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An Automated Micro-Processor Controlled Rubidium-82 Generator for Positron Emission Tomography Studies

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Radioisotope generators provide a desirable alternative to cyclotrons for the production of short lived positron emitters. A fully automated microprocessor controlled generator system for obtaining 76 sec rubidium-82 is described in detail. Column adsorbants, specifications and eluent solutions are discussed in determining generator performance for yield, breakthrough, and stability for long term use. Some examples of clinical applications in positron emission tomography are presented.

Ultra short lived radionuclides, with a half-life of a few seconds to a few minutes are readily available from long-lived parent radionuclides adsorbed to an organic or inorganic ion exchange support matrix (1-3). These radionuclide generator systems are an inexpensive alternative to an on-site cyclotron, especially for positron emitters used for positron emission tomography (PET). In PET studies it is an advantage to have very short half life positron emitters which permit the administration of 10-20 mCi of radioactivity for good statistical sampling in the reconstructed cross-sectional image while minimizing the radiation dose to the patient. An added benefit of the short half life is the rapid decay of background activity within 5-10 minutes. Repeat studies can then be performed on the same subject to obtain additional information under different physiological conditions. Some generators for positron emitters are listed in Table I. Generator produced Ga-68 is of considerable interest because of its potential for imaging thrombi formation with labeled platelets and for imaging atheroma with bifunctinal chelate labeled lipoproteins (4,5). Bifunctional chelates are also applicable to labeling monoclonal antibodies. Other positron emitters from generators, which have been studied, are Ba-128/Cs-128 (6), Fe-52/Mn-52m (7,8), and Zn-62/Cu-62 (9). The Xe-122/I-122 generator can be useful in labeling amphetamine analogs with I-122 to measure brain blood flow by PET (10,11). This chapter will discuss experience with the strontium-82/rubidium-82 generator and its operation in the automated mode for PET studies.

Experimental Studies

Rubidium-82 Generator Development. The radionuclidic properties of the 76 sec Rb-82 and the 25 day Sr-82 parent are shown in the decay scheme, Figure 1. Strontium-82 decays 100% by electron capture (E.C.) to the 1.25 min Rb-82, which decays 96% by $^{+}$ emission and 4% by E.C. to the ground state of Kr-82. The 511 keV annihilation photons are accompanied by a 777 keV gamma emission in 13% abundance. The $_{max}$ energy is 3.35 MeV.

The first Rb-82 generator was developed in 1968 with a weakly acidic cation exchange resin, Bio Rex 70, and ammonium acetate as the eluent solution (12). The development of the Rb-82 generator over a period of 14 years is outlined in Table II. Other Rb-82 generator systems were developed which used the chelating ion exchange resin, Chelex 100, and an NH_4OH-NH_4Cl eluent (13), alumina the inorganic ion exchanger (14,15) and zirconium oxide (16) using saline as the eluent solution. Recent Rb-82 generators have used a combination of alumina and Chelex 100 in tandem columns (17,18) and a SnO_2 column (19,20). Normal saline or 1.8% NaCl solutions were used as the eluent solution. The alumina column was used in an automated microprocessor controlled system (21).

The Rb-82 generator permits serial studies in the same patient as often as every 10 minutes with 20-60 mCi of Rb-82 for rapid bolus intravenous infusion. Inherent in the administration of high levels of Rb-82 activity is the need for precise flow control from an automated system to deliver the desired amount of radioactivity. The development of the alumina column parameters and the elution protocol as well as the automated microprocessor system controller are presented here. Some of the details of this system have been discussed in earlier publications (15,21). Generator produced Rb-82 is used as a diffusible flow tracer in myocardial perfusion studies and as a nondiffusible tracer in brain studies to assess blood brain barrier permeability changes in patients with brain tumors or Alzheimer's type dementia.

Production of Sr-82. An important consideration in the development of radioisotope generators is the availability, cost, and radionuclidic purity of the long-lived parent. In the case of Sr-82, the 25 day radionuclide is needed in 100-200 mCi amounts in order to provide adequate elution yields of Rb-82 from one loading of Sr-82 every three months. Initially the Sr-82 for the generator was produced at the Lawrence Berkeley Laboratory (LBL) 88-inch cyclotron by the Rb-85 (p,4n) Sr-82 nuclear reaction (12). However, because of the long irradiation time required to produce mCi amounts of Sr-82, this method was too costly for routine production of large quantities of Sr-82. Fortunately, the high to medium energy protons from the linear accelerators at the Los Alamos National Laboratory and the Brookhaven National Laboratory (BNL) are available to produce Sr-82 and other useful radionuclides in high yields.

The Sr-82 used in these studies was produced by spallation of a molybdenum target with 800 MeV protons at the Los Alamos Meson Physics Facility (LAMPF) and radiochemically separated by the Nuclear Chemistry Group at Los Alamos Scientific Laboratory (LASL) (22). The major radionuclidic contaminant in the Sr-82 is Sr-85 which is present in at least 1:1 ratio relative to Sr-82. The actual ratio depends upon the length of time after the production of radioactive strontium. Because of the 65 day half life of Sr-85 and the 25 day half life of Sr-82, the Sr-85:Sr-82 ratio increases with time. Other radionuclides found by the Hammersmith group in the processed Sr-82/85 shipment were Sr-89 (1%), Sr-90 (0.01%), Co-58 (1%) and Rb-84 (1%) from (17).

Alumina Column Yields and Breakthrough. Previous experience with the basic alumina column for the Rb-82 generator led to the design of the present column (15). The yield of Rb-82 in the column eluent is dependent on the Al_2O_3 bed volume, concentration of saline eluent, and flow-rate. These parameters also affect the breakthrough of Sr. Figures 2a and 2b show the effect of these factors for an alumina column of 0.25 to 1.00 ml, using saline solutions 1.25 to 2.00% in NaCl (15). For the 2% NaCl eluent there was a factor of 100 less breakthrough for a 25% increase in column volume from 0.75 to 1.00 ml. In the case of 1.25% NaCl eluent a 25% increase in column volume resulted in a tenfold decrease in breakthrough. The yield of Rb-82 from a 1 ml bed volume was increased by about 10% for 1.75-2.00% NaCl concentration compared to the 1.25-1.50% NaCl. The breakthrough of Al_2O_3 was 5 g/ml of 2.0% NaCl of pH 8-9. This value is one-half the allowable breakthrough for Al_2O_3 for a Tc-99m generator of 10 g/ml as set by the national regulatory agency. Because of the large amounts of radioactivity (200 mCi Sr-82 and 300-400 mCi of Sr-85) in the automated generators, a larger volume of Al_2O_3 was used is these studies to minimize breakthrough over long term use of the generator.

A stainless steel (ss) tube 3/8" o.d. with 1/16" wall thickness and 10 cm long (3.2 ml) is fitted with ss screens and Millipore prefilters at the top and bottom of the stainless steel (ss) tube which is connected by 3/8" to 1/8" Swagelok reducers to 1/8" o.d. ss tubing. All of the column components are autoclaved and assembled. The top connector and screen are removed and the column is filled with 100-200 mesh Bio-Rad basic alumina in a water slurry at pH 8-9. The alumina column is clamped between two rectangular lead plates that have been machined to fit around the ss column and placed inside of a solid lead cylinder 5 inches in diameter which has been slotted to accept the rectangular plate column shield. The shield and column are placed in a lucite enclosure behind the "hot cell" for remote pumping and loading of the Sr-82/85 as shown in Figure 3.

Loading Sr-82/85. The Sr-82/85 is shipped in a few ml of dilute HCl from LASL. The shipping shield is opened remotely and the contents of the vial are transferred to a flask. The Sr-82/85 solution is diluted with about 100 ml sterile pyrogen-free H_2O to maintain a low salt concentration and the pH is adjusted to 8-9 with dilute base. A remotely operated pumping system pumps the Sr-82/85 solution through the alumina column at a flow rate of about 1-2 ml/min. After the Sr-82/85 has been placed on the column, the flask and pumping syringe are washed two times with about 40 ml of pH 8-9 sterile water. Usually the column is left undisturbed overnight to allow the Sr-82/85 to become more firmly fixed to the alumina matrix. The column is then purged with 500 ml of 2% saline at pH 8-9 at a moderate flow rate of about 0.5 ml/sec. Quick-connects allow the column and shielding to be easily freed from the pump and connecting lines.

Construction and Operation of the Rb-82 Generator. The Sr-82/85 column and shield are then transported to the PET imaging site and the Sr-82/85 shield is lifted into a secondary lead cyclinder with 3 inch wall thickness. Quick connects are used to connect the column to the lines from the automated and microprocessor controlled pumping unit as shown in Figure 4a. An open loop (Slo-Syn) stepping motor is used to provide adequate torque and a wide dynamic speed range. A timing belt connects the stepping motor to a recirculating ball-nut and screw that moves the stainless steel piston inside of the specially machined Lexan barrel. A Bellofram rolling diaphram around the piston provides a low friction seal against airborne contamination and prevents the saline eluent solution from contacting the stainless steel piston. The motor controller is a 6800 Motorola microprocessor with 4K memory, a crystal clock, a programmable timing module, two RS-232 serial ports, and an 8-bit analog to digital converter. The controller converts input from the operator into a precise number of pulses for the stepping motor. The micro processor minimizes operator error by simplifying the controls and doing the calculations, counting, and timing. The schematic of the controller is shown in Figure 4-b.

The front panel of the controller has two four-digit thumbwheel switches and two lighted pushbutton switches. The thumbwheels determine flow rate (ml/min) and volume to be delivered (ml). One pushbutton switch initiates the pump-refill operation. The other starts the injection, or stops an injection in progress. After power-up or reset, the microprocessor initializes itself and sets up the timing module and serial ports. It then jumps into a looping program that scans the two pushbutton switches and the thumbwheel switch specifying volume. The system thus monitors changes in switch settings, scanning at greater than 1000 times per second. When a change is detected, the new setting is stored and the program enters a service routine for that particular switch. The first part of each routine is a delay that guarantees that the new setting is stable for at least 50 msec.

Another part of the loop program ascertains how much solution is left in the pump. A voltage picked off a ten-turn potentiometer, which is coupled to the piston-drive screw with a timing belt, is fed to the analog-to-digital converter and is compared with the previously stored reading from the thumbwheel switch. If the operator has requested a greater volume of solution than present in the pump, the program sets up a circuit in the programmable timing module that causes the insufficient lamp to flash twice a second. An injection cannot be started in this state; the operator must either refill the pump from the solution reservoir or change the amount to be delivered. The outlet from the pump is connected to a motor-driven three-way valve by 1/8" ss tubing and Swagelok fittings. The three-way valve allows connection to either the saline fill bottle when the controller is in the refill position or to the Sr-82/Rb-82 alumina column when the controller is in the elution position.

The filling sequence is started when the loop program has determined that the fill pushbutton has been actuated. The fill service routine turns on the refill pushbutton light, turns on the valve motor and waits for the correct valve position, then sends 100-sec pulses to the stepping motor in the reverse direction until the pump reservoir is filled; it then turns on the valve motor again, waits for correct position, turns off the refill light, and reenters the loop program. The last part of the loop program determines whether the start/stop pushbutton has been activated. If it has, the service routine reads the flow-rate thumbwheel switch and computes the period T during which pulses are sent to the stepping motor, as defined by equation (1), F is flow rate in ml/min and C, a systems constant, is calculated to be 257 pulses to deliver 1 ml of eluent. The quantity of injected solution Q ml (2) is determined by the number of pulses N sent to the stepping motor.

$$T(\text{msec}) = \frac{6 \times 10^4}{FC} \quad ; \tag{1}$$

$$Q = \frac{N}{C} \quad . \tag{2}$$

This system will perform both bolus and constant infusion studies with the microprocessor controller. In addition, variable or exponential infusion studies can be performed by using programs residing in a host computer to calculate constants which are sent to the controller through the serial port.

Elution and Breakthrough Characteristics of the Generator. The fractional elution yield and cumulative yield of Rb-82 are shown in Figure 5a,b for 2% saline bolus elutions at a flow rate of 1 ml/sec. Nine 3 ml fractions were collected over 27 sec. Each value is the mean of 3 determinations. Fractions 3-5 contain 70% of the Rb-82 available from the Sr-82 on the alumina column. The total elution yield is about 95% in nine fractions.

In some studies it is desirable to do constant infusion to achieve a steady state or equilibrium condition which is a function of input, extraction rate, tissue washout, and radioactive decay (23). Figure 6 shows the yield of Rb-82 at various elution rates to a steady-state condition. At the faster flow rate of 5.33 ml/min, there is 24% yield of Rb-82 and at the slower flow rate of 2.15 ml/min there is about 1% yield of Rb-82. The lower yield at the slower flow rate is mostly accounted for in decay during transit through the line to the patient.

The advantage of an automated precision flow controlled generator is seen in Figure 7, which shows the relationship between decay of the Sr-82 on the column and the elution time required to deliver a desired radioactive dose of Rb-82 for bolus infusion studies at a flow rate of 1 ml/sec. The elution time in sec is selected and an equivalent volume is set on the thumbwheel switches for volume desired. Normally when the conditions of delivery line volume and column characteristics are unchanged, pre-set values determined from the chart will deliver 95 ± 5% of the desired radioactive dose. The actual radioactive dose delivered is checked in three preelutions before the beginning of each day of patient studies. The history of a typical column packed with alumina and loaded 3 separate times with Sr-82/85 is shown in Table III. The generator column was used for a period of nine months or an average life of 3 months for each Sr-82 loading. The average breakthrough of Sr-82/85 for each bolus elution was about 10^{-7} for columns 10a and 10b. These columns contained about 600 mCi of Sr-82/85 at maximum activity. Thus, the breakthrough was in the 60 nCi range.

Column 10c contained an unusually large amount of Sr-85 activity of about 2 Ci. To compensate for this heavy loading, a small trapping column of 1.5 ml of alumina was placed down-stream from the main column and the breakthrough was maintained in the 30-40 nCi range. Because of the increased total volume from the addition of the second alumina column, the elution yield of Rb-82 decreased from 78% to 61% in column 10c.

Selected samples of Rb-82 elutions were analyzed for radionuclidic breakthrough by Ge/Li analysis. These results are shown in Table IV. The smaller sample numbers indicate samples taken relatively soon after loading the column with Sr when the breakthroughs are higher. As more elutions were done after the column loading, the breakthroughs of Sr-82/85 and other contaminating radionuclides decreased. Samples 75 and 76 reflect the breakthroughs from column 10c in Table III where the activity of Sr-82 and Sr-85 is 2 Ci and the breakthrough of Sr-82 and Sr-85 is 36 nCi.

Radiation Dosimetry. The radiation dose to the skeleton of a 70 kg man from 1 Ci of Sr-82/Rb-82 and Sr-85 is reported to be 71 and 7.6 mrads, respectively (17). The estimated radiation dose from 10 mCi of Rb-82 is 700 mrads to kidneys, 140 mrads to heart and 90 mrads to lungs (24). These radiation dose estimations are on the high side and in later calculations have been found to be lower by accounting for decay in vivo in transit to the specific tissues.

Clinical Studies

Heart Studies. Patients are placed in position on the Donner 280 crystal positron tomograph which is a single slice PET system with bismuth germanate (BGO) detectors (25,26). Transmission images are taken with a Ge-68 hoop source and the data are used to correct for attenuation. The patient is connected to the outflow line from the Rb-82 generator by an intravenous catheter and three-way valve. The required time in secs translated into ml required for a 20 mCi dose of Rb-82 is set on the thumbwheel switches of the microprocessor controller. The elution button is pressed in synchrony with the start of data accumulation by the computer of the PET system. For studies of myocardial blood perfusion, gated studies are performed by synchronizing to the R-wave of the electrocardiagram. Data are collected on the selected portion of the cardiac cycle. This is normally triggered on the R-wave to +70 sec. Gated studies sharpen the image by reducing blurring from the movement of the heart and permit the accumulation of input function data from the ventricular blood pool.

Rubidium-82 myocardial perfusion images are used to study patients with myocardial ischemia or infarction. An example of this study is shown in Figure 8. Three patients with known myocardial infarction were imaged with Rb-82. Twenty millicuries of Rb-82 were administered in a 20 ml bolus in 20 sec. Data accumulated from 0-90 seconds post infusion show the blood pool as the radioactivity enters the right side of the heart, flows out to the lungs, and returns to the left side of the heart. Data accumulated from 90-300 seconds reflect uptake of Rb-82 in the myocardium as distributed by blood flow. These results by a non-invasive procedure correlated with the results of catheterized contrast x-ray studies (27,28).

Figure 9 shows the results of two coronary bypass patients studied with Rb-82 and PET. The uptake of Rb-82 is shown in three 1 cm sections of the myocardium. Each section was imaged with a single bolus infusion of 20 mCi Rb-82. Patient A had blood perfusion defects in the mid and lower sections of the myocardium.

Patient B had a perfusion defect in the upper section. Quantitative information of myocardial blood flow can be obtained if the input function (the amount of radioactivity in the blood that is delivered to the tissue) is obtained. This can be done from drawing regions of interest in the blood pool and the myocardium as shown in Figure 10. The computer extracted data from the PET images provides a graphical and quantitative output for the moment to moment changes of Rb-82 activity in the regions of interest (25,28).

Brain Studies. Rubidium-82 has also been used to study blood brain barrier changes in patients with brain tumors or Alzheimer's type senile dementia (28-30). The method of study is similar to the heart studies without gating. Figure 11 shows the uptake of Rb-82 in the three levels of a brain tumor. This non-invasive procedure provides information on the size and vascularity of the tumor. In the slice OM + 10 there is a vascular rim and a necrotic center in the tumor. The metabolism of glucose was determined in the same tumor patient using ^{18}F-fluorodeoxyglucose produced on a cyclotron and the results correlated well with Rb-82 distribution.

Summary

Automated radionuclide generators capable of providing precise dose delivery of multi-millicurie amounts of short-lived positron emitters on demand from a safe and easily operated system are an attractive alternative to on-site cyclotrons for positron emission tomography. The availability of curie quantities of parent radionuclides from national laboratories and the development of microprocessor automation makes it feasible to utilize these generators in the clinical setting.

We have demonstrated the use of generator produced Rb-82 as a readily available supply of a positron emitter for PET studies. At the same time, regional suppliers of cyclotron produced positron emitters can provide on a scheduled basis metabolic substrates such as ^{18}F-fluorodeoxyglucose by taking advantage of the 110 min half life of ^{18}F. Other applications of the Rb-82 generator are; the use of Rb-82 and 2.0 min oxygen-15 labeled H_2O in dual tracer kinetic studies to obtain information on coronary blood flow, pulmonary edema, extravascular lung water (31), and the intracoronary use of Rb-82 in the single photon mode with a rotating tungsten collimator to assess myocardial blood flow (32). The use of the constant infusion method to achieve steady state conditions for the measurement of myocardial blood flow has already been discussed as a method for using slower imaging systems.

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Table I. Generators for Positron Emitters

Parent	Half-life	Decay Mode(%)	Daughter	Half-life	Decay Mode(%)	Gamma MeV(%)
Fe-52	8.3 h	(56),EC(44)	Mn-52 m	21.1 m	(98),EC(2)	1.43(100)
Zn-62	9.1 h	(18),EC(82)	Cu-62	9.8 m	(100)	0.59(22)
Ge-68	275 d	EC(100)	Ga-68	68 m	(88),EC(12)	1.08(3.5)
Sr-82	25 d	EC(100)	Rb-82	76 s	(96),EC(4)	0.73(9)
Te-118	6.0 d	EC(100)	Sb-118	3.5 m	(75),EC(22)	1.23(3)
Xe-122	20.1 h	EC(100)	I-122	3.5 m	(100)	0.56(14)
Ba-128	2.43 d	EC(100)	Cs-128	3.8 m	(51),EC(49)	0.44(27)

Table II. Rubidium-82 Generators

Column	Eluent	Rb-82 Yield (%)	Sr-82/85 Breakthrough/ml	Reference
Bio-Rex 70	NH_4Ac	72	10^{-5}	Yano 1968
Chelex 100	NH_4Cl	90	10^{-7}	Grant 1975
Bio-Rex 70	NaCl	72	10^{-7}	Yano 1979
Al_2O_3	NaCl	76	10^{-7}	Yano 1979
ZrO_2	NaCl	60-70	10^{-8}	Kulprathipanja 1979
Al_2O_3 + Chelex 100	NaCl	14-66	10-9	Horlock 1981
Al_2O_3	NaCl	80-90	10^{-8}	Yano 1981
Sn02	NaCl	70	10-9	Neirinckx 1981
Al_2O_3 + Chelex 100	NaCl	40	10-9	Vallabhajousla 1981

Table III. History of One Alumina Column and Three ^{82}Sr Loadings

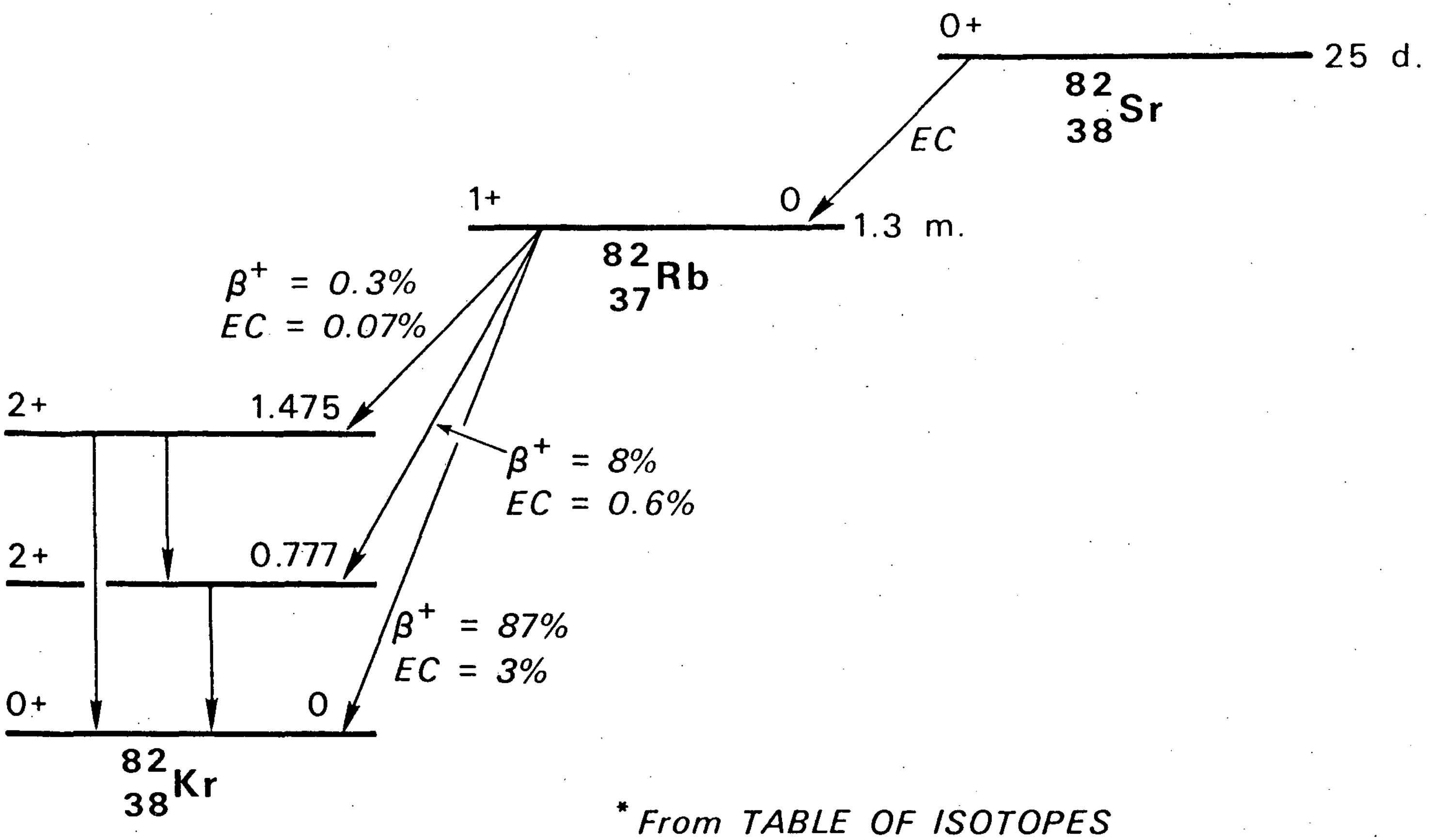
Column	Date Start	End	Sr Loading (mCi) Sr-82	Sr-85	Rb-82 Yield(%)	Sr Breakthrough (range)
10-a	8-26-81	11-20-81	197.5	439	79	$5x4x10^{-8}-1.9x10^{-6}$
10-b	11-13-81	1-18-82	132	460	78	$2.7x10^{-8}-1.7x10^{-6}$
*10-c	1-28-82	6-3-82	175	2,008	61	$5.7x10^{-9}-1.9x10^{-7}$

* Trapping column added

Table IV. Radionuclides in Rb-82 Eluates (nCi/20 ml Elution)

Date	Sample	V-48	Cr-51	Mn-54	Co-57	Co-58	Sr-82/ Rb-82	Rb-83	Sr-85
04/24/81	16	0.30	77.0	0.20		0.04	0.40	44.00	1.20
09/24/81	66		0.90	0.01	0.01	0.01	0.45	0.04	0.90
02/26/82	63			0.05	0.08	0.08	1.30	0.20	22.70
03/01/82	75			0.08	0.08	0.08	1.70	0.95	34.30
03/02/82	76			0.07	0.09	0.14	2.10	0.49	34.10
10/25/82	8	0.01	1.0	0.10			5.5	22	13.6

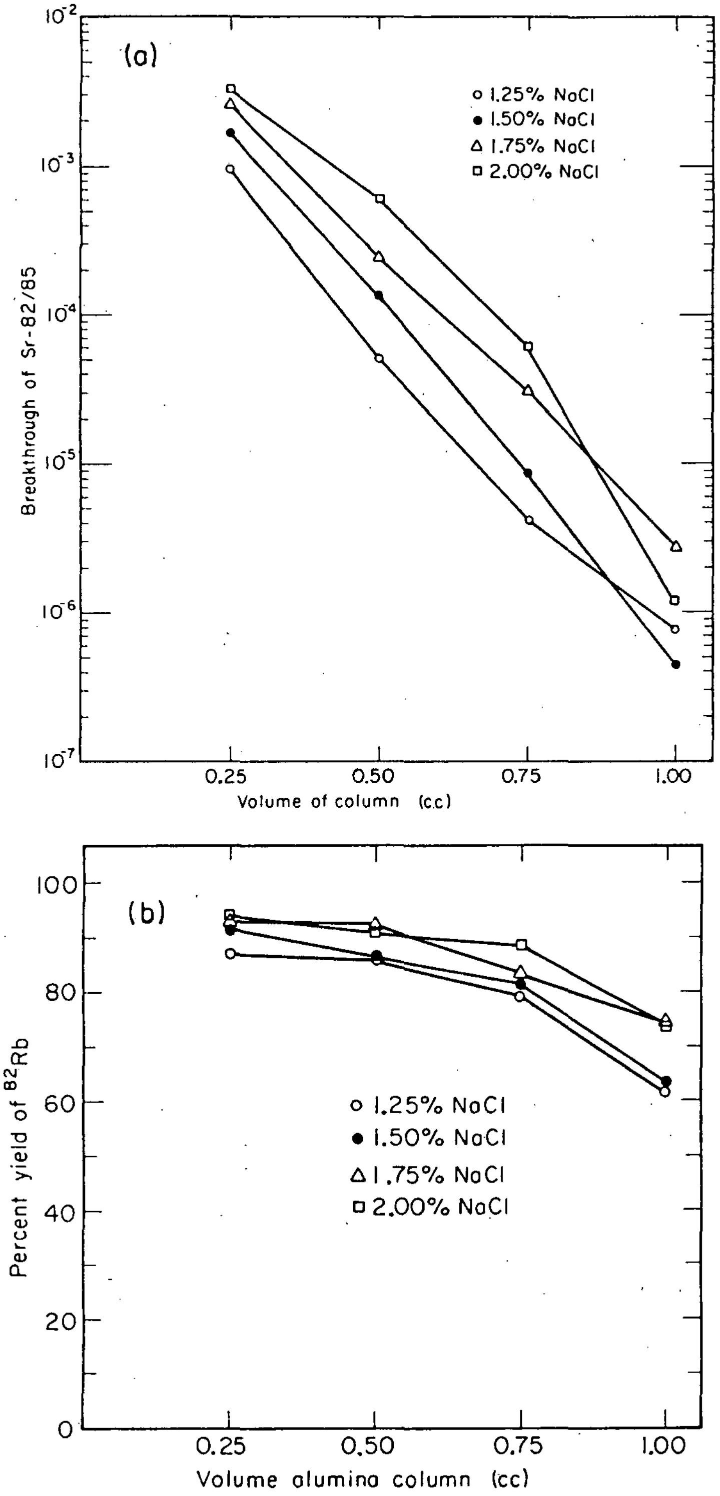
^{82}Sr-^{82}Rb DECAY SCHEME*



* *From TABLE OF ISOTOPES*
(Lederer, Hollander and Perlman, 6th Ed.)

Figure 1

XBL 7410-8112



XBL793-3250

Figure 2

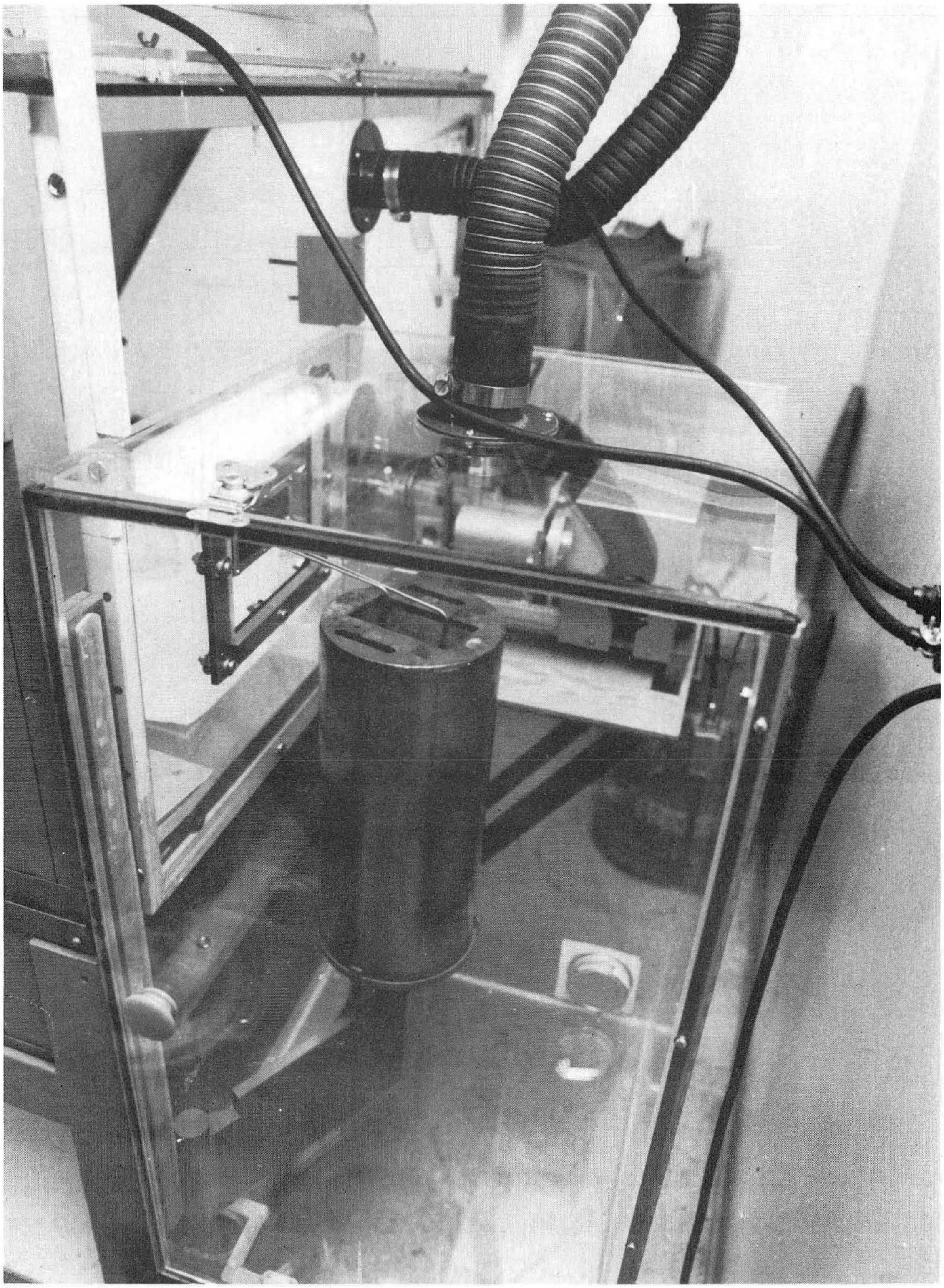


Figure 3 CBB 804-5173

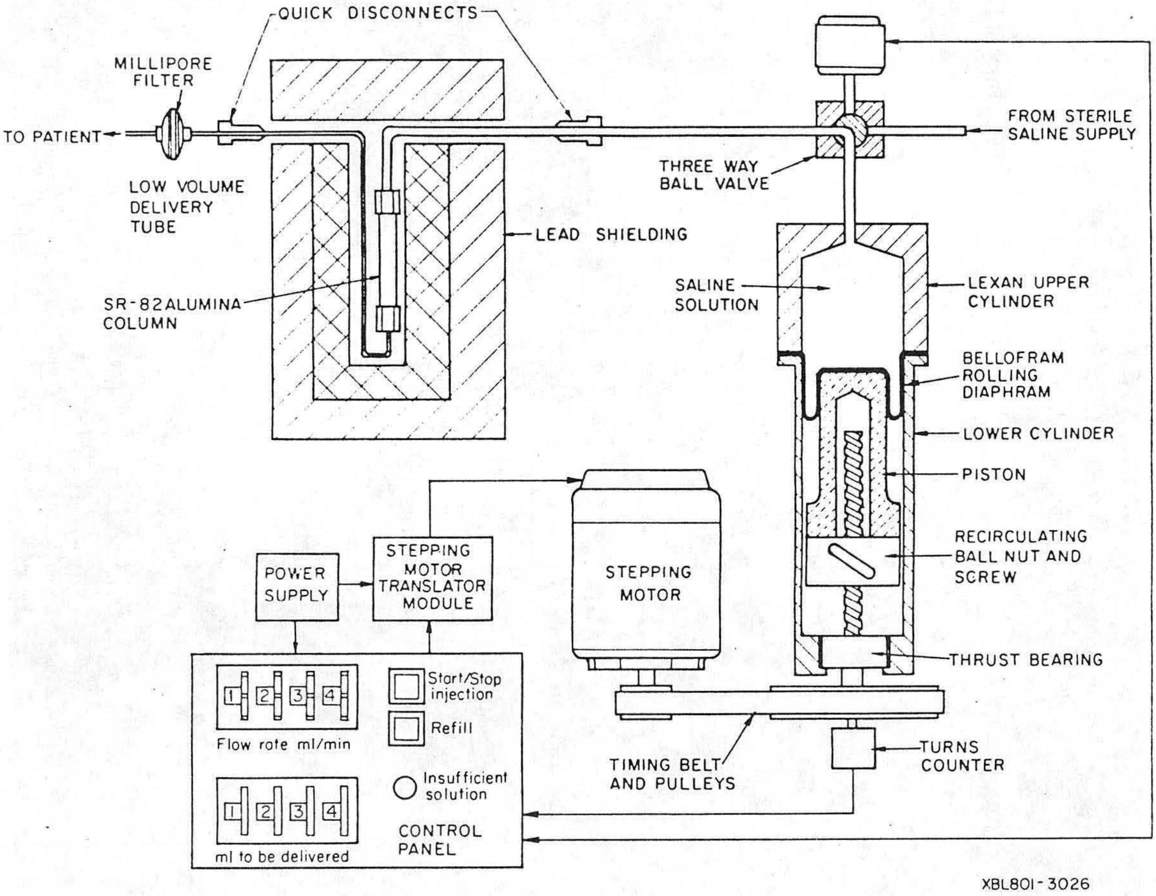
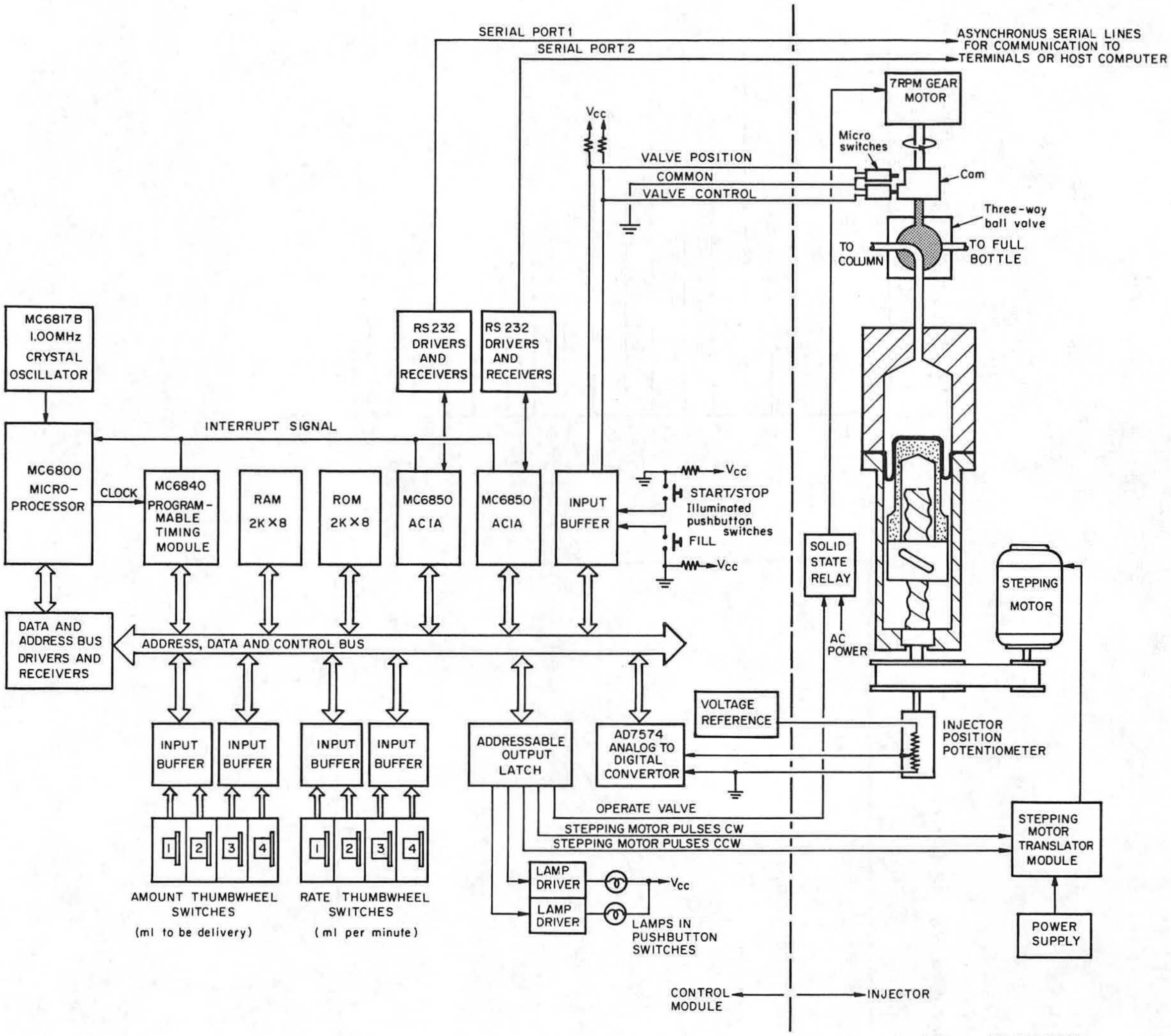

QUICK DISCONNECTS
MILLIPORE FILTER
TO PATIENT
LOW VOLUME DELIVERY TUBE
SR-82 ALUMINA COLUMN
LEAD SHIELDING
FROM STERILE SALINE SUPPLY
THREE WAY BALL VALVE
SALINE SOLUTION
LEXAN UPPER CYLINDER
BELLOFRAM ROLLING DIAPHRAM
LOWER CYLINDER
PISTON
RECIRCULATING BALL NUT AND SCREW
THRUST BEARING
STEPPING MOTOR
POWER SUPPLY
STEPPING MOTOR TRANSLATOR MODULE
1 2 3 4
Flow rate ml/min
Start/Stop injection
Refill
Insufficient solution
1 2 3 4
ml to be delivered
CONTROL PANEL
TIMING BELT AND PULLEYS
TURNS COUNTER
XBL801-3026

Figure 4-a



XBL834-3698

Figure 4-b

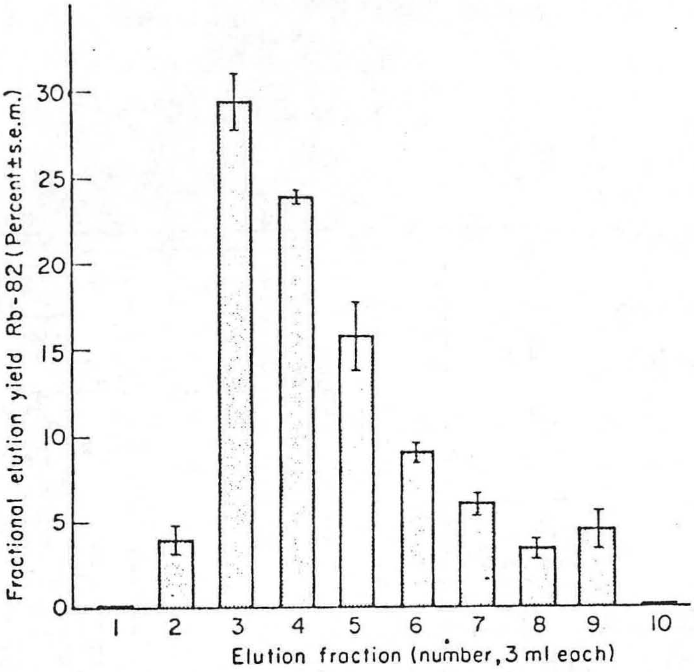


Figure 5-a

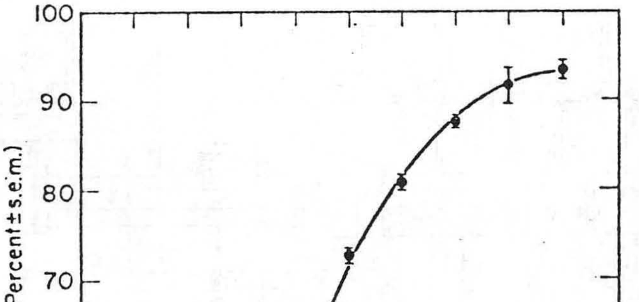


Figure 5-b

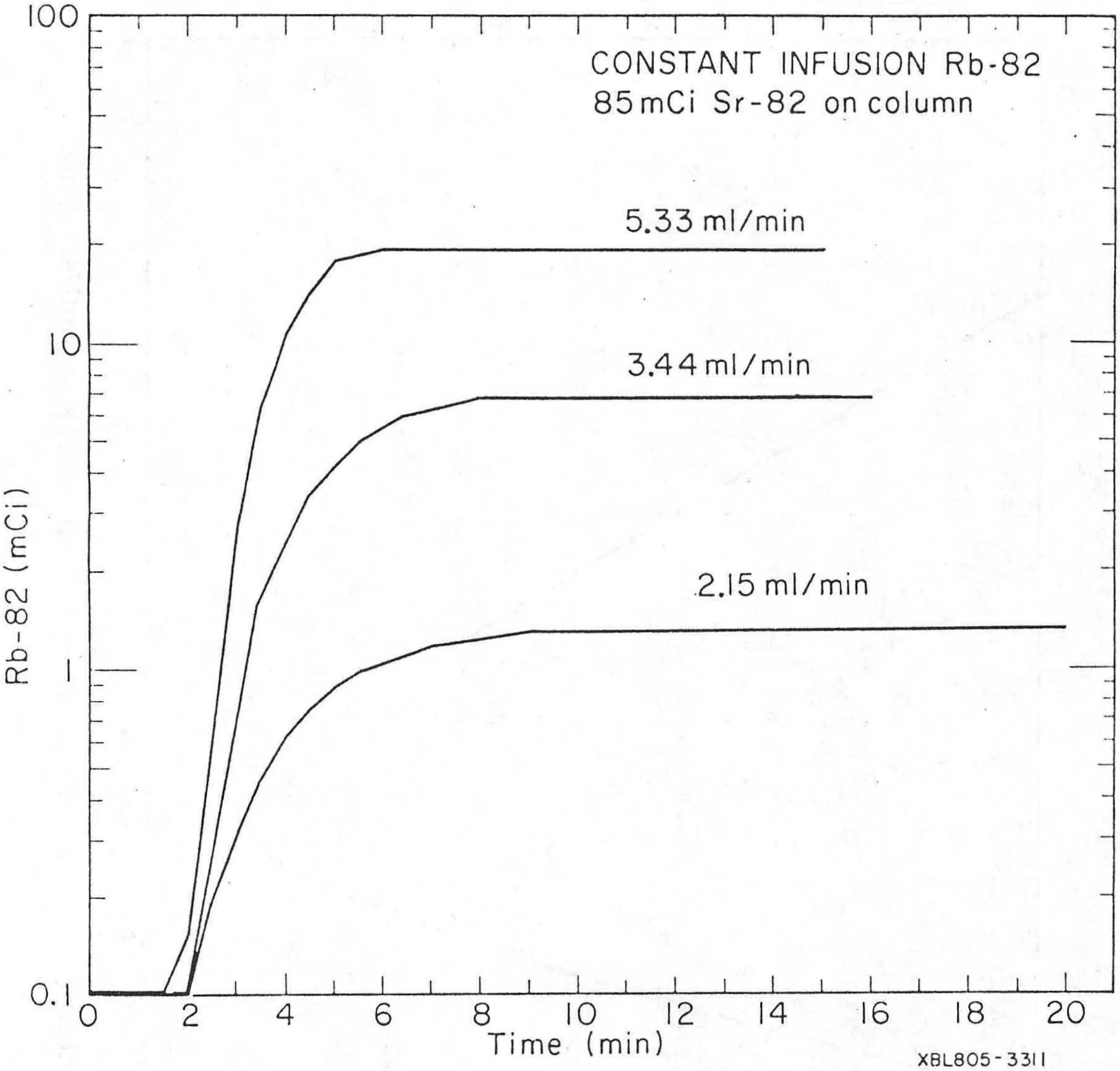
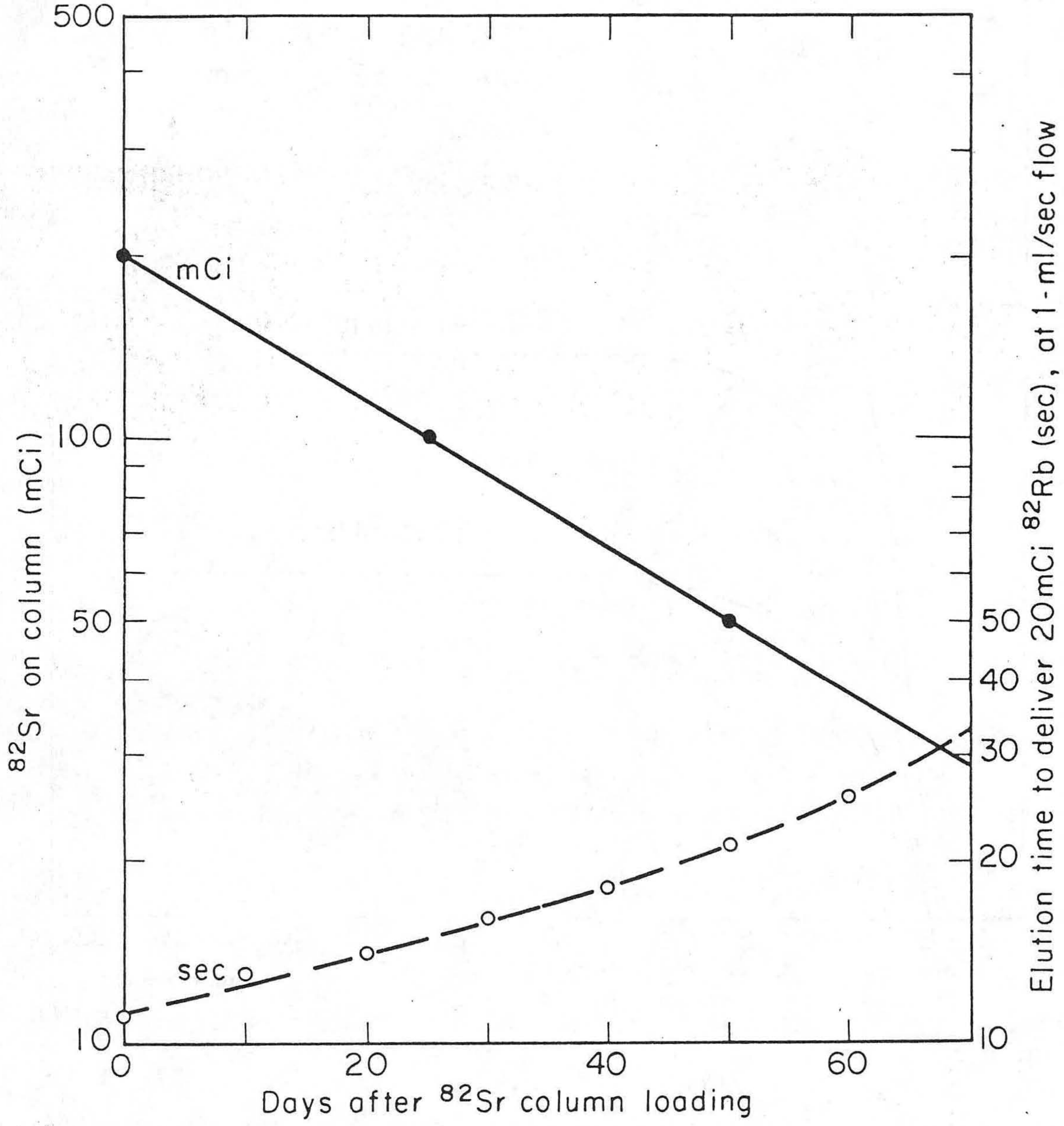
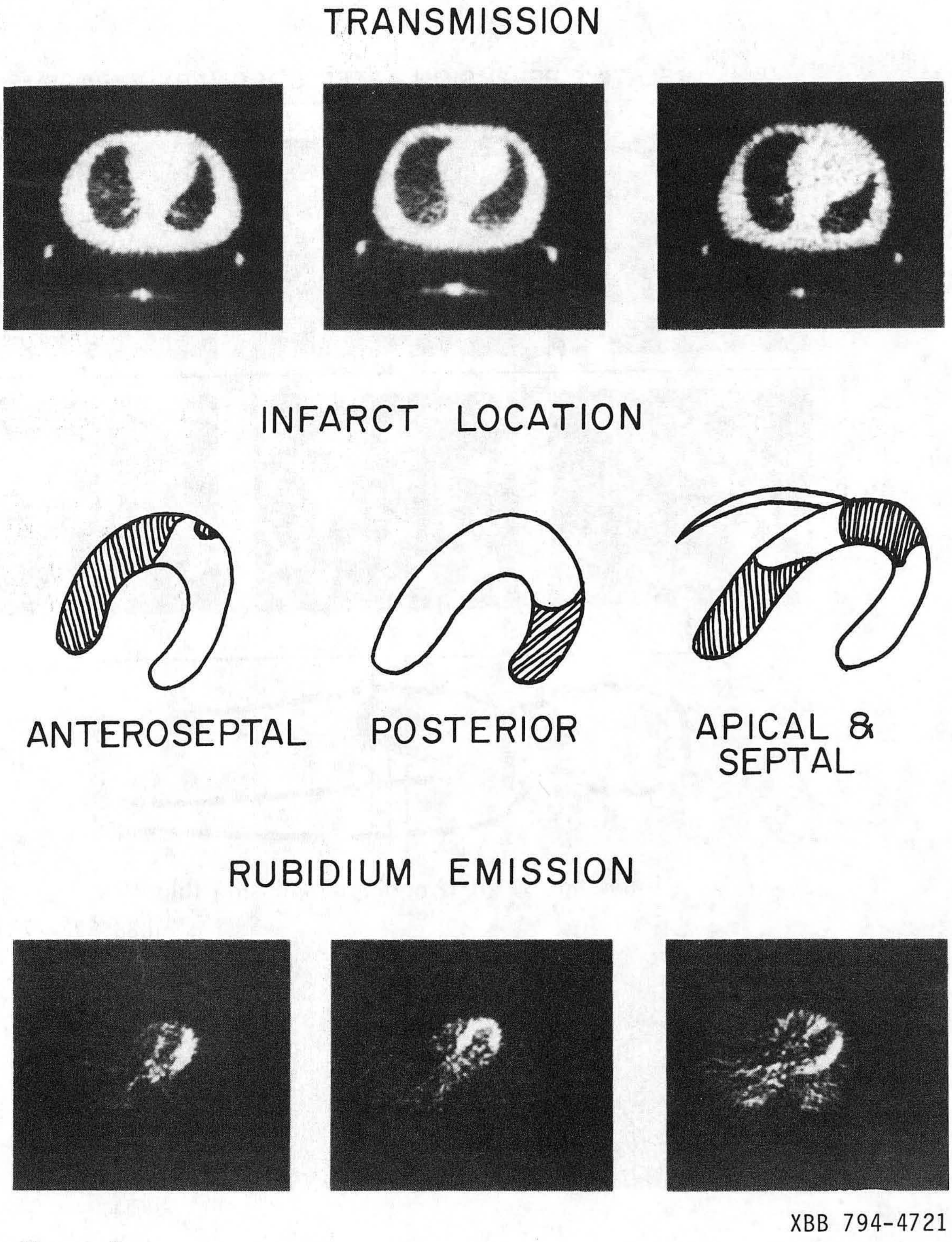

CONSTANT INFUSION Rb-82
85 mCi Sr-82 on column
5.33 ml/min
3.44 ml/min
2.15 ml/min
Rb-82 (mCi)
100
10
1
0.1
0
2
4
6
8
10
12
14
16
18
20
Time (min)
XBL805-3311

Figure 6



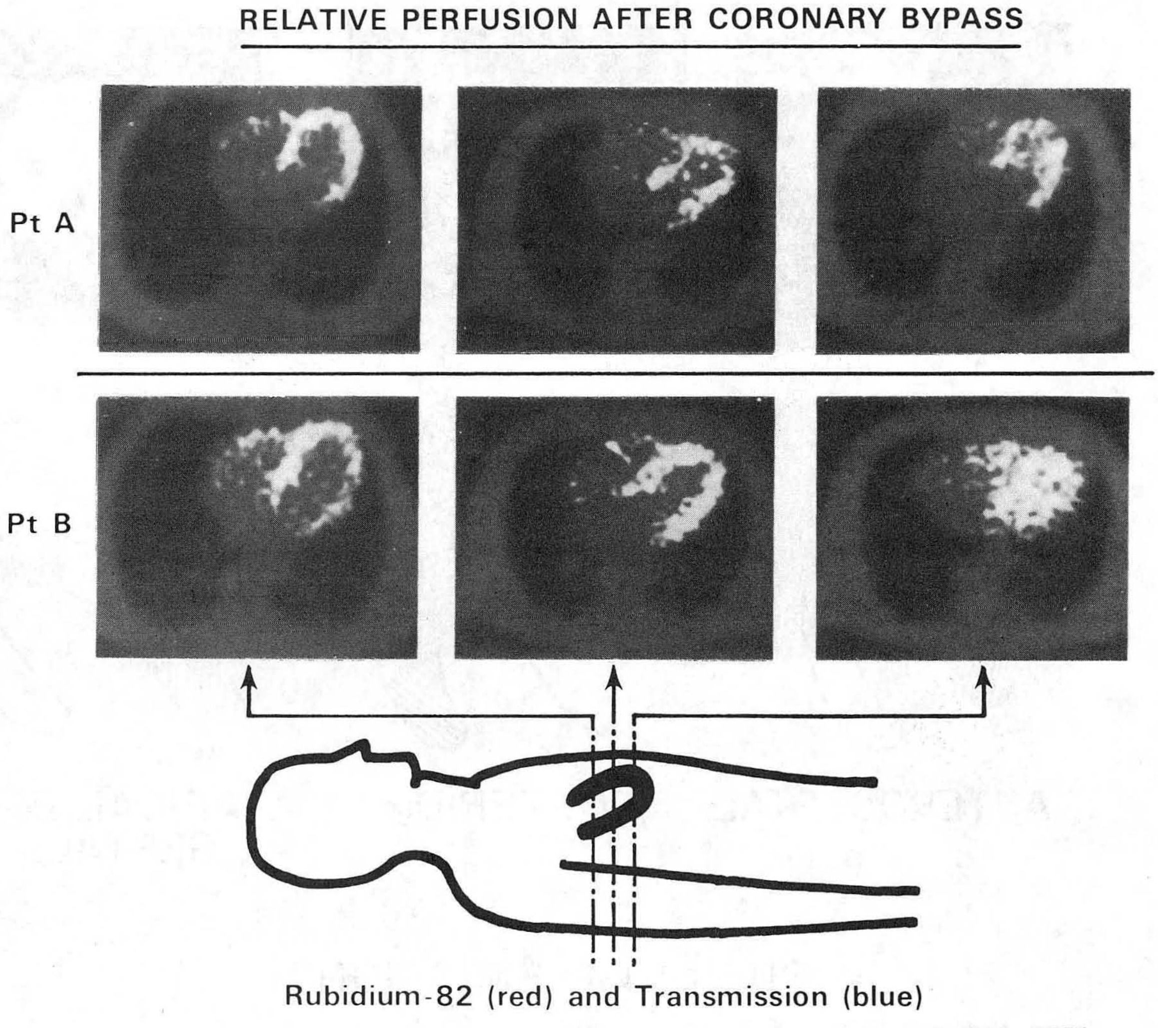
XBL822-3645

Figure 7



XBB 794-4721

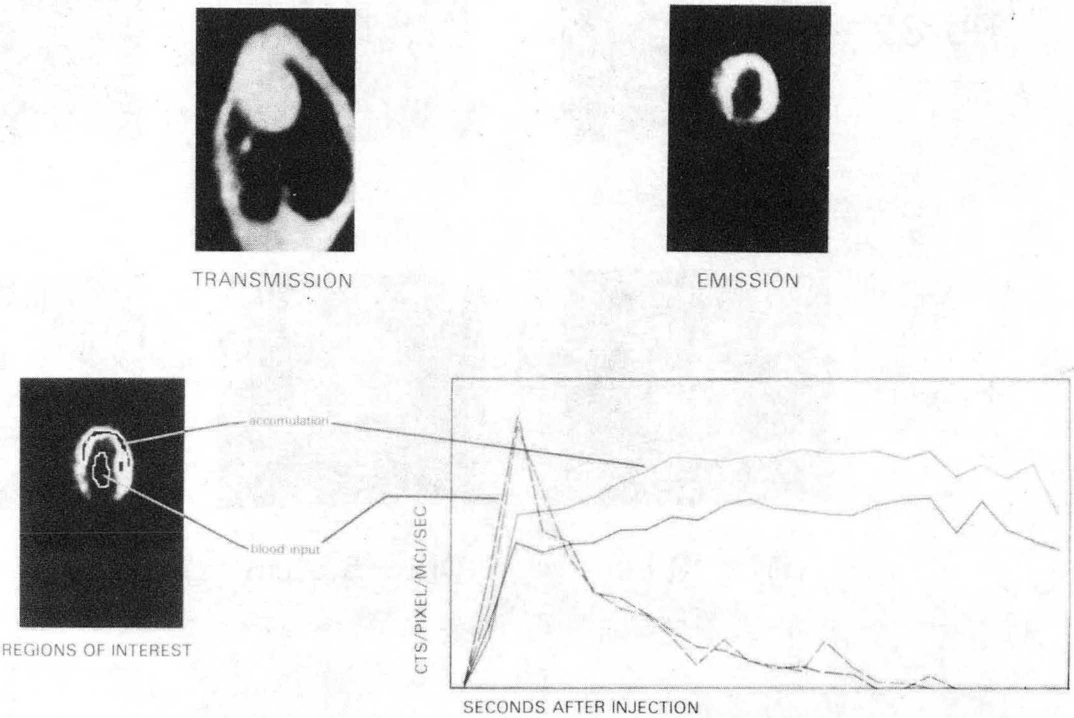
Figure 8



CBB 823-2751

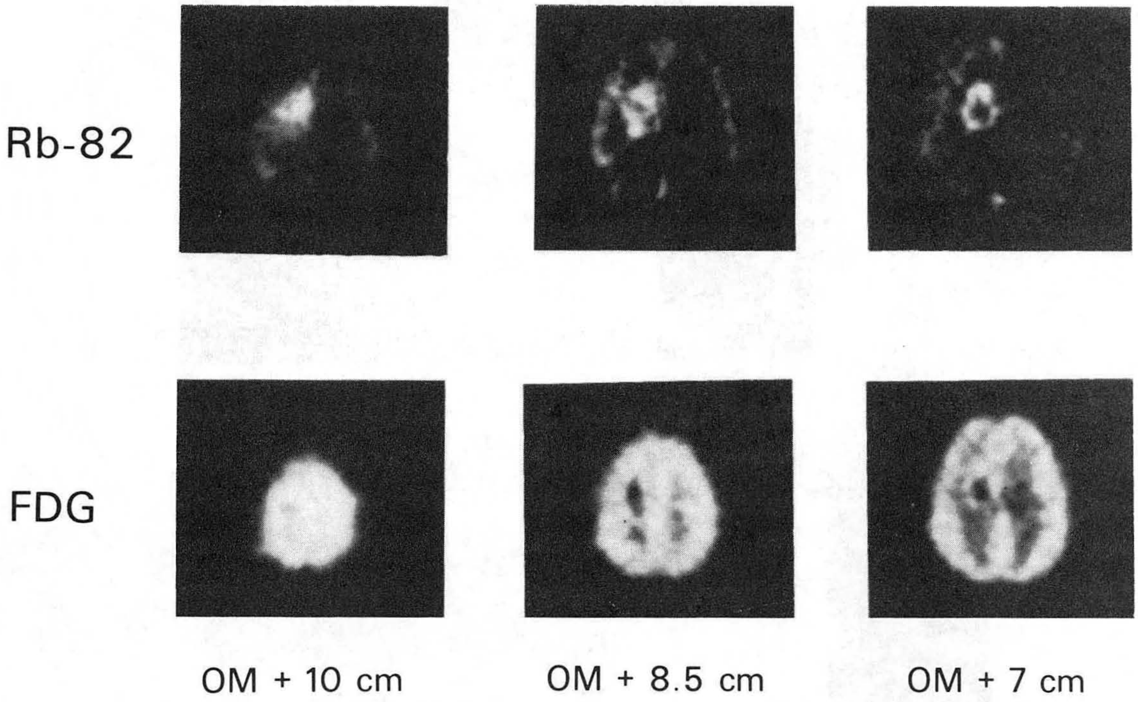
Figure 9

RUBIDIUM FLOW METHOD



CBB 815-4778

Figure 10



XBB 816-5241

Figure 11

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