.5% dose/g). The pancreas/liver ratio for ^{75}Se-β-aminoethyl selenosulfate was 3.2. The pancreas/liver ratio for rats reported in the literature using ^{75}Se-selenomethionine (currently used to image the pancreas) is 2.4.

This unusually high concentration of ^{75}Se suggests that ^{75}Se-β-aminoethyl selenosulfate could prove to be a useful alternative to ^{75}Se-selenomethionine for pancreatic imaging. The ease of preparation of ^{75}Se-β-aminoethyl selenosulfate compared to that for ^{75}Se-selenomethionine could also prove to be an attractive advantage.

Further studies during the next quarter will determine the period for maximal uptake of ^{75}Se-β-aminoethyl selenosulfate and will also compare relative tissue distribution of this agent with ^{75}Se-selenomethionine. Also, the synthesis of even greater specific activity ^{75}Se-β-aminoethyl selenosulfate ($\sim$1 Ci/mmole) will be attempted in order to increase specific uptake in target organs

TELLURIUM-123m

F. F. Knapp, Jr., and K. R. Ambrose

Studies have continued concerning the development of ^{123m}Te-labeled tissue imaging agents. Since the β-oxidation of long-chain fatty acids supplies most of the energy needs for the normal myocardium, the preparation of fatty acid analogs labeled with γ-emitting nuclides is an attractive area of research. If labeled fatty acids can be concentrated in heart tissue, then the use of such agents as vehicles for the concentration of radioactivity in the heart is an attractive approach for myocardial imaging. A wide variety of fatty acids labeled with ^{131}I, ^{123}I, ^{18}F, ^{11}C, and ^{99m}Tc have been prepared and tested for heart imaging. Nonetheless, it still has not yet been precisely established what structural perturbations can be introduced into the fatty acid molecule and still impart heart uptake. It is well established that the biological properties of many compounds are maintained when the $>C=C<$ moiety is replaced with S, Se, or Te. The substituted molecules are "isosteric" with the olefinic counterparts since the gross biological properties are still retained. Our strategy was to prepare a ^{123m}Te-labeled "isostere" of a natural fatty acid that is known to be actively concentrated and metabolized by myocardial tissue. Since oleic acid (9-octadecenoic acid) is the major serum fatty acid concentrated by the heart, we have prepared the ^{123m}Te-labeled isostere, 9-tellurahepta-decanoic acid. If the telluro analog is indeed transported *in vivo* and concentrated in heart tissue in a manner similar to that observed for oleic acid, then the excellent imaging properties of ^{123m}Te (159 keV photon; 84% abundance) may indicate that these labeled fatty acids represent a new series of potential myocardial imaging agents.

The following procedure has been developed for the preparation of ^{123m}Te-labeled fatty acids: RX(I) + Na_2Te_2(II) → R-Te-Te-R(III) → R-Te-Na(IV) + X-R'-COOMe(V) → R-Te-R'-COOMe(VI) → R-Te-R'-COOH(VII). The dialkyl ditellurides (III) were prepared by a standard procedure involving reaction of tellurium powder with a stoichiometric amount of sodium metal in liquid ammonia at -50 to -60°C followed by alkylation with the appropriate alkyl halide (I). The ditellurides were reduced with sodium borohydride to yield the sodium alkyl tellurols which were then coupled with the ω-(halo alkyl) carboxylic acid methyl esters (V) to give the telluro fatty acid methyl esters (VI) in respectable yields. The esters were used rather than the free acids since the manipulations were greatly simplified and the products could be extracted into the organic phase and most side-products could be removed by water washes. In addition, the methyl esters of the (alkyl telluro) fatty acids were subsequently found to be quite stable and could be stored for several weeks as pure oils with only minimal decomposition. The ω-bromo fatty acids used for these studies were obtained commercially and were smoothly converted to the corresponding methyl esters (V) by reaction with diazomethane. A series of ω-(alkyl telluro) fatty acids were prepared in order to investigate a variety of structural features that could potentially effect the myocardial uptake of these compounds. Our preliminary synthetic efforts have resulted in the preparation of the acids listed in Table 4. The effects of total chain length and the position of the tellurium heteroatom in the alkyl chain have been investigated. The chromatographic, ultraviolet, infrared, mass-spectral, and ^{1}H and ^{13}C nuclear magnetic resonance properties of the methyl esters and free acids have been studied, and these data are consistent with the proposed structures of these compounds.

The ^{123m}Te-labeled telluro fatty acid methyl esters were prepared in the same manner and purified by silicic acid column chromatography

Table 4. (Alkyl telluro) fatty acids prepared by basic hydrolysis of the corresponding methyl esters. The esters were synthesized by coupling sodium alkyl tellurols with ω-bromo alkyl carboxylic acid methyl esters

Telluro fatty acid	Olefinic isostere
6-Telluratridecanoic acid $CH_3-(CH_2)_6-Te-(CH_2)_4-COOH$	6-Tetradecenoic acid $CH_3-(CH_2)_6-CH=CH-(CH_2)_4-COOH$
17-Telluraheneicosonic acid $CH_3-(CH_2)_3-Te-(CH_2)_6-CH=CH-(CH_2)_7-COOH$	$CH_3-(CH_2)_3-CH=CH-(CH_2)_6-CH=CH-(CH_2)_7-COOH$
9-Tellurapentadecanoic acid $CH_3-(CH_2)_5-Te-(CH_2)_7-COOH$	9-Hexadecenoic (palmitoleic) acid $CH_3-(CH_2)_5-CH=CH-(CH_2)_7-COOH$
9-Telluraheptadecanoic acid $CH_3-(CH_2)_7-Te-(CH_2)_7-COOH$	9-Octadecenoic (oleic) acid $CH_3-(CH_2)_7-CH=CH-(CH_2)_7-COOH$

and hydrolyzed by base to the free acids. The labeled acids were then administered to female rats via the tail vein after dissolving in a pH 7.2-7.8 solution of 0.7% physiological saline containing 10% ethanol. Groups of three or four animals were used for each time point. The organs were removed and weighed and the radioactive contents then determined. The data were calculated as the percent dose/gram of tissue and are illustrated in Figs. 2, 3, 4, and 5. By a comparison of the structure-activity relationships described in the literature for the heart uptake of long-chain fatty acids, one would expect some specificity for heart concentration of the compounds under study. For instance, one would expect the shorter-chain acids not to exhibit high heart uptake

ORNL-DWG 78-19290

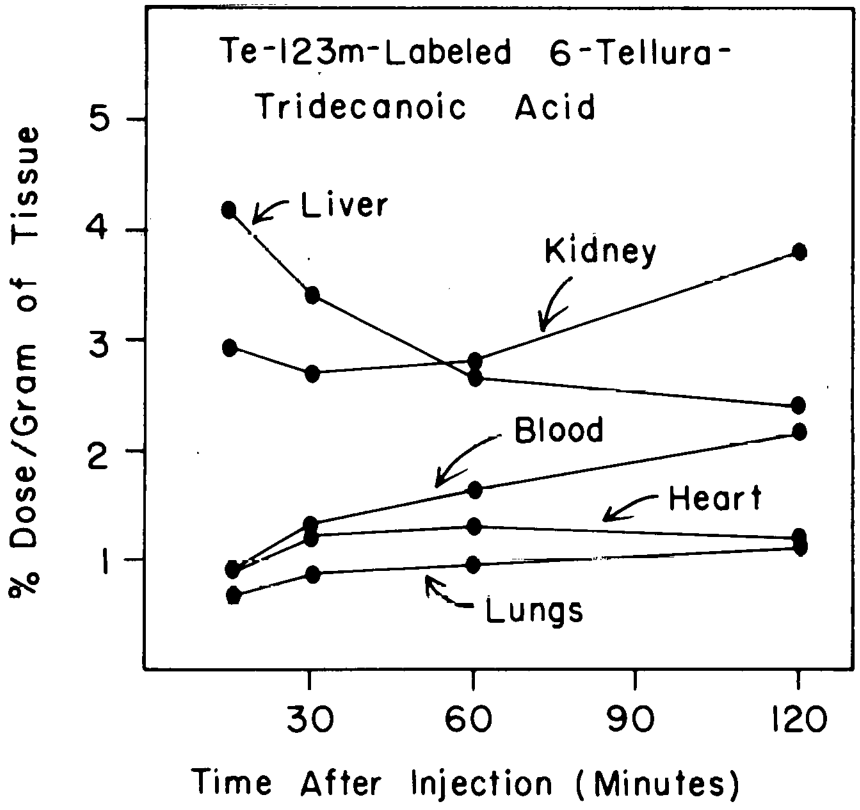


Fig. 2. Tissue distribution of radioactivity following the administration of Te-123m-labeled 6-telluratridecanoic acid.

and experiments with 6-telluratridecanoic acid (Fig.2) indicate that this compound does not show heart specificity. This telluro fatty acid is an isostere of the olefinic compound with the double bond in the unusual 6(7) position, and this structural feature may also explain the low heart uptake of the telluro fatty acid. In contrast, the ^{123m}Te-labeled isostere of oleic acid (9-telluraheptadecanoic acid) shows very high myocardial uptake (Fig. 3). Similarly, the ^{123m}Te-labeled isostere of palmitoleic acid (9-tellurapentadecanoic acid) also shows pronounced heart uptake (Fig. 4). One may also expect very long-chain fatty acids to show even greater heart uptake as a result of their slower catabolism and thus longer residence time within the heart tissue. We have also

ORNL-DWG 78-20779

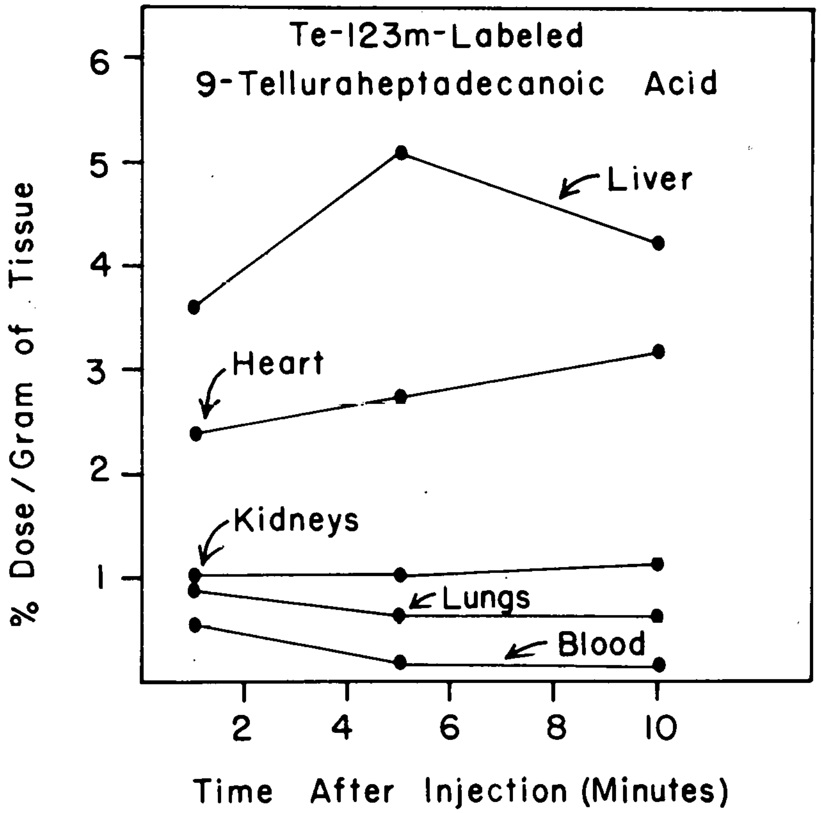


Fig. 3. Tissue distribution of radioactivity following the administration of Te-123m-labeled 9-telluraheptadecanoic acid.

ORNL-DWG 78-20778

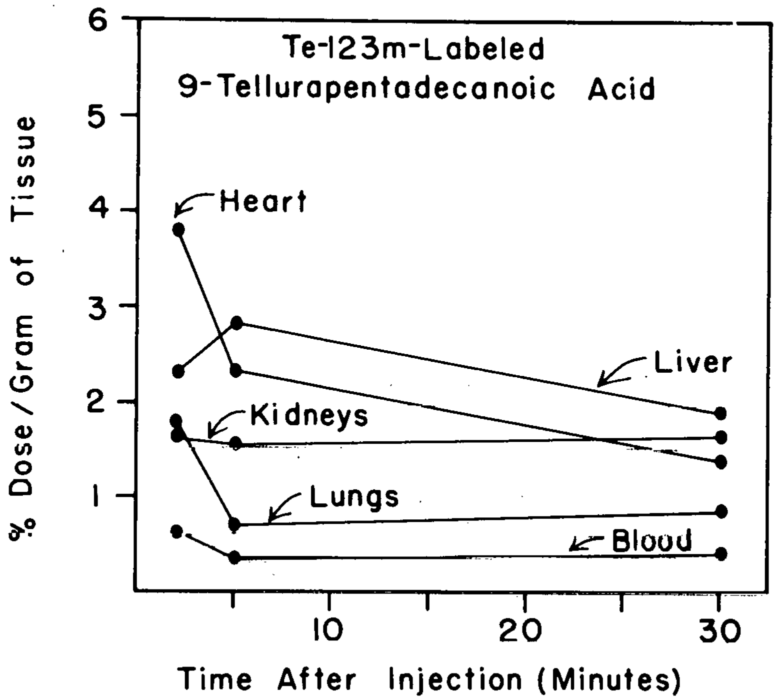


Fig. 4. Tissue distribution of radioactivity following the administration of Te-123m-labeled 9-tellurapentadecanoic acid.

found this to be the case and 17-telluraheneicosonic acid (an isostere of a $\Delta^{9,16}$-C_{22} fatty acid) shows very high heart uptake (Fig. 5). These results closely parallel, at least for short time periods, similar data reported for oleic acid, the major fatty acid concentrated and catabolized by myocardial tissue (Fig. 6). These results are encouraging and clearly indicate that the myocardial specificity for long-chain olefinic fatty acids is not destroyed by the isosteric replacement of selected double bonds with tellurium. Furthermore, the ^{123m}Te-labeled fatty acids may represent a new class of potential myocardial imaging agents. During the next quarter these studies will be extended by the preparation of other telluro fatty acids to investigate further the effects of the position of the tellurium heteroatom and the total alkyl-chain length on the myocardial specificity of such compounds.

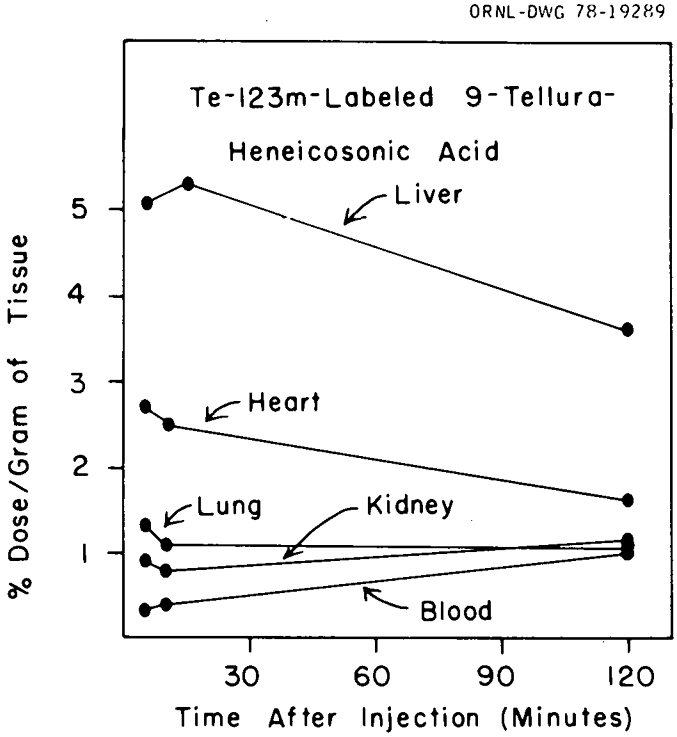


Fig. 5. Tissue distribution of radioactivity following the administration of Te-123m-labeled 9-telluraheneicosonic acid.

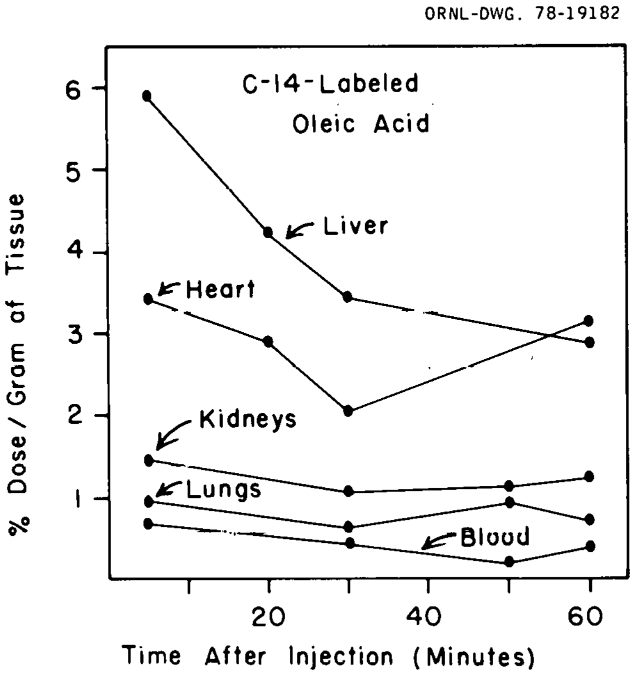


Fig. 6. The tissue distribution of C-14-labeled oleic acid administered to rats. The figure contains data plotted from selected values reported by W. H. Beirwaltes and co-workers, Journal of Nuclear Medicine, 16(9): 842, 1975.

MISCELLANEOUS

Visitors for this period included Dr. A. Perumal from the Physics Department at Johnson C. Smith University, who toured the Nuclear Medicine Technology facilities with two undergraduate biophysics students on April 28. On April 4, Dr. H. Guilford, the technical liason with Amersham Corporation, visited to discuss the production of ^{123m}Te and the potential development of ^{123m}Te-labeled radiopharmaceuticals. These discussions were continued in considerably more detail when Dr. J. A. Peacegood, from the Radiochemical Centre at Amersham, England, visited our facilities, on May 3. On May 19, Mr. R. A. Grigsby joined the Nuclear Medicine Technology Group as a summer research student. Mr. Grigsby is a graduate student in organic chemistry in the Chemistry Department at Texas A & M University, working under the direction of Dr. K. J. Irgolic. At ORNL he is participating in the synthesis of organotin and organotellurium compounds of potential interest. On April 28, P. R. Bell, distinguished scientist and lecturer, retired from ORNL. On May 18, F. F. Knapp, Jr., and J. K. Poggenburg met with representatives of the new Medical Products Division of Union Carbide Corporation and gave an overview of the nuclear medicine research and development efforts of the Nuclear Medicine Technology Group at ORNL.

Six shipments of ^{43}K were made this quarter. Four shipments were made to the National Institute for Environmental Health. One shipment was made to the University of Mississippi for their coronary disease studies. One shipment was made to the Veterans Administration Center, Wood, Wisconsin, for their study of ^{43}K uptake in the hearts of stressed rodents.

In support of the cooperative program with the ORNL Biology Division to study the translocation of asbestos fibers in rodents following deposition in transplanted tracheas, 105 mg of neutron activated chrysotile "A" asbestos fibers were supplied.

Two shipments of ^{165}Er were supplied to Oak Ridge Associated Universities to determine the potential of this nuclide for tumor localization studies using a proportional counter camera. The undesirable ^{166}Dy contaminant present in the ^{165}Er preparation reported last quarter (ORNL/TM-6410) was eliminated in the present studies by selecting Dy-free ^{164}Er neutron target material. The radiopharmaceutical quality testing and preclinical animal distribution studies have been completed in preparation for an Investigational New Drug Application to permit eventual human studies with ^{165}Er.

PAPERS AND PUBLICATIONS

Journals

R. L. Hayes, L. C. Washburn, B. W. Wieland, T. T. Sun, J. B. Anon, T. A. Butler, and A. P. Callahan, "Synthesis and Purification of ^{11}C-Carboxyl-labeled Amino Acids", *Int. J. Appl. Radiat. Isot.* 29: 186-187, 1978.

Reports

F. F. Knapp, Jr., *Nuclear Medicine Technology Progress Report for Quarter Ending March 31, 1978*, ORNL/TM-6410.

INTERNAL DISTRIBUTION

1. K. R. Ambrose
2. S. I. Auerbach
3. J. A. Auxier
4. J. M. Becker (Consultant)
5. T. A. Butler
6. J. A. Cox
7. J. M. Dougherty
8. R. B. Gammage
9. A. S. Garrett, Jr.
10. W. R. Garrett
11. J. D. Hoeschele
12-17. S. V. Kaye
18-22. F. F. Knapp, Jr.
23. E. Lamb
24. B. F. Maskewitz
25. C. H. Nowlin
26. C. L. Ottinger
27. D. C. Parzyck
28. H. Postma
29. M. E. Ramsey
30. C. R. Richmond
31. A. F. Rupp (Consultant)
32. C. D. Scott
33. W. D. Shults
34. M. R. Skidmore
35. J. B. Storer
36. P. J. Walsh
37. D. V. Woo
38. H. A. Wright
39-40. Central Research Library
41. Document Reference Section
42-43. Laboratory Records Department
44. Laboratory Records, ORNL RC
45. ORNL Patent Section

EXTERNAL DISTRIBUTION

46. S. James Adelstein, M.D., Shields Warren Radiation Lab., Boston, MA 02115
47. H. L. Atkins, M.D., BNL, Upton, NY 11973
48. A. B. Brill, MD, Vanderbilt Univ. Hospital, Nashville, TN 37232
49. T. F. Budinger, M.D., Donner Lab., LBL, Berkeley, CA 94720
50. Philip A. DeSimone, M.D., V.A. Hospital, Lexington, KY 40507
51. Paul Harper, M.D., Franklin McLean Memorial Research Institute, Chicago, IL 60637
52. R. L. Hayes, ORAU, Oak Ridge, TN 37830
53. John Hollifield, M.D., Vanderbilt Univ. Hospital, Nashville, TN 37232
54. K. J. Irgolic, Chemistry Dept., Texas A&M Univ., College Station, TX 77840
55. David E. Kuhl, M.D., UCLA, Lab. of Nuclear Medicine, Los Angeles, CA 90024
56. John S. Laughlin, Sloan-Kettering Inst. for Cancer Research, New York, NY 10021
57. A. Lengendre, M.D., UT-School of Veterinary Medicine, Knoxville, TN 37920
58. C. C. Lushbaugh, ORAU, Oak Ridge, TN 37830
59. J. N. Maddox, DOE-DBER, Washington, DC 20545
60. Office of Assistant Manager, Energy Research and Development, DOE-ORO, Oak Ridge, TN 37830
61. H. A. O'Brien, LASL, Los Alamos, NM 87545
62. J. K. Poggenburg, Medical Products Division, UCC, Tuxedo, NY 10987
63. P. Richards, BNL, Upton, NY 11973
64. A. Solomon, M.D., UT MRCH, Knoxville, TN 37920
65-91. Technical Information Center, DOE, Oak Ridge, TN 37830
92. John Venditti, National Cancer Institute, Silver Springs, MD 20910

93. H. E. Walburg, CARL, Oak Ridge, TN 37830
94. W. H. Weyzen, M.D., DOE-DBER, Washington, DC 20545
95. A. P. Wolf, BNL, Upton, NY 11973
96. Walter Wolf, University of Southern California, Los Angeles, CA 90033
97. R. W. Wood, Jr., DBER, Washington, DC 20545