Title
LUNG SCANNING WITH TECHNETIUM-99ni FERRIC HYDROXIDE MACROAGGREGAIES

Authors
Yano, Y.
Anger, H.O.
McRae, J.
et al.

Publication Date
1970-04-01

For Panel on Preparation and Control of Radiopharmaceuticals from Generator-Produced Radioisotopes in Medical Radioisotope Laboratories, Vienna, Austria, May 11-15, 1970

UCRL-19786
Preprint

c. 2

LUNG SCANNING WITH TECHNETIUM-99m FERRIC HYDROXIDE MACROAGGREGATES

Y. Yano, H. O. Anger, J. McRae, and D. Honbo

April 1970

AEC Contract No. W-7405-eng-48

LAWRENCE RADIATION LABORATORY
UNIVERSITY of CALIFORNIA BERKELEY

UCRL-19786

DISCLAIMER

Lung Scanning With Technetium-99m Ferric Hydroxide Macroaggregates[1]

Y. Yano, H.O. Anger, J. McRae,* and D. Honbo
Donner Laboratory of Medical Physics and Biophysics
Lawrence Radiation Laboratory
University of California, Berkeley, California

ABSTRACT

For scanning, technetium-99m has the useful physical characteristics of high photon yield, short half life, and an easily collimated 140-keV γ-ray emission. To utilize these advantages of ^{99m}Tc for pulmonary perfusion studies, a relatively simple and rapid procedure has been developed for preparation of ^{99m}Tc-labeled ferric hydroxide macroaggregates in the particle size range of 15 to 40 μ.

INTRODUCTION

At present two radiopharmaceutical agents are used for visualization of pulmonary blood perfusion by temporary entrapment of radioactive particles in the arteriolar-capillary bed. The first and most widely used agent is iodine-131 macroaggregated serum albumin, ^{131}I-MAA [1]. Iodine-131 decays by β-particle emission with a half-life of 8.05 days and a 264-keV γ-ray emission, 82% abundant [2]. The radiation dose to the lungs from 200 μCi of ^{131}I is about 1.2 rads [3]. This radiation dose limits the maximum amount of ^{131}I that can be given, and a relatively long time is required for each lung scan.

More recently indium-113m ferric hydroxide was introduced as a lung-scanning agent [4]. Indium-113 decays by isomeric transition with a half-life of 1.67 hours and emission of 390-keV γ-rays, 64% abundant [2]. The radiation dose to the lungs is about 0.75 rad/mCi [4]. The 390-keV γ-ray emission of ^{113m}In is relatively difficult to collimate for use with the gamma camera.

Human serum albumin has been labeled with ^{99m}Tc by the method of Stern [6], and many reports have appeared in the literature on the preparation and use of ^{99m}Tc-macroaggregated albumin, ^{99m}Tc-MAA, for lung scanning [5,7-10]. However, there are technical difficulties which preclude the use of ^{99m}Tc-MAA on a routine clinical basis.

Technetium-99m has the favorable physical characteristics of high photon yield, low radiation dose, and an easily collimated 140-keV γ-ray emission, 90% abundant [5]. It decays with a half-life of 6 h and

1. Work done under auspices of United States Atomic Energy Commission.

*Present address: University of Sydney, Department of Medicine, Sydney, Australia.

delivers a radiation dose of about 0.62 rad/mCi to the lungs of a 70-kg patient. To utilize the advantages of ^{99m}Tc for lung scanning, we have developed a relatively simple and rapid procedure for preparation of ^{99m}Tc-labeled ferric hydroxide macroaggregates that are taken up by the lungs [11].

Recently Boyd et al. have reported on the preparation of ^{99m}Tc-labeled macroaggregates of ferrous hydroxide (Tc-MAFH) [12]. They used ferrous sulfate, stannous ion, and terminal autoclaving under an inert nitrogen atmosphere to obtain a stable and sterile preparation of Tc-MAFH which has 98% uptake in lungs and less than 1% free pertechnetate.

Bruno et al. have prepared ^{99m}Tc-iron hydroxide aggregates for lung scanning [13]. They used 2 mg of ferrous iron for the preparation and found 84% uptake in the lungs and 7.5% in the liver of a rabbit 0.2 h after intravenous injection. There was about 4% free pertechnetate in the preparation.

METHODS

^{99m}Tc-ferric hydroxide macroaggregates, ^{99m}Tc-$Fe(OH)_3$-MA, are prepared by a modified application of the Reese method for making ferric (^{113m}In) hydroxide particles [14]. Sterile reagents required for the preparation are 1 N HCl, 0.65 N NaOH, 10% gelatin, isotonic saline in 1.7% gelatin solution at pH 8, $FeSO_4 \cdot 7H_2O$ solution (2 mg Fe(II)/ml N HCl), and $^{99m}TcO_4^-$ saline solution. All the reagent solutions are prepared with sterile, pyrogen-free water and passed through 0.45-μ Millipore filters.

The ferrous iron solution is prepared immediately before use. About 50 mg of reagent-grade $FeSO_4 \cdot 7H_2O$ is weighed and dissolved in about 5 ml N HCl acid. An exact dilution is calculated to make the solution 2 mg/ml in Fe(II). Two-tenths ml of this iron sulfate solution [400 μg Fe(II)] is added to 5 ml of $^{99m}TcO_4^-$-saline solution in a sterile vial. The solution is mixed and transferred through a Millipore filter into a sterile, evacuated 10-ml test tube ("Vacutainer" by Beckton, Dickinson Co.). The solution is made basic by adding 0.43 ml of 0.56 N NaOH and mixed by slow inversion for 2 min. The pH should be about 10 to 11. One ml of 10% gelatin is added to the preparation with gentle mixing for 2 min. The pH of the solution is 8 to 9.

The mixture is centrifuged in a clinical centrifuge for 10 sec at 1600 rpm, the supernatant withdrawn, and the $Fe(OH)_3$ precipitate resuspended in 5 ml of pH 8 saline solution which contains 1.7% gelatin.

The particles are sized in a hemocytometer grid using light microscopy. Free $^{99m}TcO_4^-$ content is determined by thin-layer chromatography with a 1- by 7-cm (Gelman type SG) strip in 95% methanol. Free $^{99m}TcO_4^-$ content should be less than 5%.

RESULTS

The binding of ^{99m}Tc to $Fe(OH)_3$ is dependent upon the reduction of Tc(VII), its relatively stable oxidation state, to the more reactive Tc(V)

or Tc(IV) oxidation state. The Tc(V) binds to Fe(III), and Tc(IV) is co-precipitated with $Fe(OH)_3$ as the dioxide [15].

We use ferrous iron to reduce Tc(VII) to Tc(V), from which the ^{99m}Tc-labeled iron hydroxide can be aggregated to the desired particle size range of 15 to 40 μ for visualization of pulmonary blood perfusion. Various factors such as Fe(II) concentration, pH, and "salting out" anions influence both the binding of ^{99m}Tc and the particle size of the $Fe(OH)_3$.

We have used both $FeCl_2 \cdot 4H_2O$ and $FeSO_4 \cdot 7H_2O$ as the source of ferrous iron for our preparations. The relative binding of ^{99m}Tc as a function of Fe(II) concentration either as $FeCl_2 \cdot 4H_2O$ or as $FeSO_4 \cdot 7H_2O$ is shown in Fig. 1. The average binding was 64.8 ± 1.3% with $FeCl_2 \cdot 4H_2O$ and 74.0 ± 3.0% with $FeSO_4 \cdot 7H_2O$ from six determinations of each form of ferrous iron at a concentration of 80 μg Fe(II)/ml. Most of the particles of ^{99m}Tc-$Fe(OH)_3$-MA range in size from <5 to 25 μ with Cl^- and from 15 to 40 μ with $SO_4^=$ anion. Because of the increased binding of ^{99m}Tc with $FeSO_4 \cdot 7H_2O$ and because of the desirable "salting out" effects of the $SO_4^=$ anions to produce macroaggregates of $Fe(OH)_3$ in the desired particle-size range from 15 to 40 μ, $FeSO_4 \cdot 7H_2O$ is the preferred form of Fe(II).

Free $^{99m}TcO_4^-$ is removed from ^{99m}Tc-$Fe(OH)_3$ by centrifugation similar to the method of Paoli for the removal of $^{99m}TcO_4^-$ from ^{99m}Tc-MAA [9]. This procedure for removal of $^{99m}TcO_4^-$ and the use of sterile reagents and technique are necessary because Tc(V) undergoes disproportionation to Tc (IV) and Tc(VII) upon autoclaving and increasing pH [15].

^{99m}Tc-$FE(OH)_3$-MA is prepared in the particle size range of 15 to 40 μ, as shown in Fig. 2. There is about 75% binding of ^{99m}Tc to the $Fe(OH)_3$ with 80 μg/ml of ferrous iron. After centrifugation and resuspension of ^{99m}Tc-$Fe(OH)_3$-MA, there is greater than 95% binding of ^{99m}Tc in the final product solution, as shown by thin-layer chromatography. The specific activity is about 60 μCi ^{99m}Tc per μg Fe (from a 25-ml elution of a 200-mCi ^{99m}Tc generator).

The distribution of ^{99m}Tc-$Fe(OH)_3$-MA in rats is 85 to 87% in lungs, 7 to 8% in liver, and 7 to 9% in stomach and intestines in 30 minutes after intravenous injection. These results compare favorably with the distribution of ^{99m}Tc-MAA, which show about 90% in the lungs and 3% in the liver in the same time [9].

Thirty-five patients have been studied with the ^{99m}Tc ferric hydroxide macroaggregates. Rapid sequential scintiphotos taken immediately after intravenous injection show blood flow as the ^{99m}Tc-$Fe(OH)_3$-MA flows to the right side of the heart and is carried through the pulmonary arteries to the lungs. Later scintiphotos show the final distribution of pulmonary perfusion.

In Fig. 3 anterior and posterior views of both lungs of a patient suspected to have a pulmonary embolism are shown. They were obtained using the Nuclear Chicago Pho/Gamma III and diverging collimator. An area of diminished isotope uptake is apparent in the left lung in the posterior view. Exposure time was 1 min, and approximately 100,000 dots were accumulated. The patient received 1.5 mCi ^{99m}Tc-$Fe(OH)_3$-MA.

SUMMARY

The advantages of ^{99m}Tc can be utilized for lung scanning with the compound ^{99m}Tc-$Fe(OH)_3$-MA, which is easily and rapidly prepared. There is about 85% uptake of ^{99m}Tc in the lungs with low uptake in other organs. The high photon yield and low radiation dose permit lung scans to be completed in a few minutes. Also dynamic blood-flow studies can be performed with the scintillation camera using 2- to 3-sec exposures, which visualize blood flow to the right side of the heart, pulmonary arteries, and lungs.

REFERENCES

[1] TAPLAN, G.V., DORE, E.K., JOHNSON, D.E., KAPLAN, H.S., Suspension of radioalbumin aggregates for photoscanning the liver, spleen, lung, and other organs, J. Nucl. Med. 5 (1964) 259.

[2] LEDERER, C.M., HOLLANDER, J.M., PERLMAN, I., Table of Isotopes, 6th Edition, Wiley, New York (1967).

[3] QUINN, J.L., III, HEAD, L.P., Pulmonary photoscanning: current status, Recent Advances in Nuclear Medicine (Croll, M.N. and Brady, L.W., Eds.) Appleton-Century-Crofts, New York (1966).

[4] STERN, H.S., GOODWIN, D.A., WAGNER, H.N., Jr., KRAMER, H.H., In ^{113m} --a short-lived isotope for lung scanning, Nucleonics 24 (1966) 57.

[5] HARPER, P.V., LATHROP, K.A., JIMINEZ, F., FINK, R., GOTTSCHALK, A., Technetium-99m as a scanning agent, Radiology 85 (1965) 101.

[6] STERN, H.S., ZOLLE, I., McAFEE, J.G., Preparation of technetium (Tc^{99m})-labeled serum albumin (human), Intl. J. Appl. Rad. Isotopes 16 (1965) 283.

[7] PETERSON, C.C., BONTE, F.J., Technetium-99m macroaggregated albumin: a new lung scanning agent, Intl. J. Appl. Rad. Isotopes 18 (1967) 201.

[8] KAZEM, I., GELINSKY, P., SCHENCK, P., Organ visualization with technetium-99m preparations, British J. Radiology 40 (1967) 292.

[9] DePAOLI, T., HAGER, A., NICOLINI, J.O., Albumin macroaggregates labeled with Tc^{99m}, Intl. J. Appl. Rad. Isotopes 17 (1966) 55.

[10] GWYTHER, M.M., FIELD, E.O., Aggregated Tc^{99m} labeled albumin for lung scintiscanning, Intl. J. Appl. Rad. Isotopes 17 (1966) 485.

[11] YANO, Y., McRAE, J., HONBO, D.S., ANGER, H.O., ^{99m}Tc-ferric hydroxide macroaggregates for pulmonary scintiphotography, J. Nucl. Med. 10 (1969) 683.

[12] BOYD, R.E., ACKERMAN, S.A., MORRIS, J.G., HUBERTY, J.P., Lung scanning using ^{99m}Tc-labeled macroaggregated ferrous hydroxide (Tc-MAFH) as the perfusion agent, J. Nucl. Med 10 (1969) 737.

[13] BRUNO, F.P., BROOKERMAN, V.A., ARBORELIUS, M., WILLIAMS, C.M., ^{99m}Tc-iron hydroxide aggregates for lung scanning, J. Nucl. Med 11 (1970) 134.

[14] REESE, I.C., MISHKIN, F.S., A simple way to make iron (^{113m}In) hydroxide particles, J. Nucl. Med. 9 (1968) 128.

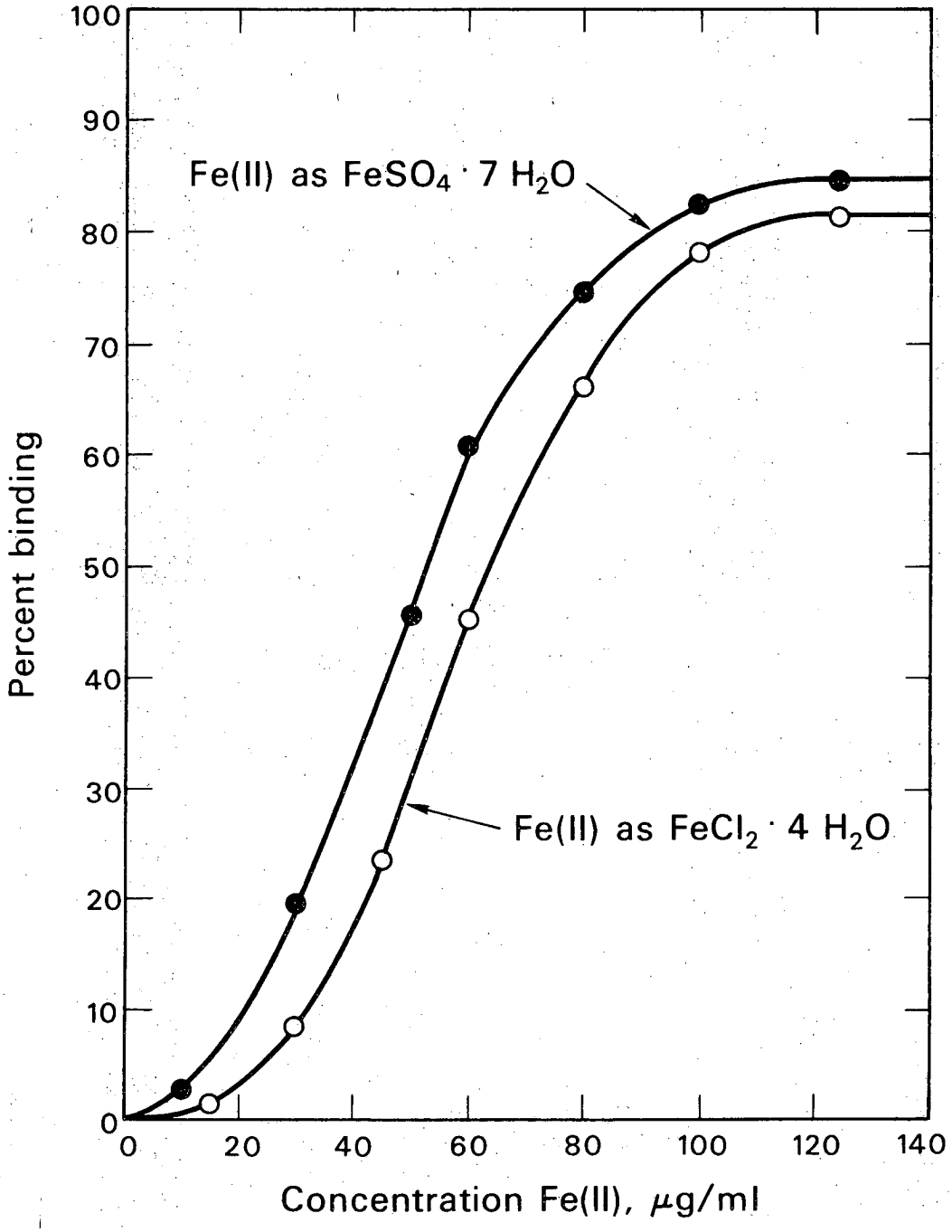
[15] ANDERS, E., The radiochemistry of technetium, NAS-NS 3021, U.S. Atomic Energy Commission (1960).

FIGURE CAPTIONS

Fig. 1. Relative binding of ^{99m}Tc to $Fe(OH)_3$ as a function of Fe(II) concentration.

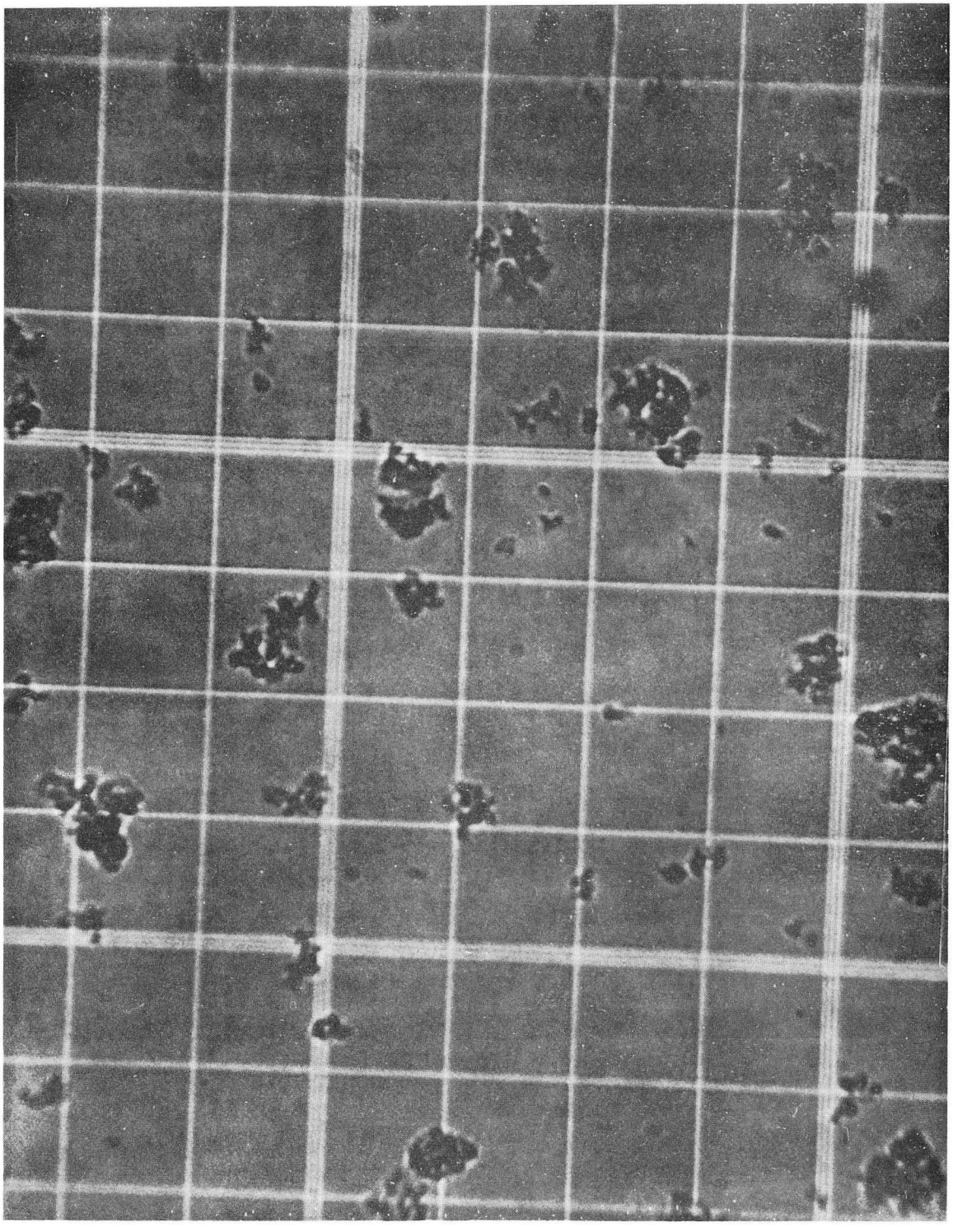
Fig. 2. Photomicrographs of ^{99m}Tc-$Fe(OH)_3$-MA showing particle sizes in the range 15 to 40 μ (small squares represent 50 μ).

Fig. 3. Anterior and posterior views of the lung using Nuclear Chicago Pho/Gamma III and diverging collimator, showing area of diminished perfusion in left lung.



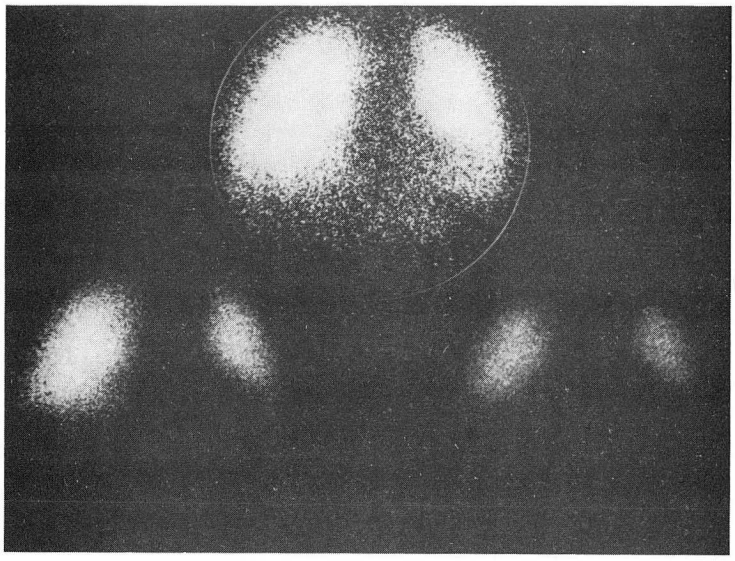
DBL 688-5396

Fig. 1

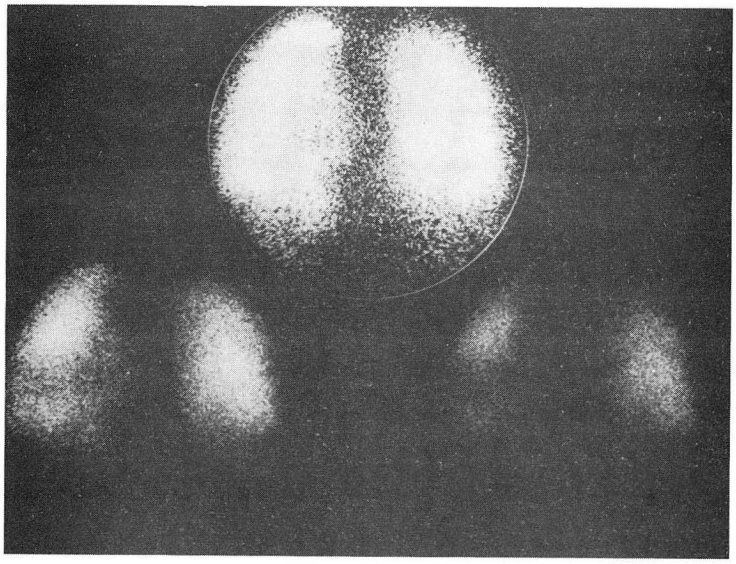


XBB 688-4868

Fig. 2



Anterior



Posterior

XBB 692-1298

Fig. 3

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