Submitted to J. of Nuclear Medicine

UCRL-19434
Preprint

c.3

CORONARY BLOOD FLOW STUDIES WITH CESIUM-129 AND THE SCINTILLATION CAMERA

Yukio Yano, Donald Van Dyke, Thomas F. Budinger,
Hal O. Anger and Patricia Chu

December 1969

AEC Contract No. W-7405-eng-48

LAWRENCE RADIATION LABORATORY
UNIVERSITY of CALIFORNIA BERKELEY

c.2

UCRL-19434

DISCLAIMER

CORONARY BLOOD FLOW STUDIES WITH CESIUM-129 AND THE SCINTILLATION CAMERA

Yukio Yano, Donald Van Dyke, M. D., Thomas F. Budinger, M. D., Hal O. Anger, and Patricia Chu

Donner Laboratory and Lawrence Radiation Laboratory
University of California, Berkeley, California 94720

December 1969

The radionuclides of Rb and Cs have been used by a number of researchers to assess coronary blood flow in both animal and human subjects. These radionuclides are extracted by the myocardium in much the same way as potassium (1, 2). Rubidium-86 was used as an indicator of coronary blood flow by determining the myocardial uptake of the isotope after intravenous injection (3, 4). Cohen et al. have used ^{84}Rb with coincidence counting technics to establish changes in the extraction ratio of ^{84}Rb by the myocardium, both for normal subjects and for those with coronary artery disease, as a function of the rate of coronary blood flow and the action of nitroglycerin (5, 6). McHenry and Knobel used ^{84}Rb with the coincidence counting and a single bolus injection technic to determine coronary blood flow as the ratio of myocardial radionuclide uptake to the integrated-time concentration curve of the first arterial circulation of the radionuclide (7).

Rubidium-82, a generator-produced isotope ($T_{1/2}$ = 75 sec) was used with the positron scintillation camera to image the myocardium after an intravenous injection (8). This method was successful for visualizing

the myocardial uptake of ^{82}Rb in animal studies, but in human subjects the uptake of ^{82}Rb by the myocardium was inconsistent.

Cesium-131, which emits 29.4-keV x rays, has been used by Carr to image the myocardium (9). About 2 hours after injection of ^{131}Cs, the myocardium was visualized and the areas of infarction appeared as a "cold" area in the scan. However, there were difficulties, attributable to attenuation of the 29.4-keV x-ray emission of ^{131}Cs by overlying body tissue. This factor led us to investigate ^{129}Cs as a scanning agent for myocardial blood flow studies.

This paper presents a method for producing and processing millicurie amounts of ^{129}Cs for studies in patients with coronary disease. Scintillation camera pictures of myocardial uptake in both animal and human subjects are presented. Experimental results of the distribution of $^{129}CsCl$ in various tissues of dogs and rats and the blood disappearance curve are also given.

Materials and Methods

The radioisotope ^{129}Cs ($T_{1/2}$ = 32 hr) decays 100% by electron capture with the emission of the following γ rays: 2% 40-keV, 3% 280-keV, 48% 375-keV, 25% 416-keV, and 5% 550-keV to stable ^{129}Xe. The 375-keV γ-ray emission can be used to obtain scintillation camera pictures. However, the 25% abundant 416-keV and the 5% abundant 550-keV γ-ray emissions require improved collimation over the standard ^{131}I collimator to obtain adequate resolution with the scintillation camera. (Collimator resolution is discussed in a subsequent section.) Cesium-129 production and the loss of resolution in camera pictures because of the high energy γ-ray emissions have been reported by Clark (10).

Cesium-129 is produced by irradiating about 200 mg of reagent grade NaI in a 0.010-inch-thick pressed powder target through a 0.005-in. Al cover foil with 35-MeV α particles in the Lawrence Radiation Laboratory 88-inch cyclotron. The nuclear reaction of the 100% abundant ^{127}I is $^{127}_{53}I(\alpha, 2n)^{129}_{55}Cs$. The threshold energy for this reaction is 14.8 MeV. The average beam current is about 12 μA, and the average yield of ^{129}Cs is about 300 μCi/uAh.

The irradiated NaI is processed in a "Berkeley box" which has 2-in.-thick Pb shielding. The NaI is washed from the powder plate with 25 ml of sterile H_2O, and a few drops of 1.0 $\underline{N}$ $Na_2S_2O_3$ are added to keep the I^- in the reduced state. This solution is filtered and the filterate is passed through an ion-exchange column which contains 6 ml of anion-exchange resin AG 1X10 in the $C1^-$ form to convert ^{129}Cs-NaI solution to $^{129}CsC1$ in saline solution. The resin column also removes ^{126}I ($T_{1/2}$=13 days), which is produced by the nuclear reaction $^{127}I(\alpha, \alpha n)^{126}I$. The threshold energy for this reaction is about 11 MeV.

Results and Discussion

The γ-ray spectrum of ^{129}Cs from a 400-channel analyzer and NaI crystal is shown in Fig. 1. The spectrum shows a strong peak at 375 keV and a weaker peak at 550 keV. The presence of long-lived ^{22}Na was established by coincidence counting, which gave a decay curve with a $T_{1/2}$ of about 2 yr. Sodium-22 is produced by the nuclear reaction, $^{23}_{11}Na(\alpha, \alpha n)^{22}_{11}Na$, which has a threshold energy of about 13 MeV. A 400-channel γ-ray spectrum taken after most of the ^{129}Cs had decayed away showed γ-ray emissions of 511 keV and 1275 keV. The amount of

^{22}Na present is 3×10^{-4} parts of the ^{129}Cs at the time of injection.

The injected dose of ^{129}Cs is 500 μCi in both human and animal studies with about 0.15 μCi of unwanted ^{22}Na. The whole-body radiation dose to a 70-kg human subject is 2.5 mrad for 0.15 μCi of ^{22}Na. For 500 μCi of ^{129}Cs, the calculated whole-body radiation dose in a 70-kg human subject is about 110 mrad.

The 32-hr half-life of ^{129}Cs is long enough to allow production of the isotope at a cyclotron and transportation to a distant cardiac center. Furthermore the decay of ^{129}Cs by 100% electron capture keeps the radiation dose within acceptable limits for coronary patients, who are usually 40 or more years old.

Animal Studies

The principal organs of uptake as determined from uptake in dogs, Table I, and the radiation dose for a comparable distribution in a human subject are given in Table II. It can be seen that 1 hr after intravenous injection the highest uptake is in the G.I. tract (28.3%), and the organ receiving the greatest radiation exposure is the kidney, with 1.32 rad for 500 μCi of ^{129}Cs. Studies were also done with rats to determine the ratio of ^{129}Cs uptake in the various organs to the uptake in blood, and the ratio of uptake in heart to uptake in liver, as a function of time after intravenous injection. Table III shows the results as the ratio of ^{129}Cs per g of organ to ^{129}Cs per g of blood and the ratio of ^{129}Cs per g of heart of ^{129}Cs per g of liver. It can be seen that the ratio of heart to blood content increases with time, and that the ratio of heart to liver content decreases with time. An optimum time to obtain the best myocardial uptake ratio would be 40 to 90 min postinjection.

Studies were done on three normal dogs, and the blood disappearance curve shown in Fig. 2 was obtained by taking 1-ml blood samples periodically for 2.5 hr after intravenous injection and counting in a well counter. There is an initial rapid disappearance phase with half-times of 2 min and 7 min, and a slower phase with a half-time of about 65 min.

Further studies on normal dogs showed myocardial uptake 1 hr postinjection. ^{129}Cs pictures of the myocardium were taken in five dogs, and 1 week later the interventricular branch of the right coronary artery was ligated. The dogs were medicated with bretyllium tosylate prior to surgery to reduce the incidence of fibrillation. Five hundred μCi of ^{129}Cs was given intravenously at completion of the operation (chest closed) and scintiphotos taken 1 hr later (1.5 hr after ligation). In four of the five dogs clearly visible negative defects were apparent in the region of the apex supplied by the ligated artery. Autopsy demonstrated a 10:1 difference in uptake between normal myocardium and the infarct. In the one dog in which no defect was apparent in the scintiphoto, autopsy demonstrated no infarct and only a 50% reduction in isotope in the area supplied by the ligated coronary artery. It was apparent that sufficient collateral circulation existed in this dog so that flow was reduced but not obliterated. The 50% reduction in uptake was not apparent in the scintillation camera picture. Figure 3 shows, top, ^{99m}Tc heart shadow transmission picture; middle, ^{129}Cs myocardial uptake 1 hr postinjection, left lateral view; and, bottom, same dog in same position 1 week later, 1.5 hr after coronary artery ligation and 1 hr

postinjection. The area of reduced coronary blood flow is indicated by the reduced uptake of ^{129}Cs.

Human Studies

Studies were done on both normal subjects and those with coronary disease. Six patients were studied after intravenous injection of 500 μCi ^{129}Cs. Three patients were normal, and three had diseases known to affect the myocardium: coronary artery disease, essential hypertension, and idiopathic myocardopathy. All three patients with myocardial pathology had cardiomegaly. Patients were counted under the camera (usually 20 min) at frequent intervals to 5 hours after injection by using the following collimators: inverted diverging, 2.2-in. without, and 2.2-in with extension (see section on Collimation). The collimators of choice are the extended 2.2-in. when the distance from the collimator to the subject is greater than 2.5-in., and the inverted diverging collimator at 2.5 in. or less. The optimum time for myocardial visualization is 45 to 90 min after injection, and the duration of counting necessary for 100,000 counts is 15 min.

There was better overall uptake of ^{129}Cs in the myocardia of normals than in abnormals. The distribution of ^{129}Cs is shown in Fig. 4 for anterior views of (A) normal, (B) cardiomegaly, (C) hypertension, and (D) coronary disease. Uptake of ^{129}Cs by the myocardium can be seen in the central portion of the pictures. Uptake of the isotope can also be seen in the liver at the lower periphery of the pictures, especially in the normal, Fig. 4-A. A definite boundary separating the area of the myocardium from the area of the liver can be seen in all the studies except the cardiomegaly (B). The patient with hypertension is also shown

in Fig. 5, which shows (top) the ^{99m}Tc transmission picture of the heart shadow, (middle) the scintillation camera picture of uptake in the myocardium, and (bottom) the whole-body scan with the Mark II whole-body scanner. The ^{99m}Tc transmission picture helps to orient the area of ^{129}Cs uptake relative to the position of the heart shadow. The whole-body scan, which shows three different intensity settings taken simultaneously and an ^{241}Am x-ray transmission of the whole-body outline superimposed on one of the views, pictures the distribution of ^{129}Cs in the heart, liver, gastrointestinal tract, kidneys, and head. Whole-body scans taken 24 hr later showed the ^{129}Cs activity widely distributed to all the soft tissues. The right heart myocardium was not visualized with ^{129}Cs as an entity distinct from the left ventricle. Myocardial ^{129}Cs concentration noticeably diminishes after a few hours, whereas the liver, gut, and stomach concentrations increase. In most of the ^{129}Cs pictures of the myocardium there is an area of reduced uptake in the upper part of the myocardium which corresponds to the blood chamber within the ventricles. This is demonstrated in Fig. 6, which shows (top) ^{99m}Tc transmission picture of the heart shadow, (middle) the uptake of ^{129}Cs by the myocardium, and (bottom) the blood pool within the ventricles shown by a dynamic study using $^{99m}TcO_4$. The lower tip of the blood activity can be superimposed on the area of diminished uptake of ^{129}Cs of the myocardium. This series of pictures was taken of a normal patient who remained in the same position beneath the camera head for all three.

Cesium-129 has potential value in quantitating coronary blood flow, imaging myocardial infarction, and assessing changes in myocardial

flow in response to drugs, diet, age, and exercise. Many of these applications can be done with the instrumentation now available. Improvements can be made by using a thicker crystal for the detector and a data readout system for quantitating activity over the myocardium.

Our series of studies is being extended to the acute myocardial infarction patients for assessment of the clinical practicality of imaging and following the progression or regression of myocardial infarctions.

Camera Collimation

The IAEA liver slice phantom was filled with 500 μCi of ^{129}Cs and pictures were taken with the scintillation camera by use of a medium-energy (0.36 MeV) 2.2-in. thick collimator (11), the medium-energy collimator plus a 1-in. extension that increases its maximum γ-ray energy to 0.44 MeV, and the inverted Nuclear-Chicago diverging collimator. When the last collimator is used, a magnified image of the heart is projected on the scintillator. The best resolution is obtained with the inverted diverging collimator when the distance from the collimator to the subject is 2.5 in. However, when the distance from the collimator to the subject is 4.5, the medium-energy collimator with extension gives the best resolution.

Summary

A method for the production of ^{129}Cs by cyclotron irradiation is described. The distribution of $^{129}CsCl$ in various tissues of rats and dogs has been determined for various time intervals after intravenous injection. Areas of myocardial infarction have been demonstrated in dogs.

Cesium-129 and the scintillation camera with suitable collimation have been used to image the myocardial distribution of coronary blood flow both in normals and in patients with coronary disease.

A greater number of patients needs to be studied to establish the clinical usefulness of ^{129}Cs in determining areas of infarction or ischemia.

Acknowledgments

The authors gratefully acknowledge the technical assistance of Dianne Peterson and Bill Hemphill in carrying out this work, which was done under the auspices of the United States Atomic Energy Commission.

TABLE 1 UPTAKE OF CESIUM-129 IN DOG, 1 hr after intravenous injection of 500 μCi of $^{129}CsCl$.

Organ	Part of injected dose (in %) for whole organ plus standard error (average for two dogs)
Heart	5.0 ± 0.5
Blood (per ml)	3.1×10^{-3}
Liver	7.01 ± 0.9
G. I. tract	28.3 ± 0.0
Kidney	9.42 ± 0.8
Lungs	2.51 ± 0.3
Spleen	9.47[a]

a. One dog.

TABLE 2 RADIATION DOSE TO A HUMAN SUBJECT (70 kg) FOR 500 μCi OF CESIUM-129.

Calculations based on organ uptake in dog

Organ	Dose (rads)
Heart	0.78
G. I. tract	1.10
Lungs	0.12
Liver	0.21
Kidneys	1.32
Whole body	0.11

TABLE 3 UPTAKE OF CESIUM-129 IN RATS AS A FUNCTION OF TIME AFTER INTROVENOUS INJECTION

Organ	Ratio $\frac{^{129}Cs \text{ per g of organ}}{^{129}Cs \text{ per g of blood}}$ plus standard error (average of two animals) after 7 min	14 min	43 min	180 min
Heart	11.9 ± 1.2	22.8 ± 0.9	29.3 ± 0.7	28.5 ± 2.5
Kidney	38.6 ± 0.2	48.3 ± 13.4	58.9 ±10.6	28.9 ± 2.5
Liver	2.49 ± 0.03	2.93 ± 0.32	6.48 ± 0.87	10.22 ± 0.38
Spleen	3.9 ± 0.62	3.78 ± 0.20	10.2	12.8 ± 0.3
Lung	5.24 ± 0.10	5.58 ± 0.13	14.1 ± 0.8	
Muscle	0.76 ± 0.14	1.20 ± 0.48	3.5 ± 1.24	5.70 ± .30
Bone	2.27 ± 0.28	2.83 ± 1.2	3.82 ± 0.47	6.52 ± 0.12
Heart:liver	4.78 ± 0.43	7.85 ± 0.50	4.60 ± 0.50	2.81 ± 0.35
%/ml blood	0.16 ± 0.04	0.20 ± 0.04	0.08 ± 0.03	0.07 ± 0.03

References

1. Donato, L., Bartolomel, G., and Giodani, R., Evaluation of myocardial blood perfusion in man with radioactive potassium or rubidium and precordial counting. Circulation 29: 195, 1964.

2. Love, W. D., Romney, R. B., and Burch, G. E.: Comparison of the distribution of potassium and exchangeable rubidium in the organs of the dog using rubidium-86. Circulation Res. 2: 112, 1954.

3. Levy, M. M., and De Oliveira, J. M.: Regional distribution of myocardial blood flow in the dog as determined by ^{86}Rb. Circulation Res. 9: 96, 1961.

4. Love, W. D. and Burch, G. E. A study in dogs of methods suitable for estimating the rate of myocardial uptake of ^{86}Rb uptake. J. Clin. Invest. 36: 468, 1957.

5. Cohen, A., Zaleski, E. J., Luebs, E. D., and Bing, R. J.: The use of positron emitter in the determination of coronary blood flow in man. J. Nucl. Med. 6: 651, 1965.

6. Cohen, A., Zaleski, E. J., Baleiron, H., Stock, T. B., Chiba, C., and Bing, R. J.: Measurement of coronary blood flow using 84-rubidium and coincidence counting methods. Am. J. Cardiology 19: 556-562, April 1967.

7. McHenry, P. L., and Knoebel, S. B.: Measurement of coronary blood flow by coincidence counting and a bolus of ^{84}Rb Cl. J. Appl. Physiol. 22: 495-500, 1967.

8. Yano, Y. and Anger, H. O: Visualization of heart and kidneys in animals with ultrashort-lived ^{82}Rb and the positron scintillation camera. J. Nucl. Med. 9: 412-415, 1968.

9. Carr, E. A., Gleason, G., Shaw, J., and Krontz, B.: The direct diagnosis of myocardial infarction by photo-scan after administration of cesium-131. Am. Heart J. 68: 627-636, 1964.

10. Clark, J. C., Matthews, C. M. E., Sylvester, D. J., and Vonberg, D. D.: Using cyclotron produced isotopes at Hammersmith Hospital. Nucleonics 25: 54-62, 1967.

11. Anger, H. O.: Radioisotope Cameras. Instrumentation in Nuclear Medicine, Vol. 1, P. 525, Academic Press Inc., New York (1967).

FIGURE LEGENDS

Fig. 1. Gamma-ray spectrum of ^{129}Cs with 400-channel analyzer and NaI(Tl) crystal. Principle peak at 375 keV.

Fig. 2. Blood disappearance curve for ^{129}Cs after intravenous injection in dogs. There are three components with half-times of 2 min, 7 min, and 65 min.

Fig. 3. Top: ^{99m}Tc point source transmission heart shadow.
Middle: lateral view, 1 hr postinjection in dog, of ^{129}Cs uptake in normal myocardium.
Bottom: after coronary artery ligation, area of diminished ^{129}Cs uptake corresponding to area of reduced coronary blood flow.

Fig. 4. Myocardial uptake of ^{129}Cs in human subjects: (A) normal, (B) cardiomegaly, (C) hypertension, and (D) coronary disease.

Fig. 5. Top: ^{99m}Tc transmission picture; middle: ^{129}Cs scintillation camera picture; and bottom: whole-body scan of patient with hypertension.

Fig. 6. Top: transmission with ^{99m}Tc of the heart shadow; middle: ^{129}Cs uptake in myocardium; and bottom: ventricle blood pool with $^{99m}TcO_4$.

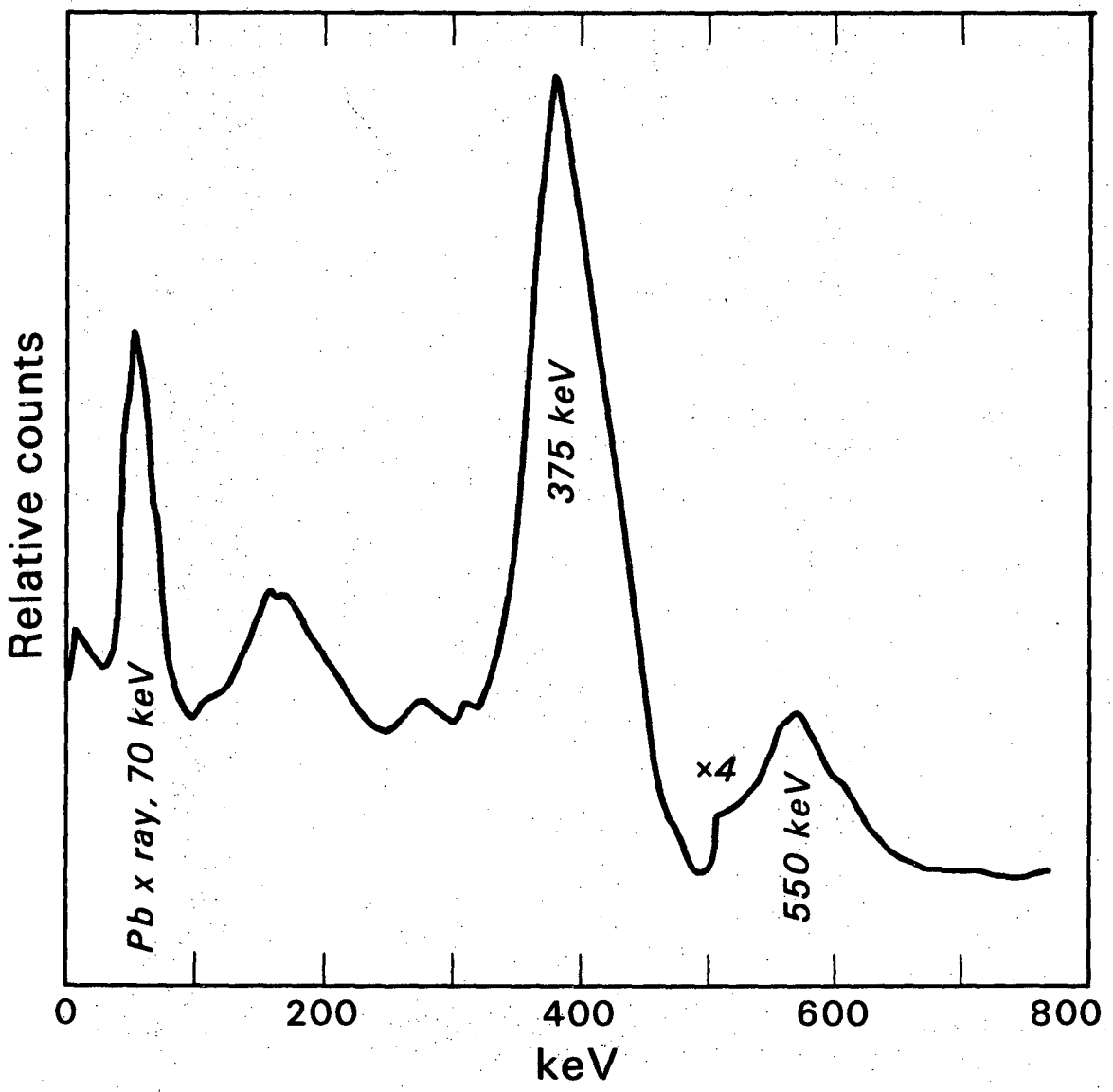
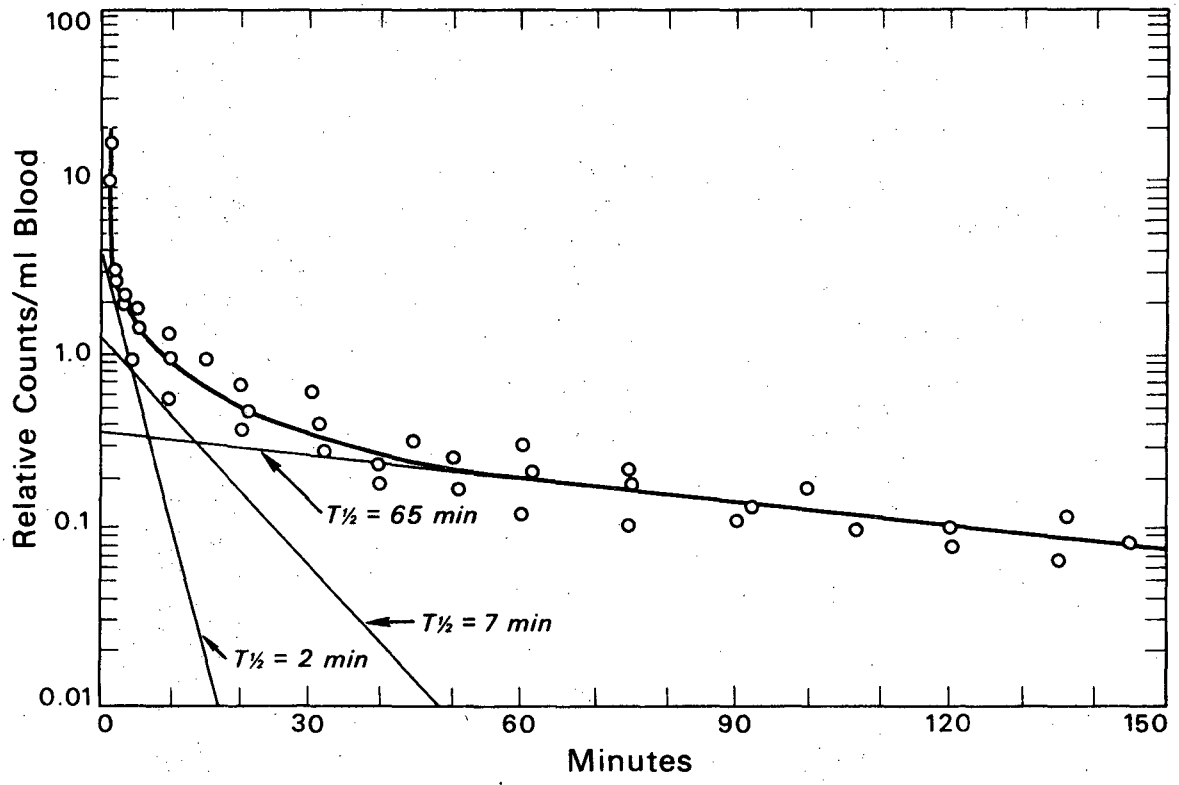
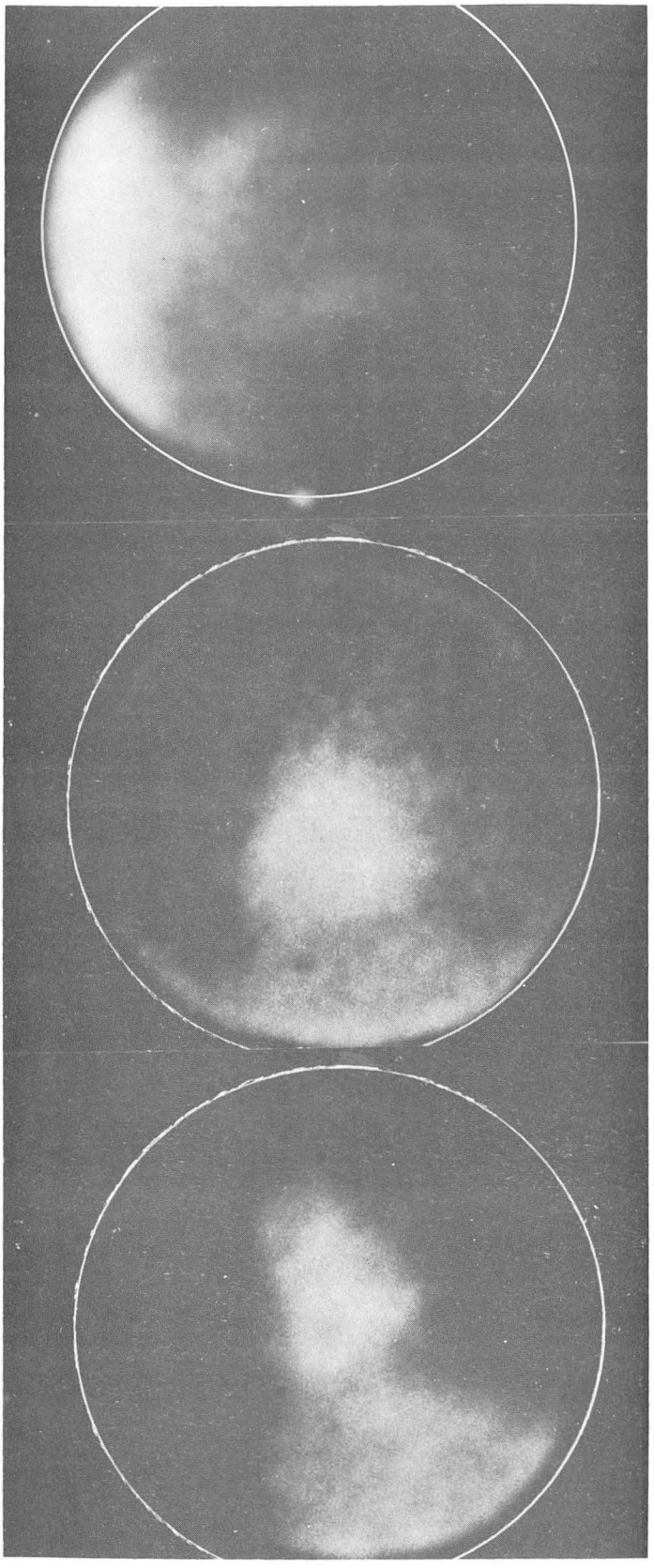

Relative counts
Pb x ray, 70 keV
375 keV
×4
550 keV
0
200
400
600
800
keV
DBL 6912-5237

Fig. 1



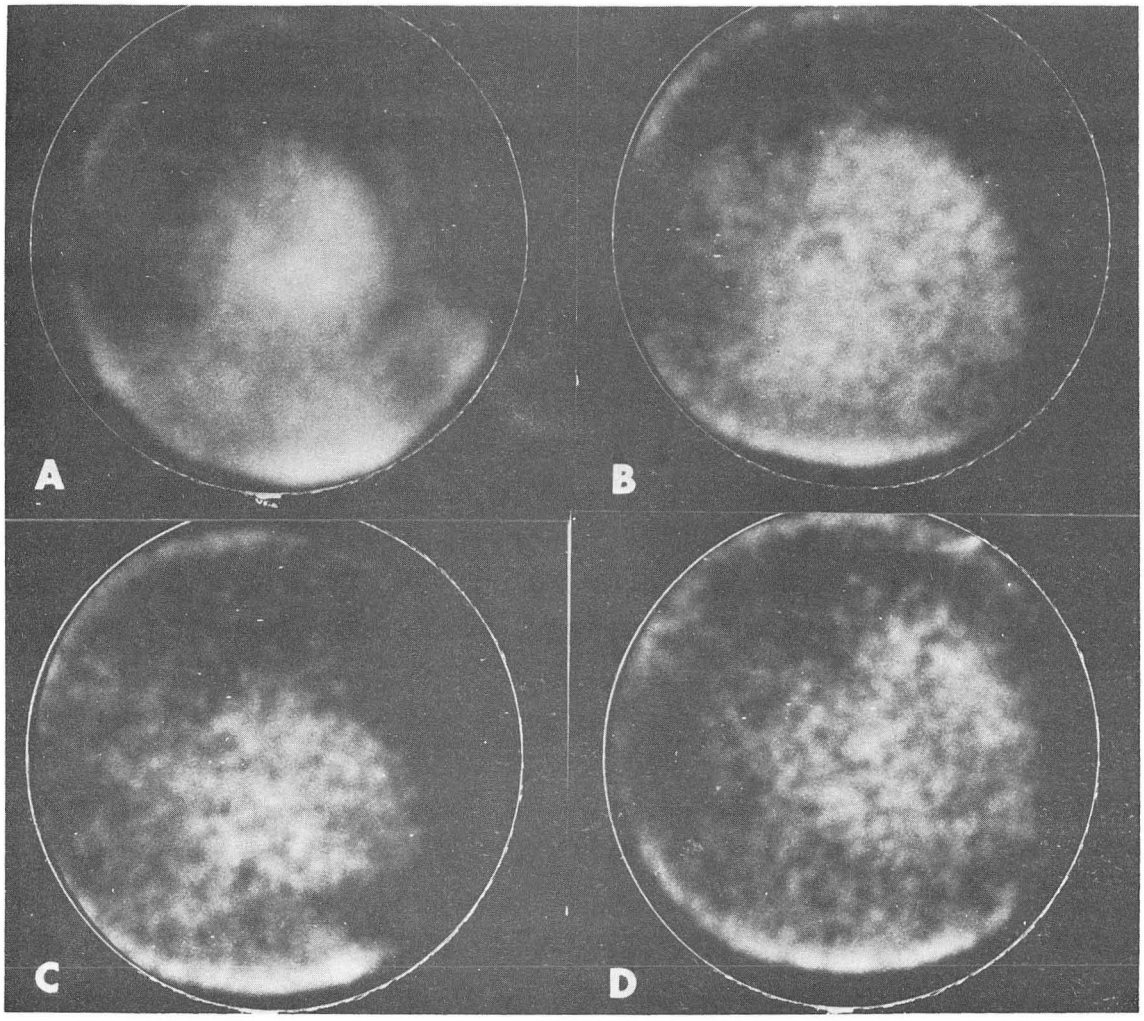
DBL 6912-5236

Fig. 2



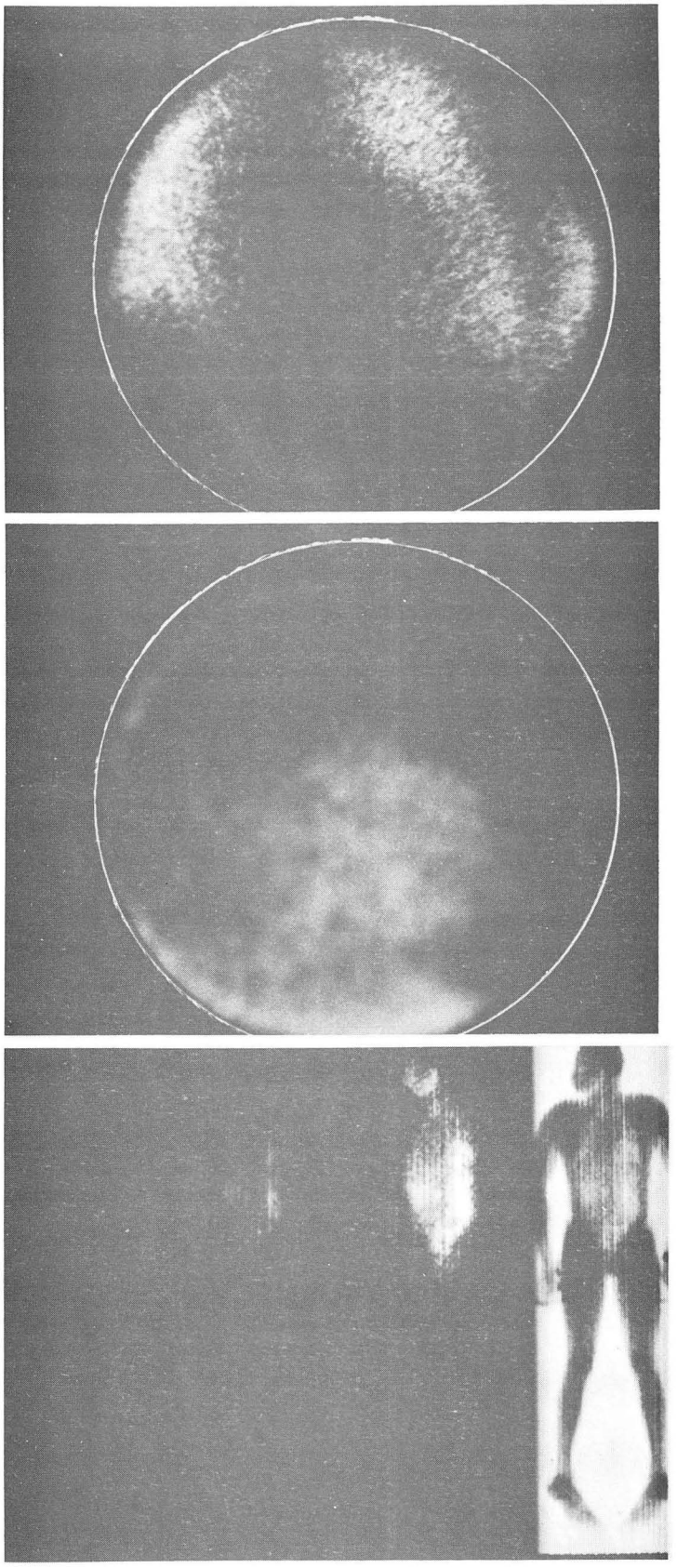
XBB 701-33

Fig. 3



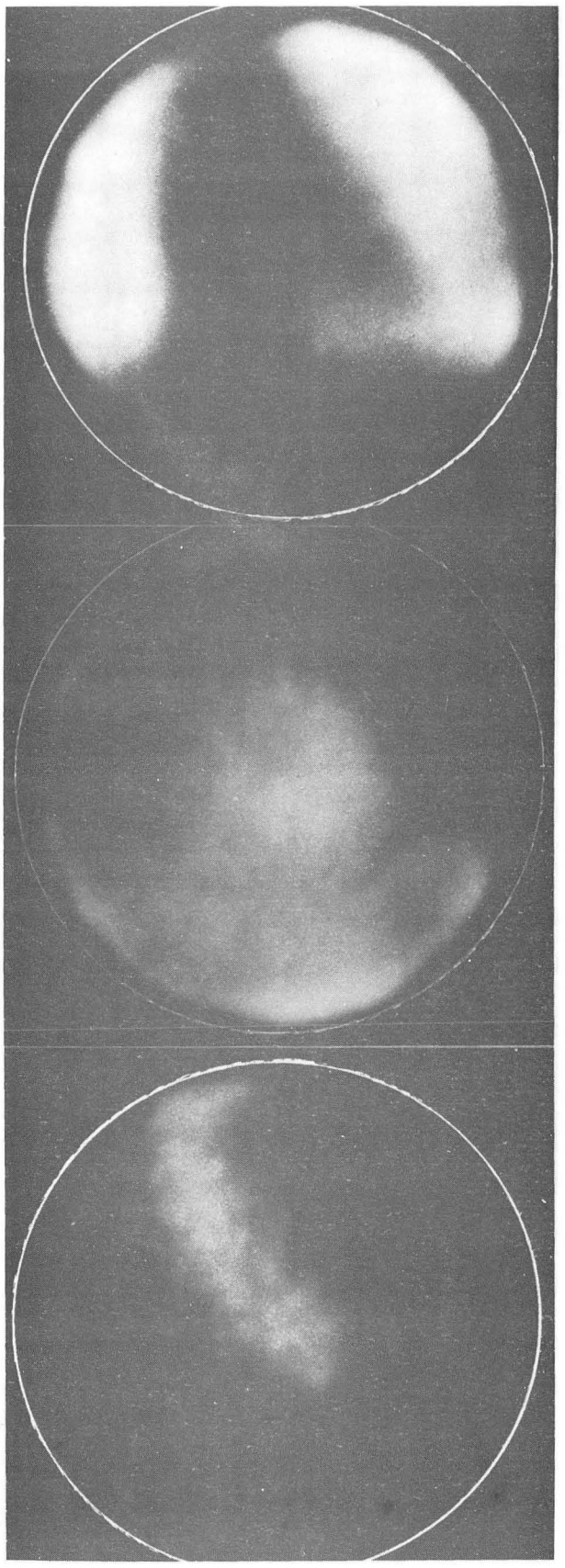
XBB 701-35

Fig. 4



XBB 701-34

Fig. 5



XBB 701-36

Fig. 6

TECHNICAL INFORMATION DIVISION
LAWRENCE RADIATION LABORATORY
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIFORNIA 94720