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PROGRESS REPORT

TO .

THE UNITED STATES ATOMIC ENERGY COMMISSION

CONTRACT AT(11-1)-3521

BIOLOGICAL EFFECTS OF RADIATION AND RELATED

BIOCHEMICAL AND PHYSICAL STUDIES

Proposal #1 Cyclotron Facility: Production of
Radionuclides, Labeled Compounds and
Fast Neutron Beams

Contract Period: September 1, 1973 to December 31, 1974

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PROGRESS REPORT

TITLE: PRODUCTION OF RADIONUCLIDES, LABELED COMPOUNDS
AND FAST NEUTRON BEAMS

<u>CONTENTS:</u>	<u>Page</u>
1. Objective	3
2. Summary of Cyclotron Use	3
3. Selenium-73 Production	8
4. Synthesis of Carbon-11 Labeled Compounds	9
a) $H^{11}CN$ and $^{11}CO_2$ Production	9
b) Valine Synthesis	10
c) α -Keto Acid Intermediate	11
d) ^{11}C -Diphenylhydantoin and ^{11}C -Hydroxyphenylphenylhydantoin	12
5. Production of ^{13}N -Ammonia and ^{13}N -Amino Acids	13
6. Chemical Form of ^{13}N in Proton Irradiated Water	19
7. Bismuth-204 Content of Bismuth-206 Preparations	20
8. Cyclotron Research and Development	21
a) Internal Beam Development	22
b) External Beam Development	23
9. References	26
10. Publications	27

1. OBJECTIVE

The operation of the cyclotron has the following objectives:

- (a) Research on nuclear reactions and target design for production of radionuclides.
- (b) Research on labeling of biologically important compounds with cyclotron produced radionuclides.
- (c) Production of radionuclides and labeled compounds for metabolic isotope research in patients and in animals carried out by the metabolic isotope study section.
- (d) Production of neutrons and charged particle radiations for biological and dosimetry research projects carried out by other sections.
- (e) Development of improved cyclotron operation and beam handling technology.

2. SUMMARY OF CYCLOTRON USE

Materials, Methods and Results

Table I summarizes the use of the cyclotron during this report period.

Of the radioisotope production runs, carbon-11 was produced by proton irradiation of nitrogen gas. If hydrogen cyanide was desired as the final product, 1% hydrogen was added to the nitrogen and the 11C -methane produced was chemically converted to H^{11}CN as described by Wolf et al. (1). One to 1.5 curies of H^{11}CN could be prepared in a forty minute bombardment at 25 μA of beam current. $^{11}\text{CO}_2$ could be prepared in slightly lower yield by using 1% oxygen plus nitrogen as the target gas. These compounds are being used as starting materials for the synthesis of other compounds for potential use as scanning agents.

The production of ^{13}N -ammonia, accomplished initially by the deuteron irradiation of methane, is now routinely produced by proton irradiation of water, followed by reduction and distillation. The static water target was found to be limited to 25 μA of proton beam current and 200 mCi of $^{13}\text{NH}_3$ after distillation. At higher beam currents the yield of $^{13}\text{NH}_3$ decreased, presumably due to cavitation in the water. This

TABLE I: SUMMARY OF CYCLOTRON USE

(May 1, 1973 - August 8, 1974)

<u>Description of Run</u>	<u>No. of Runs</u>	<u>Use (Intended Use)</u>
<u>Radioisotope Production:</u>		
¹¹ C-Cyanide	23	Organic compound synthesis
¹¹ C-Carbon dioxide	19	Organic compound synthesis
¹³ N-Ammonia	18	Methane target
	57	Water target amino acid synthesis
Oxygen-15	26	Radioactive gases
Fluorine-18	136	Water target Bone scanning
Selenium-73	10	Developmental
Iron-52	22	Erythropoietic function
Iodine-123	8	Developmental
Bismuth-206	15	Animal testing
Miscellaneous	<u>12</u>	Research and development
Subtotal	346	
<u>Other Uses:</u>		
Machine R & D	117	---
Neutron Dosimetry	21	---
Radiobiology	16	HeLa cells and mouse
Activation analysis	12	Calcium <u>in-vivo</u>
Miscellaneous	<u>7</u>	p-dose; x-ray emission
Subtotal	173	
GRAND TOTAL	519	

limit has been extended by using a recirculating water target which was tested up to 60 μ A of beam current with a proportionate increase in the activity of ^{13}N produced, corresponding to a saturation activity of 20 mCi/ μ A. The volume of water irradiated has however been increased to 150 ml and some difficulties have been experienced in modifying the reduction and distillation process to handle this five-fold increase in volume. The yield of $^{13}\text{NH}_3$ using the recirculating water target is increased from about 200 mCi to about 800 mCi at 10 minutes after the end of irradiation. It is believed that the yield of ^{18}F would also be improved by using a recirculating water target for ^3He ion irradiation, and such a target system is being designed and constructed.

Oxygen-15 as O_2 , CO and CO_2 has been produced semi-routinely for studies of the distribution of these radiochemicals when administered continuously to the lungs of dogs. Certain simplifications in the production have been adopted. For C^{15}O production, the products of the deuteron irradiation of $\text{N}_2 + 1\%$ O_2 gas were passed directly over charcoal at 1000°C . The purity of the gas was so high that it could be administered, after adding air or oxygen, directly to dogs. No oxides of nitrogen or ozone could be detected in the product. Carbon dioxide ^{15}O was made by passing the deuteron irradiated $\text{N}_2 + 1\%$ O_2 gas over charcoal at 500°C and then over copper oxide at 500°C . Pure C^{15}O_2 (1%) in nitrogen (99%) was produced and no oxides of nitrogen, $^{15}\text{O}_2$ or C^{15}O could be detected in the exit gas. The most common impurity was C^{15}O in this process, and this was found to be caused by reduction of the CuO in the furnace. The solution to this problem was to make sure the CuO was fully oxidized by passing pure O_2 over the CuO at 500°C for 2-3 hours prior to a run.

Iron-52 labeled ferrous citrate has been regularly scheduled for production weekly or whenever a suitable patient was available. Development work on the production of ^{123}I has now stopped since this radioisotope is available commercially in higher purity than it could be made on the SKI cyclotron. Bismuth-206 as bismuth citrate has been made several times for studies of its distribution in rats and in rats with transplanted or induced tumors (see Proposal No. 3).

Table II gives the yields of radionuclides produced so far with the SKI cyclotron. Also given are the method of production, the product chemical form and the impurities detected.

Table II

YIELDS OF RADIONUCLIDES WITH THE S.K.I. CYCLOTRON

Proposal #1
Progress Report
Page 6

Radio Nuclide	Half Life	Decay γ Energy (keV)	Target (1)	Production Reaction	Product Chemical Form	Yield at E.O.B. (2)		Impurities (%) (4)	
						$\mu\text{Ci}/\mu\text{A.h}$	mCi Achieved after 1 h (3)		
C-11	20 m	511	N ₂ (6)	p, α	HCN CO ₂	19000	300	---	
N-13	10 m	511	H ₂ O	p, α	N _x O _y (7)	20000	500	---	
O-15	2 m	511	N ₂ (6)	d,n	O ₂	4600	150	---	
F-18	110 m	511	H ₂ O	³ He,p	F-	6x10 ³	200	Negligible	
P-30	2.5 m	511,2240	Al	(α ,n)	PO ₃ - ₄	10000	10	---	
K-43	22 h	β^- , 370+	Ar(5)	⁴ He,n	K+	10	0.3	---	
Cr-48	23 h	300,120	Ti	³ He,2n	CrO ₂ - ₄	1.5	0.03	Cr-51-(25)	
Cr-51	28 d	320	V	p,n	--	340	3.4	---	
Fe-52	8 h	165	Cr	³ He,3n	Fe ²⁺	0.7	0.1	Negligible	
Ga-67	78 h	184,296	Zn	p,n	Ga ³⁺	77	3.8	(Ga-66)	
Ga-67	78 h	184,296	Zn	d,n	Ga ³⁺	30	1.5	(Zn-69m)	
Se-73	7.1 h	360	Ge	³ He,2n	SeO ₃ ²⁻ SeO ₄ ²⁻	250	5	Negligible	

Table I (continued)

Radio Nuclide	Half Life	Decay Energy γ (keV)	Target (1)	Production Reaction	Product Chemical Form	Yield at E.O.B. (2)		Impurities (%) (4)
						$\mu\text{Ci}/\mu\text{A}, \text{h}$	mCi Achieved after 1 h (3)	
Rb-81	4.7 h	190,450	NaBr	$^3\text{He}, 3n$	Rb+	35	0.3	---
Rb-82m	6.3 h	780,620	NaBr	$^3\text{He}, 2n$	Rb+	70	0.7	---
In-111	2.8 d	173,247	Cd	p,n	In $^{3+}$	150	7.5	In-114m(3)
I-121	2.0 h	210	Sb	$^3\text{He}, 3n$	I-	110	5	I-123(2)
I-123	13 h	160	$^{123}\text{Te}(77\%)$	p,n	I-	4000	20	I-124(0.7)
I-123	13 h	160	Sb	$^3\text{He}, 3n$	I-	24	1.2	I-124(5)
Cs-127	6.2 h	410,125	NaI	$^3\text{He}, 3n$	Cs+	43	0.4	---
Tm-167	9.7 d	208	Er-167 (91%)	p,n	Tm $^{3+}$	38	0.4	---
Hg-197	65 h	70	Au	p,n	Hg $^{2+}$	36	2	---
Hg-197m	24 h	135	Au	p,n	Hg $^{2+}$	23	1	---
Bi-206	6.2 d	70-1720	Pb	p,n	Bi $^{3+}$	100	5	Bi-207(0.02)

Footnotes:

- (1) Target is "thick" and of natural isotopic abundance unless otherwise indicated
- (2) E.O.B. = end of bombardment
- (3) Yields achieved in practice for a beam current that the target would withstand
- (4) As a percentage of the given radionuclide at E.O.B.
- (5) Not a thick target
- (6) For a flowing gas target
- (7) Nitrogen oxides are reduced to NH_3 with Devarda's alloy in basic solution.

3. SELENIUM-73 PRODUCTION

Interest in ^{73}Se has been in developing a method for the production of hydrogen selenide ^{73}Se from ^3He -irradiated germanium. It would then be possible to study the short-term in-vivo distribution of the selenide ion, which is not known, and to use $\text{Na}_2^{73}\text{Se}$ for the enzymatic synthesis of seleno-cysteine- ^{73}Se , as suggested by G. A. Russ of this laboratory. Therefore the ^{73}Se production methods previously developed were reexamined. The yield of ^{73}Se as a function of energy to 21 MeV was determined to enable optimization of target configuration. A technique to deposit rare earth oxides on gold foil (2) was adapted to prepare germanium oxide targets on copper backing, with only limited success. The germanium oxide, although sufficiently rugged to withstand target preparation and cyclotron set-up, flaked off during irradiation. A method of preparing metallic germanium by electro-deposition on copper internal target discs was developed. The electro-deposition of germanium from non-aqueous solutions, specifically ethylene glycol and propylene glycol containing germanium tetrachloride has been reported elsewhere (3). Apparatus was constructed (Fig. 1) to permit electroplating at elevated temperatures and at current densities over 1 Amp/cm².

Metallic germanium targets on copper backings were prepared at thicknesses of up to 11 mg Ge/cm² which withstood beam currents up to 300 μAmps without any discernible damage. The solvent extraction system previously used (4), although producing 90% yields and excellent purity involved the use of extremely hazardous materials (i.e. HF, HNO₃-HBr mixtures) and the evolution of many corrosive fumes (HF, Br₂, NO₂). Therefore an attempt was made to use a different procedure (5) involving the extraction of a cyclohexanone-chloro complex of selenium IV into chloroform from 8.5 M HCl, which was only partly successful. Further development of the procedure is planned to raise the yield from 30%. Methods of reducing the selenate-selenite mixture resulting from the solvent extraction, to selenide (Se^{2-}) have been mostly unsuccessful so far. The best obtained conversion to date is 20% of the ^{73}Se produced in the target converted to H_2^{73}Se using a stannous phosphate reducing agent (6). Current efforts on the selenium-73 work include: optimization of plating methods, including the effect of GeCl_4 concentration, current density and temperature; development of suitable apparatus for the remote solvent extraction of ^{73}Se to reduce mechanical losses and improve operational safety, refinement of the solvent extraction process to increase the yield, and development of an efficient method for the reduction of selenite to selenide.

4. THE SYNTHESIS OF CARBON-11 LABELED COMPOUNDS

OBJECTIVE

To develop synthetic methods for carbon-11 labeled compounds that are potentially useful for in-vivo visualization of organs or organ function tests associated with cancer.

a) H¹¹CN and ¹¹CO₂ Production

In our last proposal, one of our major goals was the production of high specific activity carbon-11 labeled hydrogen cyanide and carbon dioxide.

(1) H¹¹CN Production:

Carbon-11 is produced with the SKI medical cyclotron by the proton bombardment of nitrogen utilizing the nuclear reaction, $^{14}\text{N}(p,\alpha)^{11}\text{C}$. Previous experience has shown that the highest yield of H¹¹CN obtained by the direct nuclear recoil process was about 300 mCi, although it was considered a big improvement (compared with the 50 mCi amounts obtained earlier) in the sense of practical usefulness of carbon-11 for labeling work. This is still, however, not enough for the purpose of time consuming organic synthesis. Banfi et al., (7) have produced H¹⁴CN by catalytic conversion of $^{14}\text{CH}_4$ at high temperature in the presence of ammonia. Wolf et al., (1) have produced more than 1 curie of H¹¹CN by using a 25 MeV proton beam (degraded from 36 MeV) and pressurized target gas of N₂-H₂ (at about 14 atm.) followed by catalytic conversion of $^{11}\text{CH}_4$ at high temperature to H¹¹CN.

Since our medical cyclotron is able to produce only 14 MeV protons, the feasibility of production of a high yield of H¹¹CN has to be studied.

The new target consisted of an aluminum tube (60 cm long, 6 cm O.D., 5 cm I.D.) closed at one end with a water cooling unit and a head containing a window foil at the other. An inlet and an outlet for the target gas and a pressure gauge were provided. The target chamber was supported 1/2 inch from the beam tube exit window, and the two foils were cooled by jets of compressed air. A water cooled collimator was placed between the exit window and the beam pipe. The exit target gas passed through about 40 feet of copper tubing to the radio-chemistry laboratory, to a liquid nitrogen trap, saturated

with ammonia, and finally passed through a platinum catalyst to an absorber.

By careful study of the parameters involved in this process, it was found that with our small medical cyclotron, it was feasible to produce more than 1 curie quantities of $H^{11}CN$. The chosen parameters for this production were a target gas mixture of N_2 (95%) and H_2 (5%), at a pressure of 50 psig, a flow rate of 0.5 l/min., and an irradiation of 40 minutes duration at a beam current of 45 μ a. The produced radioactive gas containing $^{11}CH_4$ was saturated with ammonia and was converted to $H^{11}CN$ by Pt at about $1100^\circ C$. Gas chromatographic and chemical analysis showed that the $H^{11}CN$ obtained was of 95% or greater purity. At present, we are developing a method to eliminate NH_3 , because in certain syntheses the presence of NH_3 is not desirable.

(2) $^{11}CO_2$ Production:

Since $^{11}CO_2$ is one of the important precursors in labeling work, it is necessary to develop a method capable of producing high activities of $^{11}CO_2$.

The target and the apparatus used in this production were the same as for $H^{11}CN$ production except no ammonia was present. The copper oxide was employed here to oxidize CO and NO produced during irradiation to CO_2 and NO_2 . By the same methods mentioned in the above section optimum conditions for $^{11}CO_2$ production were determined. It was found that by using a gas mixture of N_2 (99%) and O_2 (1%), a pressure of 20 lbs. in the target, and a temperature of about $800^\circ C$ for the CuO, 0.8 to 1.0 Ci of $^{11}CO_2$ was obtained. Although the radioactive purity of $^{11}CO_2$ was better than 90% (determined by gas chromatographic and chemical methods), a reasonable amount of non-radioactive NO_2 was present in the final product. Nitrogen- ^{13}N and oxygen- ^{15}O were also produced but were not collected in the cold trap. Currently we are investigating the separation of $^{11}CO_2$ and NO_2 .

b) Valine Synthesis

The experience obtained from the Strecker Synthesis at this laboratory showed that it was necessary to find some new preparative methods suitable for labeling valine with carbon-11.

At present, two methods are under investigation.

(1) Via a lithio intermediate: this method can be expressed as follows:

Since isobutylisonitrile was not commercially available, this compound was prepared by means of the Hofmann reaction. Under the influence of benzyltriethylammonium chloride, the isobutylamine reacted in alkaline medium with dichlorocarbene followed by the elimination of HCl to form isobutylisonitrile, b.p. 114-5°C. 53% in yield.

The isonitrile reacted with n-butyllithium at about -60°C to form the lithio intermediate which was carboxylated with CO₂. The reaction mixture was acidified with HCl and was hydrolyzed to form valine. After recrystallization from hot absolute alcohol, the pure valine was identified by TLC by comparing it with a known sample of valine. The synthesis time was about 60 minutes not including the recrystallization which was rather time consuming. At present, we are trying to develop a quick and effective way of purifying the reaction products and hope to reduce the total synthesis time to less than 80 minutes. This time scale is considered acceptable in carbon-11 labeling work with the current yield of 11C production.

(c) α -Keto Acid Intermediate

Another method for amino acid synthesis is through

α -keto acid as the intermediate which is then transformed to amino acids by a transamination process either in-vivo or in-vitro.

At present, we are investigating the possibility of acid chloride reacting with cyanide followed by hydrolysis to α -keto.

(d) ^{11}C -Diphenylhydantoin and ^{11}C -Hydroxyphenylphenylhydantoin

OBJECTIVE

To synthesize ^{11}C -diphenylhydantoin and ^{11}C -hydroxyphenylphenylhydantoin as possible scanning agents for the brain, brain tumors or brain tumor metastases.

MATERIALS AND METHODS

In collaboration with Mr. S. Stavchansky and Dr. H. B. Kostenbauder of the College of Pharmacy, University of Kentucky, ^{11}C labeled diphenylhydantoin (DPH)(I), or dilantin (II) and ^{11}C labeled p-hydroxyphenylphenylhydantoin (HPPH)(IV), have been synthesized in 5-20 mCi batches from 300-1500 mCi amounts of H^{11}CN prepared by the method described in Section 4a in this Report.

Reaction scheme:

The $H^{11}CN$ was collected by bubbling through a solution of 5 ml 0.01 M NaOH plus 5 ml dimethylsulphoxide (DMSO) containing 0.001 moles (65 mg) of KCN. Benzophenone (I) dissolved in 5 ml of DMSO was added. These reactants were contained in the stainless steel base of a Parr pressure bomb shielded in a one inch thick lead pig, behind a 2 inch thick lead wall inside a radioactive fume hood. The lead pig was cooled with ice. After 45 minutes of bubbling, about 1 Curie of $H^{11}CN$ had been trapped in the bomb, the solvent volume was adjusted to ~10 ml. to replace that lost by evaporation and 4.5 g of ammonium carbonate powder was added. The bomb was sealed and transferred to a second lead pig heated in an oil bath to 130°C. After one hour, the bomb was cooled by transferring it back to the ice bath, and the top was removed. The contents of the bomb were poured into a beaker containing 15 ml of 1N NaOH. Twenty ml of ethyl ether were added, covered with a watch glass and stirred vigorously with a magnetic stirrer for 2 minutes. The ether phase containing benzophenone was removed by pipette, and the aqueous phase was acidified with concentrated HCl, when DPH- ^{11}C was precipitated as fine crystals. The precipitate was filtered through a Buchner funnel and washed with ethanol-water. Typical synthesis time was 70 minutes and the yield varied between 40 and 58% based on ^{11}C activity.

The metabolite of DPH, (hydroxyphenylphenylhydantoin) HPPH (IV) was also synthesized from $H^{11}CN$ and p-hydroxybenzophenone (III) in a similar manner.

RESULTS AND CONCLUSIONS

Our experience has shown that up to 20 mCi of ^{11}C labeled DPH and HPPH can be synthesized from the 1500 mCi quantities of $H^{11}CN$ obtainable from the cyclotron. Evaluation of these agents in rhesus monkeys (see Proposal 3, Section B-4) shows that the brain can be scanned satisfactorily after injections of 10 mCi. Thus it is feasible, for purposes of animal evaluation, to produce ^{11}C labeled DPH and HPPH with the cyclotron for use as brain scanning agents.

5. PRODUCTION OF ^{13}N -AMMONIA AND ^{13}N -AMINO ACIDS

^{13}N labeled ammonia, produced by the previously

described method (8) of irradiating methane gas flowing through a glass-lined target chamber, was found to be unsatisfactory as a substrate in the enzymatic synthesis of ^{13}N -amino acids. Inhibitors of the enzymatic reactions were also formed in the bombardment and the final yields of ^{13}N -amino acids were found to be too low to be used as scanning agents. This problem could have probably been overcome by purifying the ammonia by distillation, but the yield of $^{13}\text{NH}_3$ would be considerably lower than by the following method.

By the $^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$ reaction on H_2O and the subsequent reduction of the generated nitrites and nitrates by the action of sodium hydroxide on Devarda's alloy 150-250 mCi of $^{13}\text{NH}_3$ have been produced. A target chamber containing 30 ml H_2O was irradiated with 14 MeV protons at a beam current of 25 μamps for 30 min. At the end of the bombardment, the chamber was flushed with nitrogen gas and the irradiated H_2O was emptied into a flask containing 5 g NaOH pellets and 5 g Devarda's alloy. As the NaOH pellets dissolved in the irradiated solution, heat was generated and the base reacted vigorously with the alloy, evolving hydrogen gas and reducing the $^{13}\text{NO}_2^-$ and $^{13}\text{NO}_3^-$ to $^{13}\text{NH}_3$. The $^{13}\text{NH}_3$ produced from this reaction was carried by the nitrogen gas through a trap which prevented the NaOH solution from entering the condenser. The $^{13}\text{NH}_3$ vapor was condensed and passed through a capillary pipette into a 4 ml solution of buffer suitable for the enzymatic reaction. Within 10 min. after the end of bombardment, 80-90 percent of the generated oxides of nitrogen were reduced and distilled into solution. The distilled $^{13}\text{NH}_3$ was then immediately added to reaction mixtures containing enzyme, co-factors and the appropriate substrate to be aminated. At the end of incubation, the synthesized ^{13}N -labeled amino acid was separated from unreacted $^{13}\text{NH}_3$ by ion exchange chromatography.

Four amino acids have been synthesized. ^{13}N -Glutamine and ^{13}N -glutamic acid, in reactions catalyzed by glutamine synthetase and glutamate dehydrogenase respectively, have produced yields of 25-60 mCi in a 20 min. procedure of incubation and ion exchange separation for yields of 70-90 percent. ^{13}N -Asparagine and ^{13}N -valine have been synthesized in reactions catalyzed by asparagine synthetase and glutamate dehydrogenase, respectively, in yields of 1-5 mCi for a conversion rate of 5-15 percent. These compounds are currently being evaluated as tumor and organ scanning agents. The enzymatic reactions are shown in Figure 1 (see also Proposal #3 of this report).

FIGURE 1

ENZYMATIC REACTIONS

Although the enzymatic synthesis of several nitrogen-13 tagged amino acids can involve only the single step combination of $^{13}\text{NH}_3$ with a suitable substrate, the enzymatic nitrogen-13 tagging of more complex nitrogen containing compounds requires further steps of combination, separation, and purification which extend the time required for synthesis. The extended synthesis time combined with the 10 minute half-life of nitrogen-13 and the need for 5 to 10 mCi of purified compound at the time of injection make necessary the development of methods to safely produce and handle the maximum possible amount of nitrogen-13. Previous work (9) showed the yield of nitrogen-13 by proton bombardment of water utilizing the $^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$ reaction to be 20 mCi/ μAmp EOSB (end of a saturation bombardment), compared to the 3.5 mCi/ μAmp EOSB yield via the $^{12}\text{C}(\text{d},\text{p})^{13}\text{N}$ reaction with deuterons on methane. While the proton induced reaction yield is almost six times the deuteron reaction, the method is limited when a static (non-flowing) chamber is used. The work was initiated using the F-18 target chamber (10) but the 20 mCi/ μAmp EOSB yield decreased at beam currents in excess of 20 μAmp or when the beam was too sharply focused. The catalyst cup was replaced with a glass sight-tube. By this means it was determined that well diffused beams of less than 20 μAmp allowed the target water to remain quiescent except for an occasional small bubble. Currents over 20 μAmp or beams that were too sharply focused caused rapid bubbling to occur, coincident with a decrease in yield. The more violent the bubbling seemed to be, the lower the yield. A possible solution was to construct a chamber which would flow the water through the target sufficiently fast to rapidly remove any bubbles formed. Such a system, diagrammed in Figure 2, was constructed and successfully operated at currents up to 60 μAmps , reproducibly producing 20 mCi $^{13}\text{N}/\mu\text{Amp}$ at EOSB. Up to 875 mCi ^{13}N have been prepared with this target, but the conversion of the ^{13}N to ammonia is not yet entirely satisfactory.

Several methods of reduction have been attempted with the results shown in Table III. The primary difficulties encountered in adapting the Devarda's alloy-NaOH reduction are mechanical. The general scheme of operation involves placing measured amounts of Devarda's alloy and NaOH in a round bottom distillation flask which is connected to the target chamber by way of a solenoid valve and set up to

FIGURE 2
RECIRCULATING WATER TARGET SYSTEM

TABLE III: CONVERSION OF $^{13}\text{NO}_x$ TO $^{13}\text{NH}_3$

<u>Separation Method</u>	<u>% Yield</u>	<u>Comments</u>
Reduction with Devarda's alloy in strong NaOH	95%	Using 30 ml targets
Devarda's alloy - Strong NaOH	Up to 70%	Using 150 ml target
TiCl ₂ -Strong NaOH steam distillation	22-53%	High product volume (25 ml)

distill through a Kjeldahl bulb straight Liebig condenser into about 5 ml of aqueous solution to trap the ammonia. The target solution, after irradiation, is allowed to run down into the NaOH-Devarda's mixture. The water dissolves the NaOH and the resulting caustic solution reacts with the Devarda's alloy releasing considerable heat and nascent hydrogen. The hydrogen reacts with the nitrogen-13 oxides in the water to form ammonia which is then distilled by the released heat. However, the reaction is strongly dependent on the amounts of each constituent as well as the configuration of the apparatus. Current efforts are directed to achieving a reliable system to allow easy, routine operation with predictable yields of $^{13}\text{NH}_3$.

6. CHEMICAL FORM OF ^{13}N IN PROTON IRRADIATED WATER

Experiments were performed to determine the chemical form of the ^{13}N formed by proton irradiation of water.

(1) To test for $^{13}\text{NH}_3$ + dissolved gases, an aliquot of the water- ^{13}N was measured in a gamma ionization chamber, time noted, sodium hydroxide and ammonium hydroxide solutions were added, the solution boiled for 5 minutes, and the radioactivity measured again. After decay correction, this experiment indicated 22% of the ^{13}N was present at $^{13}\text{NH}_3$ or dissolved gases.

(2) Urea, HCl and NaNO_2 were added to an aliquot of proton irradiated water, and the solution boiled for one minute. The loss in radioactivity indicated 17% was neither NO_2^- or dissolved gases ($^{13}\text{N}_2$).

(3) To test for reducible NO_2^- or NO_3^- , the solution was boiled, Devarda's alloy and sodium hydroxide added and boiled again for 7 minutes. The loss in activity in the solution indicated 88% of the ^{13}N was NO_2^- or NO_3^- .

(4) To test for $^{13}\text{NH}_3$, carrier ammonium hydroxide was added followed by Nessler's reagent to precipitate NH_4OH . The precipitate was centrifuged, washed with water and recentrifuged. Only 3% of the activity was associated with the precipitate.

(5) To test for NO_2^- , an aliquot was measured, urea, HCl and NaNO_2 added, boiled for 5 minutes, and the residual activity measured. The decrease in radioactivity corrected for decay was 39%. Subtracting 19% for the dissolved $^{13}\text{N}_2$ content, the NO_2^- content was 20%.

Conclusion: Solution contains

3% $^{13}\text{NH}_4\text{OH}$

19% $^{13}\text{N}_2$

20% $^{13}\text{NO}_2^-$

59% $^{13}\text{NO}_3^-$

Gas chromatography qualitatively showed the presence of $^{13}\text{N}_2$ and $^{13}\text{NH}_3$.

By passing the irradiated water through Dowex-1 in either acidic or basic form, 99% of the activity was absorbed on the column. By passing the water through Dowex-50 in the acidic form 6.5% was retained and 93.5% appeared in the eluent. These experiments indicated that 6% of the ^{13}N activity was $^{13}\text{NH}_4\text{CH}$ and 94% was NO_3^- . These tests were performed only roughly and the results are approximate.

7. BISMUTH-204 CONTENT OF BISMUTH-206 PREPARATIONS

It was of interest to measure the ^{204}Bi (half-life 11.4 hours) content of ^{206}Bi (half-life 6.2 days) production runs, first to determine the length of time required to allow the ^{204}Bi produced to decay to negligible amounts relative to ^{206}Bi and second, to see if it would be feasible to produce ^{204}Bi with the SKI cyclotron. Two irradiations of natural lead (99.99% purity) with protons of energy 14.7 MeV were performed. The beam current was about 2 μA and the length of irradiation was

about one hour; the integrated beam current was accurately measured by a current integrator. The gross radioactivity of the irradiated lead target was measured in a gamma ionization chamber connected to an electrometer and a strip-chart recorder and the activity followed overnight and then for about 2 weeks to establish the 6.2 day component. The decay curve was plotted and resolved into its components both graphically and by computer analysis using a curve stripping program. The decay curve showed three components of half-lives 6.24 days (^{206}Bi), 13.45 hours (^{204}Bi) and 24.9 minutes (probably ^{11}C from oxygen impurity in the lead). The activities were $0.900 \times 10^{-11}\text{A}$ or 0.23 mCi of ^{206}Bi and $0.552 \times 10^{-11}\text{A}$ or 0.155 mCi of ^{204}Bi , at end of irradiation. Natural lead contains 1.48% of Lead-204. If we were to use 99% Lead-204 enriched isotope, the yield of Bismuth-204 would be 7.7 mCi/ μAh . The ^{206}Bi content would depend on the ^{206}Pb content of the enriched target. The present cost of 99% Lead-204 enriched isotope is \$75 per mg, and about 100 mg would be required to make an enriched target.

8. CYCLOTRON RESEARCH AND DEVELOPMENT

OBJECTIVE

To increase the beam current capability; to obtain higher production rates for radioactive nuclides and to provide an adequate neutron dose rate for therapeutic use.

RESULTS

The further development and improvement of the Sloan-Kettering cyclotron as outlined in the 1973 proposal have been carried out. Our cyclotron is now performing even better than it was a year ago in terms of external output and extraction efficiency. We have achieved the extraction of 400 μA of deuteron beam on an external target using a fast and simple procedure; thus 400 μA of deuteron beam will be routinely

available. The program is guided by the following principles:

1. Continue to improve various systems of the cyclotron to maintain high output capability.
2. Improve controllability to provide consistent beam quality for specific research programs.

The project deals mainly with the basic physical properties of this cyclotron. Effort has been concentrated on the studies of internal beam output, extraction efficiency and external beam control. These are described in the following sections.

(a) Internal Beam Development

Operation data before October 1972 show that the machine output was quite unpredictable after the ion source had been serviced. It became necessary to investigate the relationship between the uncertainty of beam output and the conditions of the ion source. Every changeable condition has been studied and a series of experiments on the angular coordinates of the ion source has been conducted. We discovered that the angle between the ion-source arc and the vertical axis of the acceleration plane plays an extremely important role. A rotation of 5 degrees would raise the He-3 beam current from 100 to 400 μ A. In other words, internal beam current is strongly dependent on this axial angle.

A remote control mechanism to rotate the axial angle has been designed, constructed, installed and refined during the past fiscal year. Using this new control system, we are able to obtain not only consistent machine performance but also much higher beam current output. For example, we have been able to accelerate 300-400 μ A of He-3 beam for the production of Fe-52, as compared to the 100-200 μ A previously obtainable. There has always been sufficient He-3 beam for the production of F-18, and an operational technique for the simultaneous production of Fe-52 and F-18 has been developed. In addition to higher He-3 ion beam output, He-4 output has also been greatly improved. About 400 μ A have been accelerated and 300 μ A has been extracted to the external target.

Aside from the large increase and excellent consistency of beam current output, the axial rotation control provides other very desirable features which did not exist in the past. It is now possible to add the cold cathode configuration Penning mode to the ion source control. The beam current can be increased or decreased within a fairly wide range by raising or lowering the arc voltage of the ion source when the Penning mode is used, or by rotating the axial control and adjusting the gas flow if the thermionic mode is used. These characteristics offer many advantageous features, namely:

1. A new method of machine operation; a constant orbit-dynamics method in which a fixed radiofrequency dee voltage is used and a constant extraction efficiency is maintained.

2. A practical method to investigate various extraction systems thoroughly and therefore the possibility to optimize extraction efficiency.

3. A feasible automatic control to stabilize beam current by the control of ion source voltage.

By the application of features (1) and (2), we have developed a simple operating procedure to extract a 400 μ A deuteron beam on target. Extraction of a 200 μ A H-3 beam is also found to be very fast and straightforward.

(b) External Beam Development

The extraction system consists of an electrostatic deflector, a set of harmonic coils and a magnetic channel. Each unit has been greatly modified and upgraded as follows:

(1) Deflector Gap Study

The gap of the electrostatic channel is now adjustable.

For a specific accelerated particle the electrostatic potential applied to the channel is directly proportional to its gap. In the case of extracting protons, 65 KV was used in the past. Very frequently, the condition of surfaces subjected to a high electric field suddenly deteriorated and the required voltage could not be maintained. Consequently, the scheduled program had to be cancelled. However, if the gap could be reduced, the required voltage could be lowered. The new system is able to do this, almost completely eliminating the deflector difficulty associated with proton operation. In fact, the use of protons for the production of ^{11}C and ^{13}N has increased substantially in the past year and both programs have been very successful.

The movable gap also eliminates the compromise between the deflector voltage for protons on the one hand, and the extraction efficiency for He-3 ions on the other. It is now possible to select a suitable deflector gap for each particle. In the case of extracting He-3 ions, about 10 to 15% improvement over the extraction efficiency is obtained. The unit also works much better than before when a high external beam is being extracted.

(2) Extraction Radius Study

Careful examination on the fall-off of the internal beam and on the outermost limit at which the accelerated beam can survive, before the sector focusing effect abruptly cuts it off, reveals that the original extraction radius set by The Cyclotron Corp. (TCC) was about 0.1 inch larger than it should be. We inferred that the original radius was again a compromise figure since a much higher deflector voltage would be needed if the septum is moved in 0.1 inch. Extraction of protons would then be impossible.

We have performed a series of experiments to search for a proper extraction radius for each particle. This parameter is the most important factor to determine the upper limit of the extraction efficiency. We also found that if a proper extraction radius is selected, efficiency is consistently high. It is this new information which enables us to

extract 400 μ A of deuteron beam with relative ease.

A mechanism to adjust the extraction radius will be given first priority in the development of a better extraction system. It has been designed and its construction is already in progress.

(3) Magnetic Channel Study

The original fixed magnetic channel has been redesigned and modified to a movable system. The new unit has a stepped-field gradient to provide a focusing effect on the emerging beam. Two motor driven systems have been added to alter the entrance and exit positions of the channel by remote control from the console. This device serves as an internal steering and focusing magnet to compensate for the difference in beam dynamics in order to achieve optimum extraction and at the same time to obtain maximum transmission of the external beam.

(4) Harmonic Coils Study

The dependance of the extraction efficiency on the rf dee voltage with respect to a pre-selected azimuthal angle θ of the harmonic coils' current distributing ring has been thoroughly studied. The results of this study indicate that for optimum extraction, θ should be varied as different particles are used and different dee voltages are applied. Modification of this system to change θ in steps by remote control from the console has been designed. Both a mechanical construction and an electronic control are being built.

CONCLUSION

High output and reproducibility for both internal and external beams have been simultaneously achieved. We believe that the SKI cyclotron is approaching its peak capability with increased beam currents and higher production rates for radioactive nuclides.

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Sloan-Kettering Institute for Cancer Research
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New York, New York 10021

TITLE OF PROJECT Biological Effects of Radiation and Related
Biochemical and Physical Studies:
Cyclotron Facility and Radionuclide Production

NAMES, DEPARTMENT, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS AND OTHER PROFESSIONAL SCIENTIFIC PERSONNEL (not including graduate students) engaged on the project, and fraction of man year devoted to the project by each person

John S. Laughlin, Ph.D., Member
Roy S. Tilbury, Ph.D., Associate
Thomas Y. T. Kuo, Ph.D., Associate
Alan S. Gelbard, Ph.D., Research Associate
C. T. Ting, Ph.D., Research Associate

NO OF GRADUATE STUDENTS ON PROJECT 0 NO OF GRADUATE STUDENT MAN YEARS

SUMMARY OF PROPOSED WORK (200-300 words, omit Confidential Data) Summaries are exchanged with government and private agencies supporting research, are supplied to investigators upon request, and may be published in AEC documents. Make summaries substantive, giving initially and for each annual revision the following: OBJECTIVE, SCIENTIFIC BACKGROUND FOR STUDY, PROPOSED PROCEDURE, TEST OBJECTS AND AGENTS

The objective of the proposed work is to develop methods of production using a small medical cyclotron (Cyclotron Corp. Model CS-15) of radionuclides, radiochemicals and radiopharmaceuticals for use in the early diagnosis of cancer. Interest is focused on the short-lived radionuclides which are not commercially available (e.g. ^{11}C , ^{13}N , ^{15}O , ^{18}F and ^{73}Se). We try to develop efficient methods for their production as simple chemical compounds and then develop methods for the synthesis of potentially useful compounds.

Results to date have included the preparation of 400 mCi batches of ^{13}N -ammonia by proton irradiation of water followed by the enzymatic synthesis of ^{13}N -labeled glutamine, glutamic acid, asparagine and valine. These are being evaluated as possible tumor, myocardial and pancreas scanning agents. Batches of up to 1.5 Curies of ^{11}C -labeled hydrogen cyanide have been prepared and up to 60 mCi batches of ^{11}C -labeled diphenylhydantoin or p-hydroxyphenylhydantoin have been made. The former is being evaluated as a brain scanning agent. Attempts are being made to produce ^{14}O , ^{15}O , and ^{19}O as molecular oxygen, carbon monoxide and carbon dioxide for studies of the "steady-state" distributions of these materials in-vivo. Attempts are being made to synthesize ^{18}F -labeled estradiol as a possible scanning agent.

RESULTS TO DATE

for the detection of breast cancer, metastases or hormone dependent tumors. Iron-52 is produced semi-routinely for erythropoietic studies and fluorine-18 is still produced routinely for bone scanning in Memorial Hospital. Technical improvements to the cyclotron have resulted in 4 times higher internal and external beams and improved extraction efficiencies.

	PROGRAM CATEGORY NO
BUDGET	
PRIMARY	
SECONDARY	

Signature of Principal Investigator

DATE

11/7/74

INVESTIGATOR

DO NOT USE THIS SPACE