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BIOLOGICAL EFFECTS OF RADIATION AND RELATED BIOCHEMICAL
AND PHYSICAL STUDIES

Proposal #4: Cyclotron Facility: Production of Radio-
nuclides, Labeled Compounds and Fast
Neutron Beams

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Compounds and Fast Neutron Beams

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1. Introduction

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 (5507).
- (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. Radionuclide Yields

Table 1 lists the yields of radionuclides obtained with the Sloan-Kettering cyclotron for various target materials and bombarding particles. The yield is expressed either as microcuries per microampere of beam current per hour of irradiation (as distinct from microcuries per microampere-hour) and as millicuries per hour under practical radiation conditions. The yields for ^{11}C , ^{13}N and ^{15}O from gaseous targets are calculated from activities per unit volume of target gas under flowing conditions of the gas. A few yields as indicated are for targets not thick enough to stop the beam completely. Chromium-48 has also been made by irradiating TiO_2 enriched to 80% in Ti-47 when the yield of Cr-48 was increased to $12\ \mu\text{Ci}/\mu\text{A}/\text{h}$ and the Cr-51 impurity was reduced to 1.3%.

300 mCi amounts of hydrogen cyanide - ^{11}C have been produced by irradiating nitrogen, 5% hydrogen mixtures with 14 MeV protons, similar to the method of Lamb et al (3). We have found a Pyrex glass tube to work as well as a quartz one but the temperature of the tube must be not less than 350°C and the oxygen content of the target gas must be a minimum (typically 10 ppm) otherwise CO_2 is produced. The HCN has been used to label red blood cells (see later) and to synthesize valin- ^{11}C and alanine- ^{11}C by a Strecker synthesis. These amino acids are currently being evaluated as possible pancreatic scanning agents. We are not currently using the following radionuclides for either animal or human studies but the yields have been measured and are given here for reference: ^{30}P , ^{43}K , ^{51}Cr , ^{81}Rb , ^{111}In , ^{121}I , ^{127}Cs , ^{197}Hg .

3. Production of ^{13}N -ammonia, ^{13}N -glutamine and ^{13}N -glutamate

As has been previously reported (4) ^{13}N labeled ammonia has been made by irradiating methane gas flowing through a glasslined target chamber. Yields of ^{13}N of 100 mCi have been obtained in solution a few minutes after a 30-minute bombardment at $30\ \mu\text{A}$ of deuterons (7 MeV).

Several studies have been made on the parameters involved in the production of $^{13}\text{NH}_3$ by deuteron irradiation of methane gas. When pure methane (Matheson U.H.P. grade) was used as target gas instead of C.P. grade, the yield of ^{13}N -ammonia was decreased by about a factor of 5 and a white colloidal precipitate was observed in the normal saline solution in the bubbler. This white colloidal precipitate could be removed by filtration through a 0.22 micron filter, and the precipitate was not radioactive. It was probably a polymeric product of methane produced by radiolysis.

On irradiating U.H.P. methane in an aluminum target chamber at various beam currents (5 to $20\ \mu\text{A}$), the yield of ammonia ^{13}N was found to increase from 20 to 75% and the yield of nitrogen - ^{13}N decreased from 78 to 0.25%. The hydrogen cyanide- ^{13}N content was consistently low (about 1%) in these runs. When nitrogen was added to U.H.P. methane over the range 50ppm to 25%

the $^{13}\text{NH}_3$ activity remained constant while the $^{13}\text{N}_2$ activity increased from 0.2% to 1000%. These results are shown in Table II. An aluminum target chamber (47 cm long, 5cm internal diameter) was filled with methane (Matheson Co. ultra high purity grade) by repeated evacuation and filling, using a mechanical vacuum pump. The evacuation and filling procedure was repeated until consistent results were obtained by gas chromatography of the irradiated gas. The gas was sampled after irradiation through a rubber septum by a lcc gas tight syringe, after filling and emptying 5 times. The walls of the syringe were wetted with concentrated ammonia solution prior to sampling which acted as carrier for the radioactive ammonia in the sampling procedure. This was not essential but helped the reproducibility of the sampling procedure and the subsequent gas analysis. The lcc sample of gas was analyzed by radio-gas chromatography using a thermal conductivity detector to measure gaseous constituents and a glass vial (10ml volume) inserted in the well of a 2x2 inch sodium iodide scintillation detector coupled to a single channel analyzer, ratemeter and dual pen recorder to measure radioactive constituents. Two columns were used; a Poropak QS 8ft x $\frac{1}{8}$ inch in stainless steel or glass, was used to detect air, NO , N_2O , NH_3 , H_2O , HCN , $\text{C}_2\text{H}_5\text{NH}_2$ and CH_3CN ; a column of molecular sieve 5A, 2ft. long, $\frac{1}{8}$ inch diameter in stainless steel tubing was used to separate oxygen and nitrogen. The results obtained showed that the $^{13}\text{NH}_3$ activity remained constant while the added nitrogen content of the methane was varied from 50ppm to 25%. The nitrogen ^{13}N content increased with the added nitrogen content. Small amounts of nitric oxide and nitrogen dioxide labeled with ^{-15}O was detected.

In similar but less extensive experiments no effect was found by adding oxygen or hydrogen. The only thing that did seem to affect the $^{13}\text{NH}_3$ yield was radiation dose in the form of increased beam current, or by narrower collimation of the beam. This leads us to the conclusion that $^{13}\text{NH}_3$ is formed as a product of hot atoms of ^{13}N extracting hydrogen atoms from methane or reacting with hydrogen atoms or molecules formed by radiolysis of CH_4 . Hydrogen is known to be the major product in the radiolysis of CH_4 with a variety of radiations (5). In routine production runs microgram amounts of ammonia have been detected by Nessler's reagent in the aqueous product solution. Presumably nitrogen impurities in the methane have reacted with hydrogen produced by radiolysis.

^{13}N labeled ammonia has been used to visualize the myocardium (6,7,8). The incorporation of $^{13}\text{NH}_3$ in the myocardium is thought to involve the amination of α -ketoglutarate to glutamate acid and then to glutamine in reactions catalyzed by glutamic dehydrogenase and glutamine synthetase respectively. Thus glutamate ^{-13}N and $^{13}\text{NH}_4^+$ would be expected to be incorporated at a faster rate than glutamine ^{-13}N . Indeed enzymatically prepared glutamine ^{-13}N has been found to concentrate in the liver, where it is probably catabolized to urea. The mechanism of myocardial concentration may be confirmed by the use of methionine sulfoximine

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

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	CO ₂ (6)	d,n	N ₂ NH ₃	3200	100	---	
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	(2n-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 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)	
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

Table II

RELATIVE YIELDS OF $^{13}\text{NH}_3$ and $^{13}\text{N}_2$ WHEN CH_4 , N_2 MIXTURES
 WERE IRRADIATED WITH DEUTERONS (7.5 MeV AT 5 μA FOR 5 MIN).

Nitrogen Content <u>X</u>	<u>Relative Activities (counts/min)</u>	
	<u>$^{13}\text{NH}_3$</u>	<u>$^{13}\text{N}_2$</u>
0	5000	100
1.25	3000	4000
2.5	2500	3000
5.0	3000	15000
7.5	2000	30000
12.5	1500	40000
25	4000	40000

Table III

Radionuclide yields on Irradiation of Germanium with
23 MeV ^3He ions

<u>Radionuclide</u>	<u>Half-life</u>	<u>Yield $\mu\text{Ci}/\mu\text{Ah}^*$ at EOB</u>
^{73}Se	7.1 h	250
^{73}Se	42 m	590
^{71}As	62 h	46
^{72}As	26 h	14
^{76}As	26.5 h	7

* Irradiated for 30 minutes at 1 μA .

Table IV

Cross sections at various energies for ^{16}O (^3He , p)
 ^{18}F reaction

Foil No.	He-3 Energy (MeV)	Cross-section (mb)		Other Work (1)	Markovitz (16)
		Run 1	Run 2		
1	19.7	115	180	90	65
2	18.6	132	212	95	70
3	17.4	153	238	100	90
4	16.2	200	332	150	100
5	14.8	288	442	200	110
6	13.4	307	460	300	120
7	11.9	5.4	94	350	180
8	10.2	0.27	0.2	400	250
9	8.3	---	---	500	300
Int ^d beam current (μAh)		0.2	0.1		

(1) Rautenbach (13)

Table V

Cross sections at various energies for the reaction
 $^{20}\text{Ne} (d, ^4\text{He}) ^{18}\text{F}$

<u>Foil No.</u>	<u>d Energy MeV</u>	<u>Cross-section (mb)</u>	
		<u>Run 1</u>	<u>Run 2</u>
1	6.49	293	374
2	6.06	277	349
3	5.61	265	337
4	5.13	238	293
5	4.62	217	255
6	3.13	181	209
7	2.38	102	140
8	1.51	54	62
9	0.32	4.1	2.2
Int ^d beam current (μAh)		1	0.1

which inhibits glutamine synthetase and may thus reduce uptake of $^{13}\text{NH}_4^+$ in the myocardium (9).

Ammonia- ^{13}N has also been made by irradiating water with protons, utilizing the nuclear reaction $^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$. The nitrate and nitrite ions formed initially are reduced to ammonia by reduction with zinc dust in sodium hydroxide solution, and "carrier-free" ammonia- ^{13}N is distilled over in a stream of nitrogen. The yield of ^{13}N is 20 mCi/ μA at saturation, and we have made 200mCi of ammonia- ^{13}N in the distillate 10 minutes after a bombardment at 40 μA for 30 minutes. We expect to be able to make 400mCi by this method. A small amount of ^{18}F (0.2%) was made by p,n reaction on ^{18}O , but this did not distill over.

4. Cyclotron Production of Selenium-73

Selenium -73 was produced by 23 MeV $^3\text{He}^{++}$ ion irradiation of solid germanium targets. 99.999% pure germanium ingot about 1 inch in diameter was sliced into pieces about 0.020 inch thick with a diamond cutting wheel. The germanium slice was attached to a copper plate by means of a steel ring and four screws. The germanium surface touching the copper plate was ground flat using fine carborundum polishing powder, and good thermal contact was achieved by means of a paste of gallium and indium. The assembled target was attached to the external irradiation position of the cyclotron, water cooled on the back surface, and irradiated in vacuo through a $\frac{1}{4}$ inch diameter collimator. The target could withstand 20 μA of beam current for two hours, and has withstood 40 μA for 15 minutes without damage to the germanium disc. Alternatively the target could be irradiated through a 0.0005 inch thick "HAVAR" foil (a stainless steel obtained from the Hamilton Precision Metals Co. 42.5% Co, 13% Ni, 20% Cr, 24.5% Fe) which separated the cyclotron vacuum system from the target. Then the surfaces of the target and the foil were cooled with an air jet.

The yields of the various radionuclides produced are shown in Table III. ^{73}mSe decays away rapidly and the arsenic radioactivities were removed during the chemical separation. A small amount of ^{75}Se was also produced in an amount of 0.3% of the ^{73}Se at time of use.

5. Chemical Separation of Selenium -73

The irradiated germanium target was dissolved in HF-HNO_3 mixture, then HNO_3 was decomposed by boiling with HCl .

Selenium was extracted from HCl-HBr solution into benzene in the form of $\text{SeOBr}_2(10)$. The radioactive selenium was back-extracted into slightly alkaline water. The details are as follows: the germanium target was separated from the copper target holder, and any Ga-In paste remaining on the target surface was dissolved in concentrated HCl, then washed with water. The germanium plate was then put in a polyethylene beaker, and 2 ml of concentrated HF and 2 ml of concentrated HNO_3 were added. Immediately after addition of these two reagents, a vigorous reaction took place and produced brown fumes of NO_2 . The reaction stopped in five minutes and the radioactivity was almost completely dissolved in the solution, while most of the germanium plate was still intact. Then 20 ml of concentrated HCl was added and the solution was transferred to a 200 ml Erlenmeyer flask. The undissolved germanium metal was not allowed to enter the flask. If the metal slipped into the flask, this interfered with the subsequent chemical separation. A four foot glass tube was connected to the opening of the flask using a rubber stopper, and the flask was heated on a hot plate. The temperature was controlled to allow the solution to boil but the top of the glass tubing remained cool. The solution produced brown fumes and took on a brown color, which gradually changed to yellow. After 15 minutes heating the flask was cooled with water. No radioactivity was lost during this refluxing. The solution was then washed twice with 20 ml of benzene which eliminated little radioactivity but was necessary for the perfection of the subsequent procedures. Two ml of concentrated HBr were added to the benzene-washed solution, and the extraction was carried out again with benzene. Most of the ^{73}Se was extracted into the first benzene fraction. If the HBr reagent had deteriorated by long storage and contained Br_2 , or if the refluxing was not performed properly, ^{73}Se was not extracted into the first fraction, but was extracted in the second or third fraction. Br_2 contamination in the HBr reagent could be eliminated by benzene washing of the reagent prior to use. The radioactivity of arsenic was not extracted into benzene but remained in the aqueous phase. Radioactive benzene fractions were combined and washed with 20 ml of concentrated HCl - concentrated HBr (10:1) twice, then with a 10 ml volume of distilled water twice. This water washing removed the small amount of arsenic contamination completely, and removed little selenium. If a larger volume of water was used, selenium was extracted into water also. ^{73}Se was then extracted into 10 ml of 2M NaOH twice. The recovery of ^{73}Se was more than 90%. The final preparation was free from germanium, when determined colorimetrically by the ammonium molybdate method. The chemical form of selenium at this stage was selenite (Se^{+4}). The solution was then heated on a hot plate and evaporated to dryness with no loss of radioactivity. If the solution was acidic the radio-

activity was lost by exaporation. Solution for injection was prepared by dissolving the residue in physiological saline and the pH was adjusted by addition of HCl.

When selenate (Se^{+6}) was needed, this was prepared by oxidizing selenite with nitric acid. Concentrated HNO_3 was added either to selenite aqueous solution in 1:1 ratio or to solid selenite. This was then evaporated to dryness by heating in a sulfuric acid bath at 135°C under an air stream. No radioactivity was lost by this procedure. Ion-exchange chromatography indicated complete chemical conversion of selenite into selenate by this processing. Sodium selenate- ^{73}Se solution suitable for injection was prepared by dissolving the solid residue in saline. The pH of the solution was neutral. When the carrier effect was examined in animal studies, nonradioactive sodium selenite or sodium selenate was added to the carrier-free ^{73}Se solutions.

The distribution of selenium-73 as selenite and selenate was studied in normal and tumor bearing mice. Various tumor types took up the radioselenium slowly and continuously in contrast to the rapid clearance of activity from most normal organs. Incorporation of selenium in association with protein and chondroitin sulphate synthesis in vivo was suggested(11).

6. The Use of $^{11}\text{CN}^-$ for Blood Labeling

Hydrogen cyanide ^{11}C has been produced in 100 mCi batches by proton irradiation of 5% hydrogen, balance nitrogen (3, 12). The $^{11}\text{CN}^-$ has been used to label red blood cells as follows. A 5 ml sample of blood is collected under sterile conditions and treated with sodium nitrite in order to oxidize hemoglobin (Fe^{2+}) to methemoglobin (Fe^{3+}). Sodium nitrite readily penetrates erythrocyte membranes without causing damage to the physiological function of the cells. Sodium nitrite is used clinically in cyanide poisoning in order to inhibit the preferential binding of cyanide with cytochrome oxidase (Fe^{3+}) of mitochondria in heart, liver and other critical organs which causes death. It is also well known as the safest vasodilator to relieve heart attack.

Methemoglobin has a large affinity for cyanide and forms cyano-methemoglobin. Radioactive ^{11}CN -1s added to the oxidized blood, and the cells are incubated at 49°C for 45 minutes. These tagged, damaged red cells are reinjected into the animal and scanning is started immediately. Preliminary animal studies have produced no adverse effects in 2 dogs and 3 rabbits. Spleens have been well visualized initially in rabbits but the activity disappeared from the spleen later. Human studies are required to evaluate the utility of this procedure.

7. Measurement of the Excitation Functions for the Reactions
 $^{20}\text{Ne}(\text{d}, ^4\text{He})^{18}\text{F}$ and $^{16}\text{O}(^3\text{He}, \text{p})^{18}\text{F}$

A cylindrical target chamber 2 inches I.D. and about 6 inches long was filled with about ten cylindrical boxes 1.9 inches O.D. and 1cm high. The tubular walls of the cylindrical boxes were made from aluminum tubing of 1/16 inch wall thickness, perforated with four holes 1/8 inch diameter. The ends of the cylindrical boxes were made by glueing 0.7 mil thick aluminum foil to the ends of the aluminum tubes. The beam end of the target chamber was sealed with a 0.5 mil thick HAVAR foil and the air was evacuated from the target chamber through a hole in its side, and neon gas was introduced to fill the target chamber to atmospheric pressure which was measured with a barometer. The temperature of the room was also noted. This experimental method of measuring cross sections of a gas was taken from a paper by Rautenbach et al. (13).

The target chamber was irradiated with 1uA of deuterons for 30 minutes and 15 minutes after the end of irradiation the boxes were removed and measured individually at 10cm from a sodium iodide crystal connected to a single channel analyzer set to measure the 511 KeV photopeak. The decay of each box containing any measurable radioactivity was followed for up to six hours and decay curves corresponding fluorine-18 plotted and extrapolated back to t_0 . The disintegration rate of ^{18}F at end of irradiation (t_0) was then calculated and hence the cross-section for its formation. The energy of the deuterons incident on each box of neon was calculated from tables of range and energy and the results are given in Table IV.

The experiment was repeated using oxygen gas and He-3 particles and the results given in Table V. It was calculated from these results that 1.4 times as much ^{18}F is obtained by irradiating neon

with deuterons than by irradiating oxygen with Helium-3 using our cyclotron. The cross section values in Table IV agree quite well with those from reference 13 over the energy range 18.9 to 11.9 MeV, but the values at low energy do not agree with reference 13 or indeed other literature determinations. This discrepancy occurs at the end of the He-3 particle track where the energy varies rapidly with depth of penetration. There are no known cross section values for the $^{20}\text{Ne}(\text{d}, ^4\text{He})^{18}\text{F}$ reaction with which to compare the present results. It is probably significant that in both Tables IV and V, i.e., for both reactions, the run giving the higher cross-section values was performed at the lower integrated beam current. These results are considered to be preliminary results only, and more experiments need to be done before we have full confidence in these measurements.

8. Miscellaneous Isotope Yields

(a) Mercury-197 and 197m

A piece of gold foil 0.006 inch thick was irradiated with 14.7 MeV protons at 2 μA for 30 min. Mercury 197 (half-life 65 hours) and Mercury-197m (half-life 24 hours) were measured to be produced at the rate of 36 and 23 microcurie/ μAh respectively. These yields are quite high and gold is an excellent target material, so that we could probably make 1.8 mCi of Au-197 and 1.1 mCi of Au-197m per hour of irradiation. It should not be difficult to separate carrier-free Hg-197 from gold. Hg-203 glutathione has been reported by Hara (15) to be a useful diagnostic scanning agent in differentiating between lung cancer and tuberculosis.

(b) Bismuth-206

The yield of bismuth-206 (half-life 6.2d) by proton irradiation of natural lead was measured to be 100 $\mu\text{Ci}/\mu\text{Ah}$. Bismuth-207 (half-life 30 years) was also produced as an impurity in a yield of 0.02%. The latter could be minimized by irradiating 99% enriched lead-206 available from Oak Ridge National Laboratory at \$600. per gram. We have developed methods to electroplate lead for suitable targets and to separate bismuth carrier-free from lead. We are able to make 10 to 15 mCi per hour of Bi-206.

Bi-206 has been reported by Flanigan et al. (14) to have a significantly higher uptake in spontaneous tumors in dogs than gallium-67, indium-111, ^{131}I -human serum albumin or ^{75}Se -selenomethionine. Bi-206 is a rather poor isotope for imaging, however, having 13 gamma-rays from 0.18 to 1.72 MeV. Bi-206 as citrate and chloride is being studied in rats by our metabolic isotope group.

9. Carbon-11 Labeled Compounds

This report is mainly concerned with the production of carbon-11 labeled hydrogen cyanide as well as the synthesis of carbon-11

labeled amino acids. It is hoped that these amino acids may be useful for in-vivo visualization of organs or organ function tests associated with cancer.

(A) $H^{11}CN$ Production:

Carbon-11 is produced with the SKI cyclotron. The target chamber involved in this production is described briefly as follows:

A quartz tube (1.5 inch diameter) with a 6mm diameter side tube as a gas inlet near one end, and a gas outlet tube at the other, was wrapped with a heating wire insulated with quartz wool and protected from breaking by covering with a metal cover. A metal head which was used to mount the foil window was mounted to the end bearing the gas inlet tube of the quartz tubing.

A gas mixture of nitrogen (99%) and hydrogen (1%) was used as the target gas. This gas passed through the chamber with a flow rate of 0.25 to 0.5 l/min. The recoil carbon-11 formed in the nuclear reaction, $^{14}N(p,\alpha)^{11}C$, reacted with the target gas to form $H^{11}CN$.

The optimum conditions for $H^{11}CN$ production were determined by varying the hole size of the collimator, target chamber temperature, gas flow rate, beam current and beam focus. It is found that under a high gas flow rate of 0.3 - 0.5 l/min., a well focused beam, a 1/2 inch diameter hole collimator and a high target chamber temperature (about 450°C), the highest yield of $H^{11}CN$ was obtained.

The gaseous components of the carbon-11 labeled reaction products were gas chromatographically analyzed and were found to be mainly methane (77.7%), carbon dioxide (2.9%) and hydrogen cyanide (19.4%).

At the present stage, about 300 mCi of carbon-11 labeled hydrogen cyanide has been obtained in a typical 50 minute irradiation with a 30 μA beam current.

(B) The Synthesis of Carbon-11 Labeled Amino Acids:

The synthesis of carbon-11 labeled amino acids can be achieved by reacting the corresponding aldehyde with carbon-11 labeled hydrogen cyanide and ammonium hydroxide to form the amino nitrile which was then hydrolyzed by acid to the amino acid, i.e.,

Two amino acids, dl-valine and dl-phenylalanine have been studied and they are described as follows:

(1) dl-Valine Synthesis.

During the period of proton irradiation, the target gas containing the $H^{11}CN$ was bubbled through a solution containing isobutyraldehyde and ammonium hydroxide at room temperature. After the irradiation, the reaction mixture was extracted with ether. The ether extract was then evaporated to dryness under reduced pressure. The resulting amino nitrile was hydrolyzed with 12 M hydrochloric acid. After the hydrolysis, the solution was evaporated to dryness in vacuo. An aqueous solution containing 1 mg of inactive dl-valine was added to act as carrier and the reaction mixture was separated and purified by salt retardation ion exchange (AG11A8, BIORAD Inc.). The radiochemical yield after making the correction for decay was 10% of the total yield of $H^{11}CN$ at E.O.B.

(2) dl-Phenylalanine Synthesis.

The method used in this process was essentially the same as the one for valine, except, instead of using isobutyraldehyde, phenylacetaldehyde was used. However, the radiochemical yield of this amino acid was only about 15 - 20% of that of valine.

(C) Evaluation of dl-Valine-1- ^{11}C as a Pancreatic Scanning Agent:

The preliminary study of dl-valine-1- ^{11}C as a pancreatic scanning agent was carried out by injecting this amino acid into rats through the tail veins. The animals were then sacrificed at various intervals and the radioactivities in liver, kidney, spleen, pancreas and blood were measured. The initial results showed that the relative retentions of pancreas reached a maximum around 20 to 30 minutes after injection. The relative retention is defined as the percentage of injected dose per gram of organ divided by the percentage of injected dose per gram of rat. The relative retentions of other organs and blood was initially a high value (about 5 minutes after injection), then gradually decreased and leveled off as the sacrifice time increased. The maximum of the relative retentions in liver was about 2 - 2.5 times higher than that of pancreas.

Results obtained from L-valine- $U-^{14}C$ and dl-valine-1- ^{14}C showed that the relative retentions of pancreas reached a peak value at about 35 minutes after injection of either of these two amino acids. This peak value was about 3 times higher than that of liver in the case of dl-valine-1- ^{14}C and 5 times higher for L-valine- $U-^{14}C$.

In the case of selenomethionine-⁷⁵Se which is currently being used as a clinical pancreatic scanning agent, the results showed that the highest relative retention of pancreas appeared at about 50 minutes after injection. The peak value of relative retention in liver was about 2 times higher than that of pancreas.

These carbon-14 results indicate that valine is probably a promising candidate as a pancreatic scanning agent (it is better than selenomethionine). These are only preliminary results and more work has to be done, especially to find the cause of the discrepancy of the carbon-11 and carbon-14 results before a definite conclusion can be drawn.

10. Neutron Production for Biological and Dosimetric Studies as Possible Therapy

The Sloan-Kettering cyclotron facility has increasingly contributed a larger portion of its effort to the production of fast neutron beams for several areas of experimental research. Average weekly usage has been about one-half of total machine time. Fast neutron beams have been produced by several reactions such as ⁹Be (He³, n), ⁹Be (d, n), ⁹Be (p, n) and ⁷Li (p, n). The external beam system has been modified in a way that targets can be placed at various positions along the beam line to obtain different target to skin distances and desired fields of exposure.

The dosimetry of fast neutron beams produced here has been carried on by the dosimetry research group. Neutron and gamma ray dose distributions have been studied using tissue equivalent ionization chamber, neutron insensitive chamber, thermoluminescent dosimeters and threshold detectors. The design and test of neutron collimator for biological and clinical irradiation have been in progress. Measurements of linear energy transfer (LET) distribution have been made in different depths in tissue like material and correlated with radiobiological experiments.

Fast neutron irradiations have been made with HeLa cells to study their radiobiology, and on pregnant rats to study the effect of fast neutrons on successive generations. In addition, the use of fast neutrons from the cyclotron for in-vivo activation analysis has been initiated.

The possibility of increasing beam current capacity to provide usable neutron dose rates for neutron therapy has been investigated. Due to the success of cyclotron improvement program, we have achieved in extracting about 200 microampere of deuteron or He³ -ions on a beryllium target and producing approximately 30 rad/min of neutron dose rate at target to skin distance of 100cm. With this dose rate available, it is feasible to establish a fast

neutron therapy program using the Sloan-Kettering cyclotron facility.

Some of the dosimetry measurements and analysis on this application are described in the paper: Compact Cyclotron Neutron Dosimetry, by J.S. Laughlin, T.R. Canada, L.D. Simpson, J.C. McDonald, T.Y.T. Kuo, and A. Mittleman, presented by invitation at the German-Austrian Roentgen Congress, April 14, 1973.

11. Cyclotron Research and Development

The first step improvement project for the Sloan-Kettering cyclotron as outlined in 1972 proposal has been completed. The program is guided by the following principles:

- (1) To restore the performance specification as demonstrated in the acceptance test.
- (2) To add better control over external beam.
- (3) To standardize the procedure of operation and establish diagnostic techniques.

Prior to the improvements described below, no more than 20 μ A (microampere) external deuteron beam was able to be obtained. In the case of He-3 we encountered unsatisfactory extraction efficiency of about 30% as well as low internal beam current. It should be pointed out that our cyclotron is now performing much better than when it was accepted in late 1967 from the manufacturer in terms of external output and extraction efficiency. Specifically speaking 120 μ A of proton, 250 μ A of deuteron and 200 μ A of He-3 external beam on target with extraction efficiency of 60% or higher have been achieved (Table VI).

The project deals principally with the basic physical properties of this compact cyclotron. Effort has been concentrated on the studies of internal beam output, extraction efficiency and external beam control.

(A) Internal beam development:

(a) Dee height adjustment

The top faces of both dees were found non-parallel to the median plane of the machine. The variation of dee height was as much as ± 0.1 inch. Consequently internal beam was subject to large amplitude of vertical oscillation and gradually decreased its magnitude when approaching the extraction radius. The beam was also hitting the lower part of the entrance of deflector thus

extraction efficiency was greatly reduced. This unevenness of dee height has been minimized to the order of ± 0.01 inch. The plane of the internal beam path has been made to coincide with the median plane. The particle beam suffers no loss during acceleration and enters deflector at correct height.

(b) Central region study

A series of twenty experiments on central region adjustment have been carried out to investigate the possibility of obtaining a higher machine output and better efficiency. The study involves adjustments of puller coordinate relative to the center of the magnet yoke, the first orbit shield coordinate relative to the same as well as the relative coordinates between puller and the first orbit shield. Puller structure and its holding mechanism have also been studied. This series of central region study proved to be very fruitful. The result of these studies reveals that the machine is capable of accelerating more than 300 μA He-3 internally. On the other hand, a result of the absolute efficiency study shows that 70 $\pm 5\%$ extraction efficiency is achievable if the central region is properly located. It is believed that our cyclotron should be able to deliver more than 200 μA of particle current on an external target.

(c) Ion source study

Although the central region study indicated that the machine output could be up to 300 μA or more, this output was not reproducible after the ion source had been serviced. The ion source's contribution to the uncertainty of output was therefore investigated. A series of experiments on the angular coordinates of the ion source's chimney were conducted. We found that the angle between its ion source arc column and the vertical axis of the acceleration plane is extremely important. A rotation of approximately 5° raises the He-3 beam current from about 100 μA to 350 μA . In other words, the internal beam current is strongly dependent on ion source arc column angle. A mechanism to rotate this angle has been installed. Since then (October 1972) about 200 μA of deuteron or He-3 on external target becomes routinely available.

(B) Absolute extraction study

A secondary internal probe has been installed just in front of the magnetic channel to measure the total extractible beam after the deflector. The term, "absolute efficiency" is defined as the ratio of the total extractible beam current to the internal beam measured at extraction radius. This absolute efficiency can be computed and used to reveal important machine characteristics. For example, if the beam width is narrow enough but absolute

Table VI
 SKI CYCLOTRON

		<u>P</u>	<u>d</u>	<u>He³</u>
External Beam Current				
a) Maximum achieved	μA	120*	250	200
b) Continual range†		0.001-100	0.001-250	0.001-200
Internal Current	μA			
Maximum available		>500	>500	350**
Extraction Efficiency	%	65 $\pm$ 5	70 $\pm$ 5	60 $\pm$ 5
Energy	MeV	14.7	7.9	23.2
Oscillator Frequency	MHz	23.75	12.70	16.68
Dee Voltage (RF)	KV	20-25	12-20	18-28
Deflector Voltage (DC)	KV	63	33	42
Ion Source Arc Current	nA	1-500	1-500	1-5000
Vacuum Pressure	mmHg	5x10 ⁻⁵	5x10 ⁻⁵	4x10 ⁻⁵

* Proton external current is limited by the power dissipation rating of the electrostatic deflector.

** Maximum internal He³ beam current is limited by the design of ion source.

† The continuously variable external beam current can be obtained by adjusting ion source arc voltage and current, dee voltage and external collimation.

efficiency is poor, we can predict that the deflector septum is deteriorated. On the other hand, if absolute efficiency is good but target efficiency is poor one can conclude that the difficulty must lie in the external system. With the aid of this secondary internal probe, we have been able to determine the optimum adjustment of central region, ion source position, harmonic coil, deflector, etc. These can be briefly described as follows:

(a) Central region:

Discussed in section (Ab)

(b) Ion source position:

Devices for ion source position controls (horizontally, radially, vertically and axially) have been modified and upgraded. Position monitoring devices have also been calibrated. With improvement of these controls, a central region which provides both optimum internal beam and highest extraction has been selected.

(c) Harmonic coils:

There exists only one control parameter over the harmonic coils prior to the improvement program, namely, the total current control. An additional parameter, which is the azimuthal angle of the current distribution ring, has been studied. As a result, approximately 20% more external beam can be extracted after an optimum angle is obtained.

(d) Electrostatic deflector:

A few experiments investigating the deflector gap and its interception radius for better extraction have been carried out. These two parameters happen to give rise to a complicated problem related to the operation of three types of particles (proton, deuteron and He-3). For example, if the gap is set suitable for He-3, it may require a much higher deflector voltage to extract protons, sometimes too high to be achievable. Or, if the gap is set right for protons, good efficiency for He-3 may be sacrificed. The same applies to the interception radius. Although this portion of the study has not yet been completed, we have succeeded in selecting a compromise configuration which allows us to obtain the forementioned performance. The quality of deflector septum material (tungsten) and the workmanship of fabrication are found to be very important for extracting high external currents. A septum of inferior material would not last more than two weeks. An arrangement has been made with the manufacturer to supply us in the future with the best septa available.

(C) External beam system modification

The original beam tube has been modified into a system which allows various control or monitoring devices to be adopted along the beam path.

Two slit systems, each of which can be used horizontally or vertically, have been installed at each end of the quadrupole magnets, so that the geometrical center can then be aligned with the external beam path. The quadrupole magnets are positioned so that we obtain:

- (1) best overlap between internal and external tuning.
- (2) best extraction condition which should not be sensitive to a certain range of adjustment of main magnet, deflector voltage, harmonic coil current or ion source position.

The target station has been converted to a movable unit. The whole station is laid on a platform with wheels on tracks which permit the station to be moved aside to give room for various neutron programs. The angle of the station can also be adjusted to match that of the center line of the external beam pipe. A beam profile monitor has been purchased from the Cyclotron Corp. and installed. This unit enables us to scan the current density distribution and the position of the external beam close to the target end. A movable Faraday cup has also been installed which is used for measuring target beam current when certain types of target are used which do not permit the target current to be accurately measured.

Sections of external beam pipe as well as those of magnetic channel have been insulated from electrical ground and from each other. Thus beam losses in various sections become measurable and methods of minimizing these losses can be derived. For the case of deuterons, current loss on the beam pipe has been dropped from about 45% to 3% of total extracted beam.

Two steering magnets, for horizontal and vertical steering, have also been installed downstream of the quadrupole magnets. With the proper beam pipe and target station alignment we already observe that the external beam is directed very much at the center of the target. The quadrupole magnets are found to have only a slight steering effect. Two steering magnets have been designed not only to compensate for this small effect but also to bring the beam through a 1/4" collimator. Using this system we have managed to direct about 50 μ A through this size of collimator or to a 0.0005 inch Havar foil target.

(D) Standard operating procedure and diagnostic technique

After all the forementioned studies were completed, it was noted that numerical settings of all control devices vary very little from run to run. It is therefore, quite feasible to set up a standard operating procedure which all our operators will follow. Experience shows that this approach works extremely well. The reproducibility of good quality beam has been excellent and no longer are operator dependent.

In the course of this improvement program, intrinsic machine properties have been studied. The immediate benefit from this investigation is that machine performance under certain operating conditions can be predicted and that if it does not function as expected the most probable cause of difficulty can be located. With the aid of the diagnostic techniques developed so far, the constancy of beam quality as well as reproducibility of operating condition have been well maintained.

Other very useful operation techniques have also been established. For example, a method of generating a few nanoamperes (10^{-3} μ A) of beam current for extra-low level irradiation has been derived. Simultaneous irradiation of external and internal targets has been achieved allowing F-18 and Fe-52 productions to be carried out at the same time. A technique of irradiating internal targets with 300 μ A He-3 particles has been successfully tested which will permit Fe-52 production to be doubled for the same time span as previously used.

12. Summary of Cyclotron Use (Jan. 1, 1972 to April 20, 1973)

<u>Description of Run</u>	<u>No. of Run</u>	<u>Beam on Time (h)</u>	<u>Use (intended use)</u>
F-18 production	130	457	Bone scanning
Fe-52 production	16	102	R.E.S. scanning
Radioactive gas	61	129	Lung function
C-11 cyanide	43	78	Amino acid synthesis Blood label
N-13 ammonia	70	120	Myocardial imaging Glutamine, Glutamate
Se-73	12	24	Animal tumor studies
Bi-206	7	20	Animal studies
I-123	7	13	Developmental
Cs-127 (NaI)	2	3	Developmental
Cs-127 (I ₂)	2	1	Developmental
Neon-F-18	10	8	Developmental
Miscellaneous isotope production	11	42	
Cr-48	16	59	Developmental
Neutron dosimetry	77	280	Neutron experiments
Rat irradiation	27	59	Genetic effects
HeLa cell irradiation	14	43	Radiobiology
Neutron activation	21	76	Activation studies
Machine development	40	130	Machine improvements

References

1. Laughlin, J.S., Mamacos, J.P. and Tilbury, R.S., Isochronous cyclotron installation for radionuclide production, Radiology, 93 2 (1969) 331.
2. Dahl, J.R., and Tilbury, R.S., The use of a compact, multi-particle cyclotron for the production of ^{52}Fe , ^{67}Ga , ^{111}In and ^{123}I for medical purposes, Int. J. Appl. Rad. Isotopes 23 (1972) 431.
3. Lamb, J.F., James, R.W. and Winchell, H.S., Recoil synthesis of high specific activity ^{11}C -cyanide, Int. J. Appl. Rad. Isotopes 22 (1971) 475-479.
4. Tilbury, R.S., Dahl, J.R., Monahan, W.G., and Laughlin, J.S., The production of ^{13}N labeled ammonia for medical use, Radiochem. Radioanal. Letters 8 6 (1971) 317-323.
5. Rudolph, P.S., "Radiolysis of Methane", in Radiation Chemistry, Vol. II, Hart, E.J. Ed. American Chemical Society, Washington, (1968).
6. Monahan, W.G., Tilbury, R.S., and Laughlin, J.S., Uptake of ^{13}N -labeled ammonia, J. Nucl. Med., 13 (1972) 274-277.
7. Harper, P.V., Lathrop, K.A., Krisek, H., et al. Clinical feasibility of myocardial imaging with $^{13}\text{NH}_3$, J. Nucl. Med. 13 (1972) 278-280.
8. Harper, P.V., Schwartz, J., Resnekov, L. et al. Clinical Myocardial imaging with ^{13}N - NH_3 , J. Nucl. Med. 13 (1972) 782-3.
9. Meister, A. et al, "Mechanism of inhibition of glutamine synthetase by methionine sulphoximine", in Mechanisms of Toxicity Aldridge, W.N. Ed. St. Martine Press, N.Y., (1971).
10. Tanaka, K., Bunseki Kagaku 18 (1969) 315. (in Japanese).
11. Hara, T., Tilbury, R.S., Freed, B.R., Woodard, H.Q., and Laughlin, J.S., Production of Se-73 in cyclotron and its uptake in tumors of mice, Int. J. Appl. Rad. Isotopes (in press).
12. Finn, R.D., Christman, D.R., Ache, H.J., and Wolf, A.P., The preparation of cyanide-C-11 for use in the synthesis of organic radiopharmaceuticals, Int. J. Appl. Rad. Isotopes, 22 (1971) 735-744.

13. Rautenbach, W.L., Steyn, J., Richards, D. and Smith, H.J., p 365-372, "Uses of cyclotrons in chemistry, metallurgy and biology", Edited by Amphlett, C.B., Butterworths, London, 1970.
14. Flanigan, C.V., Holscher, M.A., Dyer, N.C., et al., Experimental model for evaluation of tumour localizing Radiopharmaceuticals, J. Nucl. Med. 12 (1971) 355 (Abstract) and R. Benua personal communication.
15. Hara, T., et al., Scintigraphy of lung cancer using Mercury-203 pretreated with Glutathione, Nippon Kyobu Rinsho 29 (1970) p 525-31, in Japanese and English.
16. Markowitz, S.S. and Mahoney, J.D., Anal. Chem. 34 (1962) 329.
17. Laughlin, J.S., Canada, E.R., Simpson, L.D., McDonald, J.C., Kuo, T.Y.T., and Mittleman, A., Compact cyclotron neutron dosimetry, Presented at the German-Austrian Roentgen Congress, Vienna, April 12-14, 1973, (to be published).

Publications:

- Costeas, A., Woodard, H.Q., and Laughlin, J.S., Comparative kinetics of calcium and fluoride in rabbit bone, Radiat. Res. 46: 317-333, 1971.
- Chandra, R., Braunstein, P., Thieu, A., and Tilbury, R.S., Production of ^{167}Tm for Medical use, Int. Journal Appl. Rad. Isotopes 23: 553-556, 1972.
- Dahl, J.R., and Tilbury, R.S., The use of a multi-particle cyclotron for the production of ^{52}Fe , ^{67}Ga , ^{111}In and ^{123}I for medical purposes, Int. Journal Appl. Rad. Isotopes 23: 431-437, 1972.
- Hara, L., Tilbury, R.S., Freed, B.R., Woodard, H.Q., and Laughlin, J.S., Production of Se-73 in cyclotron and its uptake in tumors of mice, International Journal of Applied Rad. and Isotopes (In Press).
- Hoop, B., Laughlin, J.S., and Tilbury, R.S., Cyclotrons in Nuclear Medicine, chapter 12 of Instrumentation in Nuclear Medicine, Vol. II, edited by Hine, G.J., and Sorensen, J.A., Academic Press, 1973 (In Press).
- Monahan, W.G., Tilbury, R.S., and Laughlin, J.S., Uptake of ^{13}N -labeled ammonia, Journal of Nuclear Med. 13: 274-277, 1972.
- Tilbury, R.S., Dahl, J.R., Monahan, W.G., and Laughlin, J.S., Production of ^{13}N -labeled ammonia for medical use, Radiochem. Radioanal Letters 8: 317-323, 1971.

Abstracts, Conferences, Lectures and Symposia:

- Djordjevic, B., Kim, S.H., Fried, J., and Laughlin, J.S., Oxygen enhancement ratio in HeLa cells irradiated with cyclotron generated neutrons, Radiat. Res. 51: 451-452, 1972.
- Frascino, J.A., Freed, B.R., and Woodard, H.Q., Fluorine-18 in the acutely uremic rat, Presented at the Meeting of the Radiation Research Society, St. Louis, Mo., April 28-May 3, Abstract CE-10.
- Gelbard, A.S., Hara, T., Tilbury, R.S., and Laughlin, J.S., Recent Aspects of Cyclotron Production of Medically Useful Isotopes, I.A.E.A. Symposium No. SM-171, paper No. 93, Copenhagen, Symposium on New Developments in Radiopharmaceuticals and Labeled Compounds, presented March 26-30, 1973.
- Laughlin, J.S., Tilbury, R.S., Monahan, W.G., Benua, B., LaMonte, C., Dwyer, A., and Woodard, H.Q., Metabolic studies with short-lived radionuclides and their production with positive ions and neutrons.
- Mayer, K., Maughan, E., Clarke, L., Mason, M., Knapper, W., Tilbury, R., and Laughlin, J.S., Diagnosis of erythroid metaplasia by absolute assay of splenic ^{52}Fe . Annual Meeting of Society of Nuclear Medicine, June 1973.