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Nuclear Medicine Technology Progress Report for Quarter Ending June 30, 1980

F. F. Knapp, Jr.

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F. F. Knapp, Jr.

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SUMMARY

Of special significance in this progress report are the results of experiments demonstrating that the alkyl portion (R = H_3C-$(CH_2)_7$-) of 9-telluraheptadecanoic acid [9-THDA, R-Te-$(CH_2)_7COOH$] is retained in the myocardial tissue of rats to the same extent as radioactivity from ^{123m}Te-9-THDA. Tissue distribution experiments were performed in female Fischer 344 rats one hour after injection of 10-[^{14}C]-9-telluraheptadecanoic acid [H_3C-$(CH_2)_6$-$^{14}CH_2$-Te-$(CH_2)_7$-COOH, 10-^{14}C-9-THDA] and the data compared with the results of a parallel study using ^{123m}Te-9-THDA. The mean percent injected dose per gram of tissue values for the heart were 5.5 and 5.1 for ^{123m}Te-9-THDA, and 10-[^{14}C]-9-THDA, respectively, and the corresponding heart:blood ratios at this time interval were 8.9:1 and 11.2:1. These results clearly indicate that the alkyl region of 9-THDA is retained in the myocardium and that labeling of this portion of the 9-THDA molecule with radiohalogens such as ^{123}I may be an attractive approach for trapping radionuclides with more favorable radionuclidic properties than ^{123m}Te in the heart for evaluation of myocardial function.

The results of preliminary synthetic studies for the development of radiolabeled barbiturates as a new class of agents for the measurement of regional blood perfusion in the brain are also described. Since barbiturates freely pass the intact blood brain barrier, these agents have been chosen as attractive candidates for labeling with gamma-emitting radionuclides. Several new barbiturates substituted at the C-5 position with (trialkylstanna)alkyl, (alkylseleno)alkyl, and (alkyltelluro)alkyl moieties have been prepared and characterized. These compounds will be labeled in future studies with ^{117m}Sn, ^{75}Se, and ^{123m}Te and brain uptake studies performed in rats.

Studies of arsenic trioxide (As_2O_3) toxicity for human cells in the diffusion chamber assay system have continued. These studies employing $^{74}As_2O_3$ have demonstrated that uptake of radioactivity from test substances administered to rats can be detected in cells taken from the intraperitoneally-implanted diffusion chambers. Preliminary synthetic studies of gold-based antirheumatoid complexes are also reported. Several ^{11}C-labeled amino acids including ^{11}C-DL-valine, ^{11}C-DL-tryptophan, ^{11}C-1-aminocyclobutane carboxylic acid (^{11}C-ACBC), and ^{11}C-DL-1-aminocyclopentane carboxylic acid (^{11}C-ACDC) have been prepared for clinical testing at the Oak

Ridge Assoicated Universities. Platinum-195*m*-labeled-*cis*-dichlorodiammine-platinum(II) (^{195m}Pt-*cis*-DDP) has been supplied to collaborators for further testing and ^{75}Se- and ^{123m}Te-labeled long-chain fatty acids have been supplied to several medical cooperative investigators for the evaluation of myocardial function in experimental animals.

MYOCARDIAL IMAGING AGENTS - RADIOLABELED LONG-CHAIN FATTY ACIDS

F. F. Knapp, Jr. and T. A. Butler

Investigations of the heart specificity and mechanism of heart uptake of ^{123m}Te and ^{75}Se-labeled long-chain fatty acids have continued. In the Progress Report for the Quarter ending March 31, 1980 (ORNL/TM-7411), the effects of chain length and position of the selenium heteroatom on the heart uptake in rats of a series of ^{75}Se-labeled fatty acids were described. Only the selenium fatty acids with chain lengths greater than 21 carbon atoms showed significant heart uptake in rats, and ^{75}Se-13-selenaheneicosonic acid (13-SHCA) has been chosen as a representative ^{75}Se-fatty acid for further evaluation.

The pronounced and prolonged myocardial uptake of ^{123m}Te-9-THDA (ORNL/TM-6638) and ^{75}Se-13-SHCA (ORNL/TM-7411) has indicated that these fatty acids may be concentrated in the myocardium by a unique trapping mechanism. In an effort to take advantage of the more attractive radionuclide properties of radiohalogens such as ^{123}I, it was recently proposed that radiohalogenated fatty acids containing stable tellurium or selenium, such as ^{123}I-17-iodo-9-telluraheptadecanoic acid [^{123}I-$(CH_2)_8$-Te-$(CH_2)_7$-COOH], may represent attractive new agents that could be useful for measurement of regional myocardial metabolism (ORNL/TM-6916). The metabolic fate of 9-THDA in the myocardium has not yet been determined. Since loss of the alkyl portion (R) of 9-THDA [R-Te-$(CH_2)_7$-COOH, where R = H_3C-$(CH_2)_7$-] would preclude halogenation of this region of the molecule, an experiment was designed to determine if the alkyl terminus of 9-THDA was retained in the myocardium in the same manner observed for ^{123m}Te.

In an attempt to answer this question, 10-[^{14}C]-9-telluraheptadecanoic acid [H_3C-$(CH_2)_6$-$^{14}CH_2$-Te-$(CH_2)_7$-COOH] was prepared by basic hydrolysis of the purified product obtained by the coupling of 1-[^{14}C]-octyl telluro with methyl-8-bromooctanoate. One hour after administration to female Fischer rats the tissues were removed and dissolved in a commercial solubilizer; the aliquots were decolorized and then analyzed in a liquid scintillation counter. The tissues were analyzed after one hour since earlier extensive studies had indicated that myocardial uptake of radioactivity was maximal at this time interval after injection of ^{123m}Te-9-THDA. The distribution of ^{14}C in the rat tissues agrees remarkably well with similar data obtained with ^{123m}Te-9-THDA (Table 1) and indicates that the alkyl portion of 9-THDA is retained in the myocardium and is an attractive region of the molecule for labeling with radiohalogens. Chemical techniques for the introduction of terminal halides into 9-THDA and similar selenium and sulfur fatty acids are now being developed.

Table 1. Comparison of the distribution of radioactivity in tissues of female Fischer 344 rats 60 min after intravenous injection of either ^{123m}Te-9-telluraheptadecanoic acid (^{123m}Te-9-THDA) or 10-[^{14}C]-9-telluraheptadecanoic acid (^{14}C-9-THDA)[a]

Tissue	Mean percent injected dose/gram (range)		Heart:tissue ratios[b]	
	^{123m}Te	^{14}C	^{123m}Te	^{14}C
Heart	5.50 (4.44-6.19)	5.13 (4.01-5.83)		
Blood	0.62 (0.60-0.65)	0.46 (0.31-0.55)	8.9:1	11.2:1
Lungs	0.90 (0.82-0.94)	0.91 (0.67-1.16)	6.1:1	5.6:1
Kidneys	2.01 (1.85-2.12)	2.34 (2.06-2.54)	2.7:1	2.2:1
Liver	8.55 (7.70-9.83)	6.32 (5.38-7.56)	0.64:1	0.81:1

[a]Three female Fischer 344 rats were used in each study.

[b]Ratios are calculated from the mean percent injected dose per gram of tissue values.

The greater myocardial uptake of ^{123m}Te-9-THDA compared with the selenium analog, ^{75}Se-9-SHDA, was recently substantiated by a dual-labeling experiment (ORNL/TM-7223). Since ^{75}Se-13-SHCA has been shown to have the greatest heart uptake in rats of the ^{75}Se-labeled fatty acids that have been investigated, the tissue distribution of this model ^{75}Se-fatty acid has now been compared with ^{123m}Te-9-THDA in a dual-labeling experiment. The results of these studies (Table 2) substantiate the greater heart uptake of the ^{123m}Te-labeled agent. The heart uptake of the ^{75}Se-labeled fatty acid is still sufficiently high for further evaluation and will undergo extensive study as described earlier *(vide ante)*. The potential use of the ^{73}Se-labeled fatty acid for positron emission tomography of the myocardium is also a potentially important application, and a Medical Cooperative Program has been established with Drs. Rigo and Guillaume at the Cyclotron Unit in Liege, Belgium, to evaluate these agents.

Table 2. Distribution of radioactivity in tissues of female Fischer 344 rats 60 min following intravenous administration of ^{123m}Te-9-telluraheptadecanoic acid (^{123m}Te-9-THDA) and ^{75}Se-13-selenaheneicosonic acid (^{75}Se-13-SHCA)[a]

Tissue	Mean percent injected dose/gram (range)		Heart:tissue ratios[b]	
	^{123m}Te	^{75}Se	^{123m}Te	^{75}Se
Heart	5.07 (4.09-6.49)	1.97 (1.40-2.32)		
Blood	0.48 (0.44-0.54)	0.32 (0.29-0.34)	10.6:1	6.2:1
Liver	5.11 (4.73-5.33)	5.45 (5.05-5.73)	0.9:1	0.4:1
Kidneys	1.94 (1.86-2.00)	1.40 (1.32-1.49)	2.6:1	1.4:1
Lungs	0.83 (0.72-0.90)	1.04 (0.88-1.18)	6.1:1	1.9:1
Spleen	0.40 (0.33-0.46)	0.78 (0.73-0.89)	12.7:1	2.5:1
Brain	0.08 (0.07-0.09)	0.06 (0.05-0.07)	63:1	33:1

[a]Three female Fischer 344 rats were used in each study.

[b]Ratios are calculated from the mean percent injected dose per gram of tissue values.

[c]Each rat received 5.35 μCi of ^{75}Se-13-SHCA (specific activity 25 mCi/millimole) and 4.71 μCi of ^{123m}Te-THDA (specific activity 27 mCi/millimole).

NEW BRAIN REGIONAL BLOOD PERFUSION AGENTS-
RADIOLABELED BARBITURATES

F. F. Knapp, Jr. and T. A. Butler

Lipophilic agents that freely penetrate the blood brain barrier are attractive candidates for radiolabeling with gamma emitting radionuclides. These agents can be used to assess brain structure and monitor regional perfusion parameters since the distribution of many such radiolabeled agents is a function of blood flow. Various brain lesions are characterized by either increased vascularity (neoplasia) or avascularity (infarction), and measurement of the regional hemodynamics is an important diagnostic tool to detect and localize such abnormalities. A variety of lipophilic hydantoins such as phenytoin (diphenyl hydantoin), a common anticonvulsant, have been studied as regional perfusion agents. Carbon-11-labeled phenytoin localizes in brain tissue and has been suggested as a brain-scanning agent[1], along with a number of structurally-modified ^{11}C-hydantoins.[2] Other lipophilic agents that have been investigated inlcude ^{123}I-antipyrine,[3] ^{18}F-labeled antipyrine,[4] and radiohalogenated catecholamine analogs.[5] The preparation and testing of lipophilic agents radiolabeled with longer-lived gamma emitting radionuclides that freely cross the intact blood-brain barrier is also important if such diagnostic tools are to have wide distribution and availability to a large patient population.

Analogs of barbituric acid (I, Fig. 1) are widely used as both sedatives and anticonvulsants and freely cross the intact blood-brain barrier. These drugs are extremely lipophilic and are known to penetrate tissues at rates approximately proportional to the lipid solubility of their unionized forms. For these reasons the barbiturates are attractive candidates for radiolabeling with gamma emitting radionuclides and testing as brain perfusion agents. Despite the pronounced uptake and rapid clearance of many barbiturates by the brain, the potential use of barbiturates radiolabeled with gamma emitting radionuclides has not been explored. In conjunction with Dr. R. A. Grigsby, a postdoctoral fellow from Texas A&M University, an intensive program has been initiated to prepare a series of new barbiturates radiolabeled with ^{75}Se, ^{123m}Te, and ^{117m}Sn and to perform preliminary tissue

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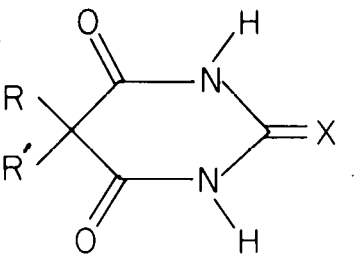

COMPOUND	R	R′	X
I	H	H	O
II	CH_3CH_2	$CH_3(CH_2)_2CH(CH_3)$	S
III	$CH_2=CH_2$	$(CH_3)_3-Si-CH_2$	O
IV	CH_3	$(CH_3)_3$ Sn CH_2	O
V	CH_3CH_2	$C_6H_5-Te-(CH_2)_4$	O
VI	CH_3CH_2	$CH_3(CH_2)_3-Te-(CH_2)_3$	O
VII	CH_3CH_2	$C_6H_5-Se-(CH_2)_4$	O
VIII	CH_3CH_2	$CH_3(CH_2)_3-Se-(CH_2)_3$	O

Fig. 1. Structures of barbituric acid (I), thiopental (II), 5-allyl-5-[(trimethylsila)methyl] barbituric acid (III), 5-methyl-5-[(trimethylstanna)methyl] barbituric acid (IV), 5-ethyl-5-[(phenyltelluro)butyl] barbituric acid (V), 5-ethyl-5-[(butyltelluro)ethyl] barbituric acid (VI), 5-ethyl-5-[(phenylseleno)butyl] barbituric acid (VII), and 5-ethyl-5-[(butylseleno)propyl] barbituric acid (VIII).

distribution studies in laboratory animals. Such studies can be expanded potentially to include barbiturates radiolabeled with a variety of other useful radionuclides such as ^{11}C, ^{123}I, and ^{77}Br.

These investigations of radiolabeled barbiturates were stimulated by the results of autoradiographic studies of brain tissue slices obtained from cats following the intravenous administration of ^{35}S-labeled thiopental (II, Fig. 1)[6] which demonstrated the pronounced accumulation of radioactivity in various brain regions. The results of a typical autoradiographic study performed by Dr. L. J. Roth in the Department of Pharmacology at the University of Chicago are illustrated in Fig. 2. The dark areas represent localization of radioactivity. The cortex, geniculates, colliculi, and white matter are labeled to varying degrees. Within one minute after administration of

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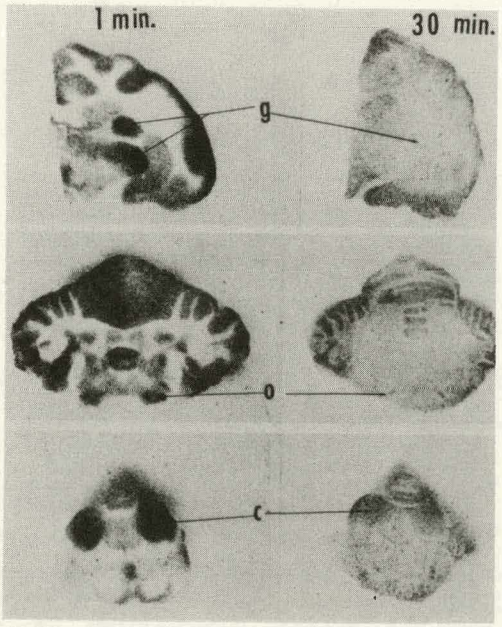

Fig. 2. Autoradiograms of cat brain slices following intravenous injection of ^{35}S-thiopental: g, geniculate bodies; o, olivary nuclei; c, interior colliculi. Source: *"Isotopes in Experimental Pharmacology,"* L. J. Roth, editor, University of Chicago Press, 1965 (reproduced with permission of the author).

^{35}S-labeled thiopental, the cortex contains significant levels of radioactivity . This accumulation of label rapidly washes out. The concentration and clearance of radioactivity after injection of ^{35}S-thiopental appears to represent a useful index of the vascularity of the various brain regions. Barbiturates radiolabeled with gamma emitting radionuclides may therefore have definite potential as a new class of clinical perfusion agents to monitor externally regional brain blood flow.

The effects of structural modifications on the pharmacological action of barbiturates are well established. As an example, replacement of the urea oxygen of the barbiturate ring system (Fig. 1) with sulfur greatly increases lipid solubility. This effect is manifested by both a more rapid onset of action and shortened duration of sedation of barbiturates containing the thiourea moiety. In addition, alkyl substitution at C-5 confers lipid solubility, and the effects of a variety of C-5 alkyl

substituents are well established. A long C-5 alkyl substituent imparts a short pharmacological effect while a short alkyl group or phenyl group at C-5 results in a long effect.

Recently, the potent barbiturate activity of 5-allyl-5- (trimethylsila) methyl barbituric acid (III) has been reported.[7] This silicone barbiturate is an isostere of 5-allyl-5-neopentyl barbituric acid and these studies further illustrate that considerable structural modification at C-5 of the barbituric acid ring system does not destroy sedative activity, and therefore brain uptake of the modified barbiturates. Since there are no useful gamma-emitting radionuclides of silicon, the chemical synthesis of tin-substituted barbiturates is being investigated as a result of interest in the potential use of the ^{117m}Sn-labeled agents for brain blood flow measurement by external counting techniques. Tin-117*m* is an ideal candidate for use in diagnostic nuclear medicine since this radionuclide has a 14-d physical half-life and decays by isomeric transition with emission of a single gamma photon with an energy of 159 keV, which is within the optimal range for efficient detection with the sodium iodide detectors presently used in clinical nuclear medicine instrumentation.

A representative tin barbiturate, 5-methyl-5- (trimethylstanna)methyl barbituric acid (IV, Fig. 1), has been prepared. Reaction of chloromethyltin (Me_3-Sn-CH_2Cl) with the sodium salt of 2-methyl-diethylmalonate gave the intermediate 2-methyl-2-[(trimethylstanna)methyl] diethylmalonate. Ring closure with urea and sodium ethoxide then gave the new tin barbiturate. Although the physical properties of the product were consistent with the proposed structure, the difficulty in preparing the Me_3-Sn-CH_2Cl intermediate, the low yield of the ring closure product, and the problems in purifying the tin barbiturate have indicated that an alternative synthetic strategy is required for the preparation of tin barbiturates. Although Me_3-Sn-CH_2Cl is a useful and versatile intermediate, it cannot be prepared by diazomethane (CH_2N_2) treatment of Me_3-Sn-Cl, but is generated by the following indirect route which is not ideally suited for radiochemical manipulations: Me_3-Sn-Cl_2 + CH_2N_2 → Me_2-Sn(Cl)-CH_2Cl → Me_3-Sn-CH_2Cl. A variety of alternative synthetic strategies are now being developed for the preparation of tin barbiturates.

Because of the potential use of ^{123m}Te, ^{75}Se, and ^{73}Se-labeled barbiturates for brain imaging studies, the preparation of several unique selenium- and tellurium-substituted barbiturates has also been recently explored. The structures of several of these new barbiturates are illustrated in Fig. 2 (V-VIII). The general procedure that has been developed for the preparation of the selenium- and tellurium-substituted barbiturates consists of initial generation of Na_2M_2 (M = Se or Te) by either reduction of the metal in dimethylformamide (DMF) with NaH or by reduction of the metal with one equivalent of sodium metal in liquid ammonia. Following alkylation with the appropriate alkyl halide, the resulting dialkyl diselenide or ditelluride products (R_2M_2) are reduced with sodium borohydride to form the reactive R-M-Na species which are coupled with the appropriate 2-(haloalkyl)-2-alkyl-diethylmalonate to yield the 2-[(alkyltelluro)alkyl]- or 2-[(alkylseleno)alkyl]-substituted 2-alkyl-diethylmalonates. Following purification by silicic acid column chromatography, ring closure is then accomplished by reaction of the diethylmalonate with two equivalents of potassium tertiary butoxide and an excess of urea in dimethylsulphoxide at room temperature. Following these procedures the homogeneous barbiturates (V-VIII) have been obtained by silicic acid column chromatography in yields of 20-30%.

The new tellurium-(V-VI) and selenium-substituted (VII-VIII) barbiturates have been characterized by elemental analyses, thin-layer chromatography, low and high resolution mass spectrometry and proton nuclear magnetic resonance spectrometry. A major goal during the next quarter will be the synthesis, purification and tissue distribution of representative ^{75}Se- and ^{123m}Te-labeled barbiturates. The octanol-water partition coefficients (K_D) will also be determined and compared with the relative brain uptake of the new barbiturates in rats to determine if the K_D values can be correlated with brain uptake.

BIOHAZARDS FROM ENERGY TECHNOLOGIES - ARSENIC TOXICITY

K. R. Ambrose and T. A. Butler

New energy technologies such as coal conversion and shale oil processing present new sources of arsenic mobilization into the envirnoment.

In an effort to understand the biological impact of this toxic pollutant, studies of the effects of arsenic on human cells have been undertaken. The interaction of arsenic with human cells in an in vivo environment using subtoxic levels of arsenic exposure has been chosen as a model experimental system. The diffusion chamber assay described in previous reports (ORNL/TM-6639 and 6771) provides a means of recovering the target cells from the in vivo environment in order to assess the biological effects of arsenic. The arsenic studies described previously (ORNL/TM-7072, 7223, & 7411) have shown that an aqueous solution of arsenic trioxide (As_2O_3) injected at subtoxic dosage into hamsters with intraperitoneally-implanted diffusion chambers can cause an inhibition of growth of the human cells inside the chambers. The extent of growth inhibition, temporary or prolonged, is dependent on the dosage employed. In addition, a linear dose-response relationship was observed for a 24-h growth inhibition assay with several selected dosages.

In order to monitor and quantitate the diffusion of arsenic into (and out of) the chamber fluid and the target cells, several of the previous studies have been repeated using ^{74}As-labeled As_2O_3. Arsenic-74 was prepared by the $^{74}Ge(p,n)^{74}As$ nuclear reaction in the 86-inch cyclotron using a natural germanium target (36% ^{74}Ge). The target material was dissolved in *aqua regia* and excess HNO_3 removed by addition of 12 *M* HCl at boiling temperature. The acid concentration was adjusted to 6 *M* HCl, 50 mg of As_2O_3 carrier added, and Cl_2 gas bubbled through the solution to maintain arsenic in the nonvolatile +5 oxidation state while $GeCl_4$ was removed by distillation. Residual Cl_2 was removed by sparging with argon gas and the arsenic reduced to the volatile +3 oxidation state by addition of HBr. The As^{3+} was then distilled into an ice-cooled water trap and the distillate treated with Cl_2 gas. This procedure removes excess HBr and reoxidizes the arsenic to +5 prior to evaporation of the solution to near dryness. The residue was dissolved in distilled water and treated with SO_2 gas at room temperature to reduce the arsenic to the +3 oxidation state. Excess SO_2 was removed by sparging with argon gas and the concentration of arsenic adjusted to 1.46 mg/ml. Analysis by spark source mass spectrometry indicated the solution to contain less than 0.5 μg/ml of germanium. The only significant contaminant was sulfur which was detected at a concentration of

~500 μg/ml. These low sulfur levels are consistent with the 625 μg/ml expected from the stoichiometric reduction of the arsenic +5 to +3 oxidation state by SO_2. Since dilute solutions of As^{3+} are completely hydrolyzed to arsenous acid, the solution was considered equivalent to water solutions of As_2O_3 used in the previous diffusion chamber studies.

Cell impermeable diffusion chambers containing Flow 2000 (human embryonic lung) cells were implanted in the peritoneal cavities of six to ten week old male hamsters. One to two days after implantation, the aqueous solution of $^{74}As_2O_3$ was injected intraperitoneally into the chamberbearing hamsters at dosages of 10 mg/kg body weight. At 4, 8, and 24 h after implantation, chambers were removed from the ^{74}As-treated and control animals and the target cells recovered from the chambers for cell enumeration under the microscope and for determination of ^{74}As activity using the autogamma counter. In addition, chamber fluid, whole blood and plasma samples, and selected organs and tissues were assayed for ^{74}As activity.

Since the ^{74}As was injected intraperitoneally, it is not surprising that at 4 h the level of ^{74}As present in chamber fluid was higher than that found in the circulating plasma of the host hamster. By 8 and 24 h however, the levels of ^{74}As activity in chamber fluid and plasma were comparable, which substantiated the fluid permeability of the diffusion chamber. At 4 h, the calculated concentration of arsenic in the chamber fluid was 2.7×10^{-5} *M*, whereas by 24 h the concentration had dropped to 5×10^{-6} *M*. At 4 h, growth inhibition was not yet manifest in the Flow 2000 cells, which have a doubling time of 20-24 h. At 24 h post injection a growth inhibition of 76% was observed in the ^{74}As treated target cells. In earlier diffusion chamber studies, a 10 mg/kg dose of As_2O_3 was observed to effect a prolonged growth inhibition of chambered target cells. Within the 3 days of assay, arsenic-treated cells never achieved the control doubling time. In studies using in vitro systems, where the arsenic concentration is static for the 24 h period, concentrations of 5×10^{-5} *M* arsenite are reported to produce irreversible inhibition of the growth of hamster cells, whereas 10^{-5} *M* concentrations produces only a temporary growth inhibition.[8]

Radioactive arsenic was also detected in the human target cells recovered from diffusion chambers of the $^{74}As_2O_3$-treated hamsters. The average

level of arsenic present in target cells at 4 h post injection was 2 ng/total cell pellet or 0.7 ng/10^4 viable cells. By 8 h there was a decrease to 0.5 ng/10^4 viable cells, which is concurrent with a slight decrease in the total number of chamber cells.

ANTIRHEUMATOID GOLD COMPLEXES

J. D. Hoeschele

Studies with antirheumatoid gold(I) complexes have continued, and the effects of structure on the tissue distribution properties of a class of complexes of the general formula, R_3PAuX, have been initiated. These types of complexes, where X = β-D-thioglucosetetraacetate (β-D-TGTA), have been chosen for investigation since Auranofin (R_3PAuX, where R = C_2H_5) is a clinically useful antirheumatoid agent now in preliminary clinical studies. The analogs that are presently under investigation contain the following alkyl (R) moieties: CH_3, *i*-C_3H_7, *n*-C_3H_7, and C_6H_5. The purpose of these studies is to determine the structure-distribution properties of the ^{195}Au-labeled complexes and to correlate these data with known antirheumatoid activity, gold serum levels and other biological and physiological data for these compounds. The synthesis of the $(C_2H_5)_3PAuCl$ and $(C_6H_5)_3PAuCl$ intermediates have been completed, and studies are now in progress to couple these intermediates with the β-D-TGTA substrate via the sulfur atom. These syntheses are complicated by the air sensitivity of the trialkylphosphine (R_3P-) intermediates and the light sensitivity of the intermediate chlorocomplexes (R_3PAuCl).

The phosphorus-31 nuclear magnetic resonance spectral data of the triethyl- and triphenylphosphine gold complexes are in good agreement with the literature data. Chemical shift (σ) values of -33.2 and -38.3 ppm were observed for the ethyl and phenyl analogs, respectively. The $(C_2H_5)_3PAuCl$ and $(C_6H_5)_3PAuCl$ intermediates were homogeneous upon thin-layer chromatographic analysis on silica gel G using toluene:chloroform:methanol (6:3:1). The relative mobility values (R_f) were as follows: $(C_6H_5)_3PAuCl$, R_f 0.74; $(C_2H_5)_3PAuCl$, R_f 0.57. Studies during the next reporting period

will be focused on completing the synthesis and purification of the intermediates and initiating the radiolabeling of these complexes.

RADIONUCLIDES FOR MEDICAL COOPERATIVE PROGRAMS

F. F. Knapp, Jr., J. D. Hoeschele, and T. A. Butler

Carbon-11

Five production runs were made for the Medical Cooperative Program with Oak Ridge Associated Universities (ORAU) to study the application of ^{11}C-labeled amino acids for tumor localization and pancreas imaging in human patients. The labeled compounds synthesized for these studies included five batches of ^{11}C-DL-valine, nine batches of ^{11}C-DL-tryptophan, six batches of ^{11}C-1-aminocyclobutanecarboxylic acid (^{11}C-ACBC), and three batches of ^{11}C-1-aminocyclopentanecarboxylic acid (^{11}C-ACPC). A new series of brain tumor uptake studies have been initiated based on the research of Dr. James Robertson at the University of Tennessee Medical College in Memphis. Dr. Robertson has found that gliomas (tumors of the brain that are frequently inoperable) are metabolicly dependent on selected amino acids and can be treated by elimination of the requisite amino acids from the diet. Measurement of the uptake of ^{11}C-labeled amino acids in such tumors offers an exciting possibility for a noninvasive method for identifying those amino acids which are essential for tumor growth.

Platinum-195*m*

One shipment each of ^{195m}Pt-labeled *cis*-dichlorodiammineplatinum(II) was supplied under the Medical Cooperative Program to the University of Arizona (Dr. Jack Hall), the University of Southern California (Dr. W. Wolf), and the University of California at Los Angeles (Dr. L. C. Ford) for continued studies relative to its antitumor properties.

Selenium-75 and Tellurium-123*m*

Collaborators were supplied radiolabeled selenium and tellurium fatty acids for further investigation as myocardial-imaging agents. The Nuclear

Medicine Division at Massachusetts General Hospital (Dr. H. William Strauss) was supplied ^{123m}Te-methyl-9-telluraheptadecanoate for heart uptake studies and also a quantity of the nonradiolabeled material for toxicity studies. Oak Ridge Associated Universities (Dr. R. Hayes) was supplied ^{75}Se-13-selenaheneicosonic acid for heart uptake studies in dogs.

Copper-64

A new Medical Cooperative Program was established with Oak Ridge Associated Universities (Dr. R. Hayes) to investigate the feasibility of preparing ^{64}Cu radiolabeled agents from a kit formulation. Cooper-64 decays in part by positron emission and such agents could be utilized for tomographic visualization of the uptake regions. One shipment of ^{64}Cu was supplied this quarter to initiate the study.

OTHER NUCLEAR MEDICINE TECHNOLOGY GROUP ACTIVITIES

Potassium-43 was supplied on a cost recovery basis through the Isotopes Sales Office to the University of Mississippi Medical Center (3 shipments) and to the National Institute of Environmental Health Sciences at Research Triangle Park in North Carolina (2 shipments).

Visitors for this period included Dr. Tsvi Sadeh from the Israel Atomic Energy Commission who visited on May 19-21 to discuss the development of selenium and tellurium radiopharmaceuticals. Representatives from Mallinkrodt Nuclear in St. Louis, Missouri, visited on May 30 to discuss the new tellurium myocardial imaging agents. On June 5-6 Dr. Robert Bittman from Queens College in New York City presented a seminar on the use of polyene antibiotics to study membrane structure. Dr. M. Guillaume from the Cyclotron Unit at Sart-Tilman University in Liege, Belgium, visited on June 12-13 to discuss collaboratives studies for the development of unique ^{73}Se-labeled agents for positron emission tomography. Dr. A. Van Wyck from the South African Atomic Energy Agency visited on June 30 for a general overview of the new radiopharmaceuticals being developed at ORNL.

F. F. Knapp, Jr. attended the Third International Symposium on Radiopharmaceutical Chemistry at the Mallinkrodt Institute of Radiology in St. Louis, Missouri, on June 16-20, and the Annual Meeting of the Society of Nuclear Medicine in Detroit, Michigan, on June 23-27.

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PAPERS AND PUBLICATIONS

Papers

A paper describing the properties of a series of ^{123m}Te-labeled fatty acids was presented at the Third International Symposium on Radiopharmaceutical Chemistry held at the Mallinkrodt Institute of Radiology in St. Louis, Missouri, on June 16-20, 1980:

F. F. Knapp, Jr., T. A. Butler, K. R. Ambrose, A. P. Callahan, L. A. Ferren, J. A. Roberts, R. A. Grigsby, and K. J. Irgolic, "Myocardial Uptake of ^{123m}Te-Labeled Long-Chain Fatty Acids: Effects of Heteroatom Position and Total Chain Length."

Four papers were presented at the 27th Annual Meeting of the Society of Nuclear Medicine held at Cobo Hall in Detroit, Michigan, on June 23-28, 1980.

J. L. Coffey and F. F. Knapp, Jr., "Radiation Dosimetry of Sn-117*m*-Labeled 23-(Trimethylstanna)-24-nor-5α-Cholan-3β-ol (Sn-117*m*-23-TSC): A Potential Adrenal Imaging Agent."

D. R. Elmaleh, F. F. Knapp, Jr., T. Yasuda, S. Kopiwoda, K. A. McKusick, and H. W. Strauss, "Te-123*m*-9-Telluraheptadecanoic Acid as Myocardial Imaging Agent."

F. F. Knapp, Jr., T. A. Butler, A. P. Callahan, and K. R. Ambrose, "Tin-117*m*-Labeled 23-(Trimethylstanna)-24-nor-5α-cholan-3β-ol (*Sn-23-TSC) Shows Significant Adrenal Uptake in Rats."

T. Yasuda, F. F. Knapp, Jr., D. R. Elmaleh, S. Kopiwoda, K. A. McKusick, and H. W. Strauss, "Biodistribution of 123*m*-9-Telluraheptadecanoic Acid: Large Difference of Uptake in Normal and Infarcted Myocardium."

Publications

D. V. Woo, F. F. Knapp, Jr., K. R. Ambrose, A. P. Callahan, and J. L. Coffey, "Radiation Dosimetry of Two New Tellurium-123*m*-Labeled Adrenal Imaging Agents: Concise Communication," *J. Nucl. Med.* 21, 454, 1980.

Reports

F. F. Knapp, Jr., *Nuclear Medicine Technology Progress Report for Quarter Ending March 31, 1980*, ORNL/TM-7072.

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