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**ORNL/TM-7072**

**Nuclear Medicine Technology  
Progress Report for Quarter  
Ending September 30, 1979**

F. F. Knapp, Jr.

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NUCLEAR MEDICINE TECHNOLOGY PROGRESS REPORT  
FOR QUARTER ENDING SEPTEMBER 30, 1979

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ORNL/TM-6639

ORNL/TM-6771

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## SUMMARY

Of special interest in this report is the demonstration of pronounced adrenal uptake in rats of  $^{117m}\text{Sn}$ -labeled 23-(trimethyl stanna)-24-nor-5 $\alpha$ -cholan-3 $\beta$ -ol. This unusual steroid is an analog of cholesterol in which the side chain terminal isopropyl group has been replaced with the trimethyltin moiety. The adrenal: blood and adrenal: liver ratios were 33:1 and 9:1, respectively, only one day after intravenous administration of the radiolabeled steroid. A variety of  $^{117m}\text{Sn}$ -labeled steroids with structural modifications of the nucleus and side chain were also prepared to determine the effects of structural modifications on the adrenal uptake of these unusual steroids. The results of tissue distribution studies in rats indicate that the important structural features required for significant adrenal uptake include an all *trans* ring juncture, an equatorial C-3 hydroxyl group, and a side chain of moderate length.

The diffusion chamber assay system (ORNL/TM-6639, 6771, and 6958) has been assessed as a means of investigating the toxicity and biological fate of trace elements from energy technologies. Diffusion chambers containing a human embryonic lung cell line were implanted in the peritoneal cavities of rats. In a preliminary experiment, the cell population in chambers from rats exposed to  $\text{As}_2\text{O}_3$  (15 mg/kg) was inhibited 48% one day after treatment compared to cells from chambers of control animals administered only saline.

In this progress report, the results of continuing studies with  $^{75}\text{Se}$ ,  $^{11}\text{C}$ , and  $^{195m}\text{Pt}$ -labeled agents are also described. Several  $^{75}\text{Se}$ -labeled long-chain fatty acids were prepared to determine the effects of total chain length and the position of the selenium heteroatom on heart uptake of this potential new class of myocardial imaging agents. Selenium-75-labeled 9-selenapentacosanic acid (isosteric chain length = 25 carbon atoms) showed the highest heart uptake of the compounds investigated. Approximately 1.4% of the injected dose was detected in the hearts of rats 30 min after injection and the heart: blood ratios were 7:1. Preliminary radiation dose estimates have been performed in conjunction with the Oak Ridge Associated Universities (ORAU) for several  $^{75}\text{Se}$  and  $^{123m}\text{Te}$ -labeled fatty acids.



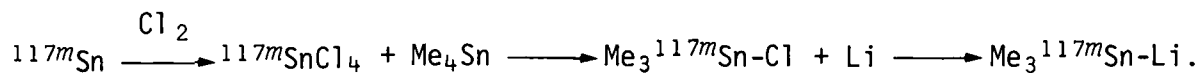
Extrapolation of rat tissue distribution and excretion data for  $^{75}\text{Se}$ -labeled 9-selenaheptadecanoic acid and  $^{123m}\text{Te}$ -labeled 9-telluraheptadecanoic acid indicate that the human liver would receive the highest absorbed radiation dose (1.4-1.7 rads/mCi).

Tissue distribution studies in rats have now been completed with the following series of  $^{195m}\text{Pt}$ -labeled chloroammine complexes:  $[\text{Pt}(\text{NH}_3)_4]\text{Cl}_2$ ,  $[\text{Pt}(\text{NH}_3)_3\text{Cl}]\text{Cl}$ ,  $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$  (*cis* and *trans*),  $\text{K}[\text{Pt}(\text{NH}_3)\text{Cl}_3]$ , and  $[\text{K}_2\text{PtCl}_4]$ . The results of these studies have demonstrated that the tissue distribution and excretion characteristics of the chloroammine complexes closely parallel their physicochemical properties. Further patient studies in a Medical Cooperative Program with ORAU have assessed the efficacy of emission computerized tomographic organ imaging with  $^{11}\text{C}$ -valine, and  $^{11}\text{C}$ -aminocyclobutanecarboxylic acid (ACBC). In addition,  $^{195m}\text{Pt}$ -labeled *cis*-dichlorodiammineplatinum(II) was supplied to a number of investigators through the Medical Cooperative Programs. Selenium-75 and  $^{123m}\text{Te}$ -labeled fatty acids were supplied for the first time through a Medical Cooperative Program with the Massachusetts General Hospital and the Harvard Medical School to determine the relative uptake of these new agents in both normal and infarcted heart tissue of rats.

#### TIN $^{117m}$

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

In an earlier report (ORNL/TM-6916), the preparation of a series of structurally modified steroids containing the trimethyltin moiety in the side chain was described. The synthesis of the  $^{117m}\text{Sn}$ -labeled steroids has now been completed, and the results of tissue distribution studies in rats have indicated that important structural features are required for the adrenal uptake of these steroids. The structural modifications that were investigated include alterations of both the steroid nucleus and side chain. The  $^{117m}\text{Sn}$ -labeled steroids were prepared by reaction of the  $\text{Me}_3^{117m}\text{Sn-Li}$  reagent with steroid substrates containing a primary bromine in the side chain. The preparation of  $\text{Me}_3^{117m}\text{Sn-Li}$  has been described in detail earlier (ORNL/TM-6639) and is summarized as follows:



The synthetic procedure has been designed such that all of the reactions are performed in a single reaction vessel, which eliminates losses from solvent extraction, purification of intermediates, and also reduces the radiation exposure. The steroid substrates and chemical yields of the  $^{117m}\text{Sn}$ -labeled steroid products are summarized in Table 1. The  $\text{Me}_3^{117m}\text{Sn-Li}$  readily reacted with the brominated steroid substrates in tetrahydrofuran at room temperature. Following hydrolysis of the reaction mixtures, the crude products were obtained by solvent extraction and purified by silicic acid column chromatography.

The  $^{117m}\text{Sn}$ -steroids were administered to rats in an ethanol-tween 80-saline emulsion by injection via a lateral tail vein. Tin- $^{117m}$ -labeled 23-(trimethyl stanna)-24-nor-5 $\alpha$ -cholan-3 $\beta$ -ol (I) showed the most pronounced adrenal uptake of the steroids investigated and the tissue distribution results are shown in Fig. 1. The adrenal uptake was high one day after administration and decreased over the seven day period. After one day, 2.5% of the administered radioactivity was detected in the adrenal glands; and after seven days, the concentration of radioactivity had been reduced to 1.9% of the injected dose. These data parallel the results observed with  $^{123m}\text{Te}$ -23-(isopropyl telluro)-24-nor-cholan-3 $\beta$ -ol (ORNL/TM-5809) in which the adrenal accumulation of radioactivity in female rats decreased steadily from 4.5% of the injected dose after one day to 2.4% after seven days. A convenient index of the adrenal selectivity of the  $^{117m}\text{Sn}$ -labeled steroids is a comparison of either the adrenal:blood or adrenal:liver ratios. The adrenal:blood ratios were calculated from the percent dose per gram of tissue values and are compared for the various steroids in Fig. 2. These data dramatically illustrate the effects of steroid structure on the adrenal uptake of the trimethyltin-substituted steroids and indicate that well-defined structural features are required for maximal adrenal uptake. From one analysis of these data it is apparent that an all *trans* ring juncture, a side chain of moderate length, and an equatorial hydroxyl group are required for adrenal specificity. Similar structure-distribution relationships have been reported earlier for a

Table 1.  $^{117m}\text{Sn}$ -labeled steroids prepared by the reaction of  $\text{Me}_3^{117m}\text{Sn-Li}$  with brominated steroid substrates

Substrate	Product	Unique structural features	Yield <sup>a</sup> (%)
3 $\beta$ -Acetoxy-23-bromo-24-nor-5 $\alpha$ -cholane	23-(Trimethyl stanna)-24-nor-5 $\alpha$ -cholan-3 $\beta$ -ol (I)	Saturated nucleus <i>trans</i> ring structure	49
3 $\beta$ -Acetoxy-24-bromo-chol-5-ene	24-(Trimethyl stanna)-chol-5-en-3 $\beta$ -ol (II)	Nuclear double bond	69
3 $\beta$ -Methoxy-24-bromo-chol-5-ene	3 $\beta$ -Methoxy-24-(trimethyl stanna)-chol-5-ene (III)	Hydrophobic C-3 substituent	34
3 $\alpha$ -Acetoxy-23-bromo-24-nor-5 $\beta$ -cholane	23-(Trimethyl stanna)-24-nor-5 $\beta$ -cholan-3 $\alpha$ -ol (IV)	<i>Cis</i> A/B ring juncture	49
3 $\beta$ -Acetoxy-17 $\beta$ -(bromomethyl)-androst-5-ene	17 $\beta$ -[(Trimethyl stanna)methyl]-androst-5-en-3 $\beta$ -ol (V)	Short side chain	35

<sup>a</sup>Chemical yield values are based upon the brominated steroid starting materials since the  $\text{Me}_3^{117m}\text{Sn-Li}$  reagent was used in considerable excess.

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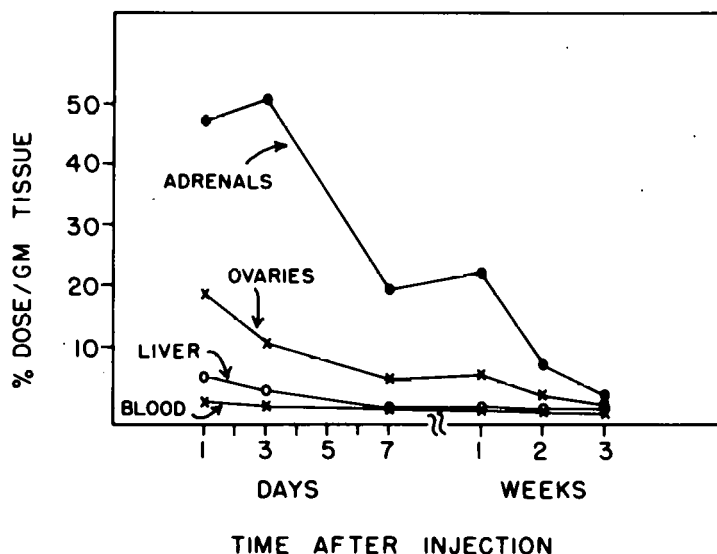


Fig. 1. The distribution of radioactivity in female rat tissues following intravenous administration of  $^{117m}\text{Sn}$ -labeled 23-(trimethylstanna)-24-nor-5 $\alpha$ -cholan-3 $\beta$ -ol (I).

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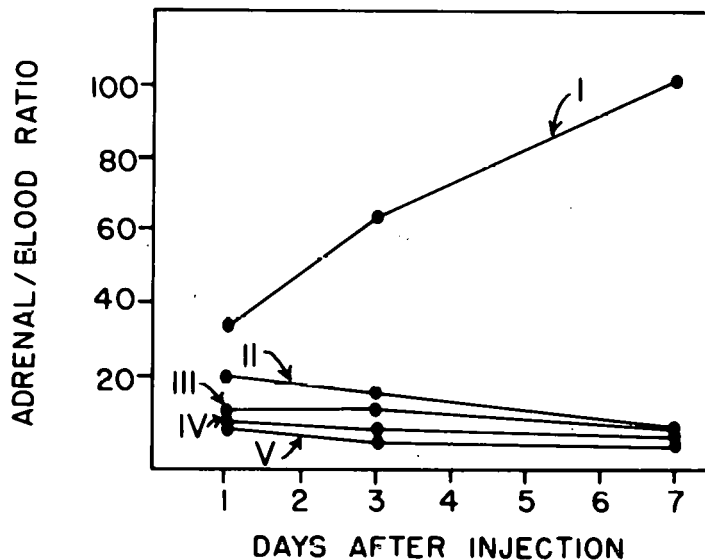


Fig. 2. Comparison of the adrenal:blood ratios at one, three, and seven days following the intravenous administration of  $^{117m}\text{Sn}$ -labeled steroids (I)-(VI) to female rats.

series of  $^{123m}\text{Te}$ -labeled steroids (ORNL/TM-6044). An additional interesting observation is the pronounced uptake of radioactivity in the spleen following administration of  $^{117m}\text{Sn}$ -labeled 3 $\beta$ -methoxy-24-(trimethyl stanna)-chol-5-ene (III) as illustrated in Fig. 3. This unexpected result probably represents sequestration by the spleen of a damaged blood cellular component that tightly binds the  $^{117m}\text{Sn}$ -labeled steroid.

The radioactive contents of the urine and feces of rats were monitored over a seven day period following administration of  $^{117m}\text{Sn}$ -labeled 23-(trimethyl stanna)-24-nor-5 $\alpha$ -cholan-3 $\beta$ -ol (I). The results of these studies (Fig. 4) demonstrate that the majority of the radioactivity was excreted in the feces. Approximately 50% of the injected radioactivity was excreted within five days. Although the identity of the radioactive contents in the feces has not yet been determined, these data suggest that the trimethyltin moiety remains attached to the steroid molecule since it is well established that neutral steroids are excreted by the fecal route.

The pronounced adrenal uptake in rats indicates that  $^{117m}\text{Sn}$ -labeled 23-(trimethyl stanna)-24-nor-5 $\alpha$ -cholan-3 $\beta$ -ol (I) is an attractive new agent for potential adrenal imaging in humans. Future studies with this agent will include attempts to image the adrenal glands of rats, rabbits, and dogs and a more detailed study of the excretion of radioactivity over a three to four week period. Studies will also be directed at identifying the radioactive species in the feces from rats administered this agent. The potential metabolism of this agent by adrenal glands will be assessed by chromatographic analysis of adrenal extracts following *in vivo* injection. The radiation dose estimates to human organs will also be calculated by extrapolation of the biological data obtained in rats to assess the potential usefulness of  $^{117m}\text{Sn}$ -labeled 23-(trimethyl stanna)-24-5 $\alpha$ -cholan-3 $\beta$ -ol (I) for potential adrenal imaging in humans.

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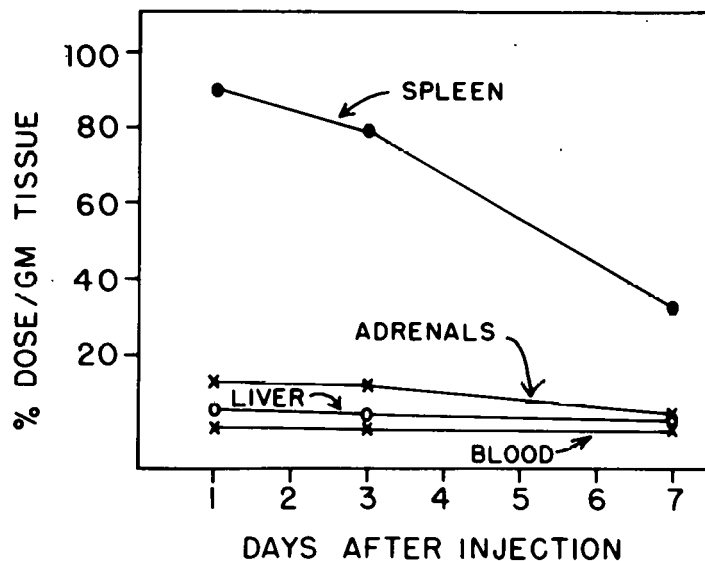


Fig. 3. The distribution of radioactivity in female rat tissues following intravenous administration of  $^{117m}\text{Sn}$ -labeled 3 $\beta$ -methoxy-24-(trimethyl stanna)-chol-5-ene (III).

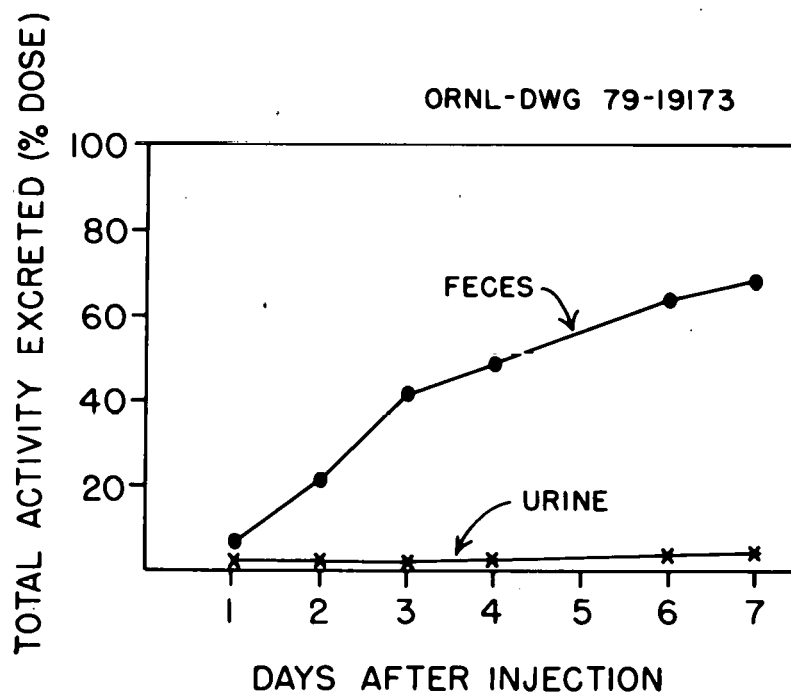


Fig. 4. Radioactive contents of feces and urine over a seven day period following intravenous administration of  $^{117m}\text{Sn}$ -labeled 23-(trimethyl stanna)-24-nor-5 $\alpha$ -cholan-3 $\beta$ -ol (I) to female rats.

## SELENIUM-75

*F. F. Knapp, Jr., K. R. Ambrose, and T. A. Butler*

The significant heart uptake of  $^{75}\text{Se}$ -labeled 9-selenaheptadecanoic acid was described in an earlier report (ORNL/TM-6916). Although the heart uptake was not as pronounced as that described for the  $^{123m}\text{Te}$ -labeled analog, 9-telluraheptadecanoic acid (ORNL/TM-6638, 6639, 6671, and 6916), the concentration of radioactivity in heart tissue was high enough to indicate that the  $^{75}\text{Se}$ -labeled fatty acid could potentially be used for heart imaging. In addition, the potential use of  $^{73}\text{Se}$ -labeled 9-selenaheptadecanoic acid for positron emission tomographic studies has been described (ORNL/TM-6958). The heart uptake of a variety of structurally modified  $^{75}\text{Se}$ -labeled fatty acids has now been investigated to determine the structural features affecting the distribution of these new agents in rats.

The  $^{75}\text{Se}$ -labeled fatty acids were prepared by the general method described earlier (ORNL/TM-6638 and 6916) which involves the coupling of alkyl selenols with  $\omega$ -bromo fatty acid methyl esters:  $\text{R-}^{75}\text{Se-H(Na)} + \text{Br-R}^1\text{-COOMe} \longrightarrow \text{R-}^{75}\text{Se-R}^1\text{-COOMe} \longrightarrow \text{R-}^{75}\text{Se-R}^1\text{-COOH}$ . The effects of both total chain length and the position of the  $^{75}\text{Se}$  heteroatom were studied. Selenium-75-labeled methyl-9-selenatridecanoate was prepared by the reaction of  $^{75}\text{Se}$ -butyl selenol with methyl-8-bromooctanoate. This fatty acid has a shorter isosteric chain length (14 carbon atoms) than 9-selenaheptadecanoic acid (18 carbon atoms). Selenium-75-labeled methyl-13-selenaheptadecanoate, an isomer of 9-selenaheptadecanoic acid, was similarly prepared by reaction of  $^{75}\text{Se}$ -butyl selenol with methyl-12-bromododecanoate. A longer chain seleno fatty acid,  $^{75}\text{Se}$ -methyl-9-selenapentacosanate (isosteric chain length = 26 carbon atoms), was synthesized by reaction of  $^{75}\text{Se}$ -hexadecyl selenol with methyl-8-bromooctanoate.

The  $^{75}\text{Se}$ -labeled fatty acids were prepared by basic hydrolysis of the methyl esters. After complexing with a 6% bovine serum albumin solution, the acids were administered to rats by injection via a lateral tail vein. The percent dose per gram of tissue values were determined at 5, 30, and 60 min after injection. These time periods were chosen since earlier

studies with  $^{75}\text{Se}$ -labeled 9-selenaheptadecanoic acid had demonstrated that optimal heart uptake was observed within the first hour after injection and the concentration of radioactivity in the heart began to decrease after one hour. The percent injected dose levels in the heart at 5 and 60 min after injection are compared for the four  $^{75}\text{Se}$ -labeled fatty acids with similar results obtained with  $^{123m}\text{Te}$ -labeled 9-telluraheptadecanoic acid in Table 2. The results of the tissue distribution studies with  $^{75}\text{Se}$ -labeled fatty acids demonstrate that heart uptake is effected by total chain length, although not as markedly as reported earlier for a series of  $^{123m}\text{Te}$ -labeled fatty acids. The longest chain  $^{75}\text{Se}$ -labeled fatty acid investigated, 9-selenapentacosanic acid, showed heart uptake that was comparable to that reported earlier for  $^{123m}\text{Te}$ -labeled 9-telluraheptadecanoic acid. Five minutes after injection, approximately 1.9% of the administered radioactivity was detected in the heart and the heart:blood ratio was greater than 7:1.

Several experiments were conducted to determine the biological fate of  $^{75}\text{Se}$ -9-selenaheptadecanoic acid in rats. Examination of the feces and urine of rats over a seven day period indicated a very rapid urinary excretion of radioactivity following administration of this agent (Fig. 5). Approximately 50% of the administered activity was excreted in the urine within one day. The rapid excretion of radioactivity would suggest that the absorbed radiation dose would not be excessive. Using excretion and tissue distribution data from rats, the radiation doses to humans from  $^{75}\text{Se}$ -9-selenaheptadecanoic acid and  $^{123m}\text{Te}$ -9-telluraheptadecanoic acid have been calculated in conjunction with collaborators at the Oak Ridge Associated Universities. The liver receives the highest calculated radiation dose for both agents:  $^{75}\text{Se}$ -9-selenaheptadecanoic acid, 1.7 rads/mCi;  $^{123m}\text{Te}$ -9-telluraheptadecanoic acid, 1.4 rads/mCi. These values are comparable to radiation dose estimates for thallium-201, an agent routinely used for the clinical diagnosis of heart disease.

In order to gain insight into the mechanism of uptake and the fate of  $^{75}\text{Se}$ -labeled fatty acids in heart tissue, it is important to identify the chemical species of the radioactivity in heart tissue following administration of the radiolabeled agent. In a preliminary experiment, rat hearts were homogenized in a chloroform-methanol mixture 30 min following intravenous



Table 2. Percent injected dose values for the heart and heart:blood ratios determined after administration of  $^{75}\text{Se}$ -labeled fatty acids to female rats. These data are compared with similar values determined earlier for  $^{123m}\text{Te}$ -labeled 9-telluraheptadecanoic acid (ORNL/TM-6916)

Radiolabeled fatty acid	Time (min)	Heart uptake (%)	Calculated heart:tissue ratios <sup>a</sup>			
			Blood	Liver	Lung	Kidney
9-Selenaheptadecanoic acid $\text{H}_3\text{C}-(\text{CH}_2)_7-\text{Se}-(\text{CH}_2)_7-\text{COOH}$	5 60	0.87 0.68	5.38 4.21	0.15 0.23	1.49 1.32	0.81 0.69
9-Selenatridecanoic acid $\text{H}_3\text{C}-(\text{CH}_2)_3-\text{Se}-(\text{CH}_2)_7-\text{COOH}$	5 60	0.63 0.27	1.93 2.65	0.37 0.39	1.43 1.39	0.74 0.56
13-Selenaheptadecanoic acid $\text{H}_3\text{C}-(\text{CH}_2)_3-\text{Se}-(\text{CH}_2)_{11}-\text{COOH}$	5 60	0.45 0.30	3.30 2.82	0.12 0.12	0.61 0.70	0.66 0.53
9-Selenapentacosanic acid $\text{H}_3\text{C}-(\text{CH}_2)_{15}-\text{Se}-(\text{CH}_2)_7-\text{COOH}$	5 60	1.9 1.2	7.27 10.29	0.38 0.30	4.77 4.96	5.79 3.66
9-Telluraheptadecanoic acid $\text{H}_3\text{C}-(\text{CH}_2)_7-\text{Te}-(\text{CH}_2)_7-\text{COOH}$	5 60	2.1 1.3	10.34 8.87	0.53 0.64	4.18 6.11	2.09 2.74

<sup>a</sup>The heart:tissue ratios are calculated from the percent injected dose per gram of tissue concentration values.

administration of  $^{75}\text{Se}$ -9-selenaheptadecanoic acid. The organic-soluble material was analyzed by thin-layer radiochromatographic analysis. The results of these studies (Fig. 6) demonstrated that radioactivity co-chromatographed with both the diglyceride and triglyceride standards. Since it is established that long-chain alkanolic acids are stored in the myocardium esterified to glycerol, these data suggest that  $^{75}\text{Se}$ -9-selenaheptadecanoic is metabolized in a similar manner. Future studies will investigate if the  $^{75}\text{Se}$ -fatty acid is further metabolized by  $\beta$ -oxidation, the normal route of fatty acid metabolism.

BIOHAZARDS FROM ENERGY TECHNOLOGIES -  
AN ASSAY SYSTEM TO EVALUATE THE  
BIOLOGICAL EFFECTS OF ARSENIC

*K. R. Ambrose*

Arsenic is recognized as a potentially hazardous trace element pollutant of the emerging coal conversion technologies. During coal combustion, arsenic is converted to volatile products; coal liquefaction and gasification processes present additional avenues for potential environmental contamination by arsenic compounds. As an example, arsenic levels can be concentrated as high as twofold in the filter cake and threefold in the char residue of the feed coal in a typical coal liquefaction process. In a coal gasification plant processing 20,000 tons of coal in a day, the amount of arsenic produced daily could theoretically be 800 lb present in gas, 1.5 lb in ash, 0.7 lb in tar and 0.5 lb in the condensate. As a result of the potential release of large amounts of arsenic to the environment, it is important to investigate the biological effects of arsenic.

The diffusion chamber assay system described in previous reports (ORNL/TM-6639, 6771, and 6958) is a method that can be used to investigate the interaction of radiolabeled pollutants with target cells within an *in vivo* environment. Under these conditions, both the metabolism of the pollutant and the excretion of the native or metabolized pollutant are possible. The potential toxicity, mutagenicity, and carcinogenicity of arsenic compounds can be studied by analyzing target cells from diffusion chambers implanted within the peritoneal cavities of rats that have been

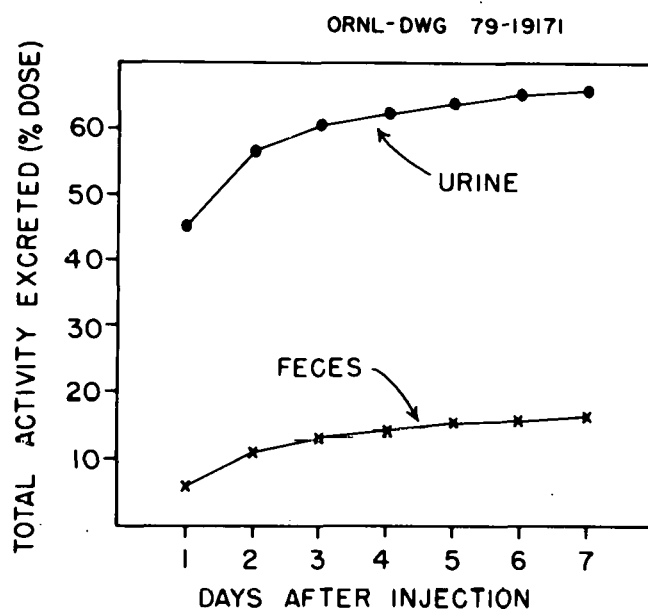
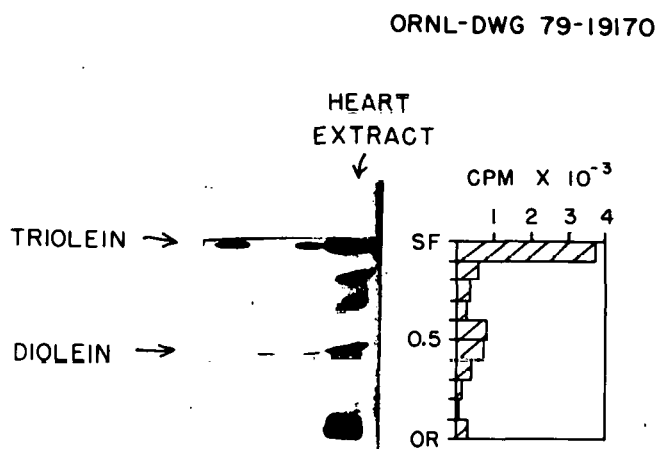


Fig. 5. Radioactive contents of feces and urine over a seven day period following intravenous administration of  $^{75}\text{Se}$ -labeled 9-selenaheptadecanoic acid to female rats.



Solvent: Petroleum Ether-Ether-Acetic Acid, 70:30:1

Fig. 6. Thin-layer radiochromatographic analysis of the chloroform-soluble extract of female rat hearts obtained 30 min after intravenous administration of  $^{75}\text{Se}$ -labeled 9-selenaheptadecanoic acid.

exposed to various arsenic compounds. Toxicity is assessed by comparing populations of the arsenic-exposed target cells to control, saline-treated populations. After exposure to arsenic *in vivo* the target cells can be tested for proliferation in soft agar *in vitro* as an index of the potential carcinogenicity of arsenic. An *in vivo* modification of the sister chromatid exchange assay can be used to assess the potential mutagenicity of the test compounds.

A human embryonic lung cell line (Flow 2000) has been chosen as a model target cell for the arsenic studies. Preliminary studies during this quarter have involved defining the optimal growth and assay conditions for Flow 2000 cells grown within diffusion chambers implanted in the peritoneal cavities of rats. In contrast to the KB tumor cells used in previous studies, the Flow 2000 cells require a higher seeding level in the chambers ( $5.0 \times 10^4$  vs  $2.5 \times 10^4$ ) and have a slower doubling time (24 hr vs 12 hr). The Flow 2000 cells also require the use of calcium- and magnesium-free media to prevent cell clumping, which can result in an inaccurate estimation of the cell population.

Following the baseline studies, an experiment was performed to determine whether an aqueous solution of arsenic trioxide ( $\text{As}_2\text{O}_3$ ) fed to chamber-containing rats would affect the growth of Flow 2000 cells within the chambers. When the target cell population from arsenic-treated rats was compared to the cell population from the saline-treated control animals, an inhibition of cell division was observed one day after treatment with  $\text{As}_2\text{O}_3$ . Growth inhibition was greatest (48%) in those animals receiving 15 mg of  $\text{As}_2\text{O}_3$  per kilogram of body weight and lowest (18%) in animals receiving the 5 mg/kg dose level. Between the first and second day post-feeding, target cells in chambers of all treatment groups (arsenic and control) underwent one doubling in accord with the previously determined doubling time. These preliminary data indicate that the arsenic feeding results in a temporary growth inhibition of human lung cells within the first 24-hr period.

Studies during the next quarter will employ  $^{76}\text{As}$ -labeled  $\text{As}_2\text{O}_3$  to determine the appearance and disappearance of arsenic in the chamber fluid and the uptake of arsenic by the target cells in the chambers. The effect

of low-level chronic exposure to  $\text{As}_2\text{O}_3$  on target cell growth will also be investigated. In addition to these studies, hamsters will be evaluated as chamber recipients for the arsenic studies since the unique binding of arsenic to rat hemoglobin would indicate that experimental data from rats should not be extrapolated to man and other mammals.

#### PLATINUM- $^{195m}$

*J. D. Hoeschele and T. A. Butler*

An earlier report (ORNL/TM-6371) described the preliminary tissue distribution data in rats for a series of  $^{195m}\text{Pt}$ -labeled-chloroamine-platinum(II) complexes. Tissue distribution studies with this important series of model complexes have been completed, and a summary of the findings is described below.

#### Syntheses

The  $^{195m}\text{Pt}$ -labeled chloroamineplatinum(II) complexes were prepared by the general reaction scheme (Fig. 7) previously reported (ORNL/TM-6371). In the present studies, the preparation of  $\text{K}[\text{PtA}_3\text{Cl}]$  and  $[\text{PtA}_3\text{Cl}]\text{Cl}$  have been improved ( $\text{A}=\text{NH}_3$ ). The amount of catalyst employed in the synthesis of  $\text{K}[\text{PtA}_3\text{Cl}]$  is now specified at 5% (w/w). In addition, two alternate synthetic routes have been evaluated for the preparation of the triamine analog,  $[\text{PtA}_3\text{Cl}]\text{Cl}$ . The first route is preferred and employs *trans*-dichlorodiammineplatinum (*trans*-DDP) as the starting material while  $[\text{PtA}_3\text{Cl}]\text{Cl}$  is prepared in the second route from *cis*-DDP. This scheme emphasizes the central and important role that *cis*-DDP has served in the development of microscale syntheses of the chloroamineplatinum(II) analogs.

#### Tissue Distribution Studies

Several observations have been made by a comparison of the distribution and retention of radioactivity in 14 tissues 24 hr after administration of the  $^{195m}\text{Pt}$ -labeled chloramine complexes to female rats. Platinum was found in all of the tissues examined for the various compounds

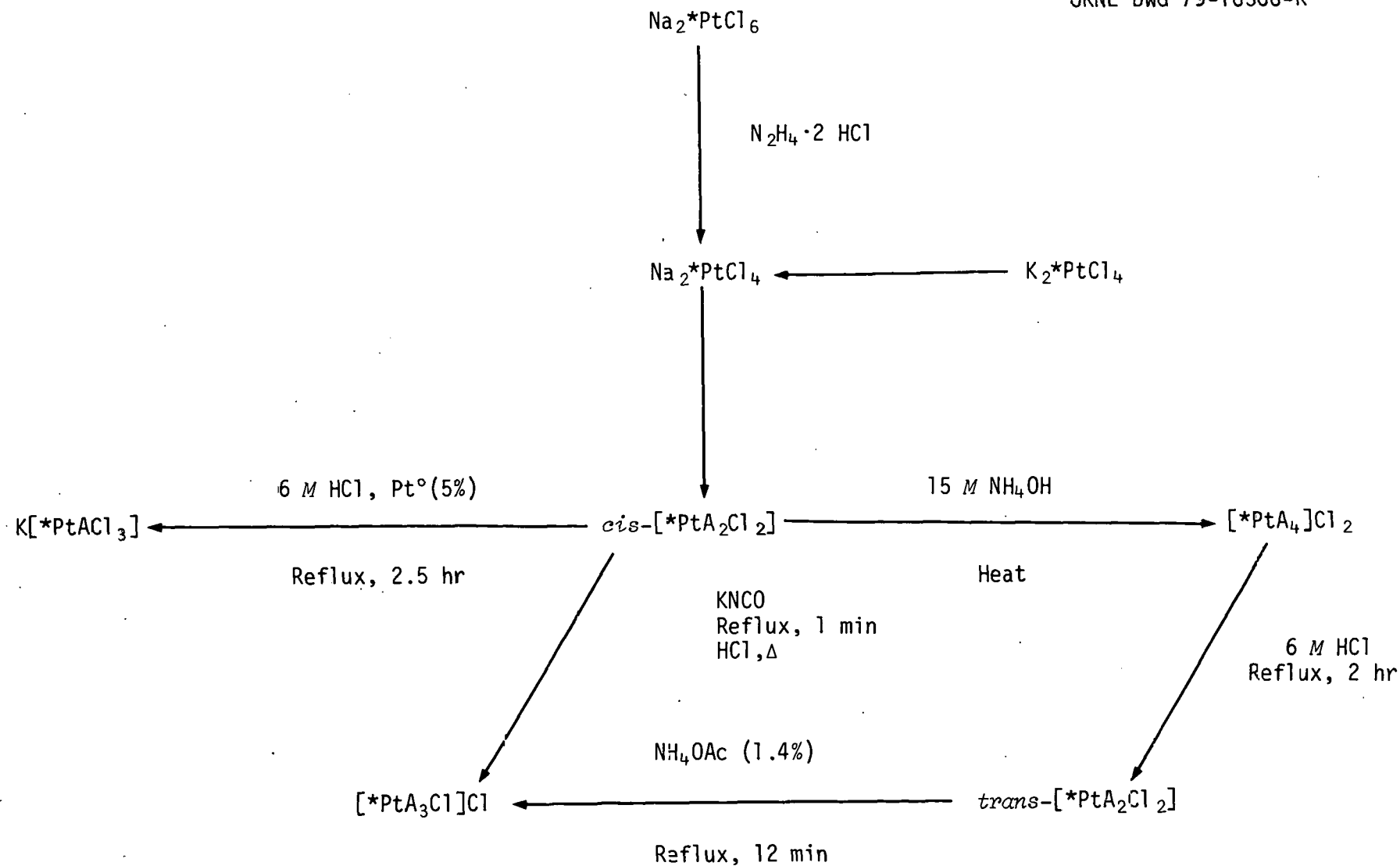
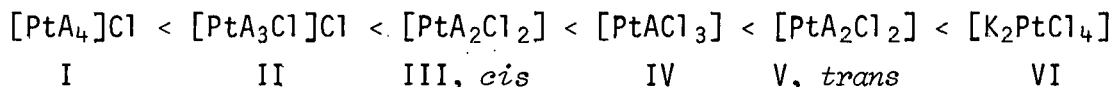
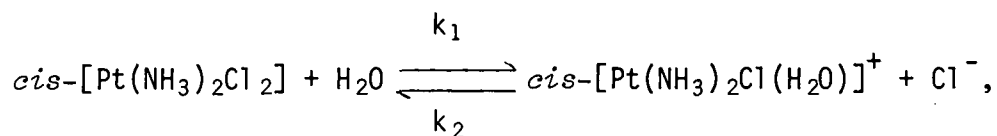


Fig. 7. The synthesis of  $^{195\text{m}}\text{Pt}$ -labeled chloroammineplatinum(II) complexes. ( $\text{A}=\text{NH}_3$ ,  $*$ = $^{195\text{m}}\text{Pt}$ ).

and the highest levels were found in kidney (0.2-4%). In general, the lowest levels were detected in the brain (0.01-0.05%). Although compound retention patterns are unique, uptake is not sufficiently high (with the exception of the kidney) nor selective enough in any given tissue to warrant consideration of any of these compounds as potential imaging agents. The average relative order of decreasing tissue levels (percent dose per gram of tissue) for the  $^{195m}\text{Pt}$ -labeled complexes in female rats is as follows: kidney > liver > lungs > genitals > spleen > blood > bladder > adrenals > colon > heart > pancreas > small intestine > skin > stomach > brain, while that for *cis*-DDP alone is: kidney > genitals > liver > adrenals > spleen > blood > lungs > pancreas > heart > brain. The rat ovary exhibited the second highest uptake of radioactivity following administration of  $^{195m}\text{Pt}$ -*cis*-DDP, and malignancies of these same tissues in humans respond well to *cis*-DDP chemotherapy. This association, however, does not imply that high tissue uptake necessarily predicts chemotherapeutic effectiveness for tumors of the same tissue origin. Tumors of the liver and particularly the kidney are of relatively low incidence, and these tissues are generally sites of relatively high uptake. This association could be more than just a mere coincidence. Another important empirical observation is that compound levels in tissues generally increase in the order:



It is significant that the general order of compound retention parallels trends both in the negative charge on the complex and the number of replaceable chloride ligands which is equivalent to the number of binding sites on the central atom, Pt(II). It is also apparent that the complexes which are retained to the greatest extent (IV, V, VI) contain more reactive chlorides by virtue of the *trans*-activating effect of mutually opposed chloride ligands. Also, the order of compound retention in the tissues more closely follows the trend in rate constants,  $k_1$ , rather than equilibrium constants,  $K_{\text{eq}}$ , for the first step of the aquation process. The aquation process is likely to be an important first step in the *in vivo* reactions of platinum(II) complexes in general and can be represented in the following way using *cis*-DDP as an example:



where  $k_1$  and  $k_2$  are first order rate constants ( $\text{sec}^{-1}$ ) for the forward step (aquation) and reverse step (anation), respectively, and the equilibrium constant is numerically equal to the ratio of  $k_1$  and  $k_2$  (i.e.,  $K_{\text{eq}} = k_1:k_2$ ). The parallel in the general order of compound retention in the tissues with trends in  $k_1$  and  $K_{\text{eq}}$  values is illustrated in Fig. 8, using retention in the kidney as a typical example of tissue retention. The values of  $k_1$ ,  $K_{\text{eq}}$ , and the average levels found in the kidney have been normalized relative to those for *cis*-DDP. Comparison of these data shows closer agreement between trends in organ retention and rate constants rather than equilibrium constants. If compound retention in the kidney paralleled  $K_{\text{eq}}$  values more closely than  $k_1$  values, a substantially lower level of retention in the kidneys would have been anticipated for *trans*-DDP. These results suggest that kinetic factors, as might have been

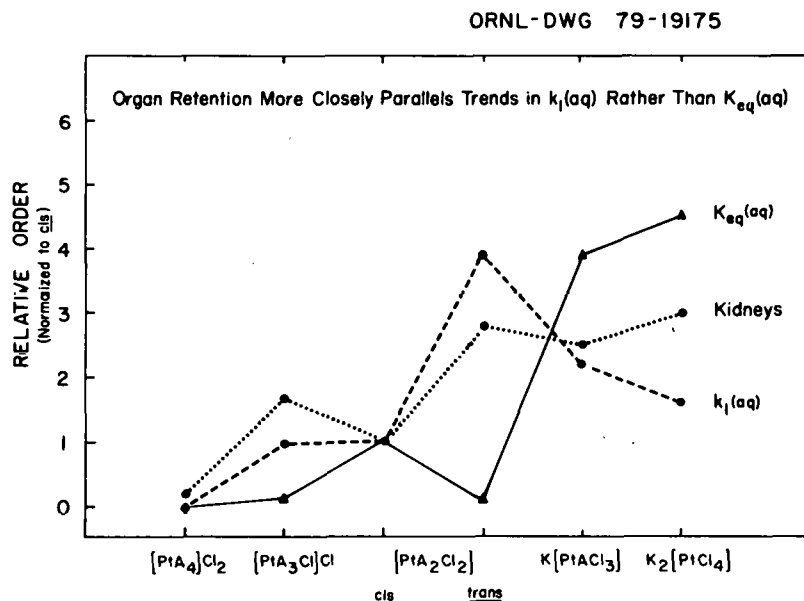


Fig. 8. Comparison of the relative order of kidney retention of  $^{195\text{m}}\text{Pt}$ -labeled chloroamineplatinum(II) complexes with the rate constants ( $k_1$ ) and equilibrium constants ( $K_{\text{eq}}$ ) for the aquation process.



predicted *a priori*, play a dominant role in the binding/retention and potential activity/toxicity of these complexes *in vivo*. The average order of compound retention in normal tissues does not parallel trends in the antitumor potential of these compounds. For example, complexes V and VI exhibit the highest tissue levels but show virtually no antitumor activity, and complex IV exhibits only marginal antitumor activity but is retained to a greater extent than *cis*-DDP, the most potent antitumor active Pt(II) complex. Certainly uptake is a necessary, but not a sufficient criterion of antitumor activity; and other criteria, such as the nature and type of binding at the target site, are far more important than uptake in eliciting antitumor activity.

Trends in the distribution coefficients,  $K_d$ , between *n*-octanol/saline and the biological half-life data,  $T_{1/2}$ , determined from cumulative urine and fecal excretion of  $^{195m}\text{Pt}$  activity are consistent with the order of compound retention. The distribution coefficient for  $\text{K}_2\text{PtCl}_4$  (VI) has not been determined. The  $K_d$  values are highest for *trans*-DDP, a neutral and non-polar analog. Adequate data are not available at the present time to evaluate the  $T_{1/2}$  for *trans*-DDP.

The relationship between tissue distribution and kinetic lability of chloroamineplatinum(II) complexes gives credence to the "Concept of the Window of Lability." Although generally applied to isostructural complexes of the same net charge, this principle is of general applicability and can be applied to the series of chloroamineplatinum(II) complexes that have been investigated. According to this concept, complexes which are chemically too inert will be too unreactive and will either not reach the target site or will not react with the target site at a sufficient rate or to a sufficient extent to elicit the critical biological response. Such inert compounds are anticipated to exhibit a short  $T_{1/2}$ , have relatively low retention in the body as well as be relatively non-toxic. On the other extreme, complexes which are chemically too reactive will be indiscriminate in their binding and will be scavenged by a host of biologically important molecules. These complexes are expected to be less active biologically, exhibit a relatively long  $T_{1/2}$ , have a high tissue retention, and be relatively toxic. Between the extremes of too inert and too reactive lies a region of optimal lability within which one would expect to find

complexes of optimal biological activity. The data for *trans*-DDP compared to  $[\text{Pt}(\text{NH}_3)_4]\text{Cl}_2$  illustrate that this concept can be validly applied to the chloroammineplatinum(II) complexes since these two complexes lie near the extremes of reactivity and toxicity and are virtually devoid of antitumor activity.

#### RADIONUCLIDES FOR MEDICAL COOPERATIVE PROGRAMS

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

##### Carbon-11

Five  $^{11}\text{C}$  production runs were made for the Medical Cooperative Program with Oak Ridge Associated Universities (ORAU) to study the application of  $^{11}\text{C}$ -labeled amino acids for tumor localization and pancreas imaging in human patients. Eight batches of  $^{11}\text{C}$ -DL-tryptophan and three batches of  $^{11}\text{C}$ -DL-valine were prepared and tested in patients at the ORAU Medical Division for tomographic visualization studies of various types of pancreatic disorders. Five batches of  $^{11}\text{C}$ -labeled 1-aminocyclobutane carboxylic acid ( $^{11}\text{C}$ -ACBC) were prepared and studied similarly for visualization of a variety of solid tumors. A total of 14 patients were examined with the  $^{11}\text{C}$ -labeled amino acids. Two preparations of  $^{11}\text{C}$ -labeled phenethylamine were utilized in preclinical studies to determine its potential application for brain function studies. The latter study includes the University of Kentucky as well as ORAU in the cooperative program.

##### Platinum-195m

Collaborators in the Medical Cooperative Program investigating platinum antitumor agents were supplied with  $^{195\text{m}}\text{Pt}$ -labeled compounds. Two shipments of  $\text{Na}_2\text{PtCl}_6$  were supplied to the University of Kentucky Medical School (Dr. P. DeSimone). One shipment of *cis*-dichlorodiammine-platinum(II) (*cis*-DDP) was also supplied to this institution for further studies of nephrotoxicity and protein binding of platinum compounds. One shipment of *cis*-DDP was supplied to the Radiopharmacy Department at the University of Southern California (Dr. W. Wolf) for radiopharmacokinetic studies. One shipment of *cis*-DDP was supplied to the Medical School at

the University of California at Los Angeles (Dr. E. Petrilli) for pre-clinical nephrotoxicity studies in dogs in anticipation that the agent will be utilized in future clinical investigations.

#### Selenium-75 and Tellurium-123 $m$

A new Medical Cooperative Program was established with the Nuclear Medicine Division of Massachusetts General Hospital (Dr. H. William Strauss) to amplify and extend the preclinical studies of a unique class of radiolabeled selenium and tellurium fatty acids as potential myocardial-imaging agents. The program was initiated by supplying  $^{75}\text{Se}$ -methyl-9-selenaheptadecanoate and  $^{123m}\text{Te}$ -methyl-9-telluraheptadecanoate. The heart uptake of these agents will be determined in normal rats and in rats that have myocardial infarctions induced by ligation of a coronary artery to determine if the fatty acids show specific uptake in normal heart tissue compared to the diseased tissue. The success of these preliminary studies will indicate if future imaging studies of infarcted dog hearts will be attempted.

## OTHER NUCLEAR MEDICINE TECHNOLOGY GROUP ACTIVITIES

Potassium-43 was supplied to several institutions on a cost recovery basis. Five shipments of  $^{43}\text{K}$  were made to the National Institute for Environmental Health Studies. Three shipments were made to the National Institutes of Health, Bethesda, Maryland, and also three shipments to the University of Mississippi Medical Center. One shipment was supplied to the University of Connecticut Medical School.

F. F. Knapp, Jr. participated in the Third International Symposium on the Chemistry of Organo Selenium and Tellurium Compounds at Metz, France, on July 9-12, and attended the Twenty-sixth Annual Meeting of the Society of Nuclear Medicine at Atlanta, Georgia, June 26-29, 1979. J. D. Hoeschele participated in the Symposium on Inorganic Chemistry in Biology and Medicine held as part of the Annual Meeting of the American Chemical Society at Washington, D. C., on September 9-14.

## PAPERS AND PUBLICATIONS

## Papers

- J. D. Hoeschele and T. A. Butler, "Correlations of Physico-Chemical and Biological Properties with *In Vivo* Biodistribution Data for Pt-195m-Labeled Chloroamineplatinum(II) Complexes," American Chemical Society Meeting, Washington, D. C., September 9-14, 1979.
- F. F. Knapp, Jr., "Tellurium-123m-Labeled Radiopharmaceuticals," Third International Symposium on Organo Selenium and Tellurium Compounds. Metz, France, July 9-12, 1979.

## Publications

- J. H. Coggin and K. R. Ambrose, "Embryonic and Fetal Determinants on Virally and Chemically Induced Tumors," *Methods in Cancer Research*, Vol. XVIII, *Oncodevelopmental Antigens*, pp. 371-389, W. H. Fishman and H. Busch, eds., Academic Press, N. Y., 1979.
- F. F. Knapp, Jr., "The Mass Spectral Fragmentation of Phenyl  $\omega$ -Dialkoxyethyl Tellurides," *Org. Mass Spectrom.* 14, 341, 1979.

## Reports

- F. F. Knapp, Jr., *Nuclear Medicine Technology Progress Report for Quarter Ending March 31, 1979*, ORNL/TM-6916.
- F. F. Knapp, Jr., *Nuclear Medicine Technology Progress Report for Quarter Ending June 30, 1979*, ORNL/TM-6958.

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