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Authors

Yano, Yukio
Anger, Hal O.

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University of California

Ernest O. Lawrence Radiation Laboratory

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VISUALIZATION OF MYOCARDIUM AND KIDNEY WITH ULTRASHORT-LIVED RUBIDIUM-82 AND THE POSITRON SCINTILLATION CAMERA[1]

Yukio Yano and Hal O. Anger

Donner Laboratory of Medical Physics and Biophysics
Lawrence Radiation Laboratory
University of California, Berkeley, California

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Abstract

Rubidium-82 decays by positron emission with a half-life of 80 sec, and is the daughter of 25-day strontium-82. The ^{82}Rb can be rapidly eluted from the parent by passing ammonium acetate solution through a suitable ion-exchange column. In dogs and rabbits, the myocardium is strongly labeled by infusing the eluted isotope into a vein for about 1 min, waiting for 2 min, and then starting an exposure with the positron camera that lasts until the isotope has essentially decayed. A relatively high uptake is obtained in heart muscle compared with skeletal muscle, and the positron camera yields an excellent image of the heart. There is little concentration of the isotope in any other organs except for the kidneys, which also exhibit a high uptake of the isotope.

Introduction

Rubidium and potassium are chemically related elements in the alkali metals group of the periodic table. The behavior of rubidium-86 and potassium-42 under biological conditions has been reported to be very similar (1, 2). Furthermore it has been reported that the myocardial uptake of ^{86}Rb after intravenous infusion is related to the rate of blood flow through the myocardium (3, 4). ^{84}Rb, a positron-emitting isotope, has been used with coincidence γ-ray detection for the determination of coronary blood flow in man (5). However, because of its relatively long half-life of 33 days and its high cost, ^{84}Rb presents disadvantages for coronary blood flow studies.

^{82}Rb has physical characteristics that are desirable for visualization of deep-lying organs. Its very short half-life offers lower radiation exposure, the possibility of quick repeat studies to obtain several views (6), and apparently very selective uptake of the isotope in the myocardium. It has a half-life of 80 sec and decays 96% of the time by positron emission with a maximum energy of 3.15 MeV. The positron is accompanied by a 0.77-MeV γ ray (9.0% abundant) to the ground state of krypton-82 (7).

^{82}Rb is produced continuously by decay of the parent isotope strontium-82, which decays by electron capture with a half-life of 25 days. When ^{82}Sr is retained on an ion-exchange column, ^{82}Rb can be milked from the radioisotope generator every 10 to 15 min. Because it is a positron emitter, it allows use of the positron scintillation camera with its high sensitivity and excellent image-forming characteristics

for deep-lying organs (8).

Materials and Methods

The parent isotope ^{82}Sr has been produced by two different nuclear reactions with the 88-inch cyclotron available at the Lawrence Radiation Laboratory in Berkeley. The first method uses the $^{80}Kr(\alpha, 2n)^{82}Sr$ nuclear reaction with a threshold energy of about 14 MeV. Natural Kr gas, 2.27% abundant in ^{80}Kr, is placed in a water-cooled gas target vessel and irradiated with 25-MeV α particles through a 0.001-in. aluminum foil window. The amount of beam current delivered to the Kr gas is limited because of the increase in pressure within the target vessel during irradiation. Although ^{82}Sr was produced in sufficient quantities to allow study of the chemical separation of ^{82}Rb from an ion-exchange column, it appears that sufficient yields of ^{82}Rb for clinical applications will be difficult to produce even with the use of an enriched ^{80}Kr gas target. The highest enrichment now available is 37.7% ^{80}Kr at a cost of $6.10 per ml. Because of the high cost and technical difficulties in irradiating ^{80}Kr, a second method of ^{82}Sr production by the $^{85}Rb(p, 4n)^{82}Sr$ nuclear reaction was investigated. The threshold energy for this reaction is about 33 MeV.

Naturally occurring Rb as RbCl, 72.15% abundant in ^{85}Rb, is irradiated with 45-MeV protons through a 0.005-in. Al cover foil. One and eight hundredths g of RbCl, equivalent to 550 mg of ^{85}Rb, is pressed into a powder target to a depth of 0.100 in. With a 2-hr irradiation delivering 20 μA-hr of beam, about 870 μCi of ^{82}Sr is recovered, which gives an adequate yield of ^{82}Rb for visualization of the heart in dogs with the positron camera.

Both methods of ^{82}Sr production also produce large quantities of ^{83}Sr with a half-life of 33 hr, which decays by positron emission to the active daughter ^{83}Rb. ^{83}Rb with a half-life of 83 days decays principally by emission of 0.53-MeV γ ray (93% abundant) to the ground state of ^{83}Kr(7). By waiting 7 to 10 days after irradiation to allow most of the ^{83}Sr to decay to ^{83}Rb, it is possible to recover nearly all of the ^{83}Rb in the first few elutions from the ^{82}Sr-^{82}Rb generator. Subsequent elutions from the generator contain only the 80-sec ^{82}Rb.

Chemistry and Ion-Exchange Column

The irradiated RbCl target material containing ^{82}Sr is washed from the powder plate into an Erlenmeyer flask with about 15 ml of H_2O. This solution is adjusted to pH 7 to 8 with a few drops of 0.1 N NH_4OH and made 0.3 M in ammonium acetate ($NH_4C_2H_3O_2$). The ^{82}Sr solution is placed on weakly acidic cation-exchange resin containing carboxylic acid exchange groups, which is available as Bio-Rex 70 from Bio-Rad Laboratories.

A specially constructed ion-exchange column is made of Pyrex glass 11 mm i.d. and 60 mm high, which is fitted with Luer-lock connections at the top and bottom.

Bio-Rex 70 of 100 to 200-mesh particle size is slurried into the ion-exchange column and washed with 0.3 M $NH_4C_2H_3O_2$. The resin column is connected to a 20-ml syringe which is automatically filled from an eluant reservoir and emptied through the isotope generator by an electric motor drive and automatic two-way valve, as shown in Fig. 1. With this automatic elution system, controlled flow of the eluant solution

under sterile conditions is achieved through a closed system. It is then possible to deliver very-short-lived isotopes from an isotope generator directly for intravenous infusion. The flow rate of the eluant is set at 0.33 ml/sec to allow for resistance to flow from the ion-exchange resin and yet deliver ^{82}Rb to the desired site before it has decayed away. As the eluate comes from the column it is delivered through intramedic polyethylene tubing of about 0.030 in. i.d. to a sterile three-way valve and Millipore filter into an intravenous catheter.

The separation of ^{82}Rb from ^{82}Sr on Bio-Rex 70 is similar to that reported by Huff and O'Brien for the separation of ^{84}Rb from an enriched strontium target (9).

As a radioisotope generator this ion-exchange system is subjected to repeated elutions with a cumulatively larger volume of eluant. The leakage of ^{82}Sr will tend to increase as the separation factor of ^{82}Rb from ^{82}Sr decreases from 10^4 to about 10^2. Present studies indicate that a total volume of about 400 ml of 0.3 M $NH_4C_2H_3O_2$ can be safely put through the resin column without significant breakthrough of ^{82}Sr to contaminate the ^{82}Rb eluate.

The yield of ^{82}Rb activity as a function of $NH_4C_2H_3O_2$ concentration is given in Table I. This data was obtained from a generator containing $\frac{1}{35}$ of the ^{82}Sr on a full strength generator. Also shown is the ^{82}Sr contamination for each elution of ^{82}Rb from the generator. It can be seen that elution with 20 ml of 0.4 M $NH_4C_2H_3O_2$ solution gives a very good recovery of ^{82}Rb (72.5%) with less than $2.0 \times 10^{-2}\%$ ^{82}Sr contamination, or about 0.02 μCi of ^{82}Sr for 100 μCi of ^{82}Rb.

Table I. Elution yields of ^{82}Rb and ^{82}Sr contamination for various concentrations of $NH_4C_2H_3O_2$.

^{82}Sr on Column (μCi)	$NH_4C_2H_3O_2$ Molarity	^{82}Rb for 20 ml Elution (μCi)	Yield ^{82}Rb (%)	^{82}Sr for 20 ml Elution (%)
24	0.15	3.43	14.3	$< 2\times10^{-2}$
24	0.20	8.35	34.8	$< 2\times10^{-2}$
24	0.30	13.4	55.9	$< 2\times10^{-2}$
24	0.40	17.4	72.5	$< 2\times10^{-2}$

Depending upon the toxicity of $NH_4C_2H_3O_2$ solution, the best concentration of the eluant should be as close to 0.4 molar as possible.

Figure 2 shows the decay curve for a typical elution of ^{82}Rb. The radio-activity increases to a maximum and then decays with a constant half-life through at least nine half-lives.

Results and Discussion

^{82}Rb obtained from the radioisotope generator was used in a series of animal experiments with rats, rabbits, and dogs. In each case ^{82}Rb was given by intravenous infusion from the pressurized ion-exchange column at a flow rate of 0.33 ml/sec. The clearance of radio-activity from the blood and uptake in specific organs was followed by sequence exposures with the positron scintillation camera.

Two ml of 0.15 M $NHC_2H_3O_2$ was used for elution of ^{82}Rb for a series of pictures of the rat. At 30 sec after injection of the isotope,

^{82}Rb activity can be seen in the general circulation. After 1 min ^{82}Rb is taken up by the kidneys and heart, where it is probably concentrated in the myocardium.

In the rabbit an infusion of 10 ml of 0.15 M $NH_4C_2H_3O_2$ led to Fig. 3, which is a posterior view. ^{82}Rb accumulation can be seen in the heart and kidneys within 2 min after injection of the activity. The picture was exposed for 1 min.

In the dog an infusion of 10 ml of 0.3 M $NH_4C_2H_3O_2$ and ^{82}Rb solution was given. The left lateral view of the chest area, beginning 2.5 min after infusion and exposed for 9.5 min demonstrates localization of ^{82}Rb $C_2H_3O_2$ in the myocardium, as shown in Fig. 4. This time of 2.5 min for clearance of ^{82}Rb from the circulation and uptake by the myocardium was established by taking a series of pictures immediately after infusion of the ^{82}Rb activity. In pictures from 15 to 60 sec after infusion of ^{82}Rb most of the ^{82}Rb is seen in the general circulation. In those taken from 60 to 120 sec ^{82}Rb is seen localizing in the myocardium. In those taken from 120 to 210 sec there is more activity in the myocardium and less in the circulation.

Another possible use for ^{82}Rb would be the visualization of the kidneys, which rapidly clear Rb from the blood during a single circulatory transit, as demonstrated by the detection of renal arterial stenosis in hypertension with radioactive rubidium (9). Furthermore Blandy et al. have shown that uptake of ^{86}Rb by the kidney is at a peak within 2 min after injection. Within 1 to 2 min the concentration of radioactivity by the kidneys is more than ten times that in the blood, liver, or muscle (11).

Summary

From the preliminary work done with the ^{82}Sr-^{82}Rb generator system in animals it appears that ^{82}Rb may prove to be of value in visualizing the myocardium and kidneys. It is fortunate that the 80-sec half-life of ^{82}Rb is long enough to allow clearance from the blood and still permit visualization of uptake in these organs.

The radiation dose to the heart and kidneys is calculated to be less than 100 mrad for 100 μCi of ^{82}Rb. The whole-body radiation exposure is less than 2 mrad.

Further development of the ion-exchange system may allow more suitable eluant solutions to be used. It is expected that important clinical applications of this new isotope will soon be developed.

Acknowledgments

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Footnote and References

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Figure Legends

Fig. 1. An automatic elution system for intravenous infusion of ^{82}Rb as a sterile solution from an isotope generator.

Fig. 2. Decay curve for ^{82}Rb obtained by milking a ^{82}Sr generator with 0.15 M $NH_4C_2H_3O_2$.

Fig. 3. Posterior view of ^{82}Rb $C_2H_3O_2$ distribution in the rabbit.

Fig. 4. ^{82}Rb uptake by the myocardium in dogs.

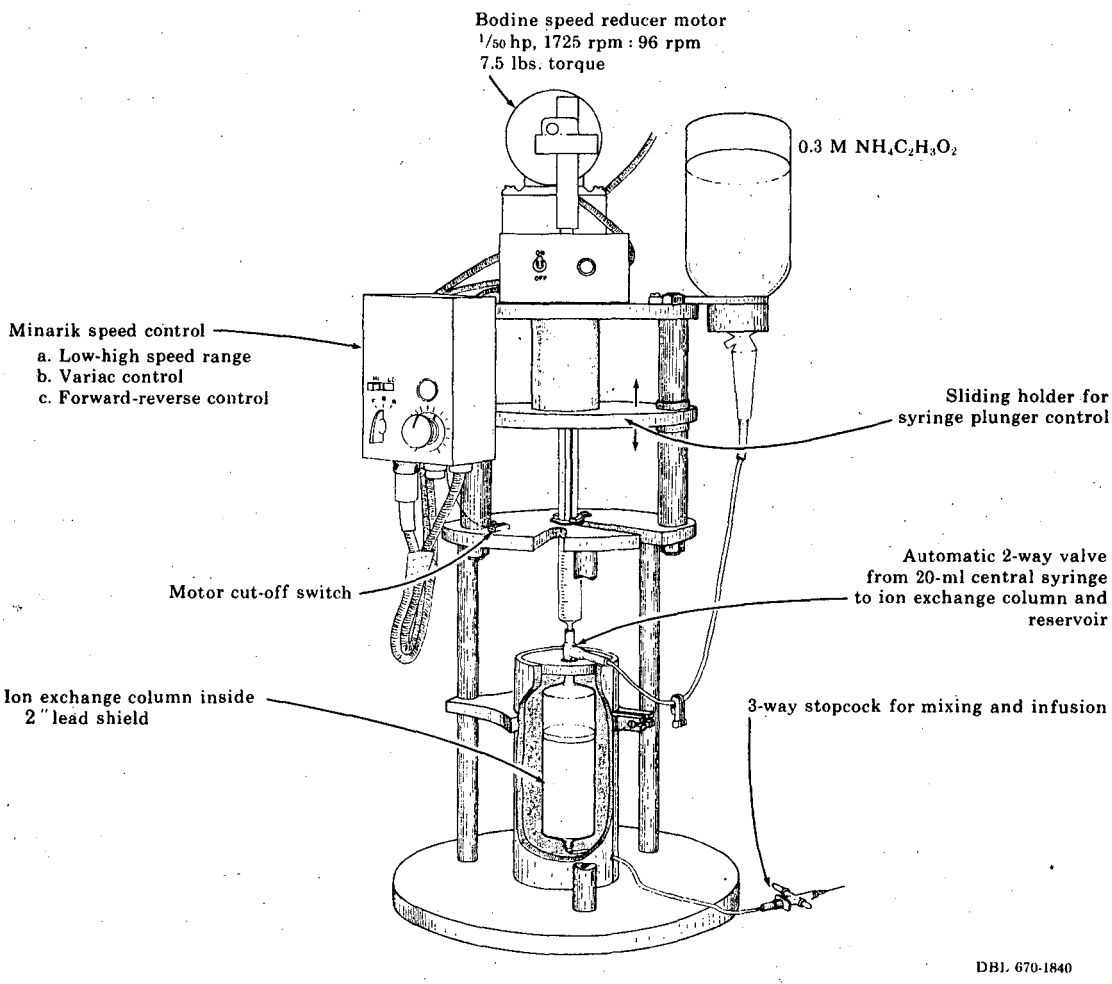
Bodine speed reducer motor
1/50 hp, 1725 rpm : 96 rpm
7.5 lbs. torque
0.3 M $NH_4C_2H_3O_2$
Minarik speed control
a. Low-high speed range
b. Variac control
c. Forward-reverse control
Sliding holder for
syringe plunger control
Motor cut-off switch
Automatic 2-way valve
from 20-ml central syringe
to ion exchange column and
reservoir
Ion exchange column inside
2" lead shield
3-way stopcock for mixing and infusion
DBL 670-1840

Fig. 1

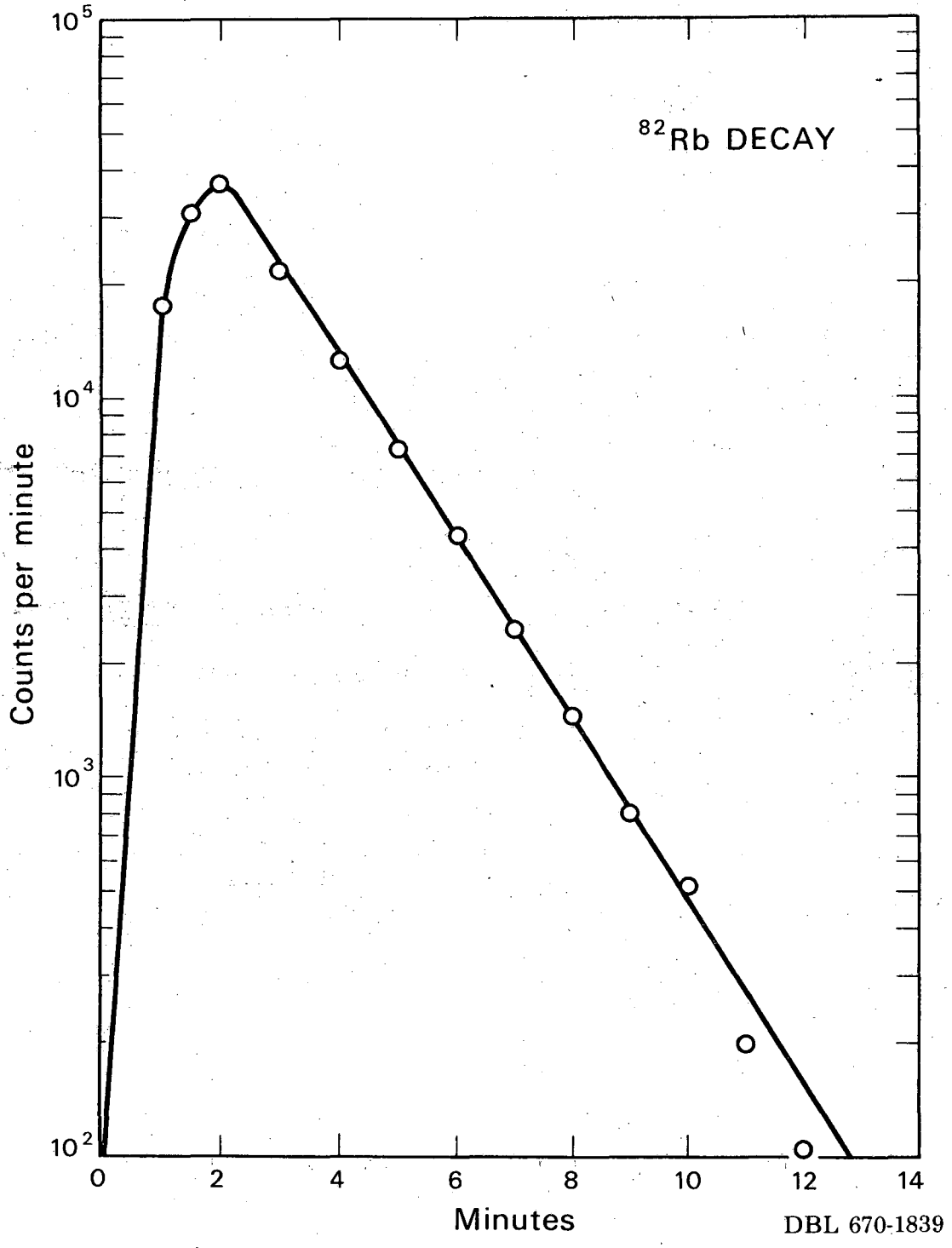
^{82}Rb DECAY
Counts per minute
10^5
10^4
10^3
10^2
0
2
4
6
8
10
12
14
Minutes
DBL 670-1839

Fig. 2

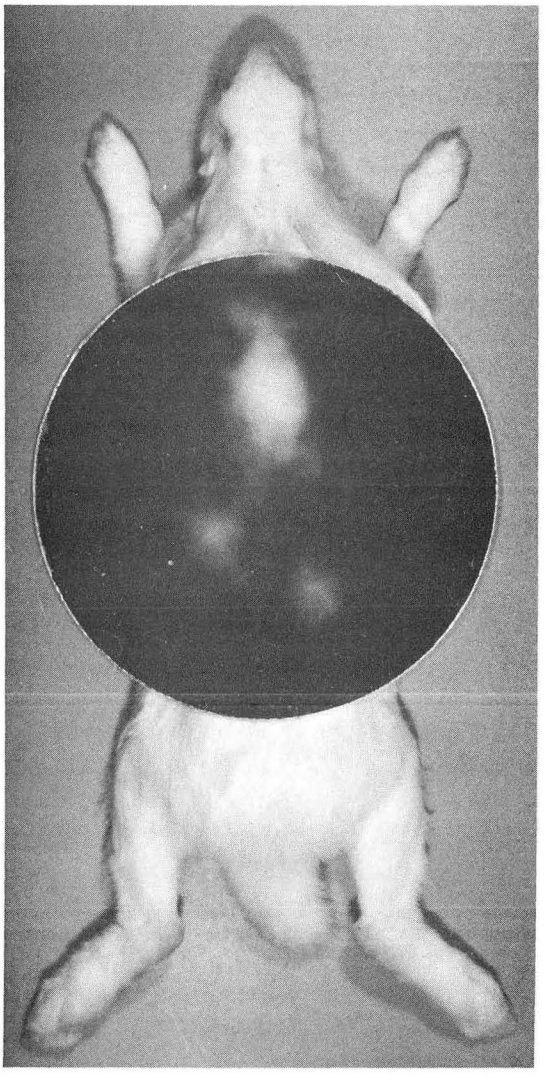

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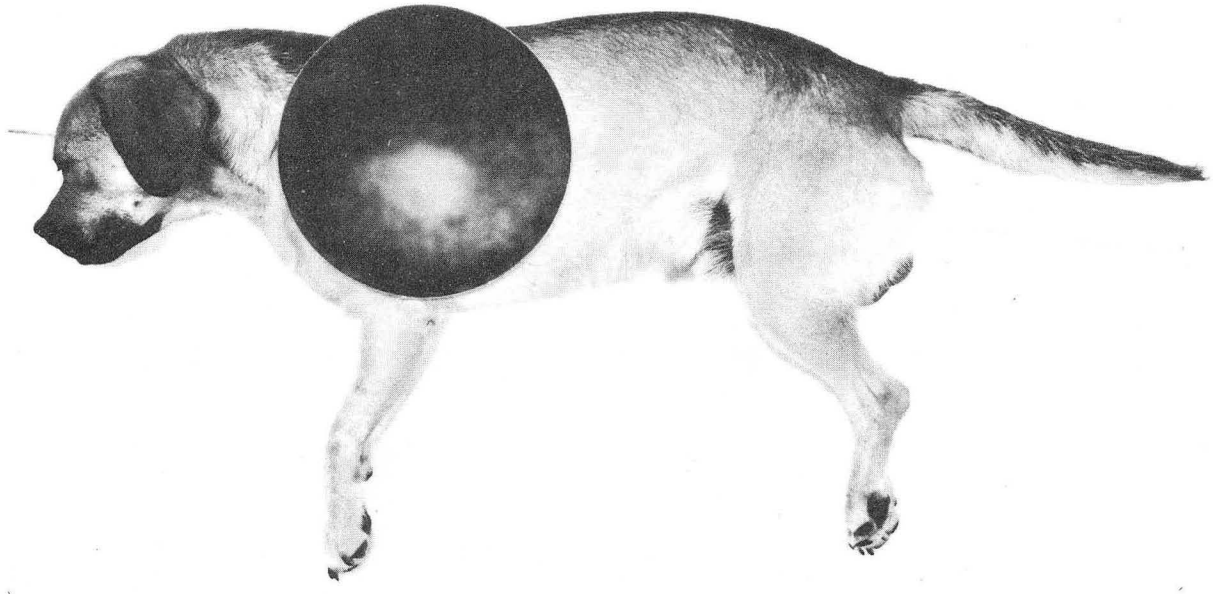
Fig. 3



XBB 679-5637

Fig. 4