

OAK RIDGE NATIONAL LABORATORY

OPERATED BY
UNION CARBIDE CORPORATION
NUCLEAR DIVISION



POST OFFICE BOX #
OAK RIDGE TENNESSEE 37830

ORNL/MIT-262

DATE: November 28, 1977

SUBJECT: Design of a Fluorine-18 Production System at ORNL Cyclotron Facility, Part 2

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MASTER

ABSTRACT

A fluorine-18 recovery system using an anion-exchange side-stream column was designed for the $H_2^{18}O$ target at the ORNL 86-inch cyclotron. The extent of radiolysis was determined and a catalyst vessel, containing a palladium catalyst, was incorporated to recombine the radiolysis product gases. The preliminary design of an externally bombarded gas target for the production of $^{18}F_2$ from $^{18}O_2$ was also completed.

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National Technical Information Service
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5285 Port Royal Road, Springfield, Virginia 22161
Price: Printed Copy \$4.00; Microfiche \$3.00

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1. SUMMARY

A previous MIT group (9) examined ^{18}F production efficiency, heat removal characteristics, and materials of construction in designing an H_2O target system for the ORNL 86-inch cyclotron facility using a 24-min proton beam of 250 μA to produce a 5 Ci of activity. Radiolysis was calculated to be significant with ~ 0.371 ml/min water decomposing to H_2 and $^{18}\text{O}_2$. Since it is costly to vent these gases ($\sim \$666$ per run), a catalytic recombination unit using 385 ml of finely-divided palladium on alumina was incorporated. The catalyst vessel also acts as a reservoir, should target water accidentally be forced from other regions of the system.

A sidestream anion exchange column was designed to recover ^{18}F , utilizing the acetate form of highly crosslinked resin. The pressure drop and flow rate, calculated to be 13.6 psi and 2.2 ml/sec, enable 99.9% of the ^{18}F to be recovered within 10 min after the cyclotron run. The total target-water inventory is 240 ml and losses are estimated to be no more than 0.75 ml/run.

An externally bombarded $^{18}\text{O}_2$ target was also designed to deliver $^{18}\text{F-F}$. Suitable conditions to yield one Ci would be a 20- μA beam current with an irradiation time of 47 min. Laboratory tests with normal water to examine efficiency of the sidestream recovery column, heat exchangers, and catalyst vessel are recommended.

2. INTRODUCTION

With the development of tomographic imaging devices, radiopharmaceuticals labeled with short-living, positron-emitting nuclides of ^{11}C , ^{13}N , ^{14}O , ^{15}O , and ^{18}F are finding increased use in medicine. Among them, ^{18}F has the longest half-life and can be attached to certain compounds with unaltered biological behavior. Fluorine-18 can be produced either with reactions such as $^{16}\text{O}(\alpha, d)$, $^{16}\text{O}(^3\text{He}, p)$, $^{20}\text{Ne}(d, \alpha)$, or $^{18}\text{O}(p, n)$ using particle accelerators or with the reaction set $^6\text{Li}(n, \alpha)t$, $^{16}\text{O}(t, n)^{18}\text{F}$ using thermal neutrons.

In a continuing project by ORNL and ORAU, an integrated modular system for synthesizing positron-emitting radiopharmaceuticals was designed. In a previous report, the design for a system utilizing H_2^{18}O as the target material was presented (9). Problems of heat removal, ^{18}F activity, target geometry, and materials of construction were investigated. However, target-water radiolysis and ^{18}F recovery processes were not examined. The decomposition of the target water by radiolysis is undesirable since it may cause pressure buildups and result in ^{18}O loss if the product gases are vented. The recovery scheme should deliver ^{18}F in the forms of anhydrous HF, fluorides, or fluorine gas, all of which can be used in syntheses of different radiopharmaceuticals.

The objectives were to determine the extent of proton radiolysis of water and its effects on the ^{18}F production system and to design a ^{18}F recovery process. Cyclotron space limitations, radiation hazards, target-water costs, and yields in radiopharmaceutical synthesis processes were considered.

3. RADIOLYSIS OF TARGET WATER

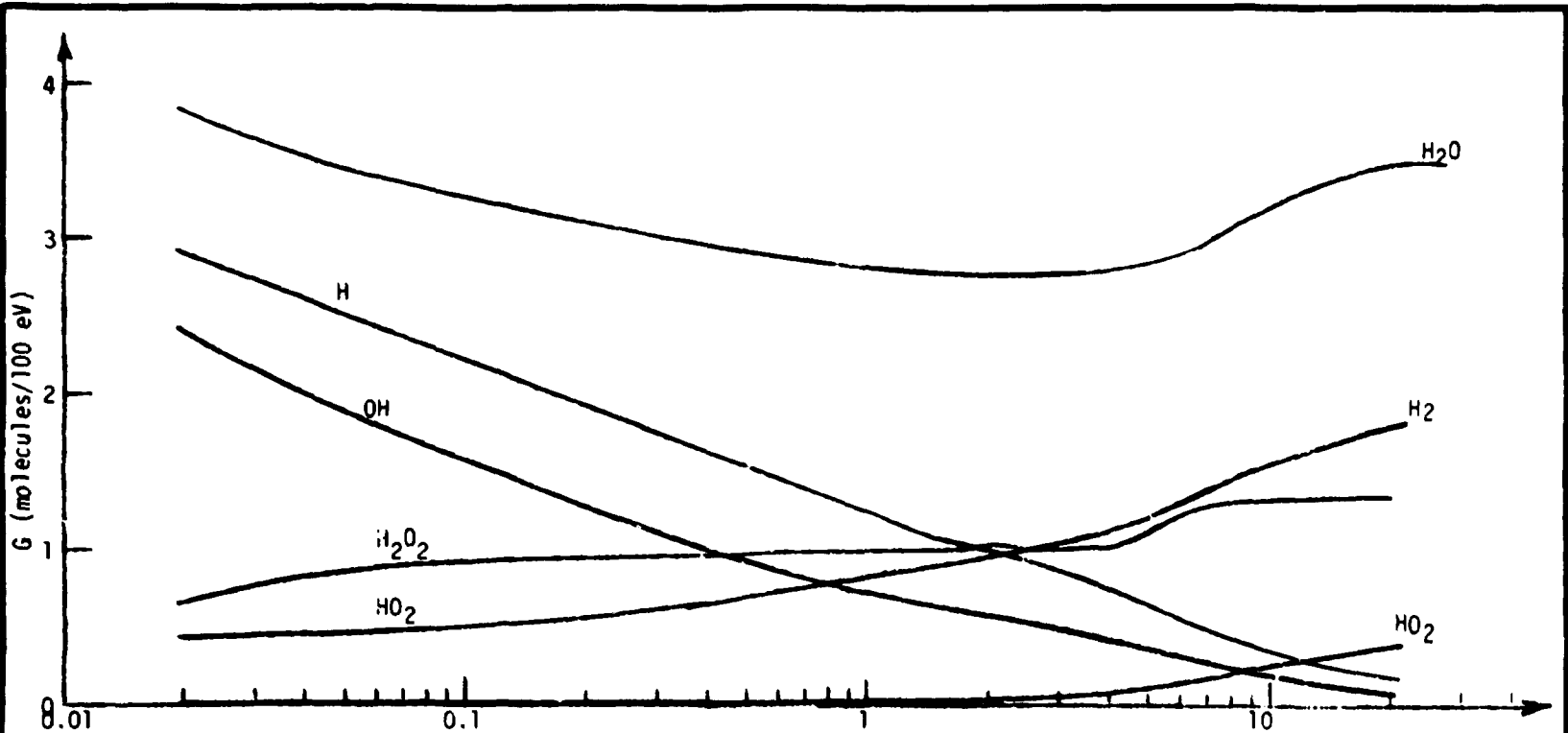
Radiolysis is the decomposition of water by high-energy radiation and can produce many products, depending on the beam energy, beam current, temperature, and nature of solutes. Molecular and radical yields can be described by G values, which represent the number of molecules or radicals formed per 100 eV deposited in the target. Values of G for water decomposition are shown in Fig. 1 as a function of $-dE/dx$, the rate at which particle beams lose their energy, also called stopping power by physicists and linear energy transfer (LET) by radiobiologists. Oxygen was found among the decomposition products and was believed to be formed indirectly as a result of the action of the radicals on the intermediate hydrogen peroxide (1).

In the proposed system, 250 μA of 22-MeV protons have a stopping power of 0.31 eV/ \AA . As they slow down, their stopping power will increase to 8.0 eV/ \AA , a maximum for protons (7). In the region from 0.3 to 8.0 eV/ \AA , average G values for H_2O decomposition and H_2 formation were 3.0 and 1.0 molecules per 100 eV deposited, respectively. From previous data (9), 3 kW would be deposited in target water. Therefore, the H_2^{18}O decomposition rate would be 5.58×10^{-2} mole/min or 1.12 ml/min, and with H_2 formation rate of 1.85×10^{-2} mole/min or 0.51 liter/min (see Appendix 10.1 for details). By stoichiometry, 0.26 liter/min O_2 would form, and venting these gases would then represent a corresponding water loss of 0.37 ml/min. With H_2^{18}O costing \$75/gm, the loss would be \$666 for each 24-min run.

A reactor vessel with palladium catalyst was designed to recover radiolysis products. In a previous work, 25-50 ml of alumina-supported palladium (1/8 x 1/8-in. pellets) was successfully used to recombine 100 ml/min of H_2 and O_2 (10). A direct scaleup results in a catalyst inventory of 385 ml to permit the same residence time for the gases.

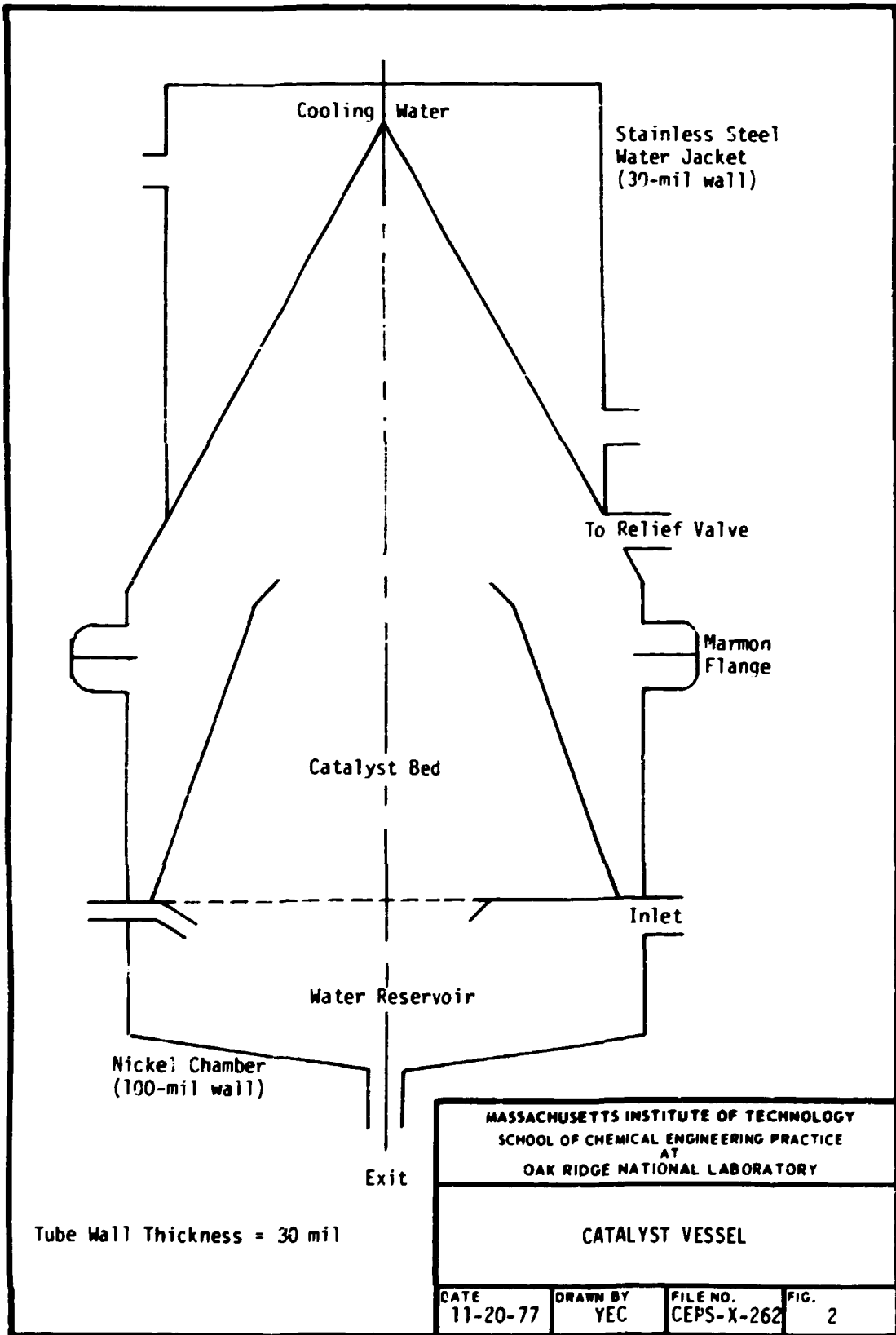
A schematic diagram of the catalyst vessel is shown in Fig. 2. The vessel volume is compact enough to be used in the cyclotron target dolly yet should provide sufficient heat-transfer surface to condense the water vapor. A perforated plate supports the catalyst pellets. Pellets form a catalyst bed shaped like a truncated cone. The condensed water will slide down the water-cooled wall of the conical section rather than directly fall into the catalyst bed.

All interior surfaces must be nickel to prevent HF damage. Walls of 100-mil thickness allow an internal pressure up to 300 psi. For safety, a pressure-relief valve set at 100 psi is located near the base of the conical



Linear Energy Transfer = $-\frac{dE}{dx}$ (eV/Å)

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WATER DECOMPOSITION YIELDS VS INITIAL LINEAR ENERGY TRANSFER (1)			
DATE	DRAWN BY	FILE NO.	FIG.
11-18-77	YEC	CEPS-X-262	1



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CATALYST VESSEL

DATE 11-20-77	DRAWN BY YEC	FILE NO. CEPS-X-262	FIG. 2
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section. Heat generated from the exothermic recombination of H₂ and O₂ would be low (0.89 W) but sufficient to keep the catalyst dry and enhance recombination kinetics.

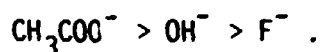
4. FLUORINE-18 RECOVERY FROM TARGET WATER

The system used to recover 5 Ci of ¹⁸F (4 x 10⁻⁹ mole of ¹⁸F) meets the following constraints:

1. Permits the production of ¹⁸F in an anhydrous fluoride form, particularly K¹⁸F or H¹⁸F.
2. Uses a quick recovery process to minimize decay of ¹⁸F activity.
3. Avoids loss or contamination of target water.
4. Fits in the limited space at ORNL's 86-inch cyclotron facility.
5. Provides radiation shielding for operating personnel.

Recovery techniques such as ion exchange, distillation, solvent extraction, and co-precipitation were considered. Ion exchange was chosen because it has been the only simple technique in which anhydrous ¹⁸F production has been demonstrated in addition to having other operation-related advantages (4). Use of a sidestream recovery system has the advantages of small column size, prolonged contact time, and small pressure drop. A mathematical model of the system indicated that a sidestream with 2% of the total flow will recover 99.9% of the ¹⁸F within 10 min after the cyclotron run (see Appendix 10.2 for details).

Since fluorine is very weakly bound by the ion exchange resin, strongly basic anion exchange resins such as Bio Rad AG1 (2) are required. The resins considered to recover fluoride ion should have the following ionic forms in order of decreasing strength:



The OH⁻ is unsuitable because it has only fair thermal stability. The F⁻ form has the drawback of diluting ¹⁸F activity with large amounts of inactive fluorine. Acetate-form resin is as efficient as the fluoride form and was therefore chosen (3). A highly crosslinked resin, such as AG1-X10 would be suitable since it expands little on hydrolysis and therefore has more ion exchange capacity per unit volume (see Table 1). The largest particle size available (50-100 mesh) is recommended to minimize pressure drop through the column.

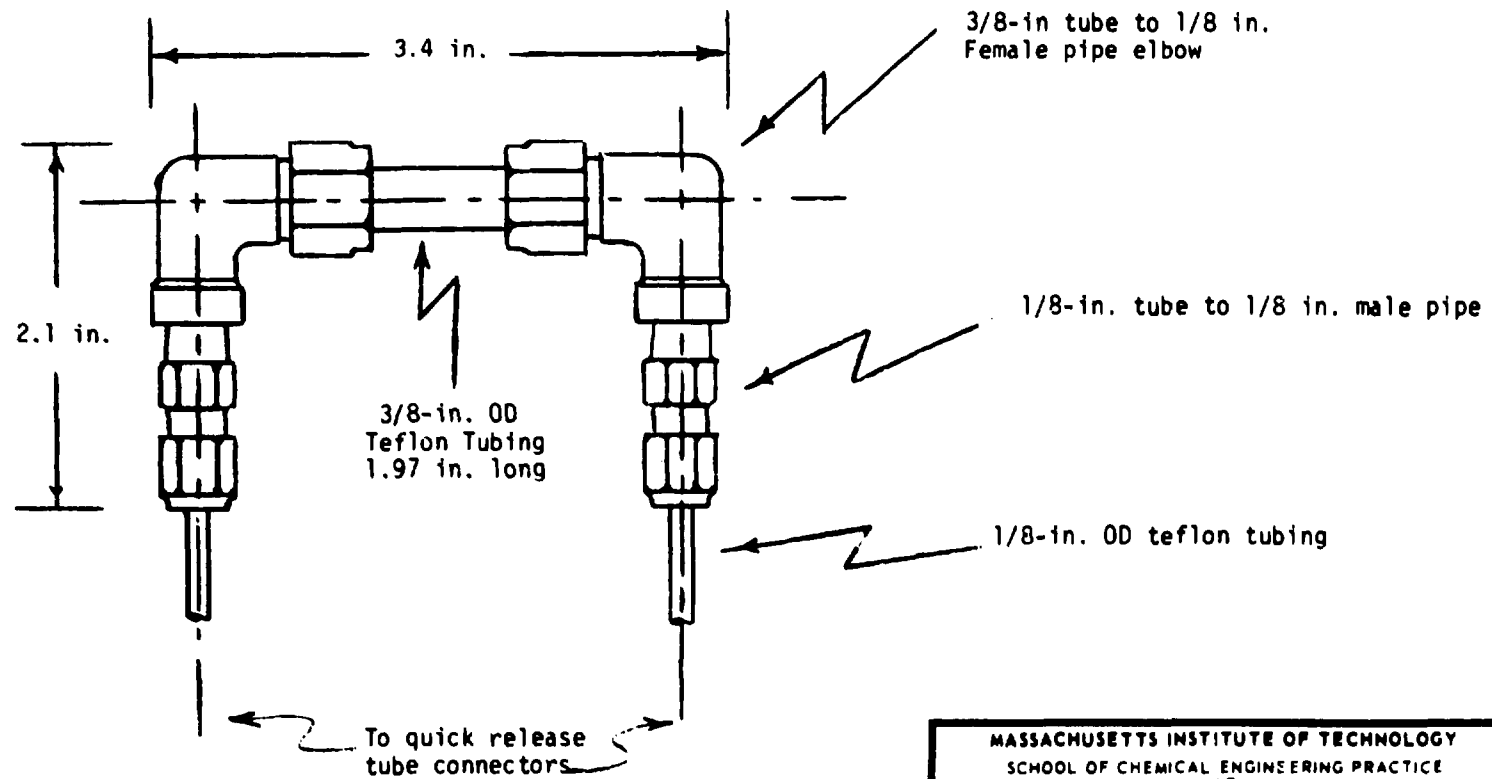
Table 1. Properties of AGI Resin as a Function of Crosslinkage (2)

<u>Resin</u>	<u>% Divinylbenzene</u>	<u>Exchange Capacity (meq/ml)</u>	<u>Water (%)</u>
AGI-X1	1	0.3	80-90
AGI-X2	2	0.7	70-79
AGI-X4	4	1.2	59-65
AGI-X8	8	1.4	39-45
AGI-X10	10	1.5	34-42

A column was designed similar to Lindner's (8), although somewhat more conservative (see Table 2). Associated connectors and fittings were then specified, as shown in Fig. 3. The pressure drop was calculated to be 13.6 psi, giving a sidestream flow rate of 2.2 ml/sec (see Appendix 10.4), which would recover 99.9% ^{18}F 10 min after the cyclotron run. Finally, a lead chamber, providing radiation protection, was designed to fit around the column (see Appendix 10.3).

Table 2. Column Design

	<u>This Work</u>	<u>Lindner (8)</u>
System flow rate	31.6 ml/sec	66.7 ml/sec
System volume	240 ml	250 ml
Column ID	0.80 cm	0.80 cm
Column length	5.0 cm	3.5 cm
Column volume	2.5 cm ³	1.75 cm ³
Exchange capacity	3.75 meq	2.28 meq
Column flow rate	2.2 ml/sec	6.7 ml/sec



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ANION EXCHANGE COLUMN AND FITTINGS

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5. COMPLETE WATER-TARGET SYSTEM

The complete water-target system, shown in Fig. 4, will fit on a one-foot-square platform built into the cyclotron dolly, with the heat exchangers fastened to the dolly leg. The procedures for system startup, column replacement, target drainage, and system drainage are described in Appendix 10.5.

In case of failure of the cooling-water system and/or the target-water circulating pump, target water would vaporize and cause a pressure increase. A check valve protects the pump and the ion exchange column from this back pressure. The catalyst vessel is large enough to contain the entire target-water inventory at a level below the catalyst bed, and a relief valve keeps the system pressure below a preset value. Any failure of that valve would be discovered before a run by flushing the system with H_2 and releasing it through the relief valve.

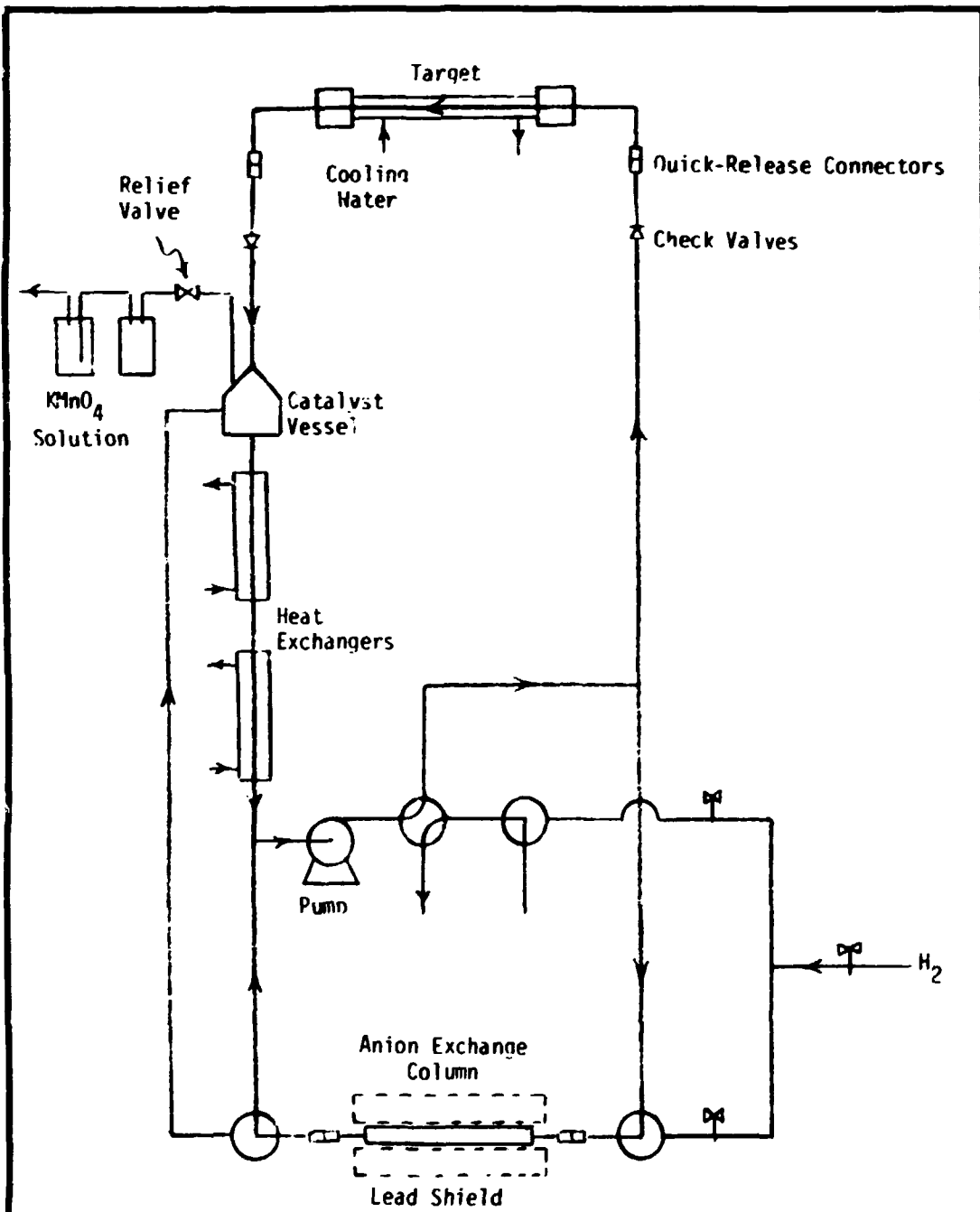
6. EXTERNAL GAS-TARGET DESIGN

It is also desired to produce $^{18}F_2$, which requires a $^{18}O_2$ target. An external gas target offers advantages of lower target inventory, no radiolysis-related problems, and fewer heat-transfer complications. However, for the 86-inch cyclotron at ORNL to deliver a 30 μA external beam, 3000 μA (full capacity) must be run internally. Current research indicates that an overall activity yield from target to patient injection is about 2% (11); thus a patient dose of 20 mCi demands 1 Ci of activity to be produced in the target (see Appendix 10.6).

The Accelerator Target Simulation (ATS) (6) package was used in the design. The proton beam leaving the interior of the cyclotron covers an area of 1 x 4 cm. The nuclear reaction cross section for $^{18}O(p,n)^{18}F$ is most pronounced in the region of 3 to 11 MeV. Therefore, a nickel window 0.063 cm thick would be suitable to attenuate the initial 22-MeV beam to 11 MeV. Using $^{18}O_2$ at 20 atm in a vessel 6.2 cm long attenuates the proton beam from 11 MeV to 3 MeV; hence a nickel vessel such as a 1 x 4 x 6.2 cm rectangular chute would be suitable (see Fig. 5). Cooling coils surrounding the vessel remove the heat generated and a port allows $^{18}O_2$ feed and $^{18}F_2$ purge. Table 3 lists beam currents and corresponding irradiation times necessary for producing 1 Ci of activity. For the proposed gas target at 20 atm, 0.75 gm $^{18}O_2$, at a cost of \$113/gm, is required.

7. CONCLUSIONS

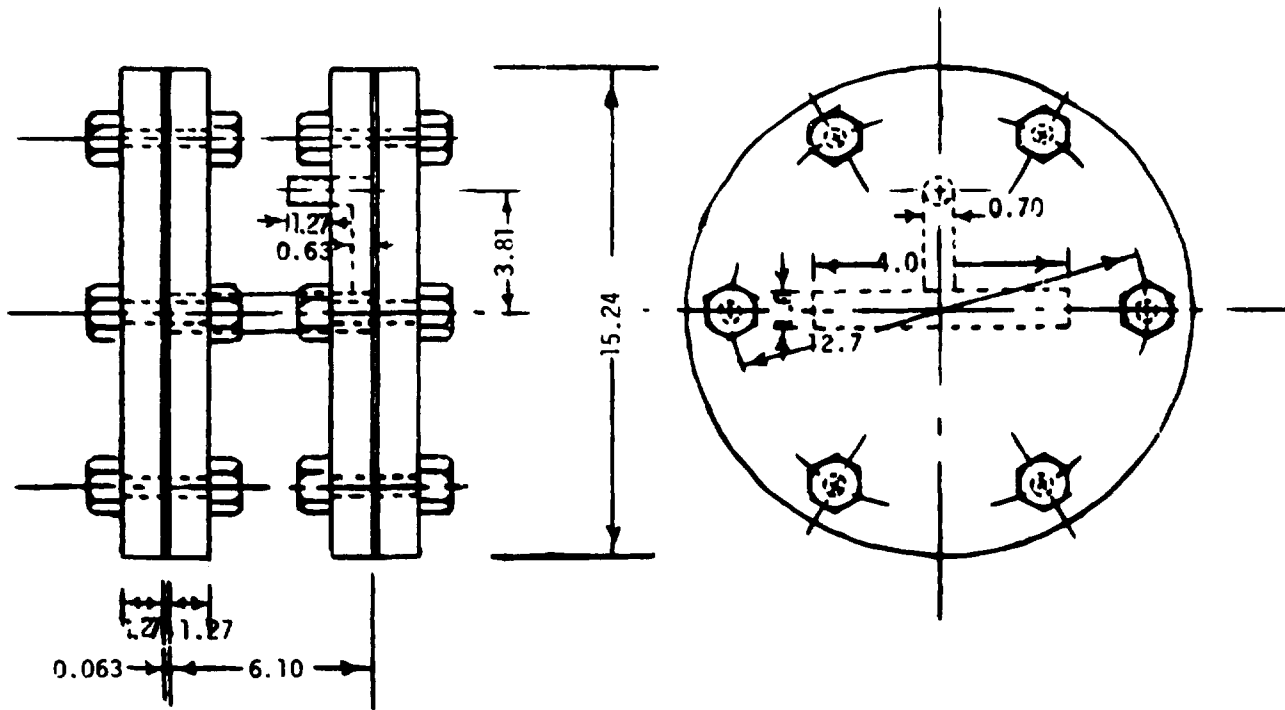
1. Radiolysis is a significant factor in the proton irradiation of target water in an ^{18}F production system.



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^{18}F PRODUCTION (WATER-TARGET) SYSTEM

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Units in cm

Target wall thickness = 0.038 (150 mil)

Material: Ni

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GAS-TARGET DESIGN

DATE 11-18-77	DRAWN BY YEC	FILE NO. CEPS-X-262	FIG. 5
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Table 3. Beam Current vs Irradiation Time to Produce
1 Ci of Activity in External Gas Target

Equation used: Final yield = $(0.197 \frac{\text{Ci}}{\mu\text{A}})(\text{beam current, } \mu\text{A})(1 - e^{-\lambda t})$
 where: $\lambda = 0.693/t_{1/2}$ ($t_{1/2} = 110 \text{ min}$)

Final Desired Yield (Curie)	Yield per 1 μA (from ATS)	Beam Current (μA)	Irradiation Time (min)
*	0.197	1	-
*	0.197	5	-
1	0.197	6	297
1	0.197	10	112
1	0.197	15	66
1	0.197	20	47
1	0.197	25	36
1	0.197	30 (max)	29

* A final yield of 1 Ci can never be achieved.

2. A sidestream anion exchange column can effectively recover ^{18}F from the water target.
3. Target-water loss is estimated to be no greater than 0.75 ml/run.
4. The system can produce the desired ^{18}F donating agents either in the form of anhydrous H^{18}F or other fluoride, such as K^{18}F .
5. An externally bombarded gas target can be used to deliver 1 Ci of ^{18}F from $^{18}\text{O}_2$ at 20 atm in a reasonable irradiation time.

8. RECOMMENDATIONS

1. Investigate the efficiency of anion exchange columns using ^{18}F -solution so that column length can be minimized to reduce inventory loss.
2. Test the proposed anion exchange column to obtain data on pressure drop vs flow rate and water-recovery efficiencies.
3. Investigate the contamination of target water brought about by resin decomposition due to high-energy radiation.
4. Run the complete system with ordinary water to test the efficiency of the heat-removal system and the catalytic reactor performance.
5. Study the feasibility of using 20% enriched H_2^{18}O as target material.
6. Examine the proposed external gas-target system for its activity yield operating under the conditions of a 20- μA beam current and 47 min irradiation time.

9. ACKNOWLEDGMENTS

The authors express their gratitude to C.J. Hohanadel and G.H. Jenks of ORNL, M.R. Skidmore of Y-12, R.R. Highfill and L.C. Washburn of ORAU, R.S. Tilbury of Sloan-Kettering Institute for Cancer Research, C.N. Wan of Brookhaven National Laboratory, and N.S. McDonald of UCLA, who supplied us with invaluable information. We are most deeply indebted to our consultants, T.A. Butler, J.K. Poggenburg, Jr., and B.W. Wieland, for their guidance and encouragement.

10. APPENDIX

10.1 Radiolysis Rate of Water

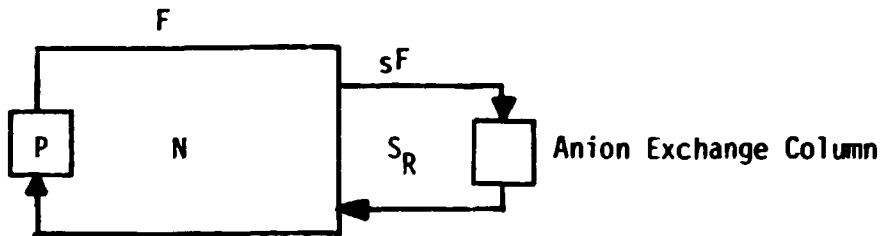
From previous calculations (9), it is known that 3000 W is deposited into the target water. This corresponds to $3000/(1.602 \times 10^{-19}) = 1.87 \times 10^{22}$ eV/sec. From Fig. 1, the average G_{H_2} is 1 molecule/100 eV. Therefore, H_2 production rate is 1.87×10^{20} molecules/sec, resulting in

$$\begin{aligned} \text{molal hydrogen production rate} &= 1.87 \times 10^{20} / (6.02 \times 10^{23}) \\ &= 3.1 \times 10^{-4} \text{ mole/sec} \end{aligned}$$

Using the ideal gas law at 62°C and 1 atm, 0.51 liter/min of H_2 will be generated.

10.2 Sidestream Recovery Model

The following equations describe the recovery of ^{18}F in the sidestream anion exchange column, assuming 100% efficiency of the resin.



The number of ^{18}F atoms in the main flow loop (N , where $N=0$ at $t=0$) is described by:

$$\begin{aligned} \frac{dN}{dt} &= P - \lambda N - \left(\frac{sF}{M}\right)\left(\frac{N}{V}\right) = P - BN \\ N &= \frac{P}{B}(1 - e^{-Bt}) \end{aligned}$$

The total number of ^{18}F atoms in both loops (T , where $T=0$ at $t=0$) is given by:

$$\frac{dT}{dt} = P - \lambda T$$

$$T = \frac{P}{\lambda}(1 - e^{-\lambda t})$$

Thus, the number of ^{18}F atoms recovered in the sidestream loop (S_R) is simply,

$$S_R = T - N = P\left(\frac{1 - e^{-\lambda t}}{\lambda} - \frac{1 - e^{-Bt}}{B}\right)$$

Given the flow rates and volumes of the final design, $V = 240 \text{ cm}^3$ and $\bar{M} = 2.2 \text{ cm}^3/\text{sec}$. These equations indicate that 91.9% of ^{18}F will have been recovered at the end of a 24-min cyclotron run. Additional calculations show that 99.9% of the ^{18}F will have been recovered 10 min later.

10.3 Lead Shield for Anion Exchange Column

To protect operating personnel from ^{18}F radiation, the lead shield shown in Fig. 6 was designed. The total weight of the shielding and column will be about 35 lb. The shielding will reduce the radiation dose from 5 Ci in the column to about 400 mr/hr at a distance of 10 in. from the lead surface.

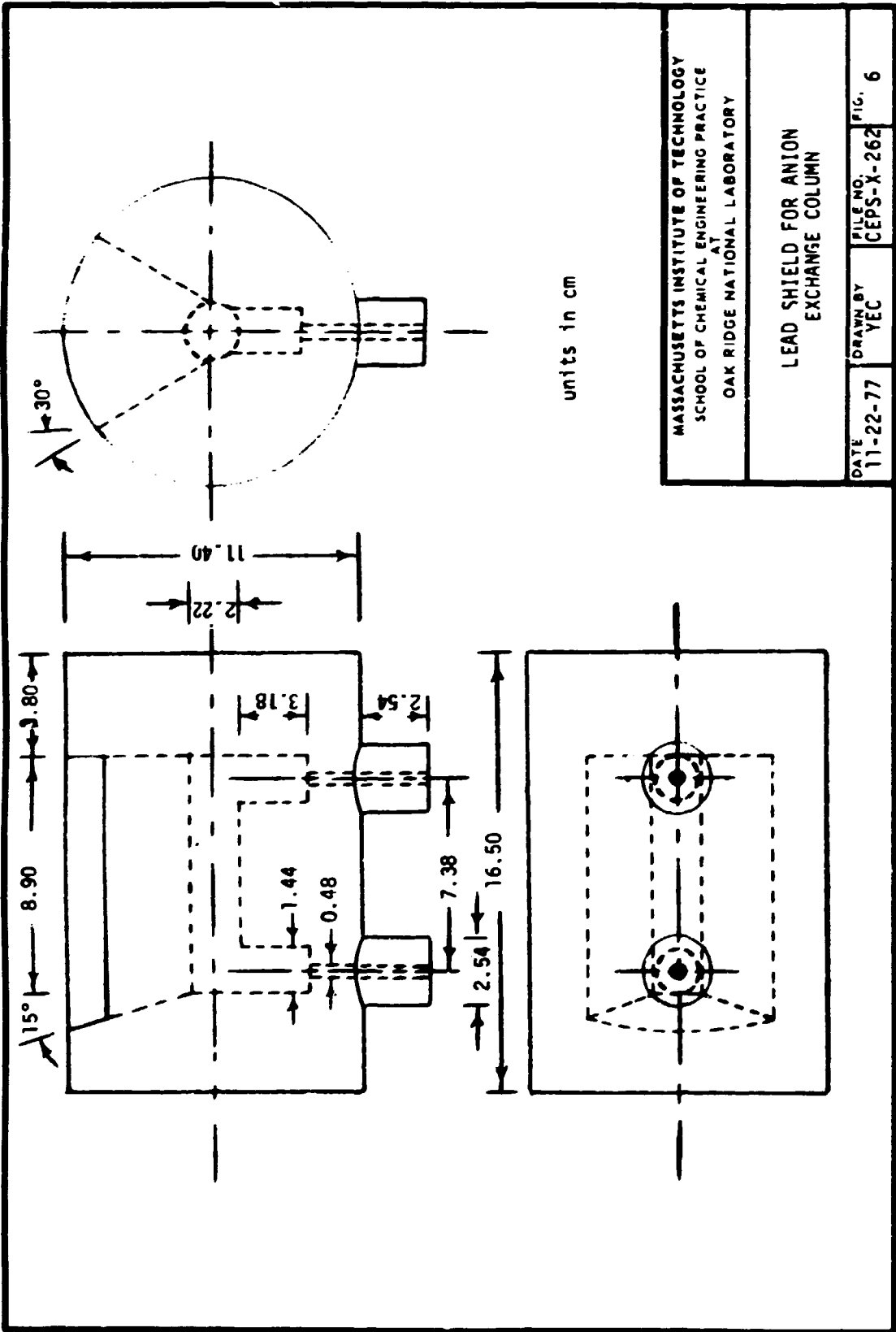
10.4 Pressure Drop vs Flow Rate of Sidestream

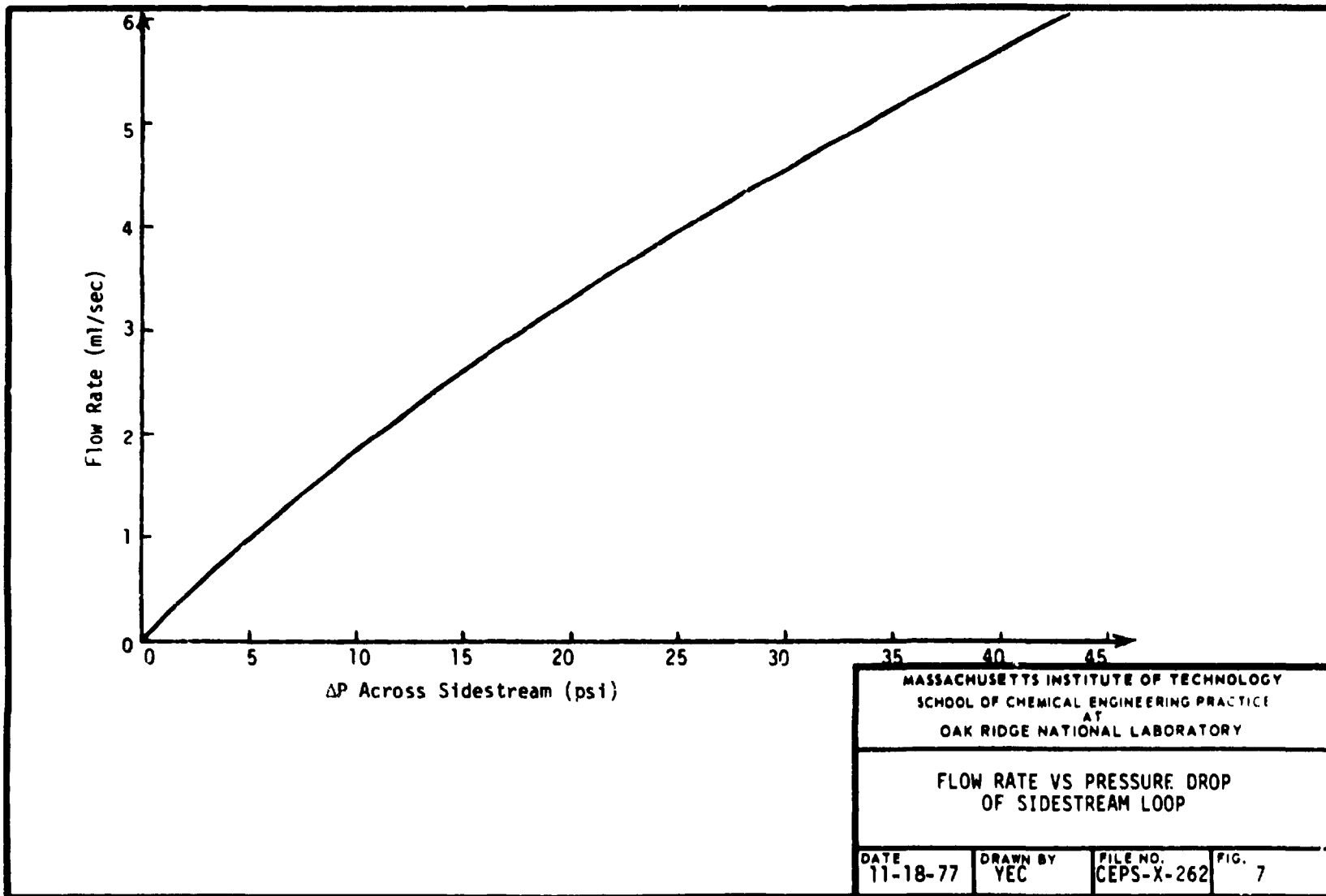
The pressure drop across the sidestream loop consists of the pressure drops in the resin column, two quick-connectors, two three-way ball valves, and the 61-cm-long, 1/8-in.-OD (30-mil wall) tubes. The calculated pressure drop is plotted as a function of water flow rate in Fig. 7.

10.5 Operating Procedures

System Startup

1. Attach a new anion exchange column to the system and surround it with the lead shield. Put freshly prepared KMnO_4 solution in the scrubbing bottle.
2. Connect the system to the target, cooling water supplies, and H_2 source.





3. Pour 240 ml target water into the catalyst vessel. Check the condition of the catalysts and replace if necessary.
4. Run the circulating pump for 3 min.
5. Flush the column with H₂ for 5 min.
6. Start the circulating pump, cooling water system, and then run the cyclotron for 24-min irradiation.
7. Let the pump run for 10 min more after ceasing irradiation.
8. Flush the column with H₂ for 5 min. Remove the column to the hot cell for synthesis.

Column Replacement

1. Attach a new column in position.
2. Follow the procedure in previous section beginning with Step 4.

Target Drainage

1. Have all valves in the system in operating positions.
2. Flush the target region with H₂ through the 4-way and 3-way valves next to the circulating pump to force the target water into the catalyst vessel.

System Drainage

1. Have all valves in the system in operating positions.
2. Flush the system with H₂ through the 4-way and 3-way valves next to the circulating pump, and run the pump to force the target water from the system.

10.6 Gas Target Activity Requirement

The following activities are required for the clinical use of 2-¹⁸F-2-deoxy-glucose (FDG) (5, 11):

	<u>Yield from Each Step</u> (%)	<u>Activity</u> (mCi)
Administered dose	-	20
Synthesis, pyranosyl to FDG (hydrolysis reaction)	60	33.3

	<u>Yield from Each Step (%)</u>	<u>Activity (mCi)</u>
Only one fluorine atom per FDG	50	67
Synthesis, glycol and $^{18}\text{F}_2$ to pyranosyl	35	190
Handling time, one half-life	50	380
$^{18}\text{F}_2$ recovery from $^{18}\text{O}_2$	65	580
Contingencies	58	1000

10.7 Nomenclature

ATS	accelerator target simulation computer code
B	$\lambda + \frac{SF}{V}$, sec^{-1}
$-\frac{dE}{dx}$	stopping power (= LET), $\text{eV}/\text{\AA}$
F	flow rate in main loop, ml/sec
FDG	2-fluoro-2-deoxy-glucose
G	number of molecules or radicals formed from decomposition per 100 eV deposited in target material
LET	linear energy transfer (= $-dE/dx$), $\text{eV}/\text{\AA}$
N	number of ^{18}F atoms in the main loop, atoms
P	rate of ^{18}F production, atoms/sec
s	fraction of F in side stream
S_R	number of ^{18}F atoms in resin column, atoms
T	total number of ^{18}F atoms in the system, atoms
t	time, sec
$t_{1/2}$	half-life, sec
V	volume, cm^3
λ	decay constant = $0.693/t_{1/2}$

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