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PROGRESS REPORT

TO

THE UNITED STATES ATOMIC ENERGY COMMISSION

CONTRACT AT(30-1)910

BIOLOGICAL EFFECTS OF RADIATION AND RELATED BIOCHEMICAL AND PHYSICAL STUDIES

Proposal #4: Cyclotron Facility and Radionuclide Production

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CYCLOTRON FACILITY AND RADIONUCLIDE PRODUCTION

Summary

1. Design of the cyclotron facility, including a small radiochemical laboratory was completed.

2. Construction of facility and assembly of cyclotron was completed.

3. Beam current and particle energy measurements were made at the cyclotron manufacturers plant in Berkeley and at Sloan-Kettering Institute (SKI).

4. A Safety Manual for the Cyclotron Facility was prepared.

5. A report describing the facility and the Radiopharmaceutical Preparation Procedures was prepared. This report outlines the procedures which will be followed in the preparation of sterile, pyrogen-free radiopharmaceuticals for human use. In particular, the nuclear characteristics, method of production, chemical and radionuclide purity, sterility and pyrogen testing, and pharmacological evaluation for sodium fluoride (F-18), potassium borofluoride ($KB^{18}F_4$), ferrous citrate (Fe-52), sodium iodide (I-123) and radioactive gas $^{15}O_2$, $C^{15}O$, $C^{15}O_2$, ^{11}CO, $^{11}CO_2$, and $^{13}N_2$ were discussed.

6. Gamma and neutron survey measurements at the facility were carried out before the acceptance tests were run.

7. The target system was completely specified, and is designed to enable solid, liquid or gaseous targets to be irradiated. Particular attention was paid to ease of target change and flexibility of target-choice. When completed, this system will also enable the absolute beam current, particle energy, beam size, position and particle distribution (profile) to be measured and monitored.

8. A liquid target chamber for irradiation of any non-corrosive, non-reactive liquid (in particular water for F-18 production) was designed and built.

9. A gas target chamber for the production of short-lived radioactive gases, e.g., $^{15}O_2$ was designed and built.

10. A solid target chamber was designed and built. This chamber was designed so that it can also be used to produce fast neutrons for neutron dosimetry studies.

11. A scattering chamber, to measure particle beam energy, was designed and built.

12. The method which we will employ to produce sodium fluoride (F-18) suitable for human use was developed. The solutions from 10 production runs have been tested for sterility, pyrogenicity and radiochemical purity, and have been shown to be suitable for human use. The development of this material is now complete.

13. A method is being developed to produce Fe-52 radiopharmaceuticals suitable for human use. Work on this is being continued.

14. An apparatus has been designed and is now being constructed to produce the following radioactive gases: $^{15}O_2$, $C^{15}O$, $C^{15}O_2$, $^{13}N_2$, $^{11}CO_2$.

15. A series of experiments have been performed to measure the yields of I-121, I-123 and I-124, using antimony targets and He-3 particles. This work is being continued.

16. A method is being developed for the rapid separation and purification of cyclotron irradiated thymidine and other organic compounds.

The SKI Cyclotron Facility

A facility to house a small cyclotron was designed. Construction of this facility, including assembly and testing of the cyclotron, was completed by November 15, 1967.

The model CS-15 cyclotron which has been installed in the sub-basement of the Kettering Laboratory of the Sloan-Kettering Institute is an isochronous, azimuthally varying field particle accelerator of modern design, also known as a sector-focused cyclotron. It was manufactured by The Cyclotron Corporation of Berkeley, California, and is described in references (1,2, and 3). It produces fixed energy external beams of protons with an energy of 14 Mev, deutrons with an energy of 8 Mev, He-3 ions with an energy of 23 Mev or alpha-particles with an energy of 15 Mev. The external beam currents for the four beam particles is in excess of 50 microamperes (μa). With suitable targets, it can produce neutrons ranging from a few Kev to over 30 Mev. A summary of the cyclotron operational values is given in Table I.

1. Description of the Cyclotron Room and Associated Laboratories

Room SC-1 in the sub-basement of the SKI Kettering Laboratory consists of a suite which houses the cyclotron, associated radiochemistry laboratory, control room and a counting room for the identification and calibration of the radionuclides produced.

a. Cyclotron Room. The physical layout for the cyclotron is shown in Figures 1 and 2. The accelerator room itself is approximately 30 feet below the street level. Shielding wall thicknesses vary from 4 to 6 feet of concrete as indicated. Further local shielding can be added to the cyclotron if, and as, required.

b. Radiochemistry Laboratory. The radiochemistry laboratory measures 18' x 13'6", and is used for carrying out the radiochemical procedures necessary to separate the desired radionuclides from the target matrix and contaminants. Two fume hoods have been provided. The smaller hood is used for development work in connection with the radiochemical separation of radionuclides. The larger fume hood, which is used for the routine production of radionuclides after

TABLE I

Summary of Measured SKI Cyclotron
Operational Parameters

Accelerated Particles	Beam Energy Mev	Beam Intensity μa	Internal Beam μa
Protons	14	60	100
Deuterons	8	60	125
He-3 Particles	23	55	120
Alpha Particles	15	>50	≈100

Beam Divergence (all particles)		0.05 Radians
Beam Energy Resolution (all particles)		0.5%
Beam Diameter (at target position)		Variable
Extraction Radius		13.5 Inches
Pole Diameter		30 Inches
Magnetic Field Strength (average)		16.5 Kilogauss
Operating Frequency:	Protons	25 MHz
	Deuterons	16.7 MHz
	Helium-3	12.5 MHz
	Alpha-Particles	16.7 MHz

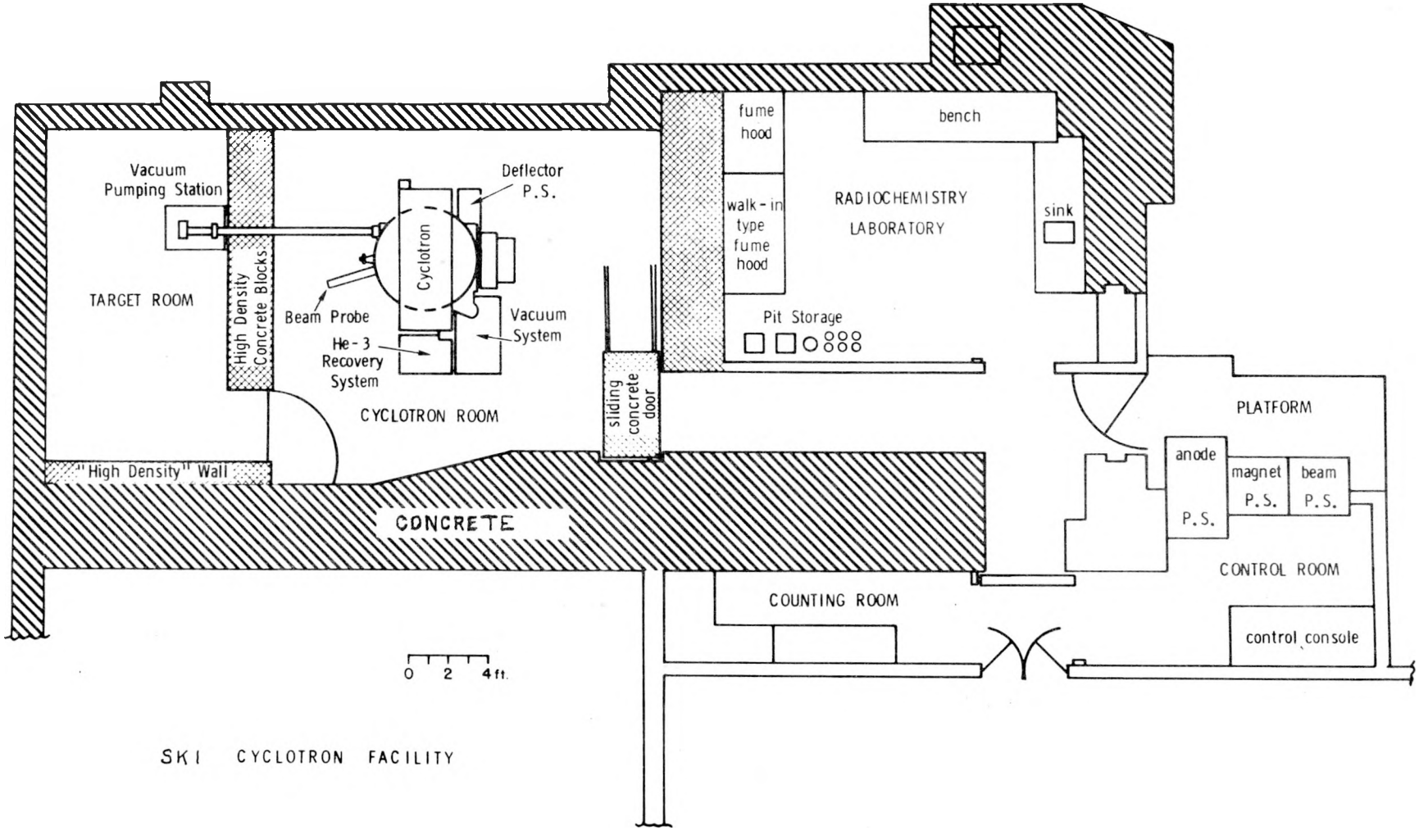

Vacuum
Pumping Station
Deflector
P.S.
Cyclotron
TARGET ROOM
High Density
Concrete Blocks
Beam Probe
He-3
Recovery
System
Vacuum
System
CYCLOTRON ROOM
sliding
concrete
door
fume
hood
bench
walk-in
type
fume
hood
RADIOCHEMISTRY
LABORATORY
sink
Pit Storage
PLATFORM
anode
P.S.
magnet
P.S.
beam
P.S.
CONTROL ROOM
"High Density" Wall
CONCRETE
COUNTING ROOM
control console
0 2 4ft.
SKI CYCLOTRON FACILITY

Figure I

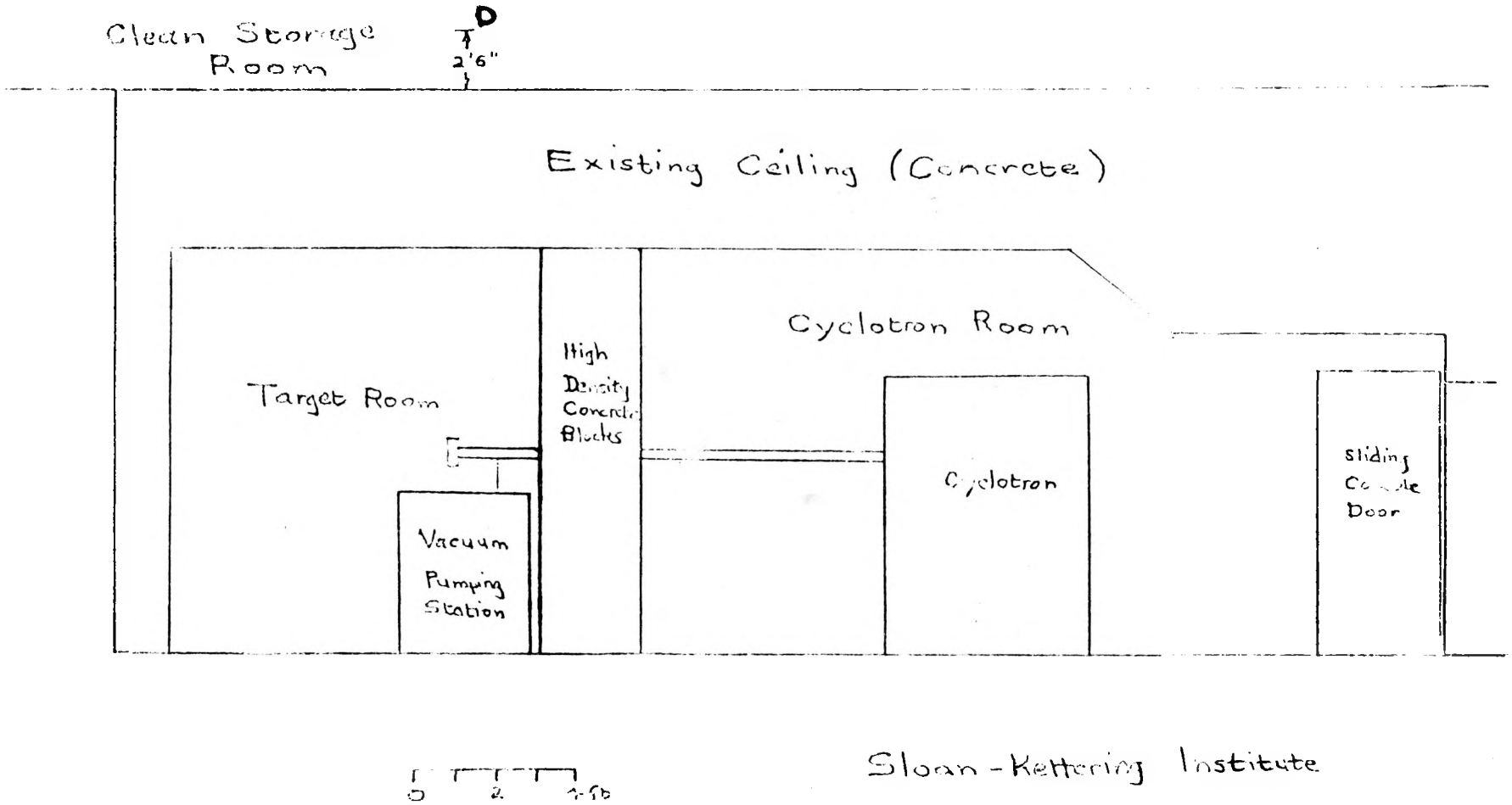

Clean Storage Room
D
2'6"
Existing Ceiling (Concrete)
Target Room
High Density Concrete Blocks
Cyclotron Room
Cyclotron
Sliding Door
Vacuum Pumping Station
Sloan-Kettering Institute
Cyclotron facility
Elevation

Figure 2

the development work has been completed, is of the "walk-in" type. The shielding, lead-glass, glassware, apparatus, etc. are set up on mobile carts, one to each procedure, and wheeled into the fume hood and "plugged-in" to the services as required.

c. Control Room. A control room houses the control console and cyclotron power supply units. A trench in the floor connects the control room with the cyclotron room, thus permitting signal cables and electrical conductors from the power supplies, control console etc. to be installed.

d. Counting Room. The counting room measures 16' x 5' and houses the calibration and scintillation spectrometry equipment. The radionuclides are identified, checked for radiochemical purity and calibrated in this area.

2. Cyclotron Operation and Characteristics

The cyclotron components arrived at SKI in June, 1967, and assembly and testing was completed by November, 1967.

Particle energy and external beam current measurements for protons, deuterons and He-3 were performed at the Cyclotron Corporation plant in Berkeley, California, prior to delivery of the cyclotron, and also at SKI after completion of assembly. The results of these measurements are shown in Table II. Full details, including graphical records of beam currents and equipment linearity and checks, are recorded in our cyclotron log book.

Beam Current

Although the contract stipulated one-hour runs for the beam current tests for protons, deuterons, and He-3, The Cyclotron Corporation agreed to extend these tests for 7 hours for each of the particles. The guaranteed beam currents can readily be exceeded, and during the course of the 7 hour runs were maintained at a value of 10% to 20% greater than the specified guaranteed values.

The beam current was measured at the external target end of the drift tube using a deep Faraday cup. The Faraday cup employed is illustrated diagrammatically in Figure 3.

The suppressor ring was maintained at a potential of +500 volts in order to prevent the escape of secondary electrons from the cup which would lead to a spurious increase in beam current. Tests indicated that this value of potential is sufficient to suppress escape of secondary electrons in the cup used. This is also shown in Figure 3.

Beam Energy

A scattering method was employed for the beam energy measurement (4). The apparatus is shown diagrammatically in Figure 4. The particle beams were elastically scattered by a thin (88×10^{-2} mg/cm^2) gold foil through 90°, and the scattered particles were detected with a 1.5 mm surface barrier detector

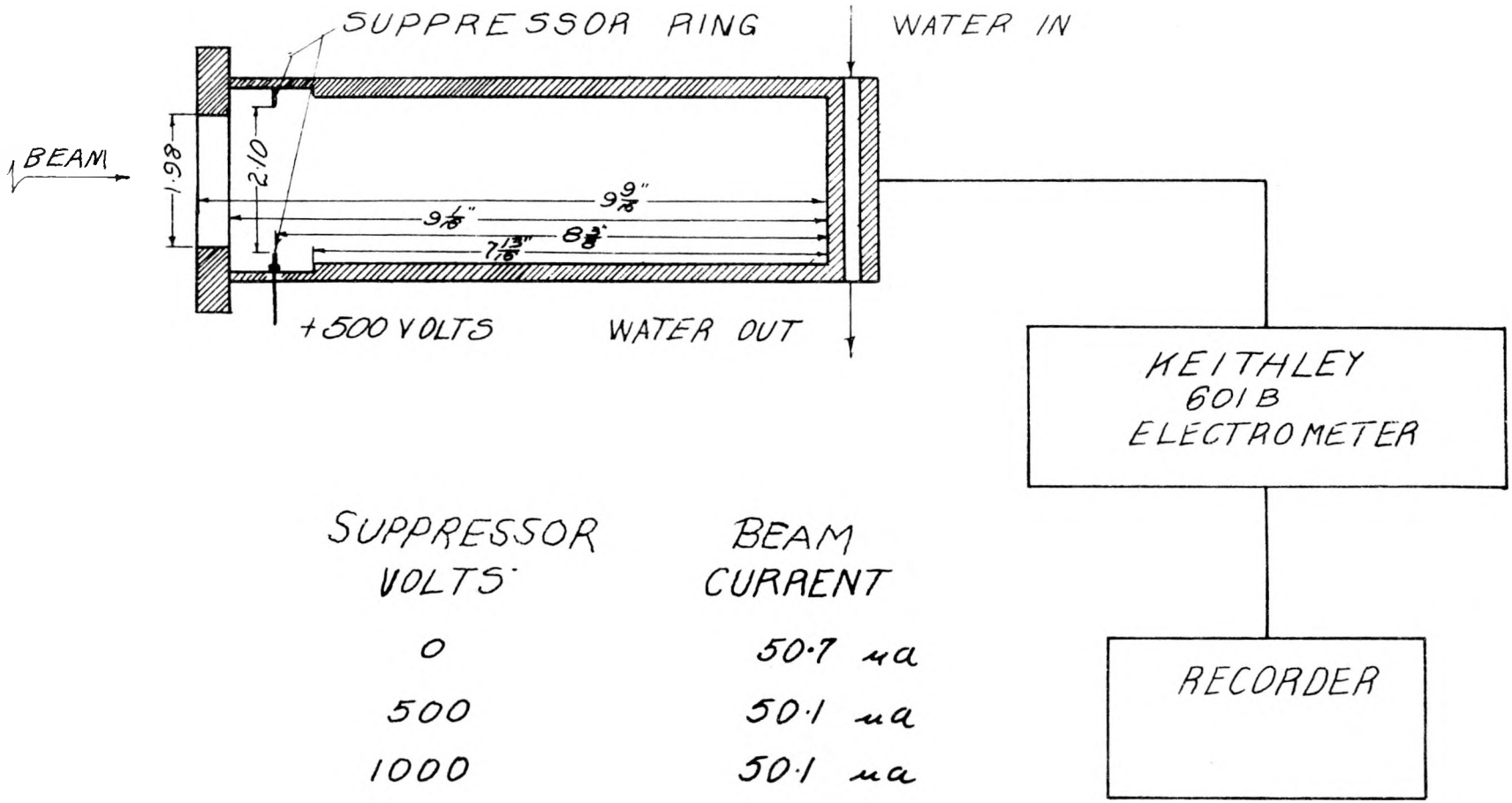
TABLE II

Cyclotron Operational Characteristics

Particles	Site	Date	Measurement	Guaranteed Value	Measured Value
protons	TCC*	5/10/67	Beam Current	50 μa	∿52 μa
		5/10/67	Energy		
			no absorber(2)**	15 Mev	14.2 Mev
			absorber(1)		14.2 Mev
	SKI*	11/10/67	Beam Current	50 μa	∿55 μa
		11/11/67	Energy		
			no absorber(1)	15 Mev	14.7 Mev
			absorber(1)	15 Mev	14.0 Mev
		11/15/67	Energy		
			no absorber(3)	15 Mev	14.7 Mev
			absorber(3)	15 Mev	14.0 Mev
deuterons	TCC	5/10/67	Beam Current	50 μa	∿ 52 μa
		5/9/67	Energy (2)	7.5 Mev	8.0 Mev
	SKI	11/13/67	Beam Current	50 μa	∿60 μa
		11/11/67	Energy (3)	7.5 Mev	7.9 Mev
		11/14/67	Energy (3)	7.5 Mev	7.9 Mev
He-3	TCC	5/12/67	Beam Current		
		5/11/67	Energy (1)	20. Mev	20.1 Mev
	SKI	11/14/67	Beam Current	50	∿55 μa
		11/14/67	Energy (3)	20 Mev	23.2 Mev

*TCC - The Cyclotron Corporation
SKI - Sloan-Kettering Institute

**The figures in brackets indicate the number of determinations made.



SUPPRESSOR VOLTS	BEAM CURRENT
0	50.7 μa
500	50.1 μa
1000	50.1 μa

BEAM CURRENT MEASUREMENT APPARATUS

Figure 3

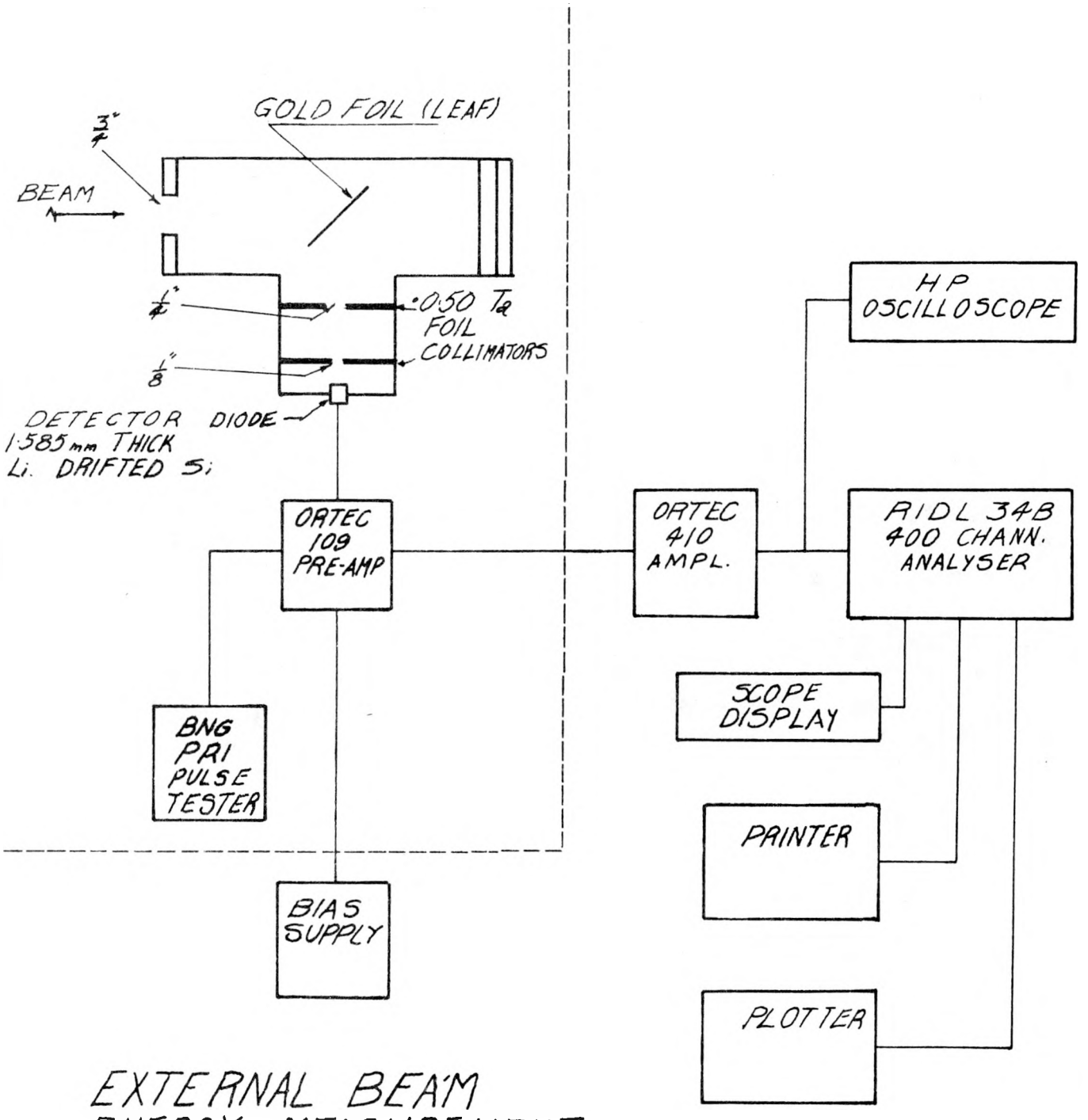

GOLD FOIL (LEAF)
3"
BEAM
.050 Ta FOIL
COLLIMATORS
1/8"
DETECTOR DIODE
1.585 mm THICK
Li. DRIFTED Si
HP OSCILLOSCOPE
ORTEC 109 PRE-AMP
ORTEC 410 AMPL.
RIDL 34B 400 CHANN. ANALYSER
SCOPE DISPLAY
BNG PRI PULSE TESTER
PRINTER
BIAS SUPPLY
PLOTTER
EXTERNAL BEAM ENERGY MEASUREMENT-SCATTERING APPARATUS

Figure 4

and also a 2 mm thick Li-drifted semiconductor detector and multichannel pulse height analyzer. The reason for scattering the beam rather than using the direct beam is that for a particle beam of 1-50 μa, the particle flux of about 6×10^{12} to 3×10^{4} particles/sec. is too great to be counted directly by a semiconductor detector. The particle flux scattered at 90°, and incidence on the detector was of the order of approximately 10^{3} particles/sec.

A correction of 1% for the protons, 2% for the deuterons and 3% for the He-3 particles was made to account for the energy loss for a scattering angle of 90° due to the single elastic Rutherford scattering.

The linearity of the system was checked with a pulse generator whose output was fed into the charge sensitive pre-amplifier both before and after each measurement calibration of the system was performed using 5.477 Mev alpha particles from AM-241.

In addition, the proton particle energy was also measured by degrading the beam to about 5 Mev with a 210 mg/cm^2 aluminum foil and using range-energy tables to obtain the undegraded proton particle energy.

Long-term Performance

In general, the cyclotron has been operating reliably, and a steady external beam of 20 μa or less can be obtained quickly and reliably. However, two components, the deflector and ion source, gave some trouble at high beam currents during prolonged use.

(1) Deflector: During the course of testing, it was found necessary to modify the original design of the septum and deflector assembly to provide for water cooling of the deflector. Concurrently, the high voltage transformer and feed through component were modified.

The reason for modifying this assembly is that while it is normally possible to extract between 45% to 60% of the external beam, about 40 μa - 60 μa of the beam is stopped by the deflector when an external beam of 50 μa or more is obtained. Without water cooling, this energy dumped on the deflector and septum was sufficient to cause some melting of the deflector so that the component lost its ability to hold high voltage of about 40 kv.

The modification to provide for water cooling was done by the manufacturer prior to the final acceptance tests, and no further problems with this component have been encountered since then.

(2) Ion Source: The source operates as a P.I.G. source at external beam currents less than about 15 to 20 μa, i.e., electrons are furnished by secondary emission from the low pressure gas. As the gas pressure is increased, the current increases, the cathodes heat up and begin to supply electrons by secondary emission.

The ion source operated reliably during the acceptance tests, but has proved to be troublesome since then. Originally, teflon insulators were used to

insulate the voltage leads but because of the small spacings within the source, the surface electrical resistance should decrease sufficiently, if degassing occurred on initially switching to the high beam current mode, so that an arc would be maintained across the teflon insulators causing breakdown of the insulators. We replaced the teflon insulators with boron nitride insulators, and this has proved to be satisfactory.

However, the cooling of the anode or chimney holding blocks was found to be insufficient for satisfactory trouble free performance. The ion source has been modified by the manufacturer and has now been replaced. The manufacturer reports that this modified source has run reliably for over 100 hours at high beam currents with little or no cathode wear.

At this time (July 15, 1968), this modified source has not been run in our cyclotron, but judging by the modifications made, it is expected to be reliable.

3. Survey Measurements

The physical layout for the cyclotron is shown in Figures 1 and 2. The cyclotron room is approximately 30' below the street level, and the external beam is directed toward solid rock. Shielding wall thicknesses vary from 4 to 5 feet of concrete as indicated. The walls are constructed of concrete of about 145 lbs/cu. ft. and also higher density solid wall or blocks of 200 to 220 lbs/cu. ft. magnetite concrete. The concrete sliding door is also of this higher density mix, the composition being as given by Aronson and Klahr (5). In addition, provision has been made for using local shielding around the target and the cyclotron itself should this subsequently prove to be necessary.

The principal protection problem arises when fast neutrons are intentionally produced by bombarding a beryllium or lithium target with an external beam current of 50 μa of He-3 particles. For normal radionuclide production, the neutron flux is an order of magnitude lower than this worst case with a lower neutron energy.

The shielding estimates were therefore based on this worst case without considering any additional local shielding around the target.

For He-3 bombarding a beryllium target, the fast neutron flux 10 cm forward of the target for a 50 μa external beam has been stated to be 2×10^{10} neutrons/cm^2/sec with a maximum energy of 28.5 Mev (6).

In order to allow for neutrons which collide with the shielding material but nevertheless escape and contribute to the dose, all neutrons were counted as if they were monoenergetic and of the maximum energy. This further results in a conservative estimate of the shielding thickness required (7).

A gamma and neutron survey was carried out when the cyclotron was first turned on during installation, using a Victoreen (Jordan) Radgun model AGB-10HG-SR for gamma dose rate measurements. A Texas Nuclear "Nemosphere" neutron dosimeter model 9140 was used for neutron dose; this instrument provides

a close approximation of total body neutron dose in the range of thermal to 10 Mev neutrons. The results are shown in Table III. The lettering in the first column refers to the measurement positions which are shown in Figures 1 and 2.

A He-3 beam of 10 μa stopped by a copper target plate was used. Background has been subtracted.

4. Cyclotron Target Design

A system has been designed to provide the capability of bombarding targets in any of the three basic states of matter; solid, liquid or gas. The system has been designed to allow:

1. rapid and easy change of targets,

2. electrical insulation of the target and holder from ground so that the assembly may be used as a Faraday cup for monitoring the relative beam intensity and

3. flexibility of target choice.

The system is conceived as three sets of components, with components of each set interchangeable when a given component in one set serves the same function in another set. Any set may be attached to the cyclotron beam tube by a Marman coupling selected as suitable for almost all uses of the external beam.

The first set is the liquid target holder, designed specifically for use in the production of F-18, but suitable for many non-corrosive or non-reactive liquids. The second set is the gaseous target holder, designed for the production of the labeled gases (e.g. $C^{11}O$, CO^{15}, ^{13}N) but suitable for use with any non-reactive gas. The third set is the holder for solid targets. This target holder not only enables the irradiation of targets in the form of solid discs and foils for isotope production, but is designed to allow the irradiation of target material to provide a fast neutron flux behind the target holder for neutron dosimetry and other experiments using neutrons.

The entire system is described in detail by drawings C-014 through C-024, and drawing C-032, which are on file.

Liquid Target Chamber (F-18)

The target chamber for liquids was designed specifically to contain water for the production of F-18 by the reaction ^{16}O (^{3}He, n)^{18}F, but may be used for the irradiation of any non-corrosive, non-reactive liquid. The target chamber shown in Figure 5 consists of a titanium target plate (item 6) to contain water for irradiation. A titanium catalyst cup (item 1) is fitted to the top of the chamber. Catalyst pellets in the form of palladium deposited on Al_2O_3 are supported on a perforated titanium disc (item 4) in the catalyst

TABLE III

Cyclotron Facility Radiation Survey

Measurement Position	Gamma dose (Radgun) mR/hr	Neutron dose (Nemosphere) nrem/hr
A: Radiochemistry laboratory	0.05	0.1
B: Sliding door	5	5
C: Passageway	0.13	0.02
D: Clean storage room (above target)	0.05	0.06

At the time of this report, the cyclotron has been used for developing the radiochemistry procedures described in other sections of this report, and high beam irradiation was not necessary since only small amounts (μCi to a few mCi) of activity were required. It is planned to carry out radiation surveys at full beam currents for all particle beams available using various target materials.

Figure 5

Liquid Target Chamber

LEGEND

Item No.	Description	Material
1	Catalyst cup	Titanium
2	Catalyst cup cover	Titanium
3	Catalyst cup cap	Titanium
4	Catalyst support	Titanium
5	End plate	Aluminum
6	Target plate	Titanium
7	Insulating spacer	Rag-filled bakelite
8	Mounting plate	Aluminum
9	Solution removal port	Titanium

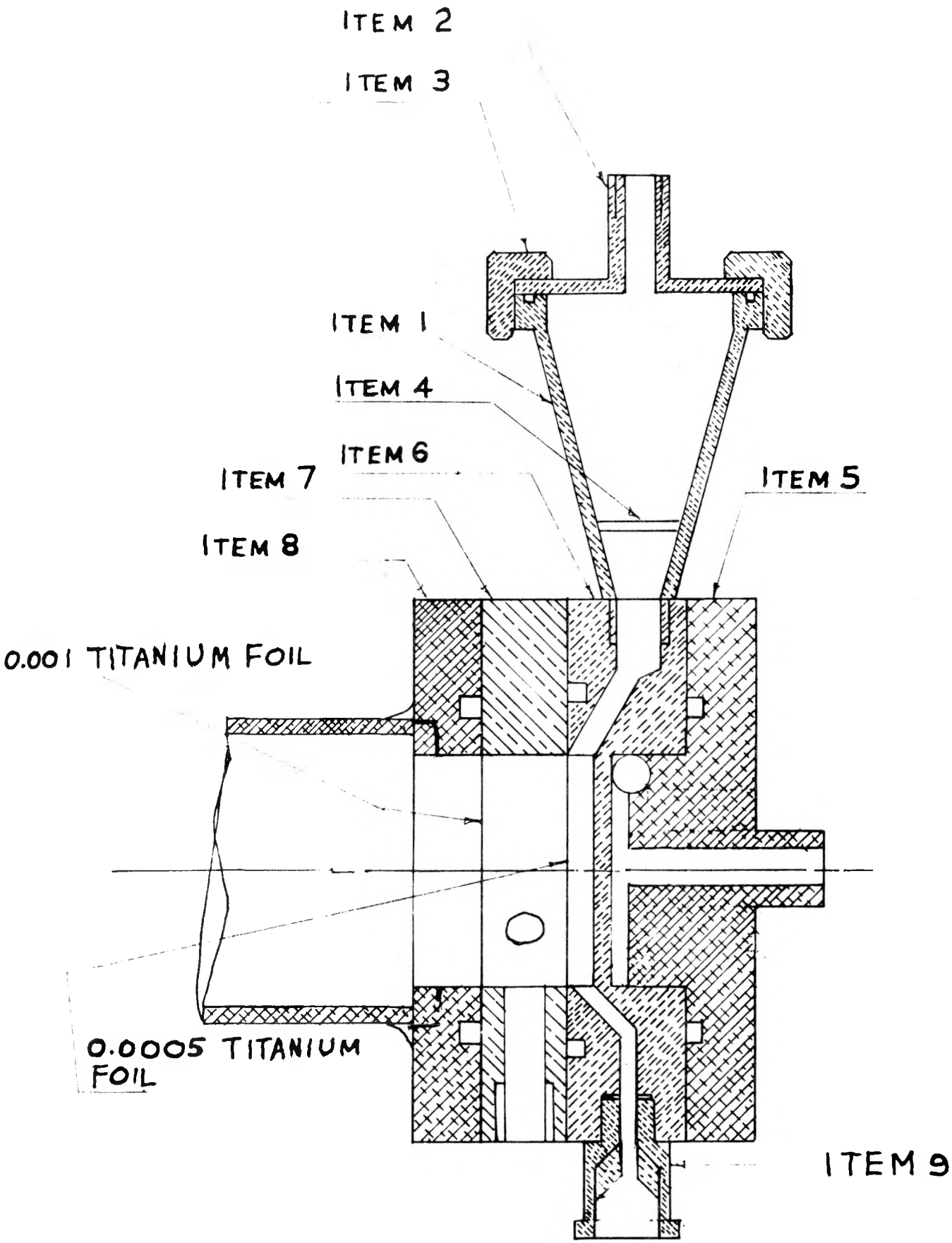

ITEM 2
ITEM 3
ITEM 1
ITEM 4
ITEM 6
ITEM 7
ITEM 5
ITEM 8
0.001 TITANIUM FOIL
0.0005 TITANIUM FOIL
ITEM 9

Figure 5

cup which is closed by a titanium cover (item 2) held in place by a titanium cap (item 3). The catalyst aids the recombination of the H_2 and O_2 produced by radiolytic decomposition during irradiation. It is estimated that about 100 ml at normal temperature and pressure of hydrogen and oxygen is produced per minute of irradiation at a beam current of 50 μA. A solution withdrawal port (item 9) is fitted to the titanium target plate, and closed with a rubber septum held in place by an aluminum crimp seal. The target water compartment is closed to the beam side by a 0.005" titanium foil which is held between a 2½" ID x 1/8" O-ring of viton rubber, which is located in a groove in the titanium target plate, and an insulating spacer (item 7). This foil retains the target liquid in the target chamber. A second titanium foil, 0.001" thick is held on the other side of the insulating spacer between the insulating spacer and an O- ring held in a groove on the bolted flange of the radioisotope target chamber flange tube (item 8). The entire assembly (except the catalyst cup assembly and solution withdrawal port) is held together by size ¼ x 3" mild steel bolts. A hose coupling mounting plate (not shown) is bolted to the target cooling plate (item 5). The target cooling plate is fastened to the back of the target plate, and sealed with an O-ring. In use, the cooling water is intended to pass in the rear of the target cooling plate and out through the two holes tangential to the back of the cooling chamber. The entire target chamber is insulated from ground by the insulating spacer and insulating sleeves around each bolt as they pass through the target chamber flange tube. The two titanium foils are cooled by passing gas, preferably helium, between the foils.

All cooling connections are made at the hose coupling mounting plate, on which the plug portion of the hansen quick disconnect fittings are attached. The water outlet connection on the hose coupling mounting plate is connected to the water inlet on the back of the hose coupling mounting plate by a length of 3/8 ID x 1/2 ID polypropylene tubing which connects from the Swagelok connector on the back of the hose coupling mounting plate to a Swagelok female connector, which attaches to the 1/4" male pipe thread on the back of the target cooling plate. After passing through the cooling chamber, the cooling water exits through the two tangential holes which are each fitted with Swagelok titanium male connectors. The target chamber is mounted on the cyclotron beam tube by attaching the Marman type flange of the radioisotope target chamber flange tube to the similar flange on the beam tube flange adapter. A captive O-ring, is used to seal the joint. A Marman flange retaining ring is used to secure the flange.

A pressure transducer, to measure the pressure, model PHF, BLH Electronics Inc., Waltham, Massachusetts, is connected to item 2, together with a pressure relief valve.

Gas Target Chamber

The target chamber for gases is shown in Figure 6 and consists of three basic components: 1) an end piece which contains a beam stopper of graphite or other material, 2) a series of gas target chambers which vary in length from 3 to 27 inches, each of which has a gas inlet and gas outlet port, and 3) a Marman flange adapter, which enables the target chamber to be attached to the end of the beam tube. These three parts are held together by bolted

TARGET CHAMBERS FOR IRRADITION OF GASES

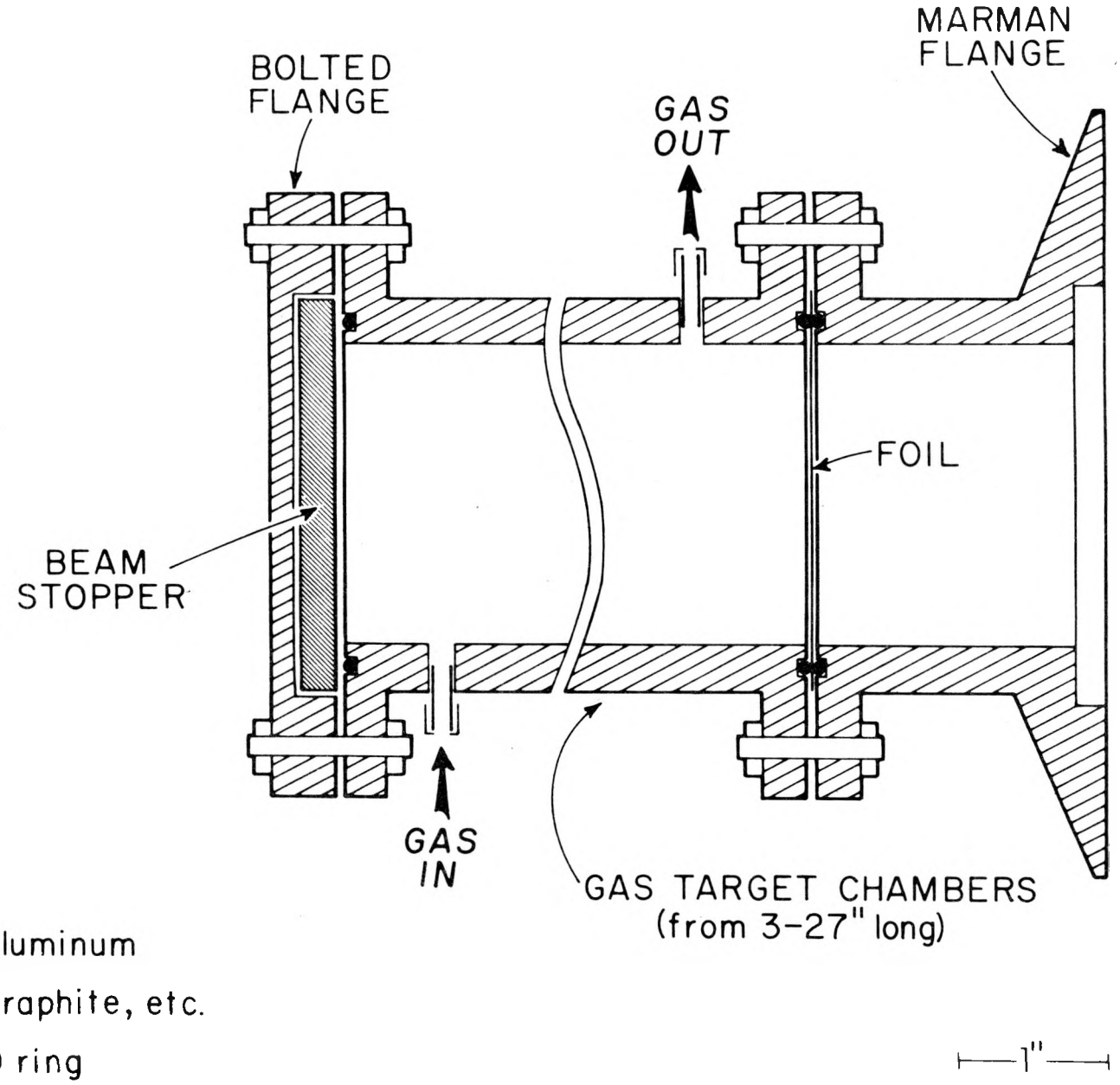


Figure 6

flanges, sealed with O-rings, and the flanges are held together by 1/4" bolts passed through 6 equally spaced holes. A foil window is held between components two and three. An insulating spacer (not shown in Figure 6) can be inserted between components 2 and 3, so that the gas target chamber can be used as a Faraday cup. The gas inlet and gas outlet connections are Swagelok quick disconnect connectors.

Solid Target Chamber

The solid target chamber shown in Figure 7 consists of two basic parts, the target holder and the target cooling plate. The target holder has provisions for a collimator in the form of a 1/4" deep recess in the beam end of the holder, and for a target plate varying in thickness from 0.001" to 0.500" and 3½" in diameter. The back of the target is maintained flush with the rear edge of the target holder by use of target spacers of the appropriate size. The target cooling plate consists of the main cooling plate, the sealing plate, and the sealing plate retainer ring. Cooling water is passed in through 4 of the radial holes at an angle of 45° to the axis of the chamber, and out through the other 4 holes. Eight plastic tubes are used to connect these 8 holes to the input and output water supply. The target cooling plate was designed so that the cooling water would flow quickly across the back surface of the target through a narrow space for the most efficient cooling. The two main components are clamped together with a Marman retaining ring (not shown). A lucite insulator in the target holder enables the solid target chamber to be used as a Faraday cup.

Scattering Chamber

The model CS-15 cyclotron is a fixed energy cyclotron. However, it is sometimes necessary to lower the particle energy in radionuclide production in order to reduce unwanted radionuclide contamination. This can be done by either:

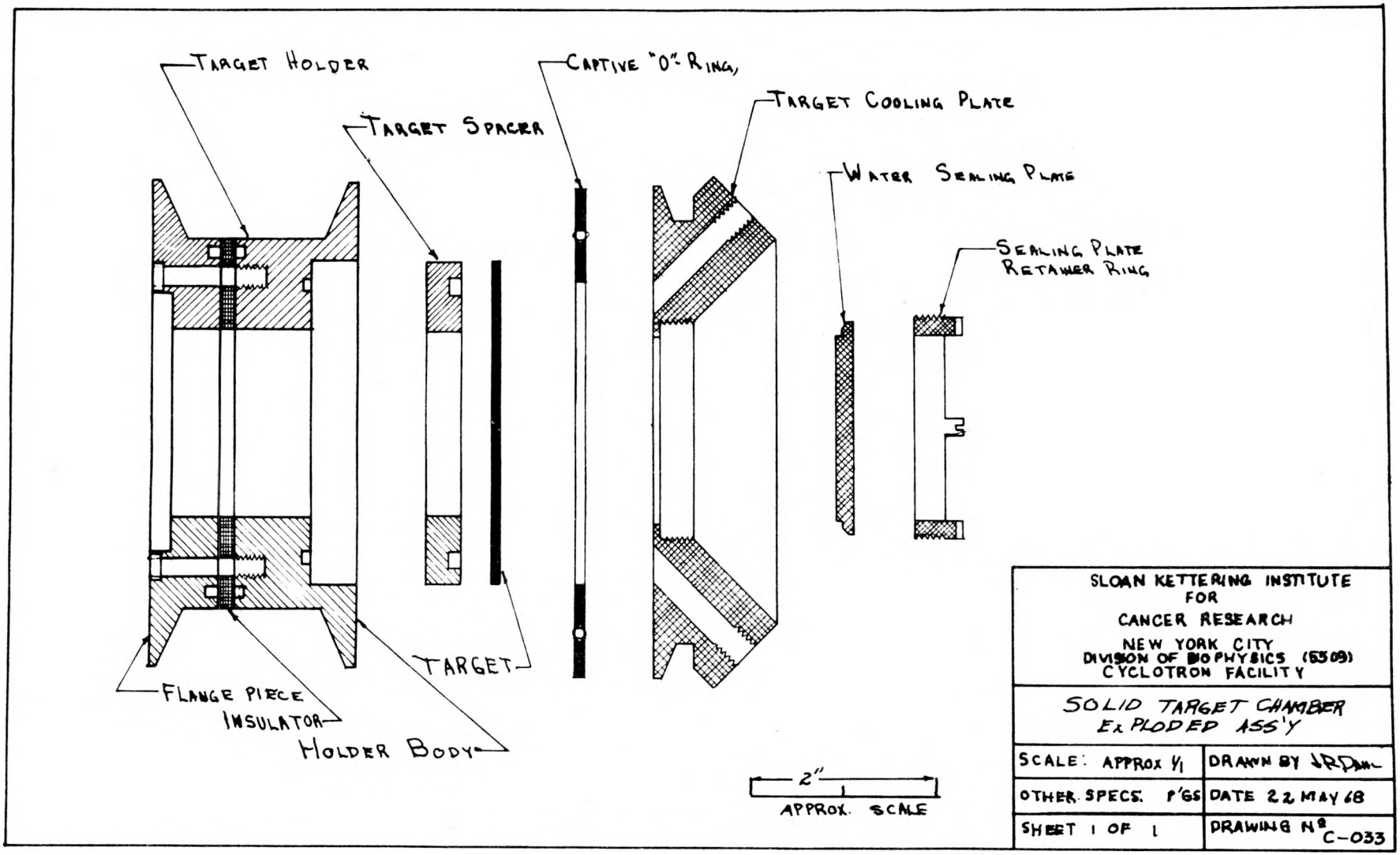
1. utilizing the internal beam probe. This is only suitable for solid target material.

2. or degrading the external particle beam with thin foils.

In addition, it is necessary to measure the particle energy for excitation function studies.

In order to measure the degraded beam energies, a scattering chamber was designed and constructed (see Figure 8). The method has been previously described.

The gold scattering foil is attached to a support which can be positioned to intercept the beam. The arm is driven by an electric motor (not shown in figure). The remote controls and position indicator are on the control console. Vacuum within the chamber is preserved by the use of a stainless steel bellows rather than by sliding O-ring seals.


TARGET HOLDER
TARGET SPACER
CAPTIVE "O"-RING
TARGET COOLING PLATE
WATER SEALING PLATE
SEALING PLATE RETAINER RING
TARGET
FLANGE PIECE
INSULATOR
HOLDER BODY
2"
APPROX. SCALE
SLOAN KETTERING INSTITUTE FOR CANCER RESEARCH
NEW YORK CITY
DIVISION OF BIOPHYSICS (5509)
CYCLOTRON FACILITY
SOLID TARGET CHAMBER EXPLODED ASS'Y
SCALE: APPROX 1/1
DRAWN BY J.R.D.
OTHER SPECS. P'GS
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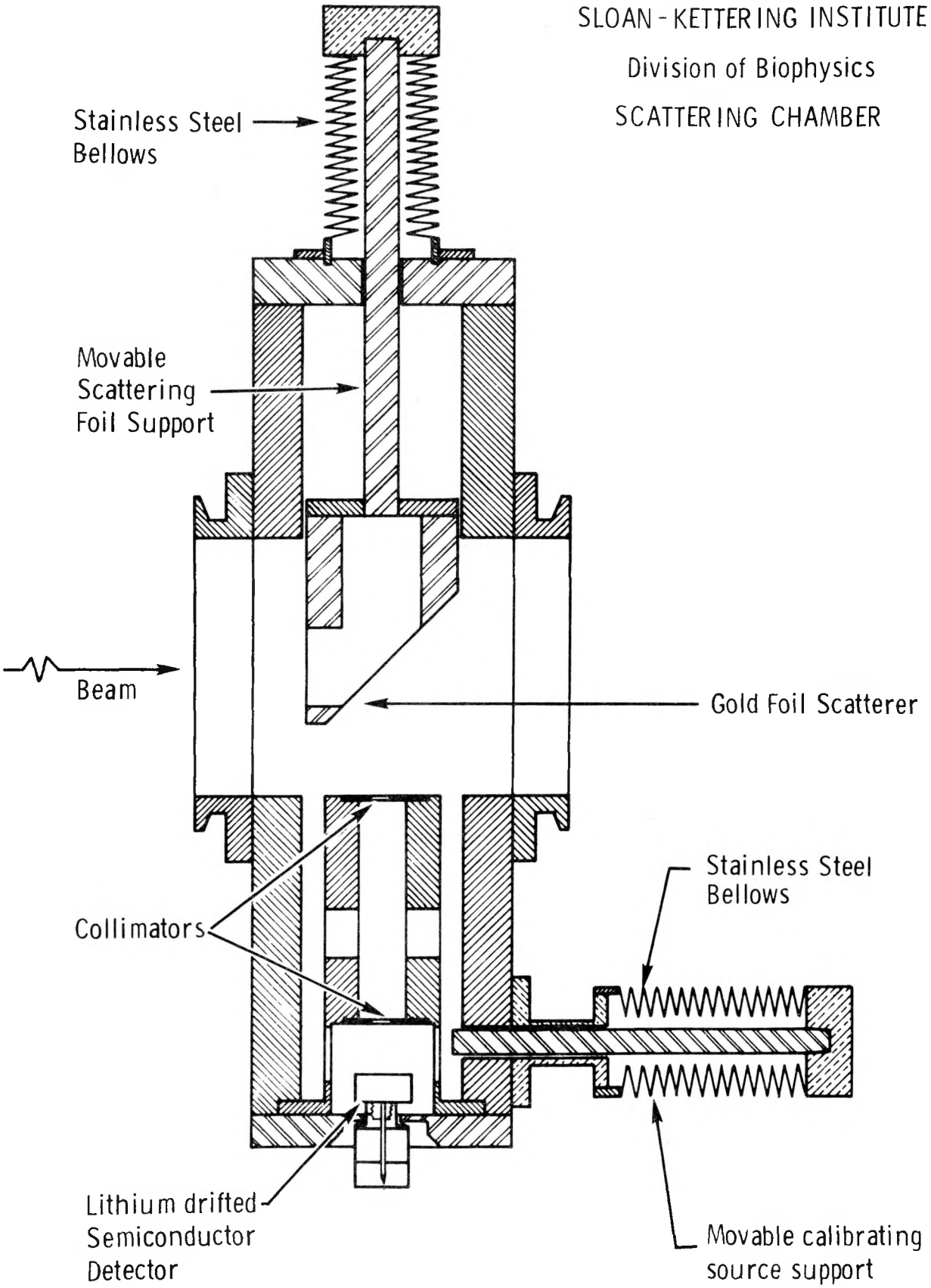
SHEET 1 OF 1
DRAWING NO. C-033

Figure 7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Division of Biophysics
SCATTERING CHAMBER
Stainless Steel Bellows
Movable Scattering Foil Support
Beam
Gold Foil Scatterer
Collimators
Stainless Steel Bellows
Lithium drifted Semiconductor Detector
Movable calibrating source support

Figure 8

A Li-drifted silicon semiconductor detector is positioned at right angles to the primary beam direction. The scattered particles are collimated by 2 tantalum collimator discs.

The energy calibration of the detector and electronic components are made by positioning an alpha-emitter such as americium-241 in front of the detector. The calibrating source is mounted on a movable support driven by an electric motor remotely controlled from the control console. A stainless steel bellows is likewise used to preserve the vacuum.

The thin (5×10^{-5} cm thick) foil can be viewed through a lucite window (now shown in diagram).

The scattering chamber can be readily and quickly attached to the beam pipe and target system by means of Marman couplings.

Radionuclide Production and Radiopharmaceutical Developments

Fluorine-18

The target chamber used for F-18 production has been described previously.

Prior to the first run, the inside of the target chamber, plus the catalyst cup and foil, were cleaned with carbon tetrachloride, detergent-water mixture in an ultrasonic bath, water, distilled water and finally sterile, pyrogen-free water. Abbott sterile, pyrogen-free water was used as target. Prior to subsequent runs, the target chambers were cleaned with 3 washes of isopropyl alcohol and 3 washes of sterile water. After each run, the F-18 solution was filtered through a 0.22 micron millipore filter, and then made isotonic with sterile, pyrogen-free sodium chloride solution. After adjusting the F-18 to the desired activity/ml, the solution was dispensed into multidose vials and autoclaved. The F-18 solution was then ready for use.

Table IV summarizes our F-18 production runs. Thirteen production runs have been completed, and the solutions from 10 of these runs have been tested for sterility and pyrogenicity and found to be sterile and pyrogen-free. The average yield of F-18 was about 7 mCi/μA.h, which is considerably higher than the yield of 1.5 mci/μA.h, obtained by using 30 Mev alpha-particles on water (8). The thick target yield of F-18 by 22 Mev ^{3}He particles on water has been calculated to be 6.9 mCi/μA.h from the published (9) excitation function for the reaction $^{16}O(^{3}He, p)^{18}F$, which is in good agreement with the measured value. The details of the calculation are given in Appendix I (see page 36).

The quantity of F-18 produced in each run was measured in a well-type gamma ionization chamber (Baird Atomic model No. 11-140), in conjunction with an electrometer (Keithley model No. 601). The ionization chamber was calibrated for F-18 relative to a standardized source of SR-85 obtained from the Radiochemical Center, Amersham, England. Equal volumes of solution were measured in the same type of vial, and a correction was made for the difference in gamma-ray abundance of the two radionuclides.

TABLE IV

Summary of Fluorine-18 Runs

Run No.	Date	Duration of irradiation (M)	External Beam Current (μA)	Volume of Target Water Recovered (ml)	Foils Used	F-18 Produced at E.O.B.(1) mCi/μA.h	Sterility Test	Pyrogen Test
1	2/28/68	41	10	8.2	Ti + Ti	7.2	--	--
2	3/14/68	32	10	8.0	Ti + Ti	8.0	--	--
3	3/19/68	35	10	8.0	Ti + Ta	7.0	Sterile	P.F.
4	4/15/68	37	6	8.0	Ti + W	7.5	Sterile	P.F.
5	4/15/68	35	10	5.5	W	9.8	Sterile	P.F.
6	4/17/68	60	10	8.9	W	7.5	Sterile	P.F.
7	4/18/68	60	10	9.0	W	6.8	Sterile	P.F.
8	4/24/68	60	10	9.0	W	6.7	Sterile	P.F.
9	5/3/68	35	10	8.5	W	6.6	Sterile	P.F.
10	5/3/68	target chamber leaked		--	--	--	--	--
11	5/3/68	35	10 (2)	8.0	W	7.0	Sterile	P.F.
12	5/3/68	35	10 (2)	9.2	W	6.8	Sterile	P.F.
13	5/3/68	35	10 (2)	8.8	W	7.4	Sterile	P.F.
14	5/7/68	60	9 (2)	8.9	W	6.5	--	--

Notes
(1) E.O.B. = End of bombardment; (2) Tantalum collimator used. 1.7" I.D.; (3) P.F. = Pyrogen free.

In order to measure any gamma-ray emitting impurities, samples of F-18 solution were measured for periods up to 67 days from the end of bombardment, on a 3 x 3 inch NaI (Tl) crystal coupled to a photomultiplier tube and a 400 channel pulse height analyzer. The gamma-ray spectrometer was calibrated by means of a set of point source gamma-ray standards obtained from the International Atomic Energy Agency, Vienna, Austria. V-48 was detected in runs 1 and 2 at a concentration of 10^{-3} microcuries/ml or 1 part per million parts of the F-18 formed at end of bombardment. The V-48 was presumably formed by ^{3}He, p) reaction on Ti-46, or (^{3}He, n) reaction on Ti-46 to produce CR-48 which then decayed with a half-life of 23 hours to V-48. V-48 has a half-life of 16 days. CR-48 was not detected in the F-18 product solution, because the F-18 activity masked any CR-48 activity that might have been present. If all the V-48 activity had been produced by decay of CR-48, the amount of CR-48 present at end of bombardment would have been 0.02 μCi/ml.

When using 0.001" tungsten foil in place of the titanium foil in the liquid target chamber, the only long-lived impurity in the F-18 product solution was Be-7 in an amount of 10^{-3} μCi/ml. This was presumed to be formed by the reaction $^{16}O(^{3}He, ^{7}Be)^{12}C$ which has a Q value of -5.57 Mev. Be-7 was subsequently found in the F-18 product solution at about the same activity/ml from runs using titanium foils, when the V-48 had decayed sufficiently.

An aged sample of F-18 product solution No. 1 was measured from time to time by liquid scintillation counting over a 70-day period, in order to set an upper limit for tritium or other soft beta-emitting impurities. Corrections were made for the V-48 and Be-7 present in the solution, and an upper limit for tritium content in the sample was set at 0.009 μCi/ml.

Iodine-123 and Iodine-121

A series of experiments have been performed to measure the yields of I-121, I-123, and I-124 in the He-3 irradiation of antimony. These experiments were done before the solid target chamber (see page 18) had been made. About 2 grams of antimony metal powder were irradiated in a Faraday cup, by compressing the powder between 2 pieces of aluminum foil. The powder was evenly distributed over a circle of 1.8 inches diameter, and irradiated for periods of 10 minutes at beam currents of 5 μa. After irradiation, the iodine was separated by dissolving the antimony in 10 ml of concentrated nitric acid plus 10 ml of saturated tartaric acid, and the iodine was distilled in a stream of nitrogen and collected in 1N NaOH solution. About 1 mg of sodium iodide was used as carrier in these experiments. The distilled iodine was repurified by solvent extraction into carbon tetrachloride and back extracted into 0.1N NaOH solution. Aliquots were taken for gamma-ray spectrometry on stainless steel planchettes, a drop of dilute nitric acid and of dilute silver nitrate added, and the sample evaporated to dryness under an infra-red lamp. Corrections were made for chemical yield when required. I-121 was measured by its gamma-ray of energy 210 Kev, (90% abundant), I-123 by its gamma-ray of energy 160 Kev (83% abundant), and I-124 by the combined 605 and 644 Kev gamma-rays, with a combined abundance of 79%. Decay curves were plotted for each of these gamma-rays, and the correct half-lives established before accepting the photopeak

areas as representing the given radionuclide. Photopeak detection efficiencies were experimentally determined by use of a set of point-source gamma-ray standards supplied by the International Atomic Energy Agency, Vienna, Austria. Activity measurements were made at a distance of 6 cm or greater (to avoid errors due to coincident summing) from a 3 x 3 inch sodium iodide crystal coupled to a photomultiplier tube and 400 channel pulse height analyser.

Irradiations were performed with increasing thicknesses of aluminum foil (0.0007 inches thick) to determine the effect of particle energy on the relative yields. The results are shown in Tables V and VI. For these experiments, no chemical separations were performed, since the iodine radioactivities could be measured in the unseparated antimony-aluminum sandwich. These results show that about 4 times as much I-121 as I-123 is produced by 22 Mev He-3 on natural antimony, and that the yield of I-121 decreases relative to that of I-123 with decreasing bombarding energy.

The I-124 yield at end of bombardment was about 5% of the I-123 at 22 Mev, and increased with decreasing bombarding energy. Thus, the I-124 content in I-123 could not be reduced by lowering the bombarding energy.

Enriched isotopes of Sb-121 and Sb-123 having abundances as shown in Table VII, were irradiated with 22 Mev He-3 particles. The gamma-ray spectra obtained from each of these samples are shown in Figures 9 and 10. The sample enriched to 98% in Sb-121 produced I-121 almost exclusively. I-123 was detected in the sample only after a decay of 22 hours, and amounted to 1.7% of the I-121 at end of bombardment.

The sample enriched to 98% in Sb-123 produced mainly I-123 and 6% I-124. The relative yield of I-123 produced by He-3 particles on Sb-121 and Sb-123 stable isotopes was calculated from the above 2 experiments to be 1:38. Thus, I-123 is produced almost exclusively by $^{123}Sb(^{3}He, 3n)$ I-123 reaction, and only 2.6% by Sb-121(He-3, n) I-123 reaction. Since I-124 is produced by (He-3, 2n) reaction on Sb-123, it is not possible to significantly reduce the I-124 contamination by irradiation of enriched isotopes of antimony instead of natural antimony. However, I-121 could be produced with less than 1% I-123 and other activities by irradiation of enriched Sb-121.

The thick target yield of I-123 was measured by irradiating a 1/8 inch thick piece of antimony metal (roughly 1" x 1") covered with a 0.0007" thick aluminum foil. The antimony and foil were measured together, and the yield of I-123 was found to be 24 μCi/μA.h. This is compared with other thick target yields in Table VII. Thus, the yield of I-123 using 22 Mev He-3 particles on antimony is lower than other methods of production. Also, the I-124 content of the I-123 is higher for 22 Mev He-3 particles on antimony than for most of the other methods given in Table VIII.

Iron-52

Fe-52 has been of interest as a radioactive tracer for at least 10 years (13), primarily because of its short halflife (8.2 h) and positron emission. It has been made by the bombardment of chromium by alpha particles

Table V

Yields of Iodine Radionuclides from He-3 Particles on Antimony with Different Thicknesses of Aluminum Absorbers

Absorber Thickness ($mg \cdot cm^{-2}$)	He-3 Energy (Mev)	Yield (μCi at E.O.B.*)		
		I-121	I-123	I-124
4.8	22.2	35	7.6	0.41
9.6	21.3	37	12.3	0.71
14.4	20.5	29	9.7	0.76
19.2	19.6	4.5	2.0	0.24
24.0	18.7	0.45	1.36	0.16
28.8	17.7	No iodine activities detected		

*End of bombardment

Table VI

Ratio of Yields of Iodine Radionuclides

Absorber Thickness (mg/cm^2)	Ratio	
	I-121/I-123	I-124/I-123
4.8	4.1	0.054
9.6	3.0	0.057
14.4	3.0	0.078
19.2	2.2	0.083
24.0	0.33	0.118

Table VII

Isotopic Abundances of Antimony-121 and
123 Enriched Isotopes

	Isotopic Abundance(%)	
Sample	Sb-121	Sb-123
Sb-121	98.4(±0.1)	1.6(±0.1)
Sb-123	1.9(±0.1)	98.1(±0.1)

Analyses supplied by Oak Ridge National Laboratory

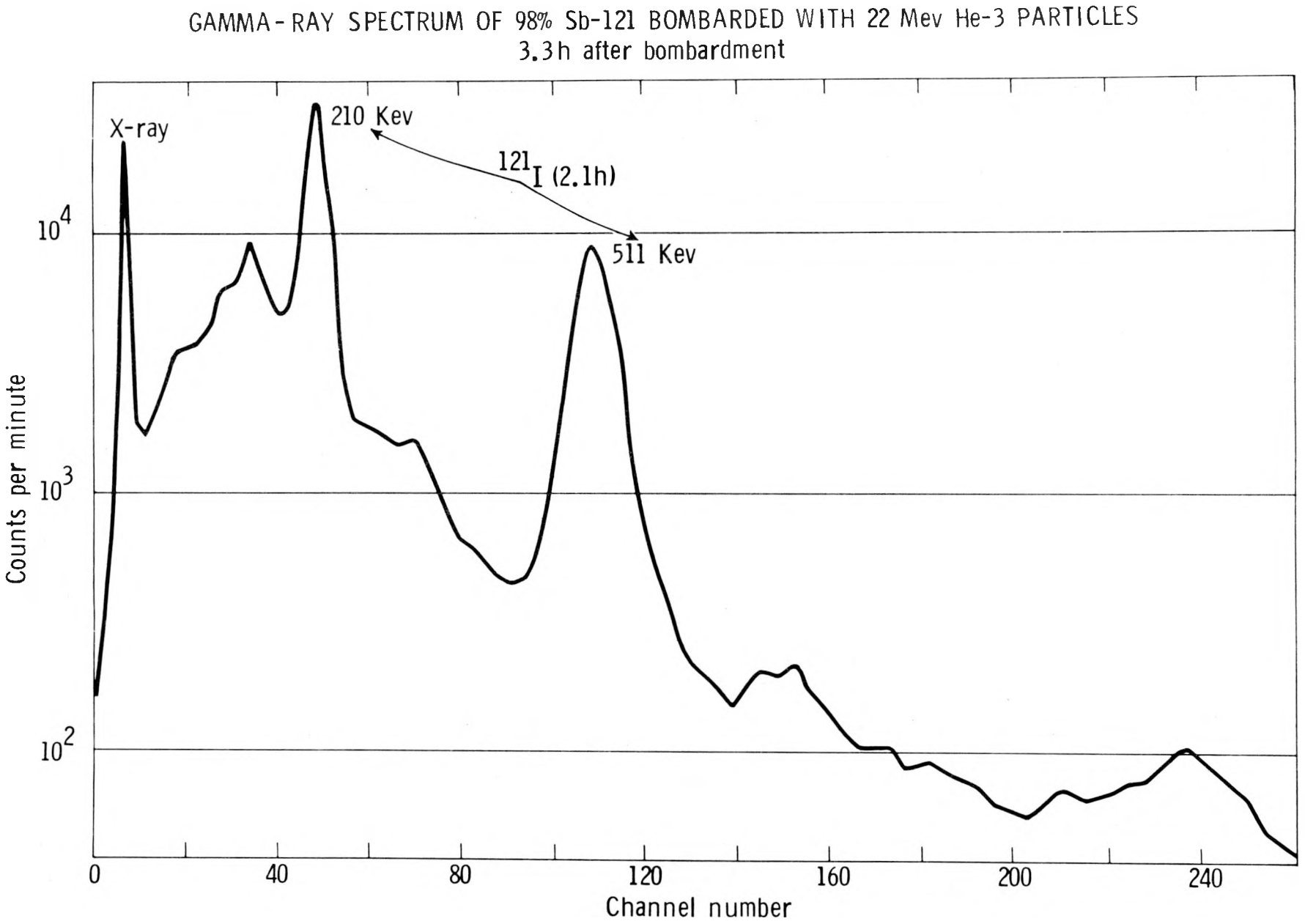
GAMMA-RAY SPECTRUM OF 98% Sb-121 BOMBARDED WITH 22 Mev He-3 PARTICLES
3.3h after bombardment
X-ray
210 Kev
121I (2.1h)
511 Kev
Counts per minute
10^4
10^3
10^2
0
40
80
120
160
200
240
Channel number

Figure 9

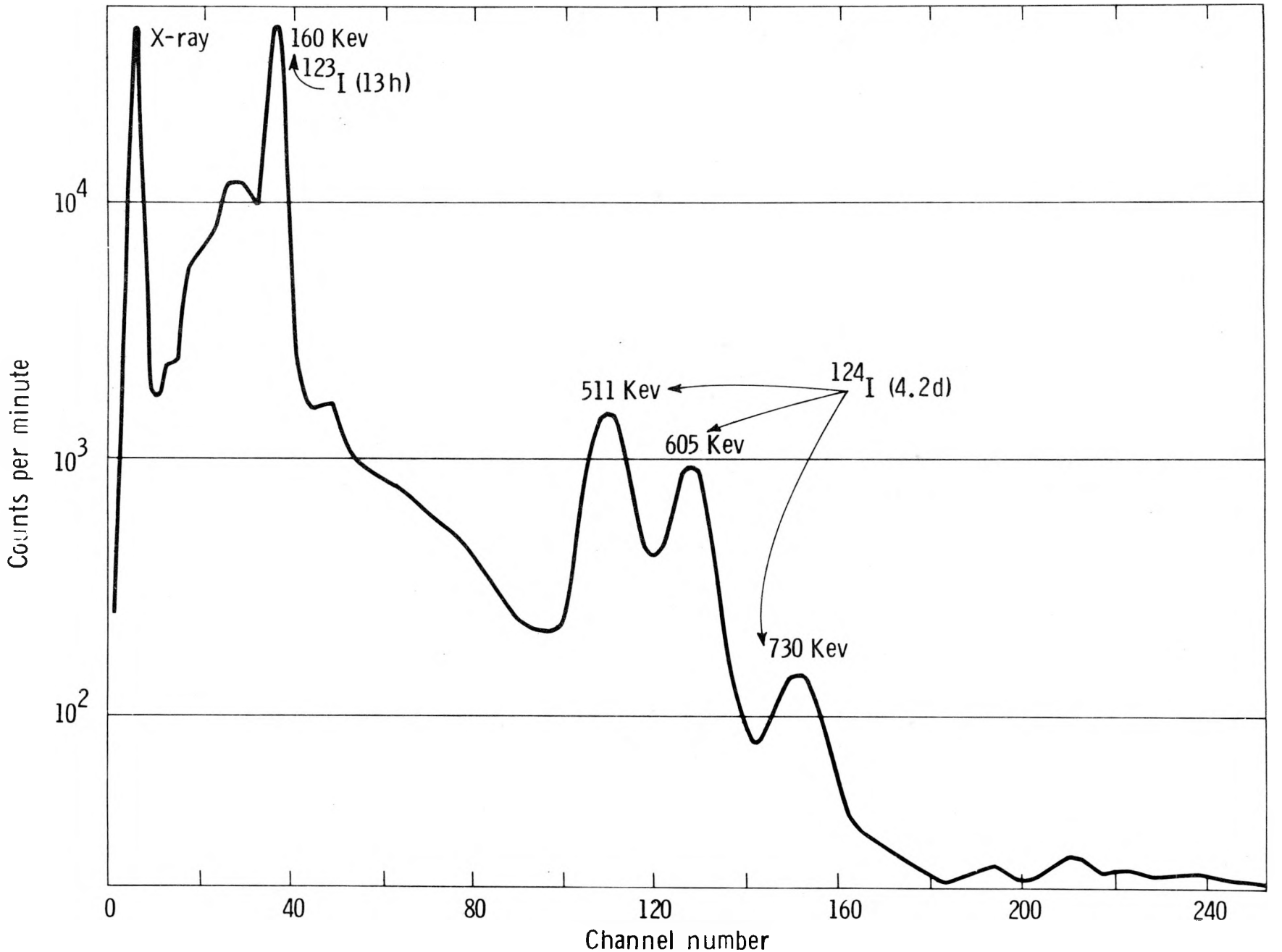
GAMMA-RAY SPECTRUM OF 98% Sb-123 BOMBARDED WITH 22 Mev He-3 PARTICLES
3h after bombardment
X-ray
160 Kev
123I (13h)
511 Kev
124I (4.2d)
605 Kev
730 Kev
Counts per minute
10^4
10^3
10^2
0
40
80
120
160
200
240
Channel number

Figure 10

Table VIII

Iodine-123 Thick Target Yields

Yield (μCi/μA.h.)	I-124 Contamination %	Bombarding Particle	Bombarding Energy (Mev)	Target	Reference
24	5	He-3	22	Sb	This work
173	small	He-3	30	Sb	(10)
20	0.5	He-4	25	Sb	(8)
200	5	He-4	40	Sb	(8)
370	0.85	protons	15.5	Te-122	(11)
70	<0.15%	He-4	40	Te-122	(12)

of 40 to 65 Mev (14,15). This method of production also produces Fe-55 as an impurity which, because of its very long half-life (2.4 y), may limit the use of Fe-52 solutions. Previous to this work, the Fe-52 has been separated from the irradiated target by solvent extraction processes, using Di-isopropyl Ether (DIPE) which require complicated remote handling apparatus.

The maximum alpha-particle energy from the SKI cyclotron is 15 Mev, and 16.9 Mev is the lowest threshold for a reaction between an alpha particle and a chromium nucleus which yields Fe-52 (^{50}Cr (α, 2n) ^{52}FE), (16). The threshold for $^{3}He^{++}$ with chromium is well below the 23 Mev of He-3 particles produced by the SKI cyclotron, and the production of Fe-52 by this method was investigated. In addition to a study of the nuclear reactions involved, the chemical separation of Fe-52 from the chromium target was also studied for the following reasons: 1) the apparatus required for the solvent extraction process is complex; 2) though not extremely dangerous, the solvent used (DIPE) is volatile and flammable; 3) the existing procedures (14,15) work best when carrier iron is added; and 4) a carrier-free method of obtaining iron from irradiated targets (17) indicated that a method could be developed which could be superior to the solvent extraction technique. The solvent extraction technique is adapted from an analytical technique dating back to 1936 (18). The efficiency of this technique depends strongly on equilibration of DIPE with a strong HCl solution (7-8M optimal), and decreases rapidly as the iron concentration becomes low ($<10^{-3}$MO (19), and is therefore not desirable for carrier free separations. Kraus and Nelson (20) give the distribution coefficient of Fe^{+3} in 8M HCl in Dowex 1 as greater than 10^{4}, and also state that Cr^{+3} is only very slightly absorbed at all concentrations.

The use of a procedure using anionic ion exchange resins to prepare solutions suitable for injection, that is, sterile and pyrogen free, has been shown not to introduce pyrogenic material from the resin, and, in fact, the resin may remove any pyrogens carried over from the target (21). The chemical separation scheme to separate Fe-52 from the irradiated chromium target is:

1. dissolve the chromium target (1-2g) in 12M HCl (25 & 30 ml).

2. evaporate the solution to near dryness and take up the residue in 12M HCl (25 ml).

3. filter the solution through a 0.22 μ Millipore filter.

4. pass the solution through a Dowex 1-X8, 100-200 mesh, chloride form ion exchange column 13 x 50 mm pre-equilibrated with 12M HCl.

5. wash the column with 30 to 50 ml 12M HCl to remove Cr^{+++}. The last portion of the eluent should be clear and colorless.

6. pass 50 ml 0.1M HCl through the column and collect this fraction containing Fe-52. The chemical yield was 90%.

Chromium targets of low purity (99+% chromium) have been irradiated, and the thick target yield of Fe-52 found to be 1μCi/μAMP.Hr.

The gamma-ray spectrum of the separated Fe-52 solution was examined with a 400 channel Pulse Height Analyser and a 3 x 3" NaI(Tl) well crystal. No impurities were detected. Mn-52 and Mn-52m were observed after several hours decay, and are expected as the decay products of Fe-52. The procedure, as outlined, requires a maximum of 3 hours for completion, and, the final procedure, including conversion of the ferric chloride to ferrous citrate, sterilization and calibration at the final solution, will add a maximum of 2 hours. At the present time, it appears that the ultimate net yield of Fe-52 from a run of 50 μAMP. for 8 hours, will be about 100 μCi, assuming 12 hours of decay and 5 hours' process time. The use of chromium targets of 99.996% purity and 1 gram mass will give a specific activity of 1μCi Fe-52/μg Fe, 815 times as high as the previous work. This relatively low yield makes it desirable to irradiate chromium in the internal beam instead of in the external beam.

Radioactive Gases

A system has been designed and is being constructed to produce the following radioactive gases: $^{15}O_2$, $C^{15}O$, $C^{15}O_2$, $^{13}N_2$, $^{11}CO_2$ and ^{11}CO. Figure 11 is a flow diagram of the radioactive gas handling system. One of four primary gases may be selected to flow into one of three cyclotron target chambers, depending on which radionuclide, O-15 N-13 or C-11 is required. If $^{15}O_2$ is required, the primary gas will be 5% O_2 plus N_2. O-15 will be produced by $^{14}N(d,n)^{15}O$ reaction, and the O-15 "hot" atoms produced will react partly with the molecular oxygen to produce $^{15}O_2$. Any oxides of nitrogen produced will be removed by absorption on active charcoal. Any ozone will be decomposed by manganese dioxide, and silica gel or "drierite" will remove water. The $^{15}O_2$ plus nitrogen will then be passed to the positron camera room, where it will be diluted in roughly a 1:10 ratio with a suitable diluent gas, passed through an ion chamber to measure its radioactivity, through a gas chromatographic analyzer to measure the chemical constituents, and finally to a breathing apparatus for patient use or to waste. If $C^{15}O$ is required, the $^{15}O_2$ is passed through charcoal at 850°C to convert it mainly to $C^{15}O$ plus a little $C^{15}O_2$, then through baralyme to remove CO_2 and then to the ion chamber. If $C^{15}O_2$ is required, the $^{15}O_2$ is converted by passing over charcoal at 500°C, and any CO produced is oxidized to CO_2 by passing over copper oxide at 850°C, and thence to the ion chamber.

If $^{13}N_2$ is required, the primary gas will be helium, nitrogen or hydrogen, and the target chamber will contain a graphite target so that N-13 will be produced by the reaction $^{12}C(d,n)\ ^{13}N$. The gas is passed over copper metal turnings at 750°C to reduce any nitrogen oxide impurities to N_2 and then through baralyme to the ion chamber.

If ^{11}CO is required, the primary gas is 5% CO plus helium, and the target chamber will contain boric oxide. C-11 "hot" atoms are generated by $^{10}B(d,n)\ ^{11}C$ reaction and the "hot" atoms react with the CO to produce ^{11}CO.

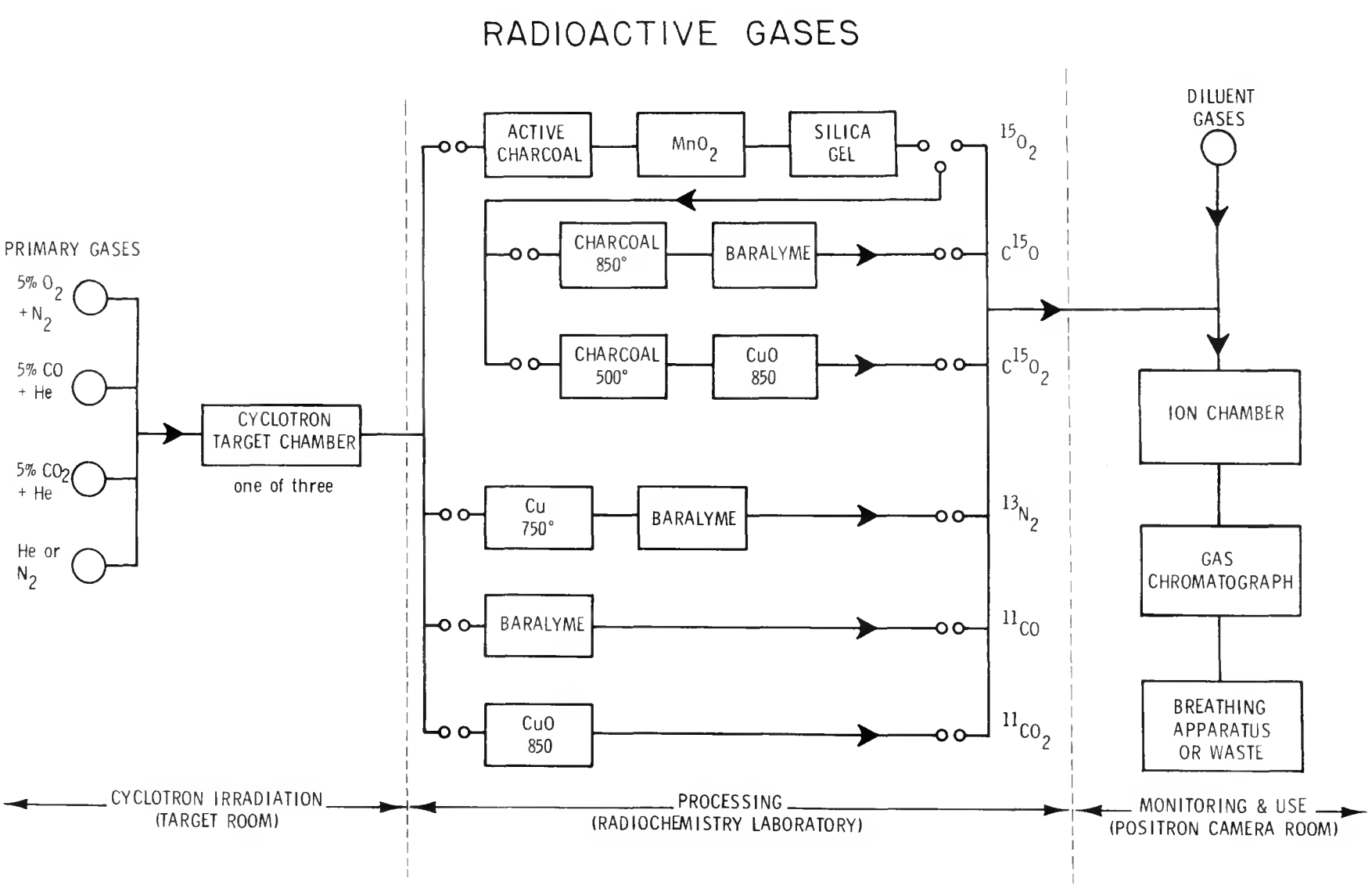
RADIOACTIVE GASES
PRIMARY GASES
5% O_2 + N_2
5% CO + He
5% CO_2 + He
He or N_2
CYCLOTRON TARGET CHAMBER
one of three
ACTIVE CHARCOAL
MnO_2
SILICA GEL
$^{15}O_2$
CHARCOAL 850°
BARALYME
$C^{15}O$
CHARCOAL 500°
CuO 850
$C^{15}O_2$
Cu 750°
BARALYME
$^{13}N_2$
BARALYME
^{11}CO
CuO 850
$^{11}CO_2$
DILUENT GASES
ION CHAMBER
GAS CHROMATOGRAPH
BREATHING APPARATUS OR WASTE
CYCLOTRON IRRADIATION (TARGET ROOM)
PROCESSING (RADIOCHEMISTRY LABORATORY)
MONITORING & USE (POSITRON CAMERA ROOM)

Figure 11

Any $^{11}CO_2$ produced is removed by baralyme, and the gas is then passed to the positron camera room. If ^{11}CO is required, 5% CO_2 plus helium is used as primary gas and after passing through the target chamber, any CO is converted to CO_2 by copper oxide at 850°C.

The chemical processing of the radioactive gases is all carried out in a single gas processing unit. A front panel on this unit is fitted with "Swagelok" quick disconnecting double-ended shut-off tubing connectors, so that the flow path of the radioactive gases can be changed quickly and conveniently. These quick disconnectors are indicated in Figure 11 by small open circles.

The gas chromatograph will be a Hewlett-Packard Model 5752B with dual thermal conductivity detectors and a gas sampling valve. Temperature programming will be possible from -78°C to +400°C. The chromatographic column used initially will be Poropak Q 16 ft by 1/4 inch, which should be suitable for most of the gas analyses required.

The gas sampling value will be connected directly into the main line of the radioactive gas handling system at any point, so that a gas analysis can be initiated simply by switching the gas sampling value from flush mode to analyze mode. The flow of gas in the main line will thus be interrupted for only a few seconds. The gas chromatograph will also be useful for the analysis of a wide variety of volatile products in our study of cyclotron-produced radiochemicals.

Carbon-11 Labeled Organic Compounds

A method is being developed for the rapid separation and purification of cyclotron-irradiated thymidine and other organic compounds. Figure 12 shows the ultra-violet absorption of eluted fractions collected from a Dowex 1 ion exchange chromatographic column (1 cm I.D. and 37 cm long). A mixture of 2 mg each of uridine and thymidine in water solution was absorbed on the top of the column and then eluted with an increasing concentration of sodium acetate solution (1.5 M initially increasing to 3 M finally). The uridine came off the column after 2 hours, and the thymidine after 2.8 hours of elution time. Uridine was used with thymidine because it occurs just before thymidine in this chromatographic scheme of separation, and so gives a sensitive test of the efficiency of separation. The eluent was pumped through the column at an estimated pressure of 20 psi by means of a Beckman solution metering pump model 746. The flow rate of the eluent was 0.7 cc/min. The figure shows that the separation was reasonably efficient, but the time taken was too long for C-11 labeled thymidine. We hope to reduce this time, by a factor of 3, by using a higher pressure system, changing the pH of the eluent, and raising the temperature of the column. Then we will be able to run samples of cyclotron-irradiated thymidine through the column, and collect any C-11 labeled thymidine. The method, if it works, should be a general method for the production of C-11 labeled aminio acids.

A solution metering pump has recently been received from the Milton-Roy Company. This pump operates at pressures up to 1000 psi, and delivers liquids at from 46 to 460 ml/hour. Pressure gauges, safety relief valves and high pressure chromatographic columns are presently being assembled to make a high pressure chromatographic system.

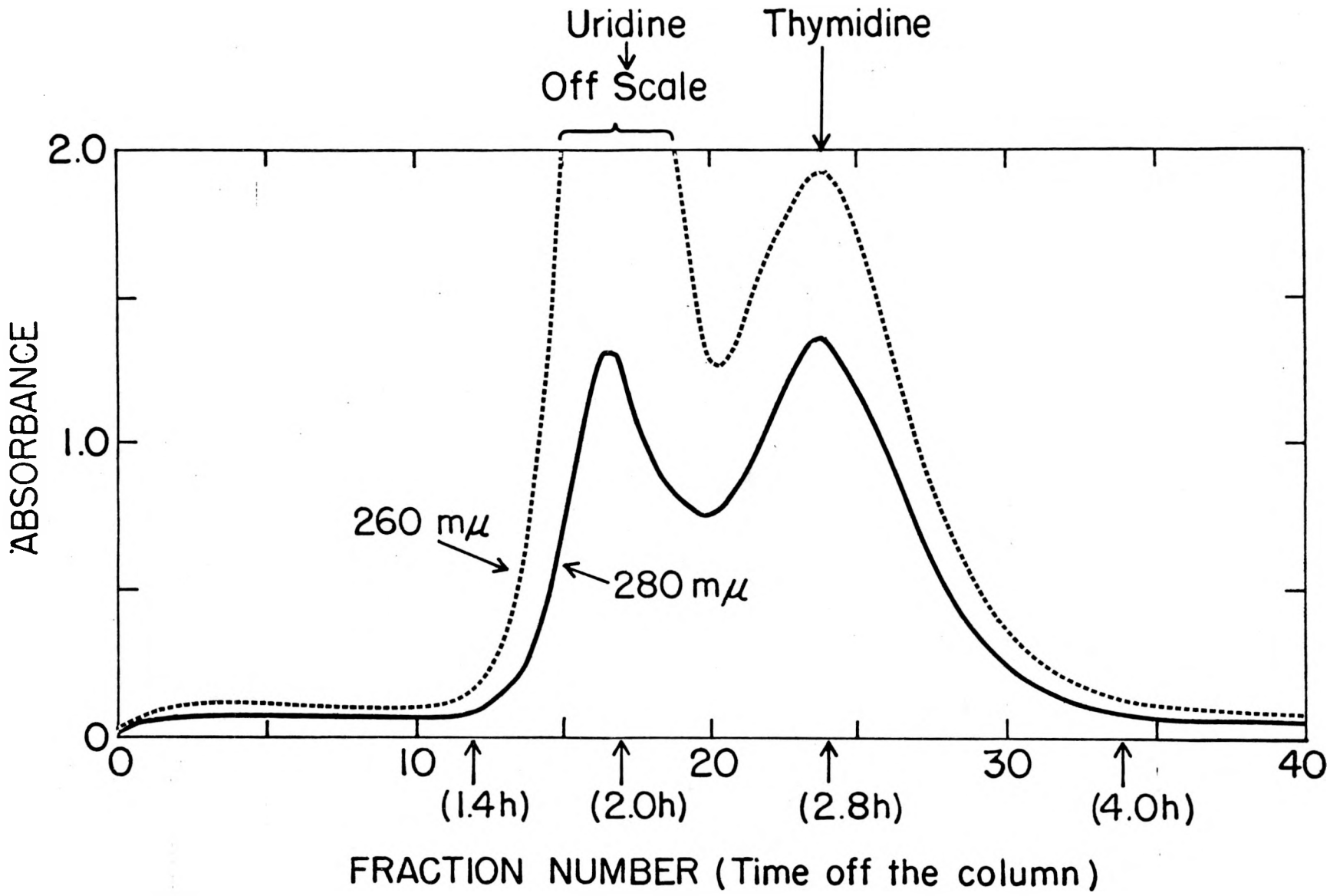
CHROMATOGRAPHIC SEPARATION OF URIDINE AND THYMIDINE
DOWEX-1-X8, 200-400 MESH. 1·5-3·0M GRADIENT ELUTION
Uridine
Off Scale
Thymidine
2.0
1.0
0
ABSORBANCE
260 mμ
280 mμ
0
10
20
30
40
(1.4h)
(2.0h)
(2.8h)
(4.0h)
FRACTION NUMBER (Time off the column)

Figure 12

Appendix I

Calculation of the Thick Target Yield of F-18 by He-3 Bombardment on Water

The average cross-section ($\bar{\sigma}$) for a charged particle reaction in a thick target is given by (22):

$$\bar{\sigma} \approx \frac{\int_E^0 \sigma_E \, E \, dE}{\int_E^0 E \, dE}$$

$$= \frac{2}{E^2} \int_E^0 \sigma_E \, E \, dE$$

$$= \frac{2}{E^2} \sum_{i=1}^{i=n} \sigma_i \, E_i \, \Delta E$$

where σ_E is the cross-section for the nuclear reaction at energy E, and ΔE is a small increment of energy as shown in Figure 13.

Numerical integration under this excitation function can be performed by Simpson's rule, so that the area of the slice shown in Figure 13 is 1/3 ($\sigma_1 + 4\sigma_2 + \sigma_3$) ΔE. A program was set up on an Olivetti Underwood computer model 101 to calculate the average cross-section for the $^{16}O(^3He,p)^{18}F$ reaction for 22.5 Mev He-3 particles. The experimental excitation function of Markovitz and Mahoney (9) was used. The average cross-section was found to be 132 mb.

The disintegration rate of F-18 at end of bombardment (D) was then calculated from

$$D = IN\bar{\sigma}R(1-e^{-\lambda t})$$

where I is the intensity of the He-3 beam, in particles/sec, N is the number of O-16 target atoms per milligram of water, R is the range of the He-3 particles in water in mg/cm^2, λ is the decay constant for F-18 and t is the duration of irradiation. The value of R was calculated from the data of Williamson et al (23), to be 59 mg/cm^2. The thick target yield of F-18 was then calculated to be 6.9 mCi/μA.h, in good agreement with the experimental yield of 7 mCi/μA.h.

Figure 13 Theoretical Excitation Function

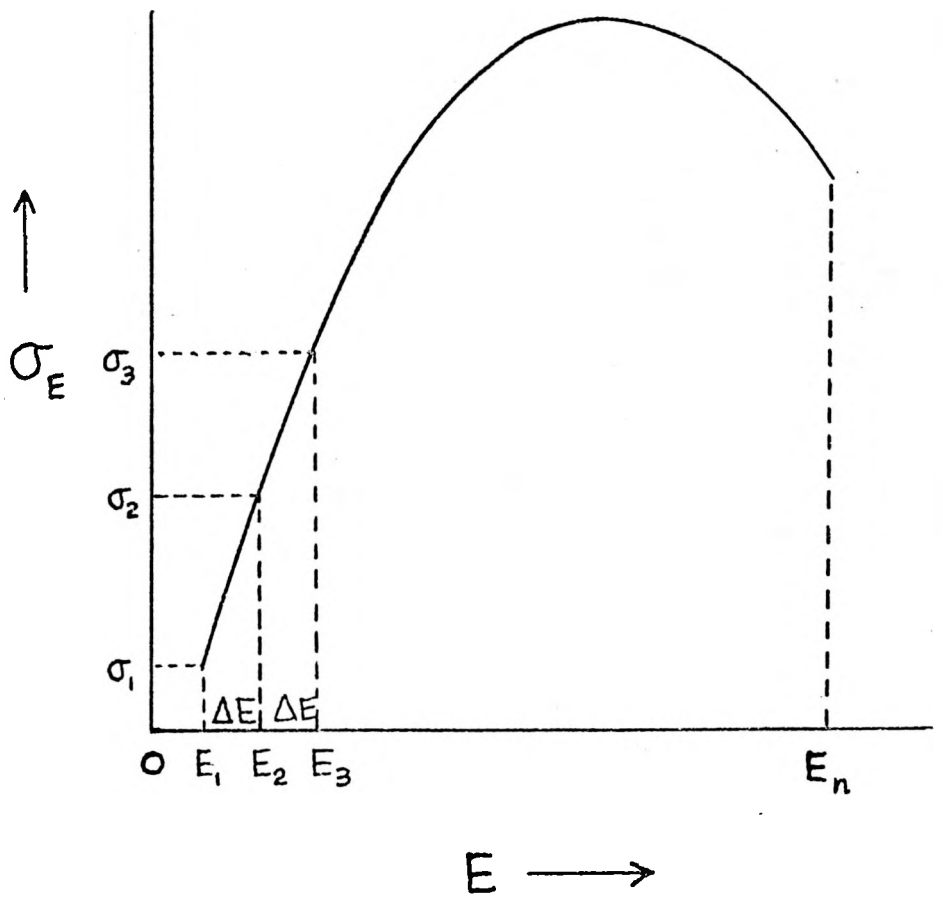

Figure 13

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