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CYCLOTRON PRODUCED THULIUM- l67 FOR BONE AUD TUMOR SCANNING

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DONNER LABORATORY

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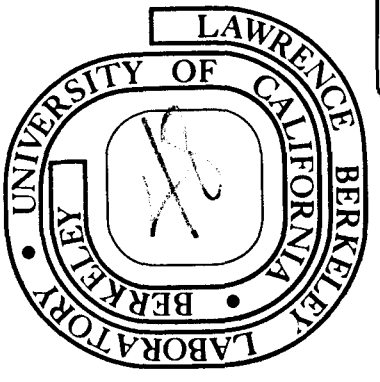

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DISCLAIMER

CYCLOTRON PRODUCED THULIUM-167 FOR BONE AND TUMOR SCANNING

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ABSTRACT

A method has been described for the cyclotron production of 9.6 day thulium-167. Ion exchange resin chromatography was used to separate the ^{167}Tm from the $HoCl_3$ target material. Distribution of the separated ^{167}Tm citrate in normal dogs and rats and in tumor bearing mice has been determined. The results of these studies indicate that ^{167}Tm is potentially useful for tumor and bone scanning.

The biological distribution of the lanthanons in rats was investigated by Durbin and coworkers in 1956.[1] They found that the lighter lanthanons were taken up primarily in the reticulo-endothelial system while the heavier lanthanons such as Dy, Tm, Er, Lu, Yb, and Tb were taken up primarily in the bone. More recently Chandra[2] on the basis of animal distribution studies of ^{170}Tm has proposed the use of ^{167}Tm for bone scanning. Hisada and coworkers[3,4] have investigated the usefulness of the heavier lanthanons such as ^{169}Yb for tumor imaging. In using ^{169}Yb citrate for scanning fifteen patients with primary lung and liver cancer they obtained thirteen positive scans.[4] Although either ^{169}Yb or ^{167}Tm should be equally effective in tumor localization, the 31.8 day half life ^{169}Yb would deliver a higher radiation dose to the patient than the 9.6 day half life ^{167}Tm. Thulium-167 decays 100% by electron capture to the metastable ^{167m}Er, T-1/2 2.3 sec, which then decays by isomeric transition to the stable ^{167}Er. The primary gamma emission of ^{167}Tm is 208 keV, 43% abundant. There is also a 532 keV gamma emission, 2% abundant. The physical characteristics of ^{167}Tm are advantageous for bone or tumor scanning because the 9.6 d half-life will allow scanning at 24-48 hours after administration to give a higher target to non-target ratio and the 208 keV photon is readily collimated and efficiently detected by the NaI(TL) crystal.

Recently we reported on our preliminary work in the cyclotron production of ^{167}Tm and its uptake in tumor mice.[5] This present report is a more complete description of our work with ^{167}Tm. We have investigated

the production of ^{167}Tm by the ^{165}Ho ($^{4}_{2}He$, 2n) ^{167}Tm nuclear reaction at the LBL 88-inch cyclotron. The ^{167}Tm was separated from the $HoCl_3$ target material by the method of Ketelle and Boyd,[6] and the biological distribution of ^{167}Tm citrate was studied in normal rats and dogs and in tumor bearing mice.

MATERIALS AND METHODS

Approximately 250 mg of $HoCl_3$ (K and K Lab) were pressed into a 0.010 inch deep powder plate holder and covered with a 0.005 inch thick aluminum cover foil. The naturally occurring ^{165}Ho is 100% isotopically abundant. The target plate was mounted on a water-cooled probe and irradiated with 30 MeV $^{4}_{2}He$ ions for up to eight hours with a beam current of 10-15 μA.

The irradiated target was allowed to stand for 2-3 days to allow the short half life 7.7 hour ^{166}Tm to decay away. The $HoCl_3$ target was then brought into solution with water and dilute HCl acid. On some occasions it was necessary to add citrate and to heat the target solution to solubilize the irradiated $HoCl_3$.

The radionuclidic composition of the ^{167}Tm target solution was determined by gamma-ray spectrometry using a Ge(Li) detector and multichannel analyzer. The separation of ^{167}Tm from the bulk of the $HoCl_3$ target material was done by using anion exchange resin AG 50x10, -400 mesh (Bio-Rad), which was placed in a glass column 1.0 cm in diameter and 45 cm high. The resin column was pre-equilibrated with 4.75% citrate solution at pH 3.4. After the ^{167}Tm-$HoCl_3$ target solution was placed on the resin bed, the citrate eluant solution was allowed to flow from a

reservoir maintained at 80-90°C through the resin column heated to the same temperature. One to two ml fractions were collected at a flow rate of 0.5 ml/min. Although the resolution of the resin column chromatography was determined by using commercially available ^{170}Tm and our reactor produced ^{166}Ho, for regular production runs of ^{167}Tm the presence of ^{165}Ho in the ^{167}Tm fractions was determined by addition of a few drops of 10% oxalic acid to bring down the Ho-oxalate precipitate. The fractions of ^{167}Tm which were collected before the first positive oxalate fraction were combined and sterilized by 0.22 μ Millipore membrane filtration.

The ^{167}Tm citrate was administered intravenously in two beagle dogs and whole body scans and scintiphotos were obtained from various times up to 24 hours later. One ml blood samples were withdrawn from various times up to 180 minutes after i.v. administration. At this time the radioactive urine was collected by catheterizing the bladder and flushing with saline solution.

Tumor bearing mice were obtained by implanting tumor cells of Ca-755 adenocarcinoma, C-1300 neuroblastoma and S-180 pleomorphic sarcoma in the right flank. Ten to fourteen days later the tumor mice were injected by tail vein with 0.15 ml of ^{167}Tm citrate and sacrificed at about 24 and 48 hours later. Samples of the blood and muscle and the entire lungs, liver, spleen, kidneys, and femur were assayed for the percent uptake of the administered dose per gram of tissue. The percent uptake in the carcass and gut was also determined.

Holmium-166 citrate in the presence of $HoCl_3$ was also administered to tumor bearing mice. The distribution of the radioisotope was determined at 24 hours to establish the effect of ^{165}Ho carrier upon the biological

uptake of the radioisotope.

RESULTS AND DISCUSSION

The production yield of ^{167}Tm was only 15-20 μCi/μAhr, which makes the availability of ^{167}Tm difficult and expensive. The machine yield was 150-200 μCi/hr, which places the cost at about $1.00/μCi for cyclotron time. Alternative production methods have been suggested which would use deuteron or proton beams to irradiate isotopically enriched ^{167}Er or ^{168}Er to produce about 60 μCi/μAh.[7] Although the yield of ^{167}Tm could be significantly improved, the increased cost of the enriched target material, about $.50/mg, would require its separation and recovery for subsequent irradiations.

Figure 1 shows the Ge(Li) gamma-ray spectrum of the unseparated ^{167}Tm 48 hours after EOB (end of bombardment). Only the gamma emissions of ^{167}Tm and ^{168}Tm were evident. The ^{167}Tm contained 0.2 percent ^{168}Tm, T-1/2 85 days.

The profile of the elution curve for separating ^{167}Tm from $HoCl_3$ is shown in Figure 2. Typically the ^{167}Tm came off in the 30-37 ml fractions and most of the $HoCl_3$ target material was removed in the fractions beginning at 62 ml. In those fractions which gave a negative oxalate test for $HoCl_3$, spectrochemical analysis was done to establish the sensitivity of oxalate precipitation at 50-100 μg $HoCl_3$/ml. Assuming the major ^{167}Tm peak to cover 7 ml, there would be at most 700 μg of $HoCl_3$ in the separated ^{167}Tm.

Two hundred microcuries of ^{167}Tm citrate were used to image the uptake in bone as seen in Fig. 3. The whole body scans were taken with the Mark II whole body scanner and scintillation camera pictures were taken

with the Donner Laboratory camera. The radioactivity has cleared from the blood and soft tissues by 24 hours to give an excellent bone scan.

The blood clearance curve as seen in Fig. 4 shows at least two components with half times of 31 minutes and 120 minutes. The total blood activity at 3 hours was 6.2 percent of the injected dose and the urinary excretion was 18.2 percent. These data are averaged results from two dogs studied with different production runs and column separations of ^{167}Tm.

The distribution of ^{167}Tm citrate in normal rats is given in Table I. These data indicate the uptake is primarily in bone (3.3-3.2 percent) and not in marrow (0.5-0.6 percent). Furthermore there is relatively low uptake in all of the soft tissues with the exception of the kidneys. This pattern of uptake appears to be consistent with most bone scanning agents.

Table II shows the distribution of ^{167}Tm citrate in tumor mice at 24 and 48 hours. The percent of injected dose/gm of tumor ranged from 0.64 percent to 0.83 percent for Ca-755 (adenocarcinoma), from 1.3 percent to 1.6 percent for C-1300 (neuroblastoma) and from 1.4 percent to 1.7 percent for S-180 (pleomorphic sarcoma).

Table III gives the ratio of tumor uptake to uptake in blood, lungs, liver, spleen, muscle and femur. The ratios of tumor to blood at 48 hours were 31.9 for Ca-755, 78.9 for S-180, and 16.1 for C-1300. The data from Tables II and III indicate that ^{167}Tm citrate compares favorably with ^{67}Ga citrate for tumor imaging. The distribution of reactor produced ^{166}Ho is shown in Table IV. The uptake of ^{166}Ho in the presence of $HoCl_3$ in tumor mice was essentially the same as the separated ^{167}Tm citrate.

SUMMARY

Cyclotron produced ^{167}Tm has the desirable physical properties of half-life, gamma energy and mode of decay to be useful for scintigraphy. The 9-6 day half life will allow production and delivery scheduling, the 208 keV gamma ray is readily collimated and yet its attenuation is minimized. Its decay by electron capture and isomeric transition of the ^{167m}Er daughter minimizes the radiation dose to the patient. The estimated radiation dose to bone of 70 kg patient from 500 μCi of ^{167}Tm is 2.3 rads. This assumes 65 percent uptake in bone and 20 percent excretion by way of the kidneys within 3 hours. The low production yield can be improved by an order of magnitude by a different nuclear reaction. The biological distribution of ^{167}Tm citrate in tumors of mice and bone of dogs indicates a potential usefulness for either tumor or bone imaging.

The value of ^{167}Tm-citrate for tumor imaging will be established by studying patients with established malignancies. These studies will be undertaken in the near future.

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Table I. Distribution of ^{167}Tm-Citrate in Normal Rats at 22 hours and 45 hours After Injection

Organ	22 hour		45 hour	
	%/Gram*	Ratio**	%/Gram*	Ratio**
blood	.006	--	.004	--
heart	.095	18.7	.129	30.0
lungs	.171	31.3	.232	57.3
liver	.219	45.8	.549	128
kidneys	.627	107	1.40	307
spleen	.180	36.1	.327	73.2
muscle of femur	.011	1.89	.034	7.25
femur and marrow	3.07	710	3.20	838
femur	3.31	760	3.20	834
marrow	.596	141	.481	96.7
gut***	1.47	--	3.20	--
carcass***	66.9	--	64.4	--

* Percent uptake of injected ^{167}Tm-citrate/gram of Organ. Above numbers represent an average of two animals

** Ratio of percent uptake of ^{167}Tm-citrate/gram of Organ: percent uptake of ^{167}Tm-citrate/gram of blood.

*** Numbers of carcass and gut represent percent uptake of injected ^{167}Tm per total tissue.

Table II. Percent/Gram, ^{167}Tm Uptake in Tumor Mice at 24 hours and 48 hours

Organ	Ca-755		S-180		C-1300	
	24 hr.*	48 hr.**	24 hr.	48 hr.	24 hr.	48 hr.
blood	0.075	0.034	0.060	0.031	0.115	0.076
liver	2.36	1.35	1.39	1.74	2.30	1.43
kidney	2.64	1.32	3.53	2.04	5.07	2.22
spleen	0.753	0.612	0.563	0.965	0.766	0.468
muscle of femur	0.682	0.309	0.310	0.367	0.424	1.49
femur	20.5	13.6	12.8	11.8	13.5	10.7
tumor	0.643	0.832	1.70	1.44	1.61	1.32
gut	0.603	0.786	1.26	0.599	0.725	0.356
carcass	2.89	2.96	2.23	2.40	2.08	1.87

* 24 hour - numbers represent average of three animals.

** 48 hour - numbers represent average of four animals.

Table III. Ratio Percent ^{167}Tm/Gram Tumor: Percent ^{167}Tm/Gram Tissue In Tumor Mice at 24 hour and 48 hour

Organ	Ca-755		S-180		C-1300	
	24 hr.*	48 hr.**	24 hr.	48 hr.	24 hr.	48 hr.
blood	7.65	31.9	28.3	78.9	10.9	16.1
liver	0.600	0.581	1.19	0.979	0.575	0.859
kidney	0.261	0.788	0.563	0.948	0.269	0.836
spleen	1.06	2.02	3.69	2.32	2.40	3.55
muscle of femur	2.51	3.61	6.40	5.08	6.40	5.08
femur	0.026	0.068	0.136	0.110	0.136	0.110
gut	1.39	1.42	3.63	2.71	2.10	3.43
carcass	0.218	0.303	0.744	0.636	0.660	0.653

* 24 hour - numbers represent average of three animals.

** 48 hour - numbers represent average of four animals.

Table IV. Percent/Gram, ^{166}Ho Citrate Uptake in Tumor Mice at 22 Hours
Numbers represent an average of two animals

Organ	Ca-755	S-180	C-1300
blood	.036	.025	.036
lungs	.617	.930	.852
liver	1.80	1.73	1.83
kidneys	4.22	3.11	14.7
spleen	.789	.771	.200
muscle of femur	.221	.117	.197
femur	3.07	6.94	8.62
tumor	.587	1.32	1.92
gut	2.75	.397	1.11
carcass	1.02	1.65	3.72

FIGURE CAPTIONS

Fig. 1. Ge(Li) gamma ray spectrum of ^{167}Tm showing gamma emissions of ^{167}Tm and ^{168}Tm.

Fig. 2. Separation of ^{167}Tm from $HoCl_3$ on cation exchange resin AG 50 x 10, -400 mesh with 4.75% sodium citrate.

Fig. 3. Composite scintiphoto (above) of a beagle dog 24 hours after i.v. administration of 200 μCi of ^{167}Tm citrate and whole body scan (below).

Fig. 4. Blood clearance curve for ^{167}Tm citrate in a beagle dog taken from zero time to 180 minutes after i.v. administration.

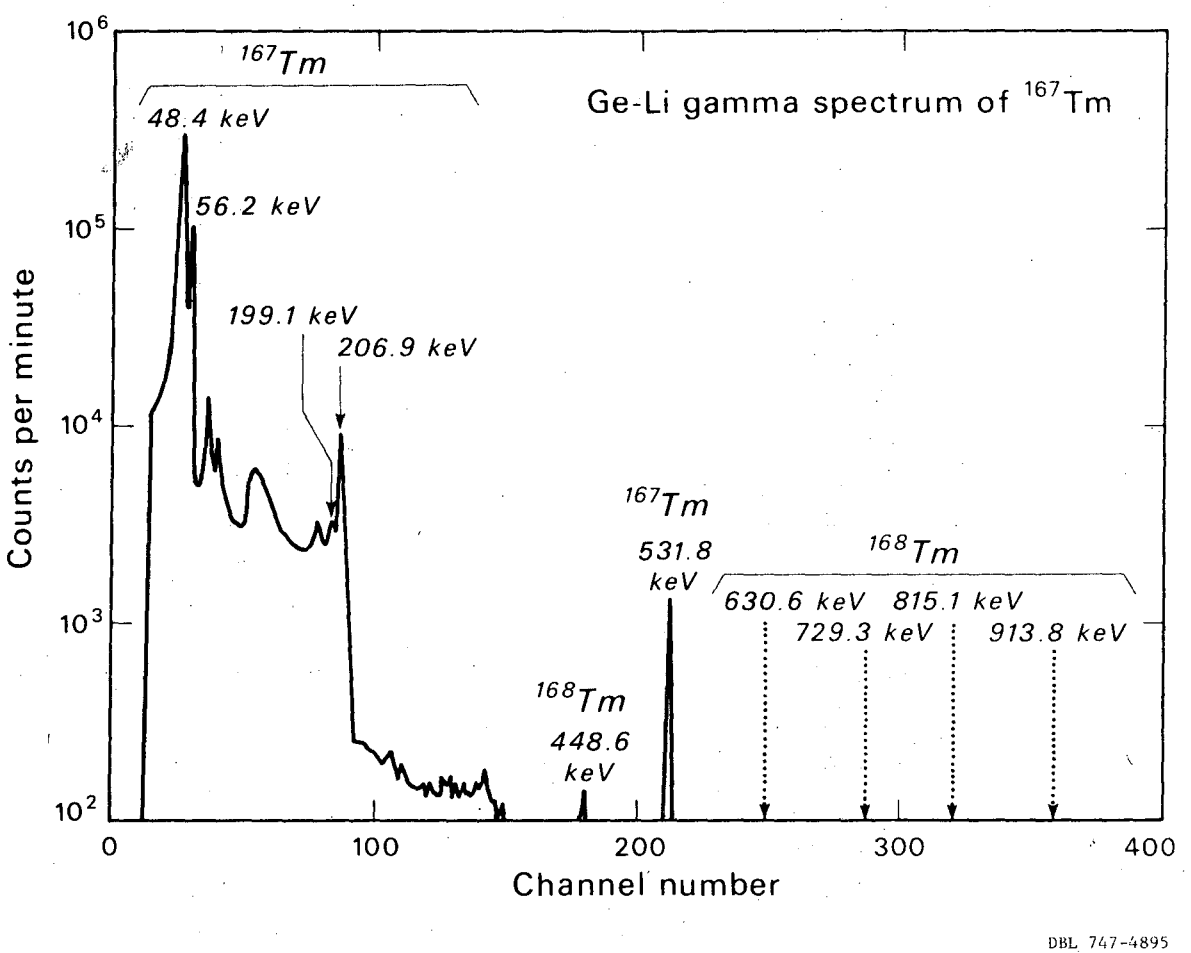
Ge-Li gamma spectrum of 167Tm
167Tm
48.4 keV
56.2 keV
199.1 keV
206.9 keV
167Tm
531.8 keV
168Tm
630.6 keV
729.3 keV
815.1 keV
913.8 keV
168Tm
448.6 keV
Counts per minute
Channel number
10^6
10^5
10^4
10^3
10^2
0
100
200
300
400
DBL 747-4895

Fig. 1

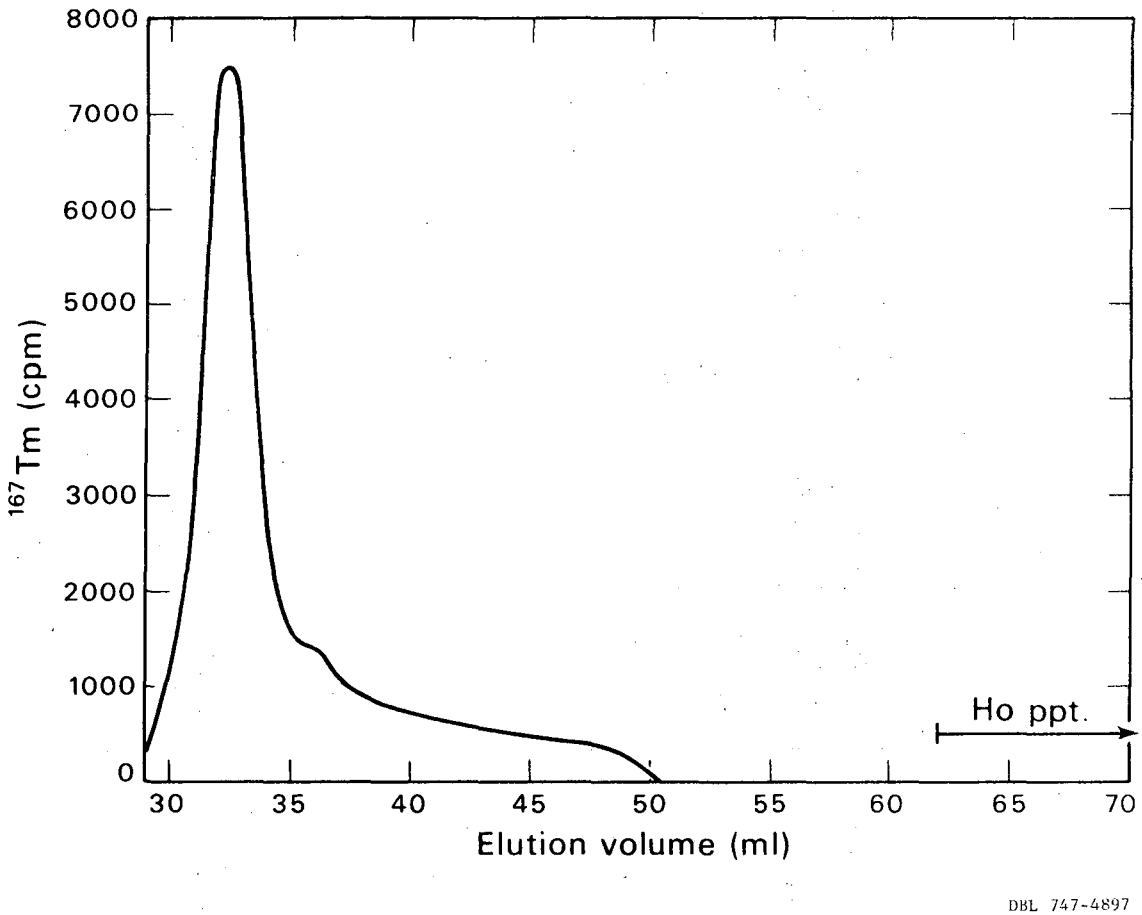
8000
7000
6000
5000
4000
3000
2000
1000
0
^{167}Tm (cpm)
30
35
40
45
50
55
60
65
70
Elution volume (ml)
Ho ppt.
DBL 747-4897

Fig. 2

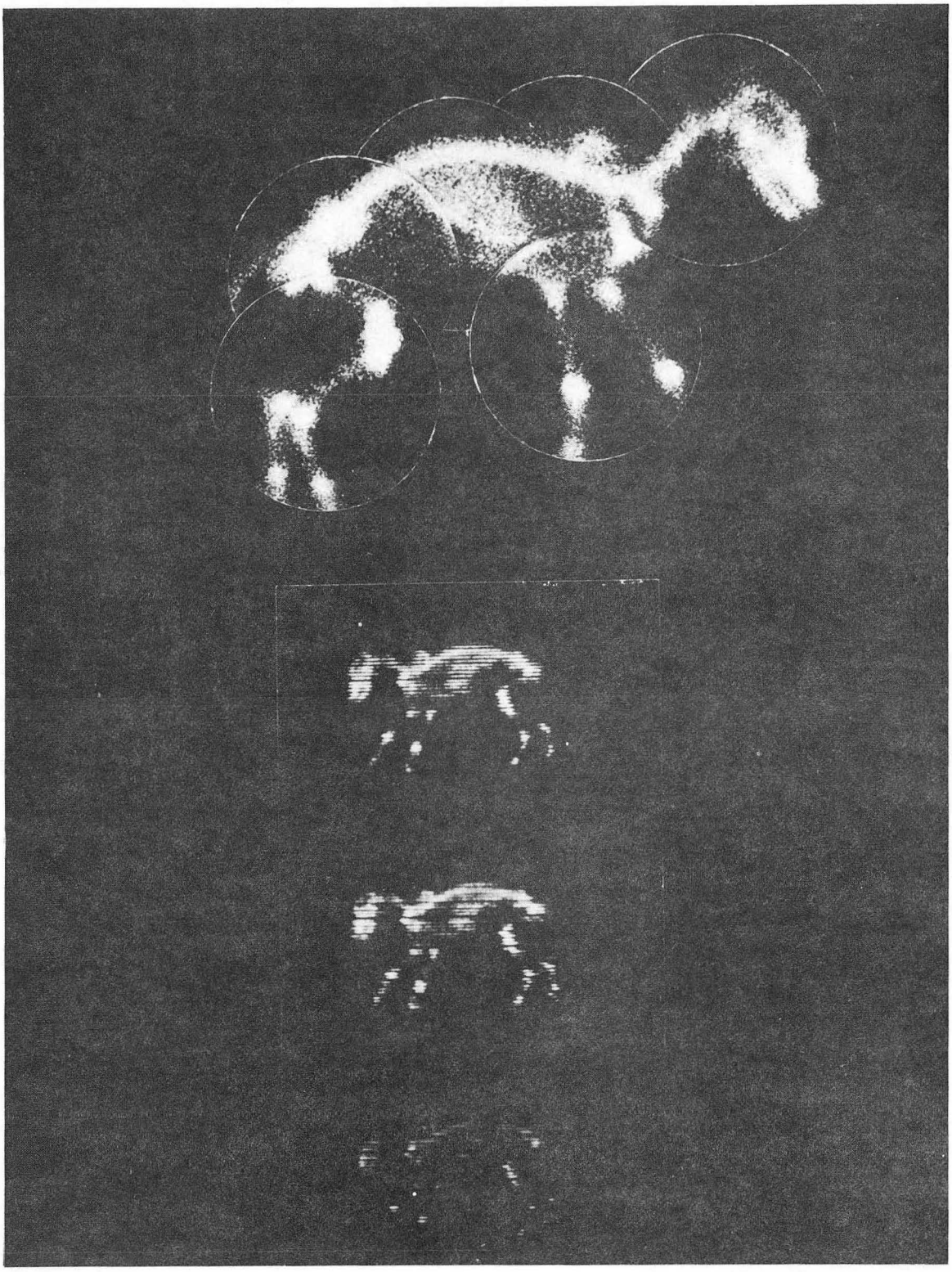

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Fig. 3

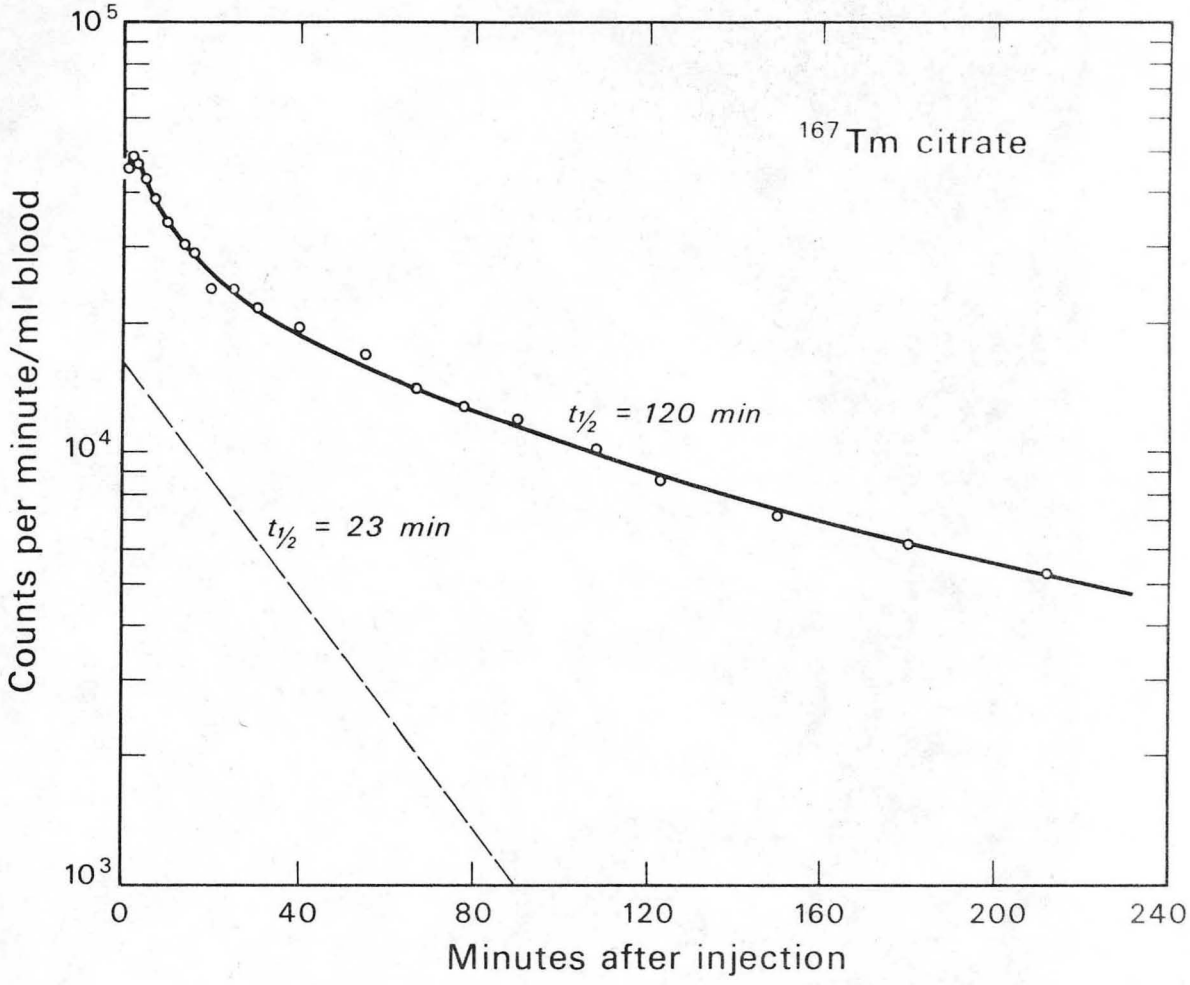
10^5
10^4
10^3
Counts per minute/ml blood
^{167}Tm citrate
$t_{1/2}$ = 120 min
$t_{1/2}$ = 23 min
0
40
80
120
160
200
240
Minutes after injection
DBL 747-4896

Fig. 4

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