ORNL/TM-6044

# Nuclear Medicine Technology Progress Report for Quarter Ending June 30, 1977

J. K. Poggenburg

OAK RIDGE NATIONAL LABORATORY
OPERATED BY UNION CARBIDE CORPORATION FOR THE ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION

## DISCLAIMER

ORNL/TM-6044

Contract No. W-7405-eng-26

HEALTH AND SAFETY RESEARCH DIVISION

# NUCLEAR MEDICINE TECHNOLOGY PROGRESS REPORT FOR QUARTER ENDING JUNE 30, 1977



J. K. Poggenburg

Work sponsored by
ERDA Division of Biomedical and
Environmental Research

Date Published - September 1977



OAK RIDGE NATIONAL LABORATORY
Oak Ridge, Tennessee 37830
operated by
UNION CARBIDE CORPORATION
for the
ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION

EB

Previous reports in this series:

ORNL/TM-5809
ORNL/TM-5936

# CONTENTS

# NUCLEAR MEDICINE TECHNOLOGY PROGRESS REPORT FOR QUARTER ENDING JUNE 30, 1977


## SUMMARY

Formation of the Nuclear Medicine Technology Group within the new Health and Safety Research Division is announced. Progress is reported for the applications of $^{11}C$, $^{195m}Pt$, $^{33}P$, and $^{123m}Te$. Of note in this report is the progress in the microscale synthesis of *cis* dichlorodiammine-$^{195m}Pt(II)$, a direct exchange method for labeling $POCl_3$ with $^{33}P$, and the successful synthesis of a $^{123m}Te$-labeled amino acid, DL-α-amino-γ-(phenyl telluro ethyl) butyric acid.


---

## REORGANIZATION

In April 1977 the Health and Safety Research Division was created from components of the former Health Physics Division, the Environmental Sciences Division, and the Operations Division. The new Division has been organized into four sections: Biological and Radiation Physics, Chemical Physics, Technology Assessments, and Biomedical Effects and Instrumentation under which this activity is organized as Nuclear Medicine Technology. It includes the former Biomedical Radioisotopes Program from the Operations Division and the Image Enhancement and Medical Instrumentation Programs from the former Medical Physics and Internal Dosimetry Section of Health Physics. The other groups in the Biomedical Effects and Instrumentation Section are: Metabolism and Dosimetry, Health Effects and Epidemiology, and Monitoring Technology and Instrumentation.

This report series is the successor to the Biomedical Radioisotope Program reports and will henceforth cover the activities in medical instrumentation.

# CARBON-11

*T. A. Butler*

After a protracted shutdown of the cyclotron for repairs, a proton beam was achieved in the latter part of this quarter and the synthesis and clinical testing of $^{11}$C-labeled compounds as tumor localization agents in collaboration with Oak Ridge Associated Universities (ORAU) were resumed.

Two human patient scans were made with $^{11}$C-1-aminocyclopentanecarboxylic acid ($^{11}$C-ACPC) and one was made with $^{11}$C-DL-valine. One preparation of $^{11}$C-DL-tryptophan was made for quality assurance testing in preparation for human clinical use. The patient scans were made at ORAU using the recently installed positron tomographic instrument (ECAT). These tomographic scans were the first obtained at ORAU with $^{11}$C-labeled compounds, and they are being evaluated to determine what information advantage this new technique offers over conventional scanning methods.

In preparation for the production of $^{11}$C-labeled glucose for radiopharmaceutical use, the uptake of $^{11}$C in a light-starved swiss chard leaf was measured. A mixture of $^{11}CO$-$^{11}CO_2$ of undetermined composition was exposed to the leaf illuminated by light from a fluorescent tube. Approximately 350 mCi of $^{11}$C was incorporated in the leaf during a 10-min exposure to the $^{11}$C gas mixture initially containing 2500 mCi of $^{11}$C. This qualitative experiment confirmed the suitability of the apparatus and technique for the proposed synthesis of $^{11}$C-glucose.

Plans for the next quarter include accelerated clinical evaluation of $^{11}$C-ACPC and $^{11}$C-DL-valine for tumor localization, first human scans with $^{11}$C-DL-tryptophan, and preclinical animal studies with $^{11}$C-glucose.

# PLATINUM-195m

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

As part of the continuing medical cooperative program to study antitumor compounds, one shipment each of $^{195m}$Pt-labeled hexachloroplatinic acid, $H_2PtCl_6$, and $^{195m}$Pt-labeled *cis*-$[Pt(NH_3)_2Cl_2]$, *cis*-DDP, was made to the University of Southern California, and one shipment of $^{195m}$Pt-labeled [Pt(*trans*-ℓ-DAC) malonate] was made to Mary Hitchcock Memorial Hospital. Each of the above $^{195m}$Pt-labeled compounds and, in addition, $^{195m}$Pt-labeled *trans*-DDP were supplied to the ORNL Biology Division for DNA binding studies. A collaborative effort with ORAU has been initiated for the purpose of investigating the subcellular distribution of *cis*-DDP.

In addition to medical cooperative activities, research efforts have centered on (a) the optimization of the microscale synthesis of $^{195m}$Pt-labeled *cis*-DDP, and (b) microscale syntheses and animal distribution studies of other key Pt(II) compounds which loom as potential second generation drugs or which may be useful in gaining insight into the mechanism of action and the structure-activity relationships of platinum antitumor drugs.

## Microscale Synthesis of *cis*-$[Pt(NH_3)_2Cl_2]$ (*cis*-DDP)

Optimization of the microscale synthesis of $^{195m}$Pt is nearing completion. Completion was anticipated this quarter, but there are a few remaining experiments needed to finalize this synthesis. Emphasis during this quarter has focused on (a) identifying and quantitating stepwise losses, (b) increasing the overall yields, (c) establishing the chemical purity of the product by spectroscopic and chromatographic techniques, and (d) demonstrating the feasibility of synthesis on a 50-μmole scale.

The present microsynthesis scheme for $^{195m}$Pt-*cis*-DDP is illustrated in Fig. 1 below and a summary of the details of synthesis (scale, yields,

losses and purity) appears in Table 1. Reference will be made to this material in the sections which follow.

| | | Approximate Losses, % |
|---|---|---|
| 1. | $Pt + \text{aqua regia} \xrightarrow{\Delta} H_2PtCl_6$ | |
| 2. | $H_2PtCl_6 + 2NaCl \xrightarrow[\text{dryness}]{\Delta} Na_2PtCl_6 + 2HCl\uparrow$ | ≤0.5 |
| 3. | $2Na_2PtCl_6 + N_2H_4\cdot 2HCl \xrightarrow{5\text{–}10^\circ C}; \xrightarrow[5\text{ min}]{85^\circ C} 2Na_2PtCl_4 + N_2 + 6HCl$ | |
| 4. | $Na_2PtCl_4 + KI_{xs} \xrightarrow[\text{ambient temp}]{} K_2PtI_4 + 2NaCl + 2KCl$ | 1.5–20 |
| 5. | $K_2PtI_4 + 2NH_3 \xrightarrow[\text{ambient temp}]{} cis\text{-}Pt(NH_3)_2I_2\downarrow + 2KI$ | |
| 6. | $cis\text{-}Pt(NH_3)_2I_2 + 2AgNO_3 \xrightarrow[\substack{50\text{–}60^\circ C \\ 5\text{–}10\text{ min}}]{\Delta} cis\text{-}[Pt(NH_3)_2(H_2O)_2]^{2+}, 2NO_3^- + 2AgI\downarrow$ | |
| 7. | $cis\text{-}[Pt(NH_3)_2(H_2O)_2]^{2+}, 2NO_3^- + HCl_{xs} \xrightarrow{\sim 50^\circ C} cis\text{-}[Pt(NH_3)_2Cl_2]\downarrow + 2HNO_3$ | 10–15 |
| 8. | Purification by recrystallization (0.1 *N* HCl or 0.15 *M* NaCl) | |
| | Total | 25–35 |

Fig. 1. Microscale synthesis of *cis*-$[Pt(NH_3)_2Cl_2]$.

Table 1. Experimental $^{195m}$Pt-*cis*-$[Pt(NH_3)_2Cl_2]$ syntheses

| | Experiment number | | | |
|---|---|---|---|---|
| | 11 | 10 | 8 | 6 |
| 1. Scale, mmoles Pt | 0.015[a] | 0.0844[a] | 0.242 | 0.120 |
| 2. Volumes, ml: | | | | |
| $Na_2PtCl_4$ solution (after reduction) | 0.5 | ? | 1.0 | 0.4 |
| Recrystallization, *cis*-DDP | 1.0[b] | 1.3 | 2.5[b] | 1.0-1.6 |
| *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ solution | - | - | 2.6 | - |
| 3. Yields, percent: | | | | |
| *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ (Step 6) | - | 78 | 70 | 87 |
| *cis*-DDP (purified) | 68 | 70 | 73[d] | 76 |
| 4. Losses, percent: | | | | |
| Formation, *cis*-$Pt(NH_3)_2I_2$ (Steps 3-5) | 33[e] | 20.3 | 15.8 | 16 |
| Conversion, *cis*-$Pt(NH_3)_2I_2 \rightarrow$ *cis*-DDP (Steps 6-8) | 15 | 8 | 12 | |
| 5. Accountability, percent: | - | 100 ± 2 | - | 100 ± 2 |
| 6. Purity: | | | | |
| Absorbance ratio $\left(\frac{300\text{ nm}}{246\text{ nm}}\right)$[f] | 4.34 | 4.2 | 4.1 | 4.0 |
| Chromatographic homogeneity: | | | | |
| Number of spots ($R_f$ value) | | 1 (0.33) | 1 | 1 |
| Percent at origin | | 2.0 | | |

[a] Stable Pt added.

[b] Physiological saline, 85°C.

[c] 0.1 *M* HCl at 95°C.

[d] Based on portion of product.

[e] Incorrect stoichiometry accounts for abnormally high ion.

[f] Recorded on Beckman DB. Ratios of 4.5 are observed for pure compounds using a Cary instrument, but only ~4.2 using a Beckman DB.

Increased yields

Yields of *cis*-DDP, previously in the range of 40-60%, have been increased to ∿72% (average of four recent syntheses). The improvement in yield is principally the result of: (a) maximizing the concentrations of Pt(IV) and Pt(II) ($\geq$0.24 *M*) employed in steps 3 and 4, respectively, and (b) general minimizing of solution volumes in all subsequent steps, particularly in the washing and recrystallization operations.

Identification/quantitation of stepwise losses. Average stepwise losses are listed in Fig. 1 and stepwise losses for the four individual experiments are listed in Table 1. (Hot-cell processing losses are not included in the losses considered here.) Minor losses ($\leq$0.5%) are incurred in the removal of residual $NO_3^-$, introduced on dissolution of platinum in aqua regia, and in the subsequent transfer of $Na_2PtCl_6$ solution (0.5-1.0 ml) to screw-capped 15-ml centrifuge tubes in which all synthetic/purification steps are performed. Presently, steps 3-5 account collectively for as much as 15-20% loss; however, it appears certain that the majority of this loss occurs in step 4. Quantitation of the extent of reduction (step 3) by absorption spectrophotometry will pinpoint the high loss step. Optimization of this step will complete the work planned for $^{195m}$Pt-labeled *cis*-DDP. Conversion of *cis*-$Pt(NH_3)_2I_2$ to pure *cis*-DDP (steps 6-8) involves ∿10-15% loss, 1/3 of which results from washing and recrystallization. Minimizing losses in this part of the synthesis is critically dependent upon minimizing solution volumes. The intrinsic solubility of *cis*-DDP in 0.1 *N* chloride ion media contributes significantly to the losses incurred during washing and/or recrystallization. Appreciable reduction in loss at this stage might be possible if the conversion of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ to *cis*-DDP (steps 7 and 8) is carried out in physiological saline and the resultant saline solution is passed through (or contacted with) a mixed-bed resin in the NaCl form. This procedure could eliminate both the washing and recrystallization steps.

Feasibility of 50-μmole synthesis scale. The feasibility of synthesizing *cis*-DDP at the 50 μmole scale has been demonstrated (cf. Table 1, Synthesis

No. 11). Both yield (68%) and purity of material are excellent. Consequently, it is entirely possible that the microsynthesis could be reduced further to a scale of 25 μmoles (or less). At this scale of synthesis it becomes practical to consider incorporating $^{197}Pt$ (β,γ-emitter, $T_{1/2}$ = 20 hr) into *cis*-DDP in order to prepare a high specific-activity product. The calculated specific activity of reactor-produced $^{197}Pt$ is considerably higher (100-200X) than $^{195m}Pt$ (1.0 mCi/mg Pt). High specific-activity $^{197}Pt$-labeled *cis*-DDP could have potential utility in clinical pharmacodynamic studies, therapeutic studies (radio- plus chemotherapy), and studies of tissue localization (e.g., in kidney), particularly for electron microscopy and autoradiographic (EM-ARG) techniques.

Purity of $^{195m}Pt$-labeled *cis*-$[Pt(NH_3)_2Cl_2]$. Platinum-195m-labeled *cis*-DDP meets the well defined purity criteria established for stable *cis*-DDP.[1,2] Preparations exhibit major absorption maxima at 300 and 365 nm and an absorbance ratio $\left(\text{As } \frac{300}{246}\right)$ of 4.2 ± 1. (Absorbance ratios ≥4.5 are observed for pure compounds using a Cary spectrophotometer but only ∿4.2 on our Beckman DB spectrophotometer.) Purity evaluations employing paper chromotography indicate that a typical compound exhibits a single homogeneous spot with an $R_f$ value of 0.33-0.36, using 2-in. Whatman 3MM paper. Eluents used were 9:1 acetone:X (X - $H_2O$, 1 *M* HCl) at 21°C. Two percent of the applied compound (∿9 μg total) remains at the origin for the 9:1 acetone: 1 *M* HCl mixture, whereas ∿6-8% remains when using 9:1 acetone:$H_2O$.

## Microscale Synthesis of $^{195m}Pt$-*trans*-$[Pt(NH_3)_2Cl_2]$(*trans*-DDP)

A microscale synthesis (∿0.1 mmole) of *trans*-DDP has been developed for studies of the mechanism of action of platinum antitumor drugs in conjunction with the ORNL Biology Division.

*Cis*- and *trans*-DDP are geometrical isomers of the composition $[Pt(NH_3)_2Cl_2]$. Whereas *cis*-DDP exhibits potent antitumor activity, *trans*-DDP exhibits no antitumor activity. This drastic difference in biological activity for structurally similar compounds has stimulated comparative investigations

into the binding of these isomers with DNA and precursor species. *Trans*-DDP was synthesized for use in these studies. The two synthesis schemes examined are outlined below.

Scheme A:

(1) $Na_2PtCl_4 + NH_4OH_{(xs)} \xrightarrow[50°C]{aq.} [Pt(NH_3)_4]Cl_2 + 2NaCl$

(2) $[Pt(NH_3)_4]Cl_2 + HCl\ (6\ M) \xrightarrow{reflux} trans\text{-}[Pt(NH_3)_2Cl_2] + 2NH_4Cl$

Scheme B:

(1) $cis\text{-}[Pt(NH_3)_2Cl_2] + NH_4OH_{(xs)} \xrightarrow[50°C]{aq.} [Pt(NH_3)_4]Cl_2 + NH_3 \uparrow$

(2) $[Pt(NH_3)_4]Cl_2 + HCl(6\ M) \xrightarrow{reflux} trans\text{-}[Pt(NH_3)_2Cl_2] + 2NH_4Cl$

Platinum-195m-labeled *cis*-DDP or $Na_2PtCl_4$ can be used as suitable starting materials. Both are prepared as described above in the synthesis of $^{195m}$Pt-*cis*-DDP. Both synthesis schemes have their individual merits. Scheme B is preferred if *cis*-DDP is prepared at the same time, particularly since a purified and assayed starting material would be available. Yields are high in both schemes and quantitative in the case of B.

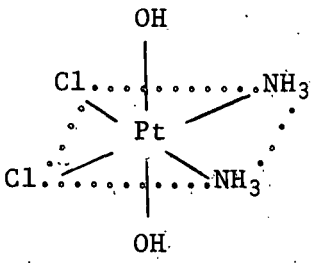
## Microsynthesis of *cis-trans*-$[Pt(NH_3)_2Cl_2(OH)_2]$

A microscale synthesis of $^{195m}$Pt-labeled *cis-trans*-$[Pt(NH_3)_2Cl_2(OH)_2]$ was developed for in-house uptake-distribution studies and testing of the premise that this compound may derive its antitumor activity by virtue of a stereo-specific reduction *in vivo* to active *cis*-DDP. The distribution data will be presented in the next progress report.

This compound can be considered to be the parent of a family of Pt(IV) antitumor drugs having the general formula *cis-trans*-$[PtA_2Cl_2(OH)_2]$ (A = $NH_3$, amines). These compounds are sufficiently soluble to be administered intravenously, exhibit reasonable therapeutic indices (5-12),

and appear to offer some promise as clinical alternatives to *cis*-DDP, particularly the analogs A = $NH_3$, isopropylamine, and cyclopentylamine. The microscale synthesis was adapted from that reported for the analog [Pt en $Cl_2(OH)_2$]. The synthesis scheme is as follows:

$$cis\text{-}Pt(NH_3)_2Cl_2 + H_2O_2 \xrightarrow[\text{warm}]{(30\%)} cis\text{-}trans$$




1. 1 milliliter of 30% $H_2O_2$ plus a small volume of water (~0.5 ml) was added to solid $^{195m}$Pt-*cis*-DDP (12.3 mg) and then the mixture was warmed. The slurry gradually transformed into a clear pale yellow solution, and no crystallization of product occurred on cooling to 0°C.

2. 37.6 mg stable *cis*-DDP was added plus additional $H_2O_2$ (30%), and the slurry was warmed. *Cis-trans* [$Pt(NH_3)_2Cl_2(OH)_2$] began to crystallize out soon after the stable *cis*-DDP dissolved.

3. The product was washed twice with water.

## PHOSPHORUS-33

*D. V. Woo*

The inert atmosphere glove box is now operational. Although the auxiliary cooling for removal of furnace heat from the synthesis of labeled $^{33}PCl_3$ has not yet been installed, the box can be used for the handling of oxygen-sensitive and/or radioactive compounds.

Efforts to optimize the microscale synthesis of $^{33}$P-labeled cyclophosphamide continued during this quarter. The labeled alkylating agent will be tested for synergistic radiotoxic and cytotoxic activity. Initial syntheses of labeled compound resulted in very low radiochemical and

chemical yields (<5%). Major losses in radiochemical yield occurred during initial incorporation of the $^{33}P$-label from $^{33}POCl_3$. Losses in chemical yield occurred during the last stage of the synthesis in the reaction of *bis*(2-chloroethyl)phosphoramide dichloride with 3-amino-1-propanol in the presence of triethylamine. The choice of reaction solvent was found to be important during the last step of this reaction. The use of dichloromethane resulted in a significant amount of the *bis*(2-chloroethyl)-amine being produced, indicating that acid hydrolysis was occurring between the phosphorus-nitrogen bond. This results from the partial solvation of the triethylamine hydrochloride salt generated within the reaction solvent. Substituting the solvent p-dioxane alleviates this problem because the triethylamine salts formed will precipitate from solution. The change of reaction solvents led to the decision to isolate and purify the intermediate *bis*(2-chloroethyl)phosphoramide dichloride by chromatography procedures described previously in order to prevent possible side products from interfering with the final reaction. Further experimental syntheses with unlabeled material by this approach have resulted in a significant improvement in chemical yields.

Various techniques were evaluated for the synthesis of radiolabeled $^{33}POCl_3$. Initially the reaction of $PCl_5$ with $P_2O_5$ in an inert solvent appeared favorable, but further studies resulted in variable chemical yields with a maximum yield of 30% (assayed by infrared spectrophotometry). Although this procedure is considered entirely feasible as a method analogous to the synthesis of $^{33}PCl_3$ via a $^{33}PCl_5$ intermediate, it was decided to test methods for the direct conversion of labeled starting material (aqueous $H_3{}^{33}PO_4$) to $^{33}POCl_3$ with a minimum of reaction steps. One such procedure evaluated involved the direct interaction of $H_3{}^{33}PO_4$ and $H_2O$ with $PCl_5$ to produce labeled $^{33}POCl_3$ in carrier $POCl_3$ by the reactions:

1. $H_3{}^{33}PO_4 + 3PCl_5 \rightarrow {}^{33}POCl_3 + 3POCl_3 + 3HCl$

2. $H_2O + PCl_5 \rightarrow POCl_3 + 2HCl$

The experimental procedure consisted of the following:

a. Lyophilization of an aqueous solution containing carrier-free $H_3{}^{33}PO_4$ plus a known amount of $H_3PO_4$ carrier to a small volume (0.1 ml).

b. Careful addition of $PCl_5$ (during an alternating freeze-thaw cycle of the lyophilized solution) based on the molar quantity of $H_3PO_4$ carrier and the $H_2O$ remaining after lyophilization.

c. Vacuum distillation of the $POCl_3$.

Experimental runs using carrier-free $H_3{}^{33}PO_4$ without added carrier $H_3PO_4$ resulted in <1% incorporation of the radiolabel. Addition of carrier improved the radiochemical yield slightly (5%). Increasing the reaction time from 4 to 16 hr after addition of the calculated amount of $PCl_5$ further improved yields to ∿31%. Poor radiochemical yields were mainly attributed to the relative rates of reaction for equations (1) and (2) above. The selective hydrolysis of $PCl_5$ (Eq. 2) appears to be the preferred reaction which proceeds at a much faster rate, thereby producing unlabeled $POCl_3$ rather than the labeled product. The number of experimental manipulations (lyophilization, addition of $PCl_5$, and vacuum distillation), however, was judged to be a serious disadvantage.

A more promising procedure thus far is a direct exchange reaction. This synthesis depends upon an apparent exchange of OH radicals in carrier-free $H_3PO_4$ with Cl atoms on the $POCl_3$ carrier via an undetermined intermediate species. The carrier-free $H_3{}^{33}PO_4$ is initially evaporated on the interior of a glass ampul by vacuum distillation. A known quantity of $POCl_3$ is transferred to the ampul, and the ampul is sealed under vacuum with a torch. The glass ampul is then placed in a screw-top stainless steel cylinder which is heated in an oven at ∿120°C for 4 days. Upon being opened, the ampul is placed into a specially designed apparatus, and the $POCl_3$ is vacuum distilled into an appropriate receiver ampul. Experimental runs starting with 500 μCi of carrier-free $H_3{}^{33}PO_4$ and 167 mg of $POCl_3$ have resulted in 75% labeling efficiency.

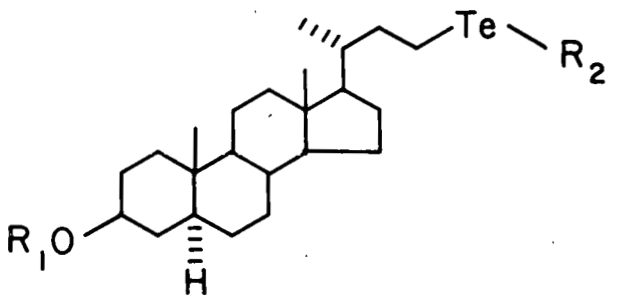
Plans during the forthcoming quarter are to optimize all reaction conditions to improve radiochemical yields in the synthesis of $^{33}P$-labeled $POCl_3$ and cyclophosphamide.

## TELLURIUM-123m

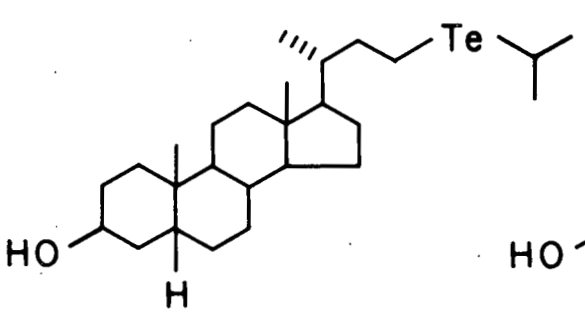
*F. F. Knapp and K. R. Ambrose*

### Tellurium-123m-Labeled Steroids

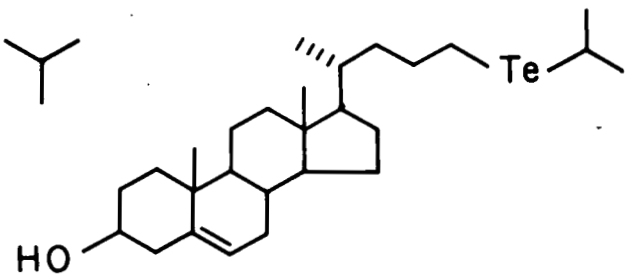
Studies were continued concerning the effect of structural modifications of telluro steroids on the ability of rat adrenals to concentrate the $^{123m}Te$-labeled compounds *in vivo*. One new telluro steroid has been prepared in which the tellurium moiety is present in a shortened sidechain (VI, Fig. 2). In this analog the 17β-sidechain is shorter (i.e., 17β-isopropyl telluro methyl) compared to our original $^{123m}Te$-labeled adrenal agent (I) in which the 17β-sidechain is considerably larger (17β-isopropyl telluro isobutyl). This new analog was prepared by a route analogous to that used to prepare 3β-hydroxy-24-(isopropyl telluro)-chol-5-ene (V). A commercial sample of etienic acid methyl ester (methyl-3β-hydroxy-17β-carboxyl-androst-5-en-oate) was converted to the corresponding 3β-methyl ether which was then reduced with a metal hydride to yield 3β-methoxy-17β-(hydroxy methyl)-androst-5-ene. Treatment with triphenyl phosphonium dibromide generated from triphenyl phosphine and carbon tetrabromide gave 3β-methoxy-17β-(bromo methyl)-androst-5-ene which was the desired substrate for coupling with sodium isopropyl tellurol. The latter reaction was conducted in the usual manner to yield 3β-hydroxy-17β-(isopropyl telluro methyl)-androst-5-ene (VI) which was purified and fully characterized. The $^{123m}Te$-labeled analog was prepared by the same methods. The results of tissue distribution experiments and rectilinear scanning studies using $^{123m}Te$-labeled (VI) are discussed below. In addition, discussions of similar studies using several of the other telluro steroid analogs that were begun in the last Quarterly Report are completed below.



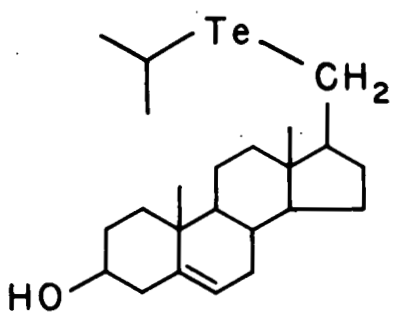

| | $R_1$ | $R_2$ |
|---|---|---|
| I | H | $i-C_3H_7$ |
| II | $CH_3$ | $i-C_3H_7$ |
| III | H | $C_8H_{17}$ |




IV




V




VI

Fig. 2. The Structure of Several New Steroids Containing the Tellurium Heteroatoin in the C-17 Sidechain.

3β-Hydroxy-24-nor-23-(octyl telluro)-5α-cholane (III)

Tissue distribution studies using $^{123m}$Te-labeled (III) indicated that intravenous administration resulted in slow accumulation of radioactivity in rat adrenals. Seven days after injection, the adrenal/tissue ratios were similar to ratios obtained one day after administration of $^{123m}$Te-labeled 3β-hydroxy-24-nor-23-(isopropyl telluro)-5α-cholane (I). These results were corroborated by rectilinear scans of rats injected with $^{123m}$Te-labeled (III) and indicate that this agent would not be effective for early adrenal visualization.

3β-Hydroxy-24-(isopropyl telluro)-chol-5-ene (V)

The rectilinear scans of both male and female rats following injection of $^{123m}$Te-labeled (V) indicated very rapid adrenal concentration of radioactivity. The results of tissue distribution experiments correlated well with the rectilinear scan data, indicating a high concentration of radioactivity in the adrenals and also the ovaries of female rats. Since $^{123m}$Te-labeled (I) and (V) are the only two analogs we have found that show a high adrenal uptake, a comparative study was performed to determine the relative adrenal uptake of these two agents in both male and female rats. The results of these studies (Table 2) indicate that $^{123m}$Te-labeled (V) concentrates somewhat better in rat adrenals. Because this analog is much less expensive to prepare than (I) these data would suggest that $^{123m}$Te-labeled (V) should be used for extensive studies in larger animals (*vide infra*).

Table 2. Adrenal/tissue ratios of % dose/g following intravenous administration of the $^{123m}$Te-labeled steroids[a]

| Compound | Females | | Males | |
|---|---|---|---|---|
| | I | V | I | V |
| | Day 1 | | | |
| Blood | 55.7 | 63.7 | 49.3 | 39.5 |
| Liver | 39.0 | 36.3 | 34.1 | 19.8 |
| Ovaries | 5.3 | 7.0 | - | - |
| Kidneys | 42.7 | 69.6 | 30.5 | 39.9 |
| Lungs | 24.7 | 23.2 | 19.4 | 13.4 |
| | Day 7 | | | |
| Blood | 129.7 | 182.5 | 59.4 | 125.8 |
| Liver | 127.5 | 133.1 | 61.7 | 60.9 |
| Ovaries | 9.4 | 6.7 | - | - |
| Kidneys | 50.6 | 72.0 | 19.6 | 40.7 |
| Lungs | 141.1 | 79.8 | 60.8 | 43.8 |

[a]The data presented for each time period are the mean from three animals. The standard deviations were generally less than 10% of the mean values.

3β-Hydroxy-17β-(isopropyl telluro methyl)-androst-5-ene (VI)

The chemical synthesis of (VI) has been described earlier in this report. Tissue distribution experiments with $^{123m}$Te-labeled (VI) have demonstrated a very low adrenal and ovarian uptake of radioactivity. It is interesting to note that seven days after injection of the labeled steroid the majority of the radioactivity accumulated in the adipose tissue. In fact, after seven days the concentration of radioactivity in the adipose was greater than that in the adrenals and ovaries. It is not clear what these results mean, and they may suggest *in vivo* instability of the labeled steroid. The rectilinear scan data were similar to the tissue distribution results and indicated that there was no tissue-specific localization of this analog.

In summary, we have now essentially completed our preliminary studies involving a new class of neutral steroids labeled in the sidechain with the $^{123m}$Te nuclide (Fig. 2). These studies have defined certain struc-

tural features that determine the ability of rat adrenals to concentrate these substances *in vivo*. Although none of these analogs have been found to concentrate in rat adrenals more effectively than (I) it has been demonstrated that the uptake of (V) is very similar. Using both $^{123m}$Te-labeled (I) and (V), clear images of both the adrenal glands and the ovaries of rats have been obtained using both a rectilinear scanner and an RC type proportional counter. More recently, the adrenal glands of rabbits have successfully been imaged using a rectilinear scanner and a gamma camera. In addition, the tissue distribution of radioactivity in a dog following injection of $^{123m}$Te-labeled (I) indicated high adrenal/tissue ratios after nine days (i.e., adrenal/liver ratio = 29:1). In the next quarter we will continue these studies in dogs using both $^{123m}$Te-labeled (I) and (V), and we will also attempt to image dog adrenals using several different instrumental techniques. Our success in imaging rat and rabbit adrenals suggests clinical trials in humans and, therefore, animal toxicity studies should be undertaken. The $^{123m}$Te-labeled (V) appears to concentrate marginally better than (I) in rat adrenals (Table 2), and more importantly, it is prepared from a less expensive steroid substrate. Consequently, a large-scale synthesis of (V) was recently initiated for toxicity tests in laboratory animals. Its gross toxicity will be determined in test animals, and also, histopathological examination will be conducted using the adrenal glands and other organs isolated from animals treated with large doses of (V).

## Tellurium-123m-Labeled Amino Acids as Potential Pancreatic Imaging Agents

Considerable effort has been devoted toward developing techniques for the chemical synthesis of $^{123m}$Te-labeled amino acids. Telluro amino acids have not been previously prepared and these compounds are of interest as potential pancreatic imaging agents. The early diagnosis of pancreatitis and pancreatic carcinoma is a common clinical problem. The use of $^{75}$Se-labeled selenomethionine (V.b., Fig. 3) was originally developed because of the biological importance of methionine and the availability of the gamma-emitting $^{75}$Se nuclide. Furthermore, $^{75}$Se was readily incorporated into

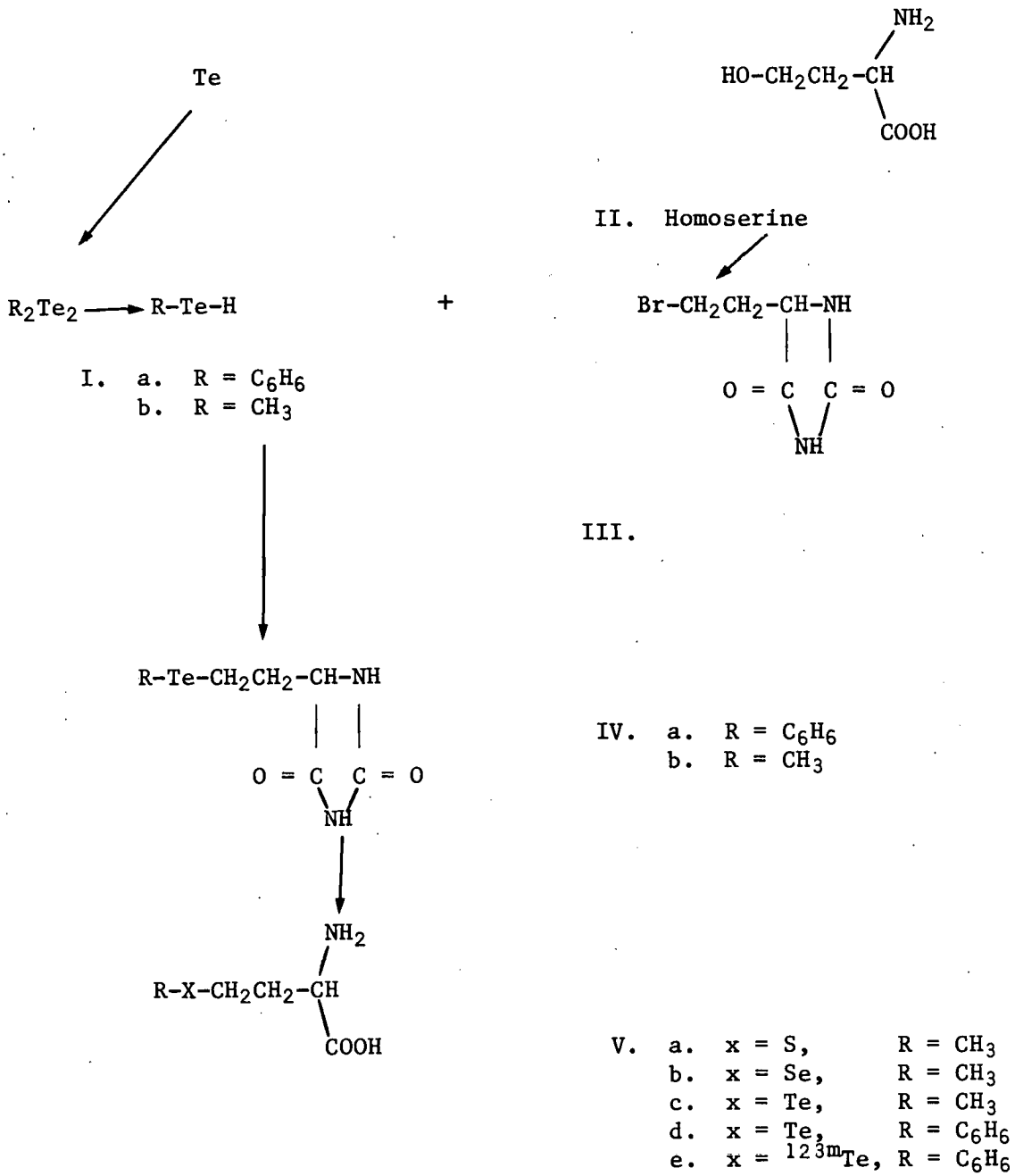



Fig. 3. The Synthesis of Telluro Amino Acids.

selenomethionine by both microbiological and chemical methods. Selenomethionine (V.b.) behaves similarly to methionine (V.a.) *in vivo* and is concentrated in a number of animal species by the pancreas and other tissues that are involved in active protein synthesis. The multiple high-energy gamma emissions of $^{75}Se$, however, result in poor images with an unnecessary radiation dose to the patient. To alleviate these disadvantages the use of $^{123m}Te$-labeled telluromethionine (V.e.) has been suggested as a superior alternative for pancreatic imaging. Attempts to prepare $^{123m}Te$-labeled telluromethionine by microbiological techniques have been unsuccessful. Our successful experience with the preparation of the $^{123m}Te$-labeled steroids prompted further exploration of the synthesis of telluro amino acids.

Our first attempts to prepare telluro amino acids by methods involving the introduction of the benzyl telluro moiety were unsuccessful. The failure is due primarily to the extreme instability of dibenzyl ditelluride. In addition, the benzyl methylene carbon-tellurium bond is unstable even in simple benzyl alkyl tellurides. These properties preclude the preparation of the requisite benzyl telluro intermediates which serve as substrates for the du Vigneaud reduction and subsequent transformation to the desired methyltelluro products. These combined facts dictated devising an alternative strategy. Our early studies of factors affecting the formation and stability of ditellurides and tellurides proved that phenyl akyl tellurides are much more stable than simple dialkyl tellurides because of the stabilizing effect of the aromatic ring. Thus a scheme was devised for the preparation of a representative α-amino acid containing the phenyl telluro moiety (Fig. 3). The method developed should be of general applicability for the synthesis of a variety of telluro amino acids. Its success results from strictly avoiding any attempts to isolate the tellurol intermediates. Such intermediates (I) are quite useful synthetically when generated *in situ*, however, and are formed by reduction of the precursor ditellurides under an inert atmosphere. For the preparation of a model telluro amino acid, diphenyl ditelluride was reduced with sodium borohydride in methanol under an argon atmosphere. The resulting phenyl tellurol was then coupled with 5-(bromoethyl) hydantoin (III) which was

conveniently prepared by known methods from DL-homoserine (II). The reaction resulted in a high yield of 5-(phenyl telluro ethyl)-hydantoin (IV.a.). This unusually substituted hydantoin is stable when stored in the dark as a solid at 4°C. It was fully characterized and exhibited the expected physical and chemical properties. Treatment of this hydantoin with 1 *N* NaOH in a teflon-lined bomb at 160°C resulted in hydrolysis to DL-α-amino-γ-(phenyl telluro) butyric acid (V.d.). Although some decomposition was detected, the product was isolated in reasonable yield and was fully characterized by the usual methods. The $^{123m}$Te-labeled amino acid (V.e.) was prepared from reactor-produced $^{123m}$Te. The microscale synthesis of diphenyl ditelluride was accomplished by reaction of the $^{123m}$Te with phenyl magnesium chloride. The $^{123m}$Te-labeled diphenyl ditelluride was then reduced, coupled with the hydantoin, and the labeled butyric acid (V.e.) then obtained by the methods described above. The physical properties of the labeled amino acid were indentical to those determined for the unlabeled product, and radiochemical homegeneity was established chromatographically. The tissue distributions of the labeled amino acid are presently under investigation using Fischer strain rats.

Using this same methodology we are now attempting to synthesize telluromethionine (V.c.). Special precautions must be taken in this case because of the high volatility of dimethyl ditelluride and methyl tellurol (I.b.). In addition, the 5-(methyl telluro ethyl) hydantoin (IV.b.) must be isolated by a different method from that used to isolate 5-(phenyl telluro ethyl) hydantoin (IV.a.). Dimethyl ditelluride has been prepared by reaction of methyl iodide with sodium ditelluride. Reduction of the ditelluride to methyl tellurol with subsequent coupling with 5-(bromo ethyl) hydantoin (III) then gave (IV.b.). The 5-(methyl telluro ethyl) hydantoin has been purified and characterized. The best conditions for hydrolysis of this intermediate to telluromethione (V.c.) must now be determined.

In summary, the methodology has now been developed for the preparation of telluro amino acids. The first such compound, DL-α-amino-γ-(phenyl telluro ethyl) butyric acid, has been prepared. The synthesis is easily adapted to the microscale and, providing the requisite halo-alkyl

hydantoin intermediates are available, the preparation of a variety of telluro amino acids is possible.

During the next quarter it is anticipated that several of the required hydantoins will be prepared and their coupling with phenyl tellurol and other tellurols will be studied in detail. The tissue distribution of any new telluro amino acids prepared will be studied by making the $^{123m}$Te-labeled analog.

## IMAGING AND INSTRUMENTATION

*P. R. Bell*

The conversion of the Oak Ridge Imaging System (ORIS) programs from the PDP-8 to the PDP-11 language has begun using a borrowed PDP-11 computer. Since inception of ORIS, the 16-bit word has become the standard in nuclear medicine imaging systems. In order to make our developments available for clinical evaluation, the conversion to the clinically used PDP-11 has been undertaken. A considerable part of the matrix convolution program, which is used both for antiscatter and antipenetration calculations and for the two-dimensional polynomial least squares smoothing and bounding, has been translated. The procurement of a floppy disk drive has made possible accelerated progress in adapting the OS/8 input/output methods to the RT-11 monitor used with the PDP-11. A few of the many undocumented procedures necessary for successful use of RT-11 have been located.

An RK8E disk pack containing an ORIS system and source files has been prepared for Dr. David Schurr of the Kaiser Permanente Medical Group at Oakland, California, in response to a request through the Biomedical Computing Technology Information Center. This will provide a complete system, after minor additions or modifications to suit their hardware.

The success of the two-dimensional least-squares matrix method for data smoothing has encouraged us to begin development of a three-dimensional

analagous method, two-space dimensions, and time for smoothing and bounding of dynamic sequences. The data are so sparse in dynamic sequence that every effort is needed to improve the reliability of the results. The matrix array will have 343 elements and thus the direct method may need speeding up by three orthogonal two-dimensional fits.

## MISCELLANEOUS

Two shipments of $^{64}Cu$ were supplied to ORAU to study the tissue distribution of high specific-activity $^{64}Cu$ citrate and $^{64}Cu$ bleomycin in tumored rats. Copper-64 is a positron emitter (19%) and may have potential as a positron tomographic agent for detection of cancer.

Two shipments of $^{18}F$ as $Na^{18}F$ were made to ORAU for use in animal studies using the ECAT scanner.

High specific-activity $^{141}CeCl_3$ was made by the nuclear reaction

$$^{139}La(n,\gamma)^{140}La(n,\gamma)^{141}La \xrightarrow{\beta^-} {}^{141}Ce$$

and purified by HDEHP solvent extraction. The preparation will be tested in a cooperative study with Dr. Nathaniel Revis of the Biology Division to measure myocardial uptake in connection with infarct studies in a rat model. Cerium-141 was chosen because of its imaging properties.

Nine shipments of $^{43}K$ were made this quarter. Four shipments to University of Mississippi were used for radioisotope imaging in heart disease studies in comparison with $^{201}Tl$. Three shipments to Brookhaven National Laboratory were used in their studies of exchangeable electrolytes in human subjects. Two shipments to City College of New York were used for imaging studies.

Visitors this period include: Dr. John Bevin, from Proctor and Gamble Maimi Valley Laboratory, to discuss their results on toxicity studies with $^{33}P$-labeled EHDP; Dr. Archie Prestako, Bristol Laboratories, to discuss the availability of $^{195m}Pt$-labeled compounds; and Dr. Charles Weems, a

reproductive endocrinologist from the Division of Agriculture of Arizona State University, who wanted to discuss possible radioisotopic imaging techniques for monitoring changes in blood flow to ovaries as a function of administration of various prostaglandins. Dr. Philip DeSimone and John Butts of the V. A. Hospital, Lexington, Kentucky, and Dr. Jack Coupal, radiopharmacist, and Richard Yanzey, radiopharmacy graduate student, from the University of Kentucky visited along with Dr. Stephen Krauss, University of Tennessee Memorial Research Center and Hospital, to discuss possible clinical research with platinum chemotherapy compounds. Dr. Krauss is actively testing *cis*-DDP in human clinical trials. The Kentucky group also spent another session in the laboratory reviewing the synthesis of *cis*-DDP.

K. R. Ambrose, F. F. Knapp, and J. K. Poggenburg attended the Annual Meeting of the Society of Nuclear Medicine in Chicago, June 20-23, where two papers were presented by the Group.

## PAPERS AND PUBLICATIONS

### Papers

F. F. Knapp, Jr., and Kathleen R. Ambrose, "Tellurium-123m Labeled 24-Nor-23-(Isopropyl Tellura)-5α-Cholan-3β-ol: A New Potential Adrenal Imaging Agent," 24th Annual Meeting of the Society of Nuclear Medicine, Chicago, June 20-23, 1977.

F. F. Knapp, Jr., and A. P. Callahan, "The Synthesis of Tellurium-123m Labeled Steroids," 24th Annual Meeting of the Society of Nuclear Medicine, Chicago, June 20-23, 1977.

G. A. Andrews, K. F. Hübner, L. C. Washburn, B. W. Wieland, W. D. Gibbs, R. L. Hayes, T. A. Butler, and I. R. Collman, "Clinical Studies of C-11-Labeled Amino Acids," poster session at the 24th Annual Meeting of the Society of Nuclear Medicine, Chicago, June 20-23, 1977.

## Journals

F. F. Knapp, Jr., and Kathleen R. Ambrose, "Tellurium-123m Labeled 24-Nor-23-(Isopropyl Tellura)-5α-Cholan-3β-ol: A New Potential Adrenal Imaging Agent," *J. Nucl. Med.* 18(6), 600 (1977).

F. F. Knapp, Jr., and A. P. Callahan, "The Synthesis of Tellurium-123m Labeled Steroids," *J. Nucl. Med.* 18(6), 610 (1977).

G. A. Andrews, K. F. Hübner, L. C. Washburn, B. W. Wieland, W. D. Gibbs, R. L. Hayes, T. A. Butler, and I. R. Collman, "Clinical Studies of C-11-labeled Amino Acids," *J. Nucl. Med.* 18(6), 638 (1977).

F. F. Knapp, Jr., and G. J. Schroepfer, "Mass Spectrometry of Sterols: Electron Ionization Induced Fragmentation of C-4 Alkylated Cholesterols," *Chem. Phys. Lipids*, 17(4), 466-500 (1976).

## Reports

J. K. Poggenburg, Biomedical Radioisotope Program Progress Report for Quarter Ending March 31, 1977, ORNL/TM-5936 (June 1977).

## REFERENCES

1. National Cancer Institute Purchase Specifications for *cis*-$[Pt(NH_3)_2Cl_2]$.

2. J. D. Hoeschele, unpublished work; and Clinical Brochure for *cis*-Dichlorodiammineplatinum (II), NSC-119875 (Aug. 1974).

3. F. Basolo, et al., *J. Am. Chem. Soc.*, 72, 2433 (1950).

## INTERNAL DISTRIBUTION

1. K. R. Ambrose
2. S. I. Auerbach
3. J. A. Auxier
4. J. M. Becker (Consultant)
5. P. R. Bell
6. T. A. Butler
7. W. R. Casto
8. K. Cowser
9. J. A. Cox
10. D. E. Ferguson
11. R. B. Gammage
12. W. R. Garrett
13. J. D. Hoeschele
14. S. V. Kaye
15. F. F. Knapp, Jr.
16. E. Lamb
17. T. A. Lincoln
18. P. Nettesheim
19. C. H. Nowlin
20. C. L. Ottinger
21. C. H. Patrick
22-26. J. K. Poggenburg
27. H. Postma
28. M. E. Ramsey
29. C. R. Richmond
30. A. F. Rupp (Consultant)
31. M. R. Skidmore
32. M. J. Skinner
33. J. B. Storer
34. D. V. Woo
35. H. A. Wright
36-37. Central Research Library
38. Document Reference Section
39-40. Laboratory Records Department
41. Laboratory Records, ORNL RC

## EXTERNAL DISTRIBUTION

42-43. Technical Information Center, ERDA, Oak Ridge, TN 37830
44. D. C. Davis, ERDA-ORO, Oak Ridge, TN 37830
45. J. A. Lenhard, ERDA-ORO, Oak Ridge, TN 37830
46. J. N. Maddox, ERDA-DBER, Washington, DC 20545
47. W. H. Weyzen, ERDA-DBER, Washington, DC 20545
48. R. W. Wood, Jr., ERDA-DBER, Washington, DC 20545
49. T. F. Budinger, M.D., Donner Lab., LBL, Berkeley, CA 94720
50. R. L. Hayes, ORAU, Oak Ridge, TN 37830
51. C. C. Lushbaugh, ORAU, Oak Ridge, TN 37830
52. H. A. O'Brien, LASL, Los Alamos, NM 87545
53. P. Richards, BNL, Upton, NY 11973
54. Harold L. Atkins, M.D., BNL, Upton, NY 11973
55. A. P. Wolf, BNL, Upton, NY 11973
56. H. E. Walburg, CARL, Oak Ridge, TN 37830
57. A. Solomon, M.D., UT-MRCH, Knoxville, TN 37920
58. A. Legendre, M.D., UT-School of Veterinary Medicine, Knoxville, TN 37920
59. John Venditti, National Cancer Institute, Silver Springs, MD 20910
60. S. James Adelstein, Shields Warren Radiation Lab., Boston, MA 02115
61. David E. Kuhl, UCLA, Lab. of Nuclear Medicine, Los Angeles, CA 90024
62. John S. Laughlin, Sloan-Kettering Inst. for Cancer Research, NY, NY 10021
63. Paul Harper, M.D., Franklin McLean Memorial Research Institute, Chicago, IL 60637
64. Walter Wolf, University of Southern California, Los Angeles, CA 90033
65. Philip A. DeSimone, M.D., V. A. Hospital, Lexington, KY 40507
66. John Hollifield, Vanderbilt University Hospital, Nashville, TN 37232
67. Bertrand Brill, M.D., Vanderbilt University Hospital, Nashville, TN 37232