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TECHNETIUM-99m FERRIC HYDROXIDE MACROAGGREGATES FOR PULMONARY SCINTIPHOTOGRAPHY[1]

Yukio Yano, James McRae, Deanna S. Honbo, and Hal O. Anger

Donner Laboratory of Biophysics and Medical Physics
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August 12, 1968

ABSTRACT

For scanning, technetium-99m has the useful physical characteristics of high photon yield, low radiation dose, and an easily collimated 140-keV gamma-ray emission. To utilize these advantages of ^{99m}Tc for lung scanning, a relatively simple and rapid procedure has been developed for preparation of a ^{99m}Tc-labelled compound that is specific for lung uptake. A detailed chemical method is presented for preparation of ^{99m}Tc-labelled ferric hydroxide macroaggregates in the particle size range of 20 to 50 μ, with a specific activity of about 60 μCi ^{99m}Tc/μg Fe. Gamma camera pictures and tomographic scans of pulmonary blood perfusion in animals and human subjects are presented.

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 364-keV gamma-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-113m decays by isomeric transition with a half-life of 1.67 hours and emission of 390-keV gamma rays, 64% abundant (2). The radiation dose to the lungs is about 0.75 rad/mCi (4). The 390-keV gamma-ray emission of ^{113m}In is relatively difficult to collimate for use with the gamma camera.

Human serum albumin has been labelled 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 (11).

Technetium-99m has the favorable physical characteristics of high photon yield, low radiation dose, and an easily collimated 140-keV gamma-ray emission, 90% abundant (5). It decays with a half-life of 6 hours and delivers a radiation dose of about 0.62 rads/mCi to the

lungs. To utilize the advantages of ^{99m}Tc for lung scanning, we have developed a relatively simple and rapid procedure for preparation of ^{99m}Tc-labelled ferric hydroxide macroaggregates that are taken up by the lungs.

METHODS

We prepare ^{99m}Tc-ferric hydroxide macroaggregates, ^{99m}Tc-$Fe(OH)_3$-MA, by a modified application of the Reese method for making ferric (^{113m}In) hydroxide particles (12). Sterile reagents required for the preparation are 1 N HCl, 0.56 N NaOH, 10% gelatin, isotonic saline in 1.7% gelatin solution at pH8, $FeSO_4 \cdot 7H_2O$ solution (2 mg Fe (II)/ml N HCl), and $^{99m}TcO_4^-$ saline solution. All the reagents are prepared with sterile distilled water and passed through 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. An exact dilution is calculated to make the solution 2 mg/ml in Fe(II). Two-tenths milliliter 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, stoppered 10-ml test tube ("Vacutainer" by Beckton, Dickinson Co.). The solution is made basic with 0.43 ml of 0.56 N NaOH and mixed by slow inversion for 3 min. The pH should be 11 to 12 or adjusted with a few drops of NaOH if necessary. One ml of 10% gelatin is added with gentle mixing for 2 min.

The mixture is centrifuged in a clinical centrifuge for 10 sec at 1600 g, the supernatant withdrawn, and the $Fe(OH)_3$ precipitate

resuspended in pH8 saline-gelatine solution in a volume to give the desired activity per ml of solution.

The particles are sized on a hemocytometer, 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 AND DISCUSSION

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 states. The Tc(V) binds to Fe(III), and Tc(IV) is coprecipitated with $Fe(OH)_3$ as the dioxide (13).

The most commonly used reductants for ^{99m}Tc labelling are ascorbic acid in the presence of Fe(III) and thiocyanate ion in hydrochloric acid solution (14). However, these reducing agents interfere with the formation of $Fe(OH)_3$ macroaggregates by forming complexes with Fe(III). Therefore, we use ferrous iron to reduce Tc(VII) to Tc(V) from which the ^{99m}Tc-labelled iron hydroxide can be aggregated to the desired particle size range of 20 to 50 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. 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 (15) to produce macroaggregates of $Fe(OH)_3$ in the desired particle-size range from 20 to 50 μ, $FeSO_4 \cdot 7H_2O$ is the preferred form of Fe(II).

Free $^{99m}TcO_4^-$ is removed from $^{99m}Tc\text{-}Fe(OH)_3$ 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 (13).

$^{99m}Tc\text{-}Fe(OH)_3$-MA is prepared in the particle size range of 20 to 50 μ as shown in the photomicrograph Fig. 2. There is about 75% binding of ^{99m}Tc with 80 μg/ml of ferrous iron. After centrifugation and resuspension of $^{99m}Tc\text{-}Fe(OH)_3$-MA, there is greater than 95% binding of ^{99m}Tc in the final product solution, as shown by thin-layer chromatography, with a specific activity of about 60 μCi ^{99m}Tc/μg Fe (for a 25-ml elution from a 200-mCi ^{99m}Tc generator).

The distribution of $^{99m}Tc\text{-}Fe(OH)_3$-MA in rats is 85 to 87% in lungs, 7 to 8% in liver, and 7 to 9% in stomach and intestines within 30 minutes after 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).

The uptake of $^{99m}Tc\text{-}Fe(OH)_3$-MA in the lungs of a rat is shown in Fig. 3. These are anterior views exposed for 1 min with the Donner Laboratory scintillation camera using (A) multichannel and (B) pinhole collimation. The injected dose was 200 μCi in 0.2 ml containing 12 μg Fe.

Studies were done with ^{99m}Tc-Fe(OH)$_3$-MA in a human subject who had carcinoma of the lung. Before injection of the radioactivity, a transmission picture (Fig. 4) was taken with the scintillation camera by placing a disk source of ^{99m}Tc below the patient according to the method of Anger and McRae (16). This allows positioning of the heart and lungs for the subsequent emission pictures. Note the lesion shown in the left lung. Two mCi of ^{99m}Tc in 1.4 ml (65 μg Fe) were injected into the antecubital vein.

Figure 5 (A through F) is a dynamic blood-flow study 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. View F shows the uptake of activity by the right lung in the same relative position as shown by the transmission picture. This patient showed no blood flow to the left lung which remained as a "cold" area throughout the study. These pictures are anterior-posterior views, each exposed for 3 sec and taken with 0.3-sec intervals between exposures.

The patient was repositioned to place the right lung completely in the field of view for Fig. 6 which is an anterior-posterior view taken 10 min post-injection and exposed for 1 min showing localization of the isotope in the right lung. There is also a small amount of uptake in the liver.

Figure 7 is a 6-plane scan of the same patient taken with the newly developed Multiplane Tomographic Scanner (17). These six images are obtained from a single scan of the chest area and are focused at successively deeper planes in the lung. The first image is 1 inch below the chest surface and the last image is at a depth of

6 inches. The scanning time was 15 min and about 120,000 counts were recorded.

Figure 8 is a posterior multiplane tomographic scan showing uptake of the compound in the lungs. The right lung base is higher than the left, and there is no detectable uptake in the liver. The standard P-A and right lateral chest X rays were normal, but a prone X ray showed the right diaphragm to be 2.5 cm higher than the left diaphragm. There was normal diaphragmatic movement on both sides. The patient was referred for study because of pain over the lower right chest.

SUMMARY

The physical advantages of ^{99m}Tc can be utilized for lung scanning with this new 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 insignificant uptake in other organs. The high photon yield and low radiation dose permits lung scans in a few minutes. Also dynamic blood-flow studies can be performed with the scintillation camera using 2- to 3-sec exposures. This preparation can also be used to advantage with the Multiplane Tomographic Scanner to obtain high resolution tomographic images of the lungs.

FOOTNOTE AND REFERENCES

[1]This work was done under the auspices of the U. S. Atomic Energy Commission.

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FIGURE LEGENDS

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 20 to 50 μ range (small squares represent 50 microns).

Fig. 3. Uptake of ^{99m}Tc-$Fe(OH)_3$-MA in rat lungs, 1-minute anterior-posterior gamma-camera picture; A. Multi-channel collimator, B. 1/8-inch pinhole collimator.

Fig. 4. Transmission picture with disk source of ^{99m}Tc; anterior-posterior view of chest area.

Fig. 5 (A through F). Three-second blood-flow studies, anterior-posterior view, gamma-camera pictures with multichannel collimator.

Fig. 6. Anterior-posterior view, 1-min exposure, upper chest area, 10 min post injection.

Fig. 7. Anterior-posterior view with the tomographic scanner over the chest area.

Fig. 8. Posterior multiplane tomographic lung scan.

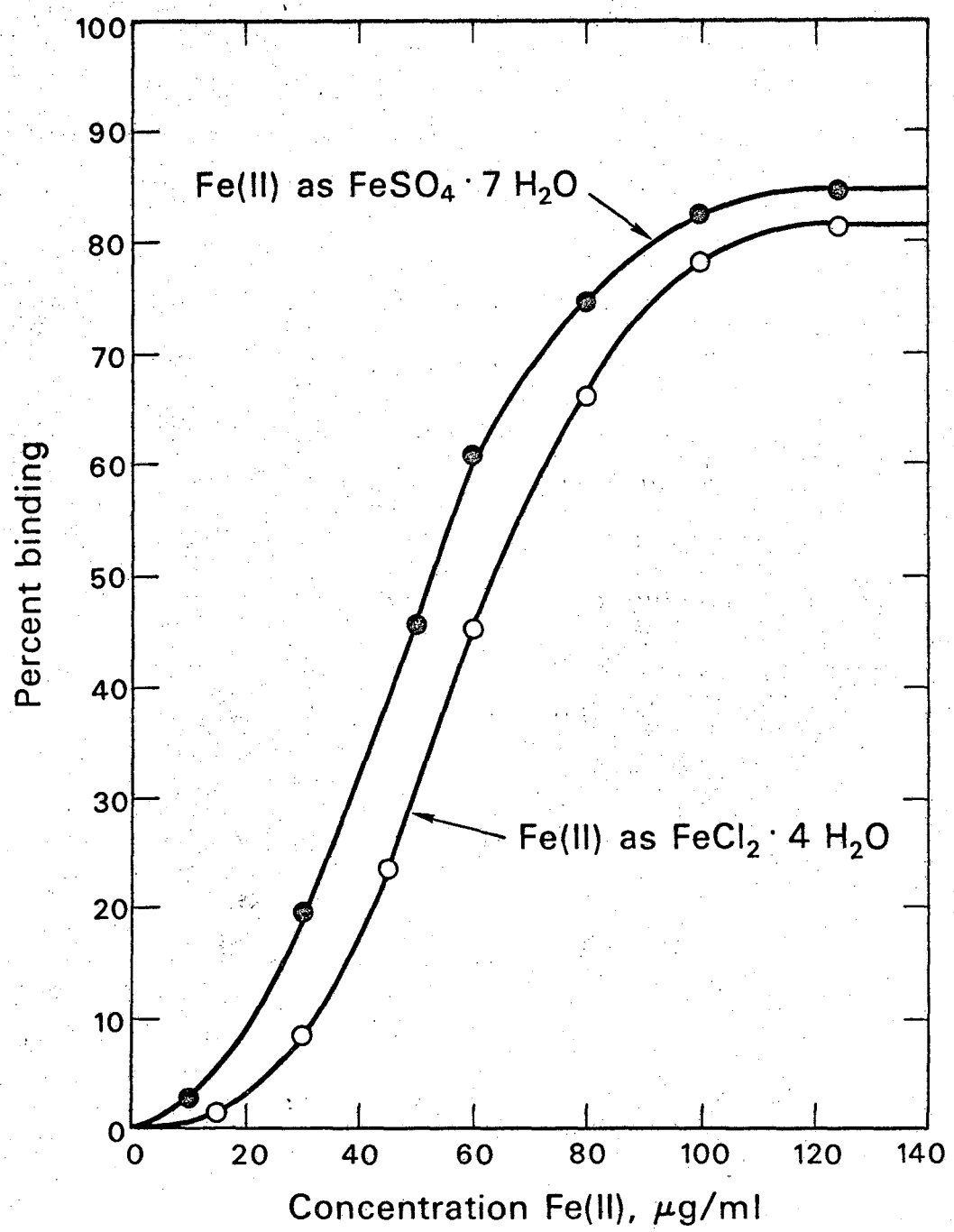

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Fig. 1

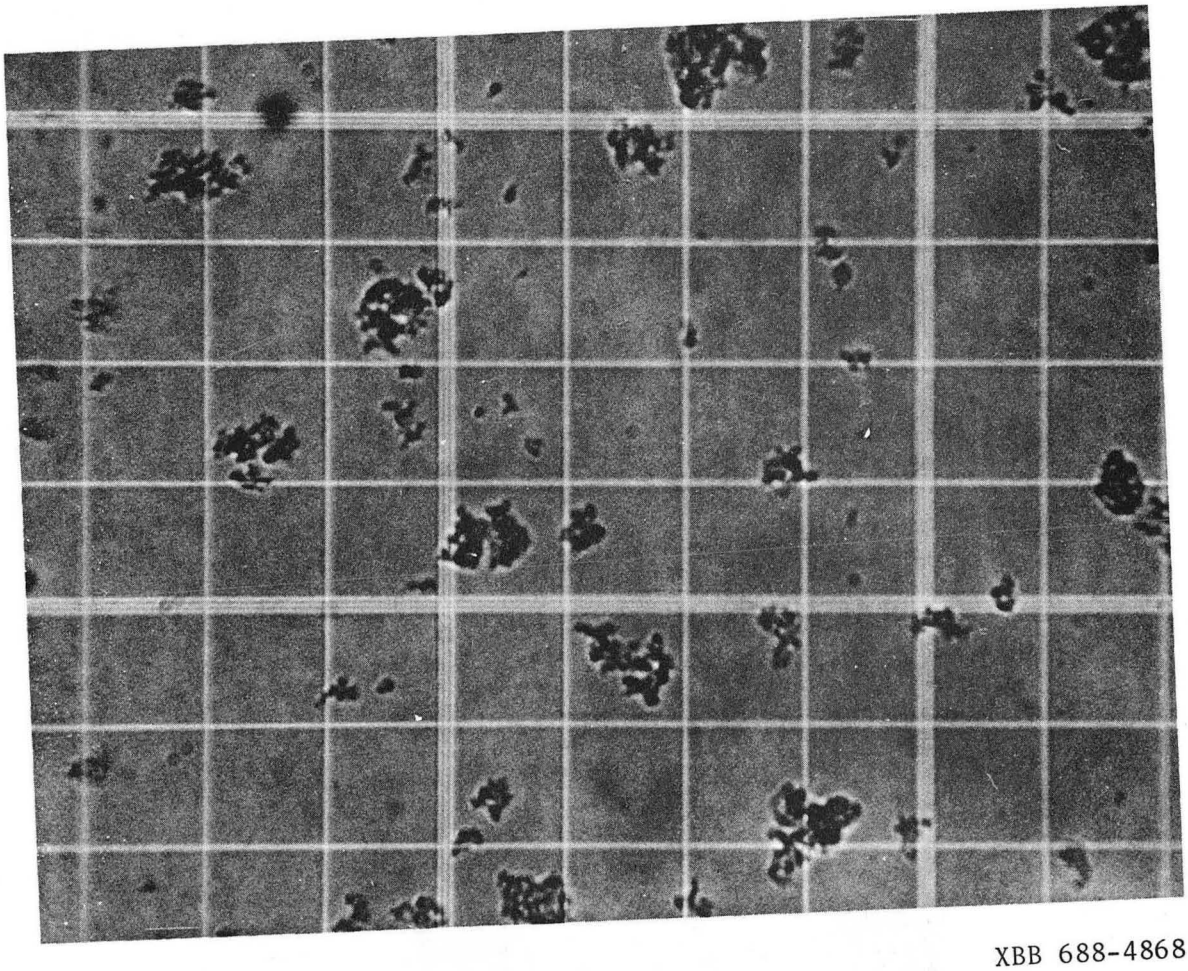

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Fig. 2

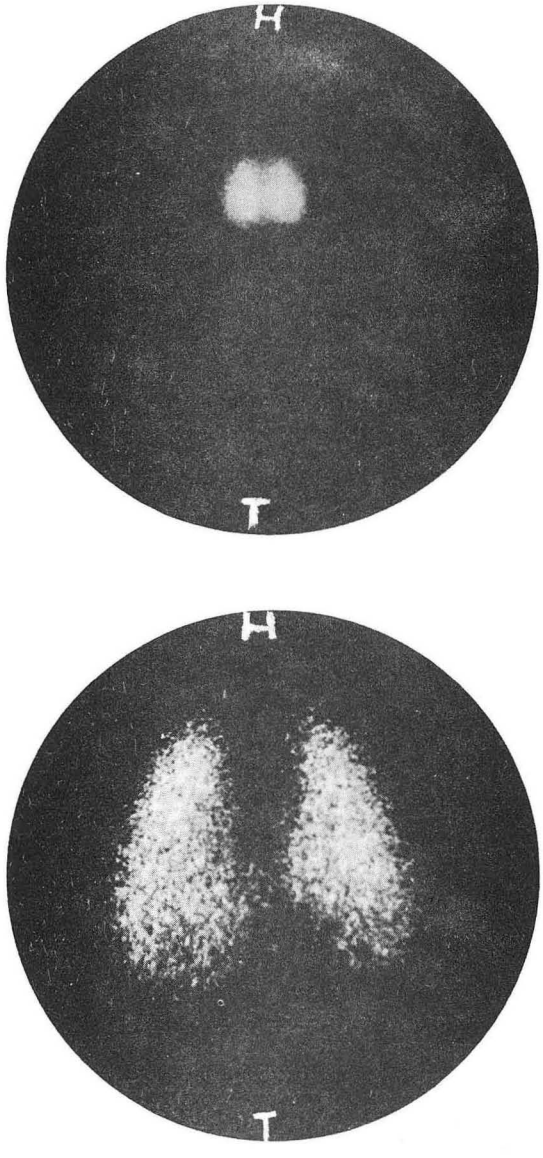

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Fig. 3

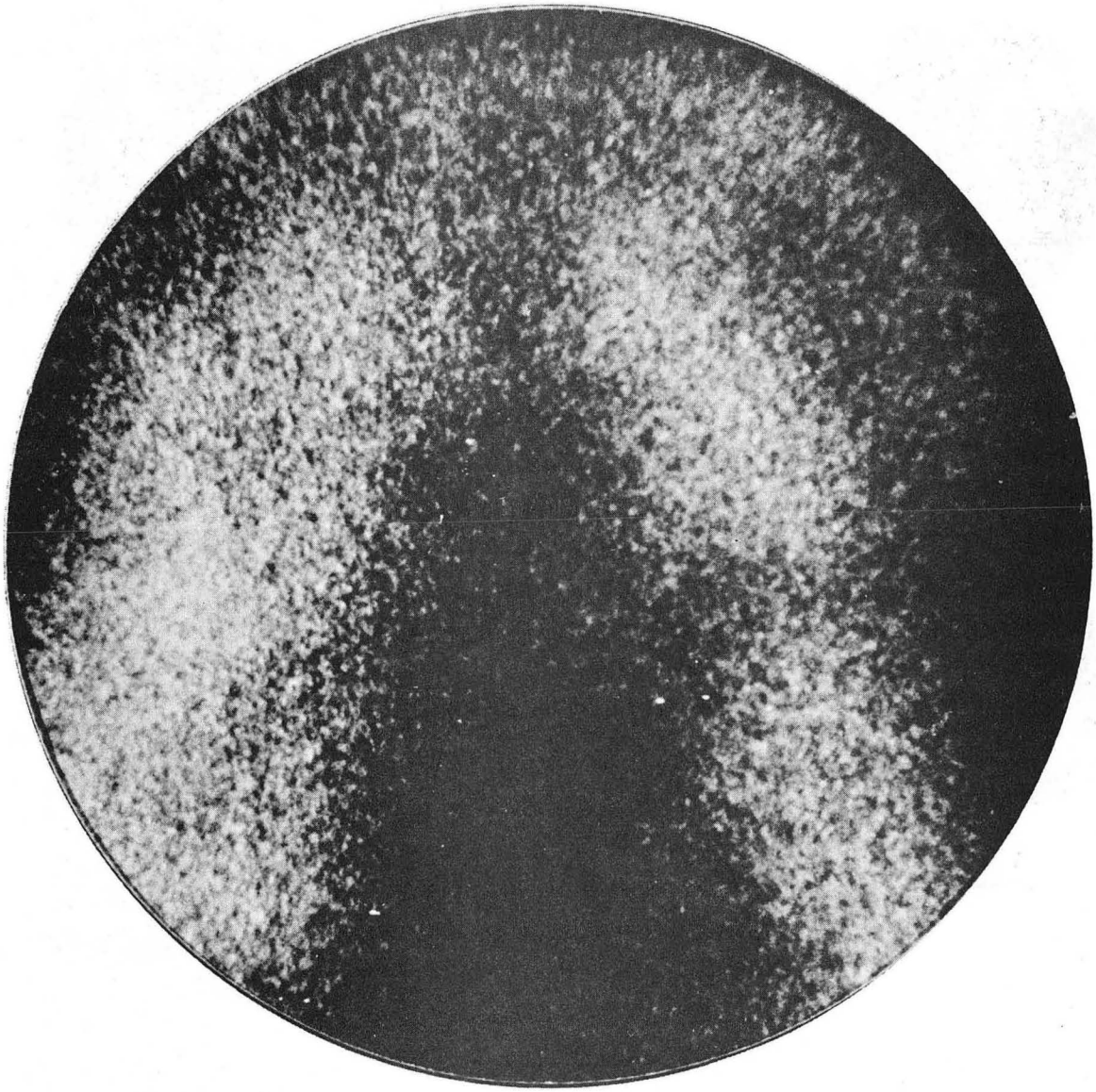

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Fig. 4

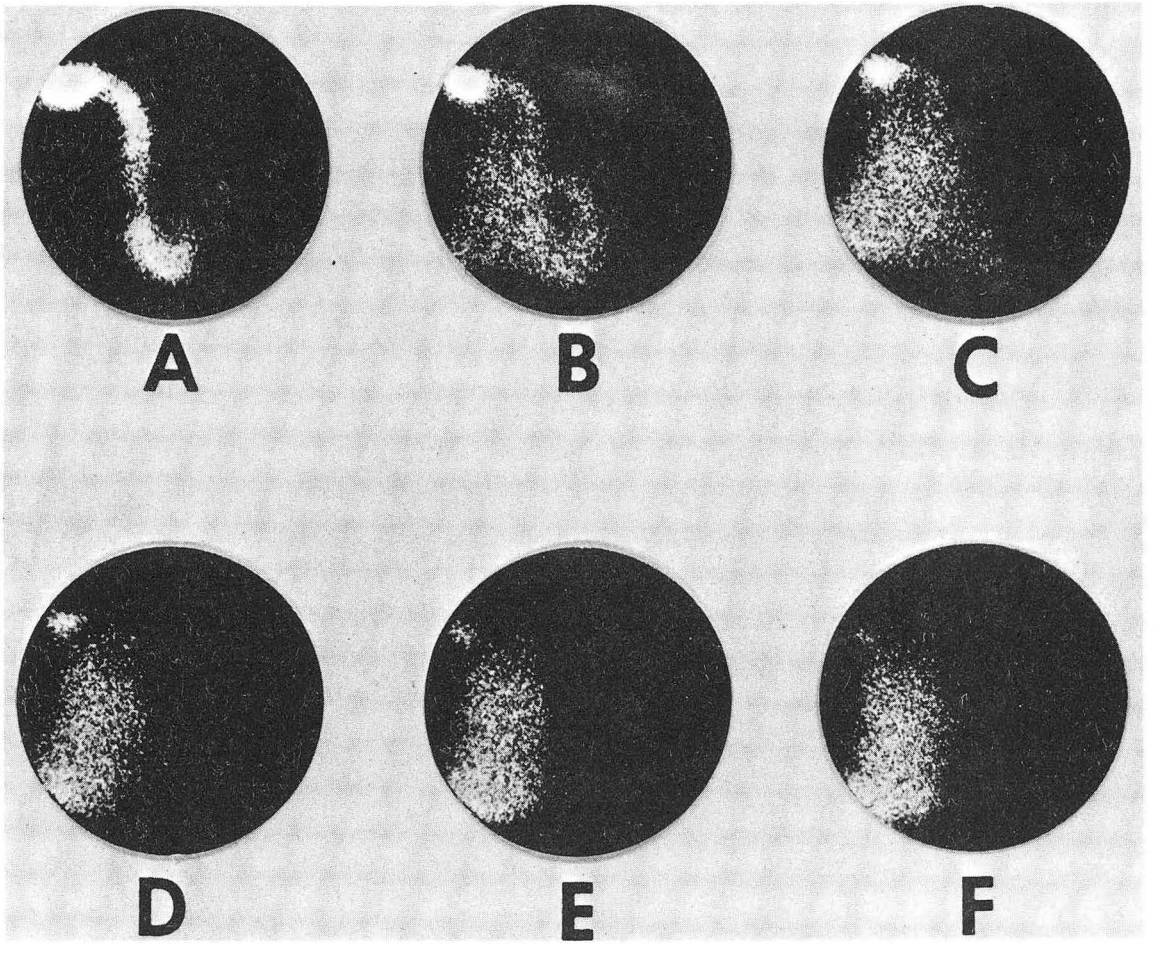

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Fig. 5

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Fig. 6

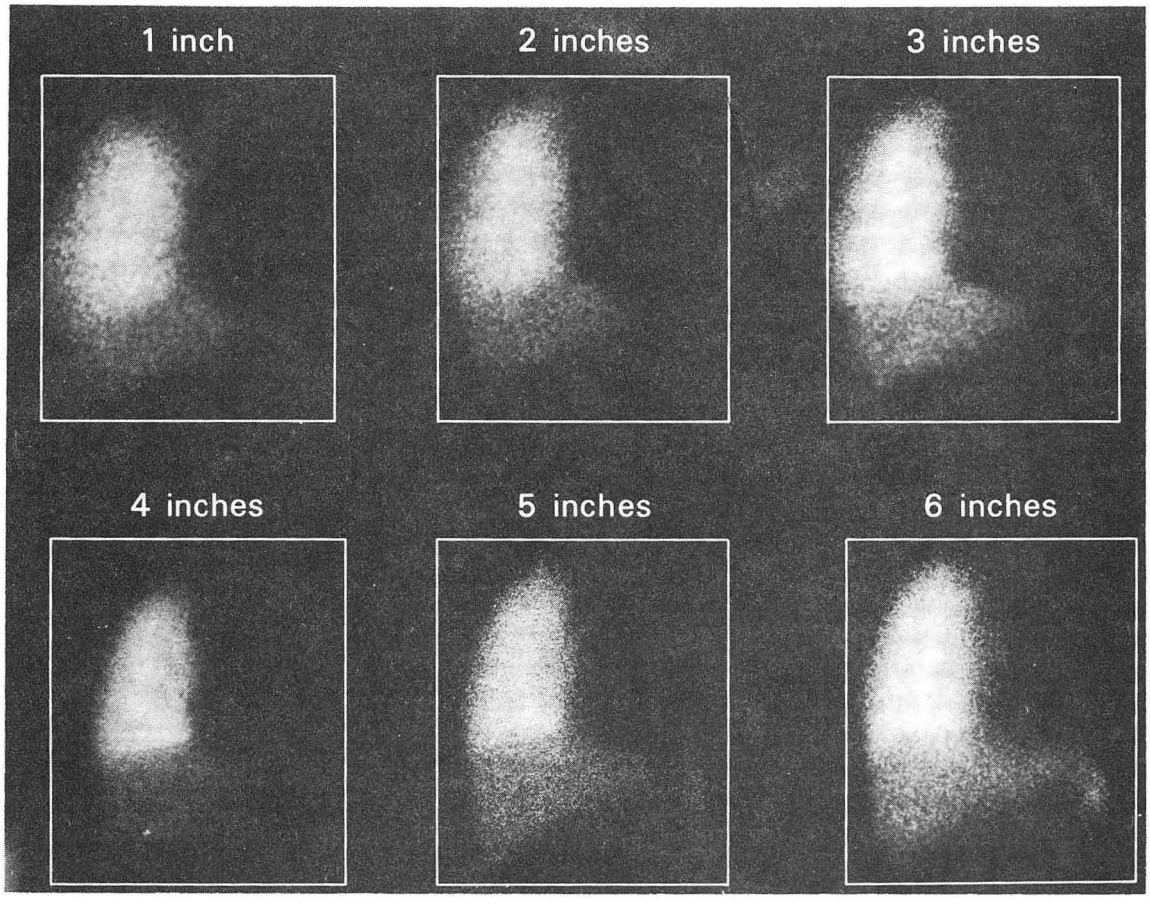

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Fig. 7

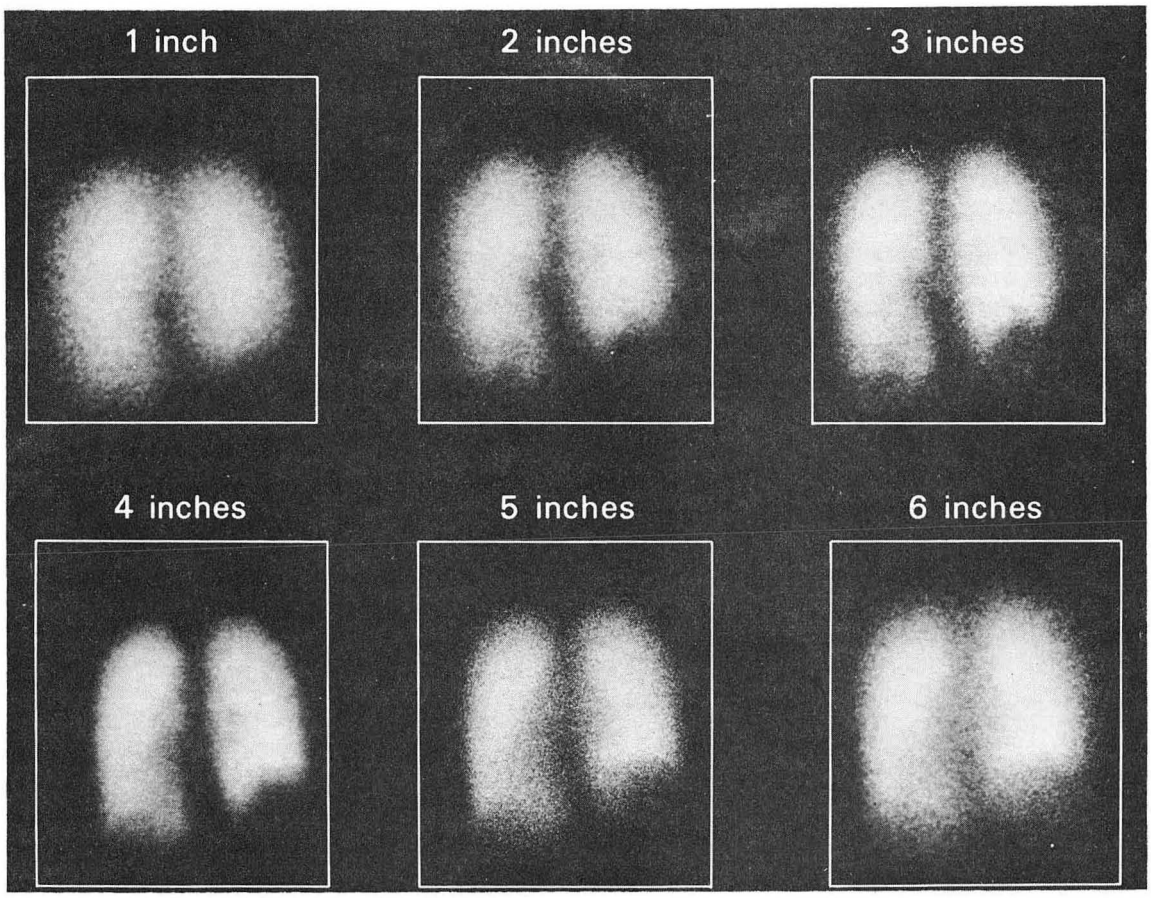

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Fig. 8

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