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TIN-117m: PRODUCTION, CHEMISTRY, AND EVALUATION AS A BONE-SCANNING AGENT*

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Abstract

Cyclotron and nuclear reactor methods of producing ^{117m}Sn were compared. Reactor production gave the highest yield. Of several chelates studied, in rats ^{117m}Sn tartrate gave the highest bone uptake (55%) with less than 5% uptake in soft tissue. Because of a favorable half-life of 14 days and emission of 158 keV photons, ^{117m}Sn is considered as a possible bone-scanning agent. Scintillation camera and whole-body scan pictures show uptake of ^{117m}Sn-tartrate in bone of beagle dogs. Radionuclidic purity, chemical toxicity, and absorbed radiation dose are within limits acceptable for human use.

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The early detection of metastatic bone lesions could be greatly facilitated if a radionuclide with suitable physical and chemical characteristics for bone scintigraphy were readily available. Although ^{18}F and ^{99m}Tc-labeled bone-seeking agents such as polyphosphates[1] and diphosphonates[2] appear to be very promising for bone scintigraphy, an "off-the-shelf" radiopharmaceutical would be useful either for those not close to an ^{18}F supplier or those not prepared to do ^{99m}Tc labeling of bone-seeking agents.

Tin-117m has some characteristics which make it desirable for bone scintigraphy: (1) It can be reactor produced, and with a half-life of 14 days it offers a possibility for commercial availability. (2) Its photon emissions of 158 keV (87 per cent abundant) are ideally suited for imaging with gamma cameras; (3) it decays 100 per cent by isomeric transition to stable ^{117}Sn, and (4) it has a high affinity for bone when it is administered as a tin chelate.

Investigations have been made on the production and chemical form of ^{117m}Sn that provides a useful bone-scanning agent.

Materials and Methods

Production of ^{117m}Sn

Three methods of producing ^{117m}Sn were investigated. In the first method isotopically enriched ^{116}Sn (98.5 per cent) was obtained as tin metal from AERE* at a cost of $0.95/mg and the ^{116}Sn (n, γ) ^{117m}Sn nuclear reaction was investigated in the General Electric Test Reactor† which has a thermal neutron flux of 5.4×10^{14} n/cm^2/sec. To obtain ^{117m}Sn of relatively high specific activity, 50 mg of ^{116}Sn were irradiated for periods up to 30 days. The target material was dissolved in concentrated HCl, and the chemistry of separation and preparation of ^{117m}Sn compounds were carried out with the acid solution of ^{117m}Sn.

Two methods of cyclotron production were investigated in an effort to obtain "carrier-free" ^{117m}Sn: In one method, $InCl_3$ (obtained from K and K Laboratories) was used as the target material for the $^{115}_{49}In(^4_2He, \underline{pn})\ ^{117m}_{50}Sn$ nuclear reaction using 25-MeV ^4_2He particles from the LBL 88-in. cyclotron. The $InCl_3$ target material was dissolved in 7.5 N HCl and a few drops of 30 per cent H_2O_2 were added. Chemical separations were made by extraction into a solution of 83 per cent 2-ethyl-2-hexanol and 17 per cent petroleum ether to separate the indium target material from the radionuclides of Sn and Sb[3].

In the second method of cyclotron production, isotopically enriched ^{114}Cd (90-99 per cent), obtained from ORNL+ as CdO was

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†Vallecitos, California.

+Oak Ridge National Laboratories.

used for the $^{114}_{48}Cd(^{4}_{2}He, \underline{n})\ ^{117m}_{50}Sn$ nuclear reaction using 25-MeV $^{4}_{2}He$ particles. The CdO target material was dissolved in 8 $\underline{N}$ HCl and the ^{117m}Sn extracted into MIBK (methyl-isobutyl-ketone)[4].

The recovered ^{117m}Sn was assayed by counting the 158-keV photons on a multichannel analyzer using a NaI(Tl) crystal. Gamma spectroscopy was used to determine the radionuclidic purity of the separated ^{117m}Sn.

The half-life of the radionuclides produced by these methods was obtained by counting both the separated and unseparated samples of ^{117m}Sn for a period of at least 420 days.

Chemical preparations and their distribution in animals

Various chelates of ^{117m}Sn and ^{113}Sn were evaluated in a total of 20 Sprague-Dawley rats each weighing 200-250 g and in 2 beagle dogs each weighing about 10 kg. Preparations of ^{117m}Sn and ^{113}Sn as tartrate or citrate, and ^{113}Sn as HEDTA (N-hydroxyethylene-diaminetriacetic acid) in 5:1 and 10:1 molar ratios of chelating agent to tin were administered intravenously. The distribution of ^{117m}Sn was determined at 3 and 20 h after administration; ^{113}Sn was assayed at 19 hr. Two rats were assayed for each preparation and at each time interval. The rats were sacrificed under ether anesthesia, and the various organs and blood samples in plastic vials were counted in a well-counter. Distribution studies were also done using commercially available ^{113}Sn ($T_{1/2}$ 115 days, 390-keV photons from In-113m daughter) prepared and counted under the same conditions as ^{117m}Sn.

The Donner Laboratory scintillation camera[5] and Mark II whole-body scanner[6] were used to image the in vivo distribution of the radiopharmaceutical.

In addition, blood disappearance curves of ^{117m}Sn as tartrate and citrate chelates were obtained in studies with beagle dogs. After the intravenous administration of 100-200 μCi of ^{117m}Sn, 1-ml blood samples were obtained periodically for up to 3 h. The blood samples were counted and the data plotted on semilogarithmic paper. The data were also analyzed by using a computer program for a two-compartment model as described by Parker[7] for determining the extraction efficiency of bone as a per cent of cardiac output.

The per cent excretion of the radiopharmaceutical by the kidneys was determined by catheterizing the bladder 3 h after intravenous administration of the ^{117m}Sn tartrate or citrate and determining the total activity in the urine.

Toxicity studies of tin tartrate were carried out in 21 Sprague-Dawley rats by administering intravenously up to 5000 times the proposed human dose of stannous tartrate or stannic tartrate. Tin was given in concentrations ranging from 2 to 18 mg/kg. The rats were kept under observation for up to 3 months, then sacrificed, and macroscopic examinations were made of the various organs.

Results and Discussion

Production

Although the cross section for thermal neutron activation is only 6 mb for ^{116}Sn, the reactor production of ^{117m}Sn was adequate with

a thermal neutron flux of 5.4×10^{14} n/cm^2/sec; one mCi of ^{117m}Sn/mg Sn was obtained from a 30-day irradiation. Thus, if 250 μCi were to be used for a 70-kg human patient, 0.25 mg of Sn would be administered, which would be 3.5 μg/kg—or at least 1000 times below the toxic response level. This projection of toxicity was based on the assumption that there would be a comparable toxicity for tin compounds in man as there was in our rat studies which showed no adverse effects at the 4.2 mg/kg concentration.

The yield of ^{117m}Sn from either of the two cyclotron production methods was very low. In the $^{115}_{49}$In ($^4_2$He, pn) $^{117}_{50}$Sn irradiation, the predominating reactions were $^{115}_{49}$In($^4_2$He,2n)$^{117}_{51}$Sb, and $^{115}_{49}$In ($^4_2$He, n) $^{118}_{51}$Sb. This was evidenced by the activities found in the organic and acid phases after solvent extraction. There was a predominating activity, with $T_{1/2}$ of 5.0 h and gamma emission of 254 keV, which appeared to be ^{118}Sb. There was also a radionuclide with a $T_{1/2}$ of about 2 h and gamma emissions of 158 keV and 511 keV, which appeared to be ^{117}Sb.

In the $^{114}_{48}$Cd ($^4_2$He, n) $^{117m}_{50}$Sn irradiation, ^{117m}Sn was obtained, though in low yield. However, there was also the $^{114}_{49}$Cd ($^4_2$He, p) $^{117m}_{50}$In nuclear reaction occurring, as evidenced by a $T_{1/2}$ 2.0-h activity with gamma emissions of 314 and 565 keV. In the MIBK-extracted phase there was 92 per cent recovery of ^{117m}Sn which was about 3 μCi per μAmp-h. The yield of ^{117m}Sn might be increased with a lower-energy $^4_2$He particle (< 25 MeV) but it appears unlikely that enough ^{117m}Sn could be produced by cyclotron irradiation to warrant further efforts.

For the reactor-produced ^{117m}Sn, which has a specific activity of about 1 mCi/mg, short-lived radionuclides of ^{117m}In ($T_{1/2}$ 1.93 h) and ^{117}In ($T_{1/2}$ 45 min) were produced possibly by the (n, p) nuclear reaction on ^{117}Sn (0.47 per cent in the isotopically enriched ^{116}Sn). These indium activities decayed to ^{117m}Sn and ^{117}Sn respectively and their chemical separation was not necessary. A few days after the end of the irradiation, gamma spectroscopy of the unseparated ^{117m}Sn from a reactor production run indicated mainly the 158-keV gamma emission of ^{117m}Sn. However from about 225 to 400 days after the irradiation when the ^{117m}Sn activity had decayed away, an 88-keV photon was observed. This long-lived radionuclide was determined to be ^{109}Cd from the decay curve of ^{117m}Sn (Fig. 1), which indicates a straight line decay curve with a $T_{1/2}$ of 14 days for a period of at least 70 days and a $T_{1/2}$ of 1.2 yr for a period of about 240 to 420 days after the irradiation. These data were obtained on ^{117m}Sn from a two-day irradiation.

Data were also obtained on ^{117m}Sn from a 30-day irradiation. Although not shown here, the decay curve from 94 to 250 days after the irradiation revealed only two components with a $T_{1/2}$ of 14 days and a $T_{1/2}$ of about 1 year. This long-lived activity was not found in the MIBK-extracted ^{117m}Sn. If ^{117m}Sn is used in human studies, an MIBK extraction procedure to remove the unwanted ^{109}Cd will probably be necessary.

The gamma spectrum and decay scheme of ^{117m}Sn are shown in Fig. 2. Only the 158-keV gamma emission was seen for ^{117m}Sn from a typical production run. The decay scheme[8] shows two transitions, M-1 and M-4, with two gamma emissions in cascade. The

combined gamma-emission intensity is 0.89/dis. The combined $e_{\overline{K}} + e_{\overline{L}} + e_{\overline{M}}$ is 1.11/dis where the $e_{\overline{K}}$ is 0.77/dis, the $e_{\overline{L}}$ is 0.27/dis and the $e_{\overline{MN}}$ is 0.07/dis[9]. The high internal conversion ratio of the M-4 transition greatly increases the radiation dose from ^{117m}Sn.

The estimated radiation dose to a 70-kg patient would be 1.98 rad to bone and 0.78 rad to kidneys from 250 μCi of ^{117m}Sn-tartrate. This assumes that there is 50 per cent excretion and 50 per cent uptake in bone 3 h after intravenous administration and that the effective half-life in bone is the same as the physical half-life.

Table 1 shows the uptake of ^{117m}Sn as a 5:1 molar ratio of citrate or tartrate in rats at 3 and 20 h after intravenous administration. The relatively high uptake in femur (about 2.2 per cent of the injected dose/g of femur) and the low uptake in blood and soft tissues at 3 h indicate high bone uptake which would be advantageous for bone scanning.

A similar distribution was observed when commercially available ^{113}Sn was administered at 10:1 or 5:1 molar ratios of citrate, tartrate or HEDTA (Table 2). These data indicate an uptake in the femur which is comparable to ^{18}F. Tin tartrate at the 10:1 molar ratio has the highest uptake in femur of the various chelates of ^{113}Sn. The data in Tables 1 and 2 do not account for 100 per cent of the injected activity because the amount excreted in the urine was not determined and the uptake in the various organs was per gram of tissue (except for carcass and gut) and not for the total activity in each organ. These data only indicate the general trend of uptake for various conditions of preparation and time of study. The bone-to-blood ratio of

120:1 for the ^{117m}Sn-tartrate at 3 h was adequate for good bone imaging. At 20 h the bone-to-blood ratio was twice the ratio at 3 h.

The blood disappearance curve for the ^{117m}Sn tartrate (Fig. 3) has at least two components, with $T_{1/2}$ of 9 min and $T_{1/2}$ 113 min. Although the citrate curve was plotted it was not analyzed for the component half-times.

The kinetics of some bone-seeking radiopharmaceuticals (Table 3) were obtained by computer analysis of blood disappearance and urinary excretion data for beagle dogs by using the method of Parker[7] for a two-compartment model. Tin-117m tartrate was taken up by bone with nearly the same efficiency as ^{18}F and with 2 to 3 times the efficiency of ^{99m}Tc-Sn-EHDP, a ^{99m}Tc-Sn(II)-diphosphonate complex[2]. The renal clearance of ^{117m}Sn tartrate was about the same as ^{18}F but less than the ^{99m}Tc-Sn-EHDP. The total per cent of the injected dose of ^{117m}Sn tartrate going to bone was nearly the same as ^{18}F but about 2-1/2 times the ^{99m}Tc-Sn-EHDP. These data indicate that ^{117m}Sn tartrate is an excellent bone-scanning agent in the beagle dog.

Figure 4 shows the distribution of ^{117m}Sn tartrate in a beagle 24 h after intravenous administration of 100 μCi. The whole-body scan is shown, together with the composite of the lateral view taken with the scintillation camera. Scans were also done up to 2 weeks after intravenous injection of ^{117m}Sn tartrate, and the ^{117m}Sn activity was still retained in the bone.

Summary

The advantages of ^{117m}Sn for bone scanning are (1) reactor production and 14-day half-life, (2) 158-keV photons, (3) good uptake in bone, and (4) acceptable radiation dose to the patient for 250 μCi dose administered intravenously.

However, the two major disadvantages of ^{117m}Sn for bone scintigraphy are (1) the 100 per cent conversion of the M-4 gamma transition, which greatly increases the radiation dose, and (2) the low neutron activation cross section, which reduces the yield of ^{117m}Sn, thereby increasing its cost and decreasing its specific activity.

A nuclear reactor with a neutron flux greater than the 5.4×10^{14} $n/cm^2/sec$ would greatly increase the usefulness of ^{117m}Sn as a bone-scanning agent by increasing the yield and specific activity of ^{117m}Sn.

The toxicity data indicate a safety factor of at least 10^3 when 250 μCi of ^{117m}Sn/0.250 mg of Sn would be administered intravenously to a 70-kg patient.

Acknowledgment

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Table 1. The uptake of ^{117m}Sn as 5:1 molar ratio chelates of tartrate or citrate expressed as per cent of injected dose per g rat tissue at 3 and 20 h after i.v. administration.*

ORGAN	CITRATE		TARTRATE	
	3 h	20 h	3 h	20 h
Blood	0.011 0.012	0.005 0.004	0.019 0.016	0.007 0.005
Heart	0.014 0.015	0.021 0.017	0.026 0.022	0.024 0.009
Lungs	0.041 0.036	0.032 0.030	0.057 0.047	0.030 0.032
Liver	0.050 0.038	0.049 0.035	0.048 0.045	0.048 0.065
Kidneys	0.545 0.594	0.382 0.299	0.696 0.607	0.405 0.383
Spleen	0.019 0.020	0.030 0.027	0.048 0.032	0.031 0.029
Muscle of femur	0.005 ---	0.010 0.013	0.014 0.007	0.011 0.044
Femur+marrow	2.20 ---	2.81 2.22	2.04 2.26	4.05 2.39
† Carcass	52.7 36.1	46.0 44.8	47.0 44.1	58.0 52.5
† Gut	1.47 0.94	3.38 2.32	2.65 2.91	4.82 3.78

*Two rats were assayed at each time for each compound; the individual values are given.

†Per cent uptake of administered ^{117m}Sn per total tissue.

Table 2. The uptake of ^{113}Sn as 5:1 or 10:1 molar ratio chelates of tartrate, citrate, or HEDTA as per cent of injected dose per g rat tissue at 19 h after i. v. administration.*

Organ	TARTRATE		CITRATE		HEDTA	
	10:1	5:1	10:1	5:1	10:1	5:1
Blood	0.014 0.010	0.012 0.010	0.012 0.013	0.011 0.008	0.006 0.005	0.022 0.025
Heart	0.012 0.018	0.011 0.013	0.013 0.013	0.010 0.009	0.007 0.005	0.016 0.016
Thymus	0.009 0.100	0.009 0.006	0.007 0.007	0.007 0.006	0.008 0.006	0.006 0.015
Lungs	0.026 0.047	0.022 0.027	0.027 0.032	0.021 0.019	0.018 0.023	0.025 0.064
Liver	0.027 0.044	0.033 0.028	0.033 0.029	0.030 0.026	0.030 0.024	0.035 0.028
Kidneys	0.730 0.869	0.693 0.800	0.687 0.565	0.605 0.576	0.540 0.517	0.703 0.630
Spleen	0.027 0.034	0.028 0.028	0.026 0.023	0.022 0.019	0.021 0.019	0.029 0.031
Muscle sternum	0.052 0.006	0.007 0.005	0.006 0.007	0.005 0.005	0.003 0.002	0.003 0.025
Sternum	0.358 0.397	0.476 0.336	0.322 0.443	0.281 0.236	0.254 0.308	0.299 0.429
Ribs	0.132 0.227	0.215 0.163	0.234 0.268	0.067 0.111	0.065 0.169	0.106 0.105
Muscle of femur	0.042 0.010	0.004 0.008	0.005 0.024	0.004 0.007	0.037 0.037	0.004 0.007
Femur + marrow	2.59 2.93	2.33 2.31	2.03 2.68	2.10 1.78	2.17 1.95	2.09 2.25
Marrow	0.282 0.304	0.097 0.069	0.154 0.423	0.226 0.389	0.216 0.415	0.180 0.126
Femur	3.02 3.47	2.48 2.76	2.51 2.99	2.50 1.63	2.47 2.35	2.18 2.43

*Two rats were assayed for each preparation of each compound.

Table 3. Kinetics of some bone-seeking radiopharmaceuticals in beagle dogs as determined by computer analysis of blood-disappearance and excretion data for a two-compartment model.

	^{117m}Sn		^{99m}Tc-Sn-EHDP*		^{18}F	
	Tart.	Cit.				
Sex	(F)	(F)	(F)	(M)	(F)	(M)
Wt. (kg)	10.4	11.8	8.1	12.0	10	12.7
Bone Clearance (% est. C.O.)†	1.4	1.0	0.34	0.41	1.6	2.2
Renal Clearance (% est. C.O.)	1.3	0.8	1.7	1.6	1.2	1.1
Per cent to Bone	53	55	17	20	57	67

*Ethane-1-hydroxy, 1-1 diphosphonate labeled with ^{99m}Tc using Sn(II).

†Per cent of estimated cardiac output.

FIGURE CAPTIONS

Figure 1. Decay curve of the unseparated ^{117m}Sn produced by a 2-day irradiation of 98 per cent enriched ^{116}Sn; O—O decay of ^{117m}Sn, ■—■ decay of ^{109}Cd.

Figure 2. Decay scheme (top) and gamma spectrum (bottom) of ^{117m}Sn.

Figure 3. Blood disappearance of ^{117m}Sn as citrate or tartrate up to 3 h after i.v. injection into two beagle dogs.

Figure 4. Whole-body scan (top) and scintillation camera (bottom) pictures of ^{117m}Sn tartrate 24 h after i.v. injection into a beagle dog.

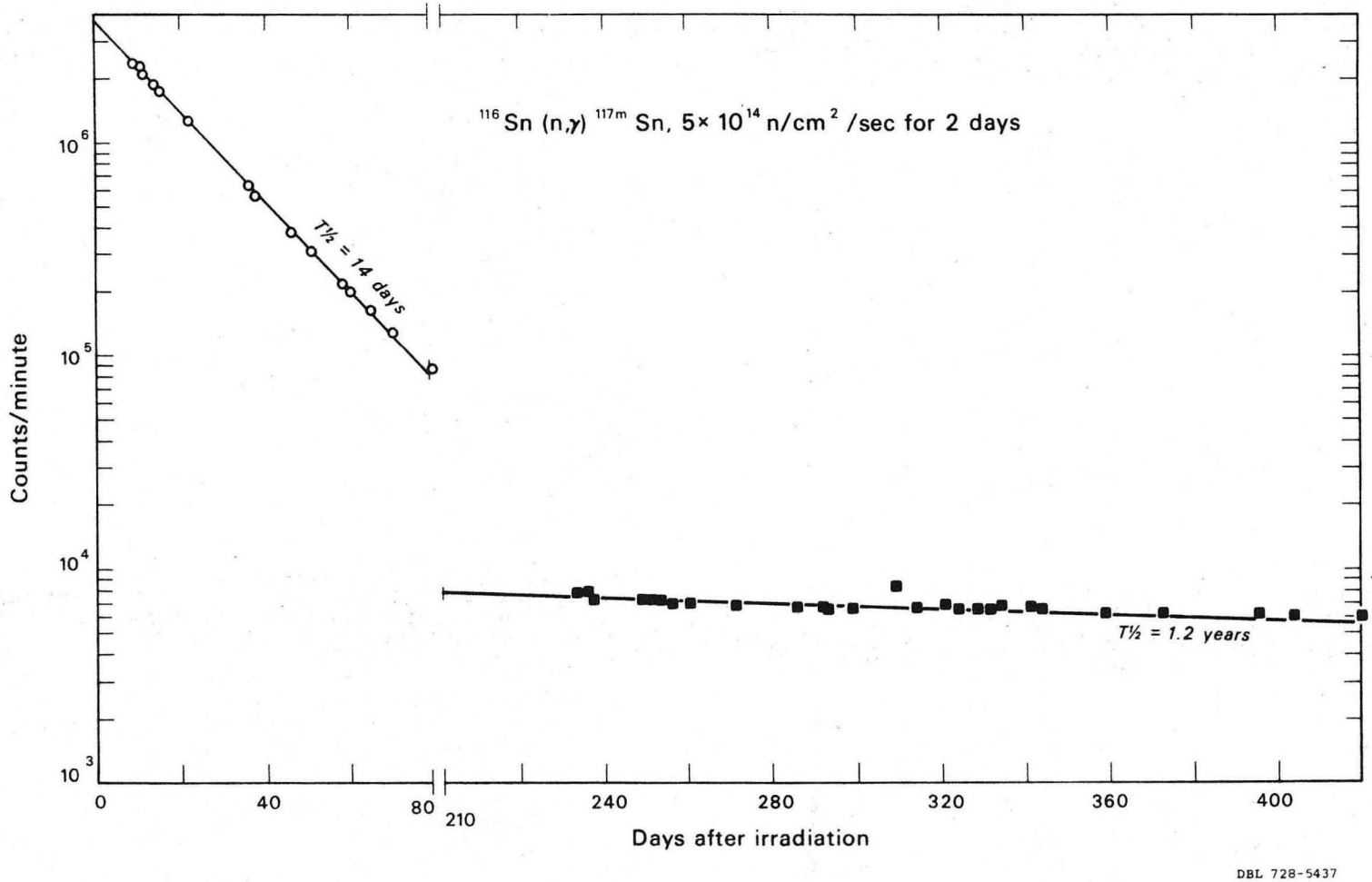
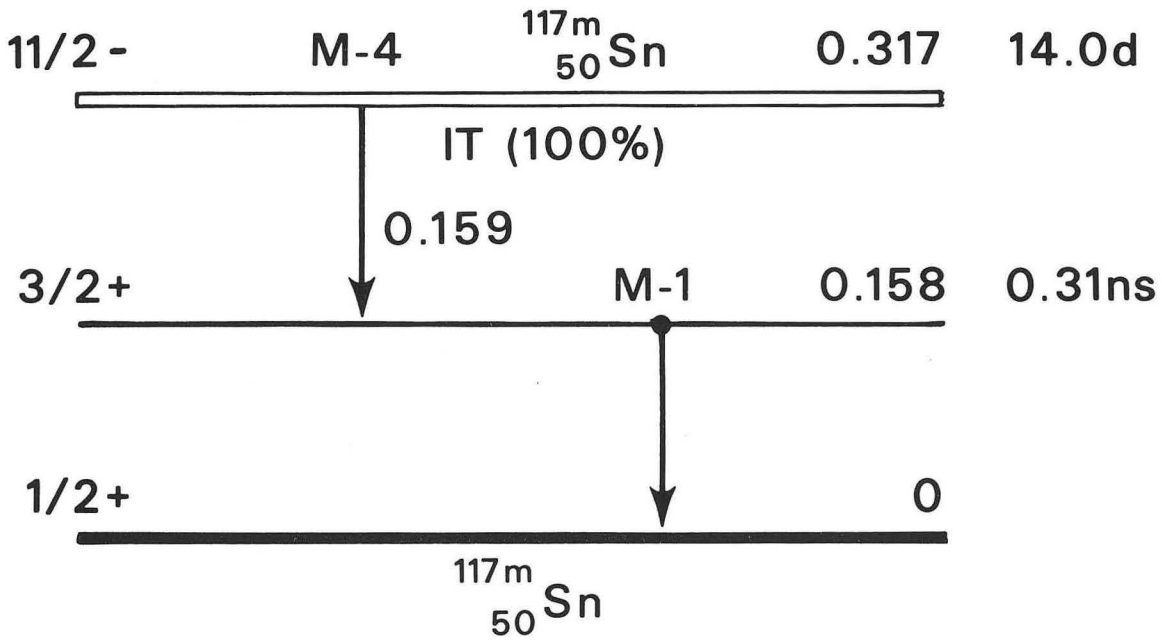
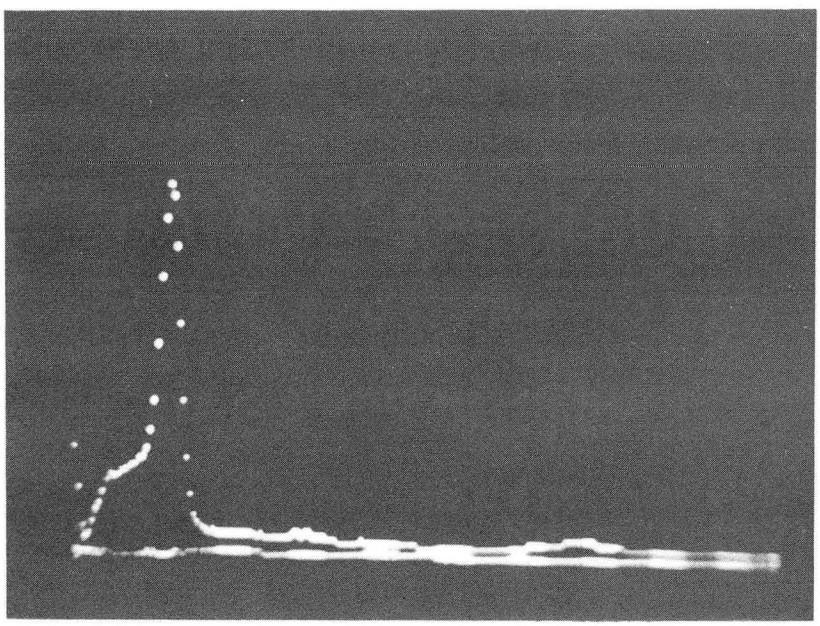

^{116}Sn (n,γ) ^{117m}Sn, 5× 10^{14} n/cm^2 /sec for 2 days
T½ = 14 days
T½ = 1.2 years
Counts/minute
10^6
10^5
10^4
10^3
0
40
80
210
240
280
320
360
400
Days after irradiation
DBL 728-5437

Fig. 1

DECAY SCHEME



GAMMA SPECTRUM



158 keV

XBB 727-3695

Fig. 2

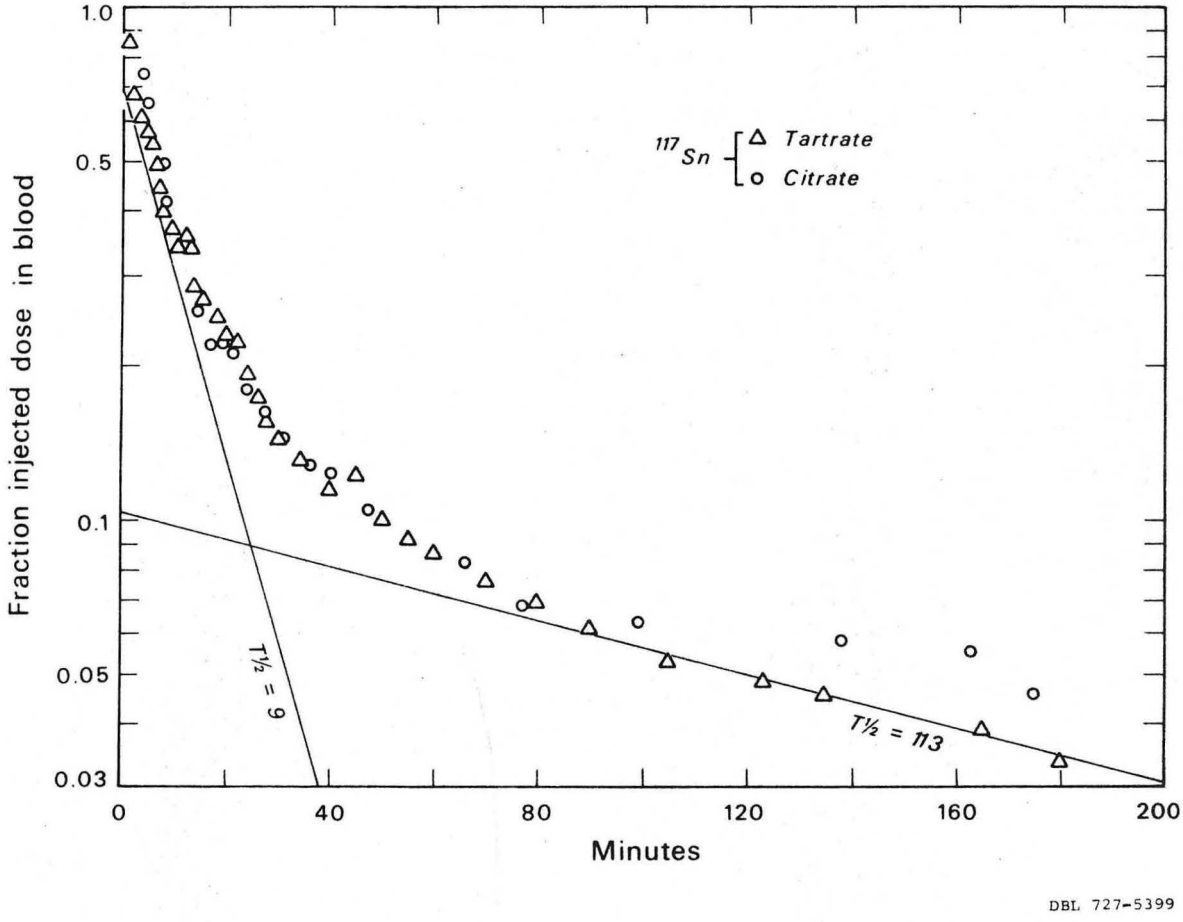
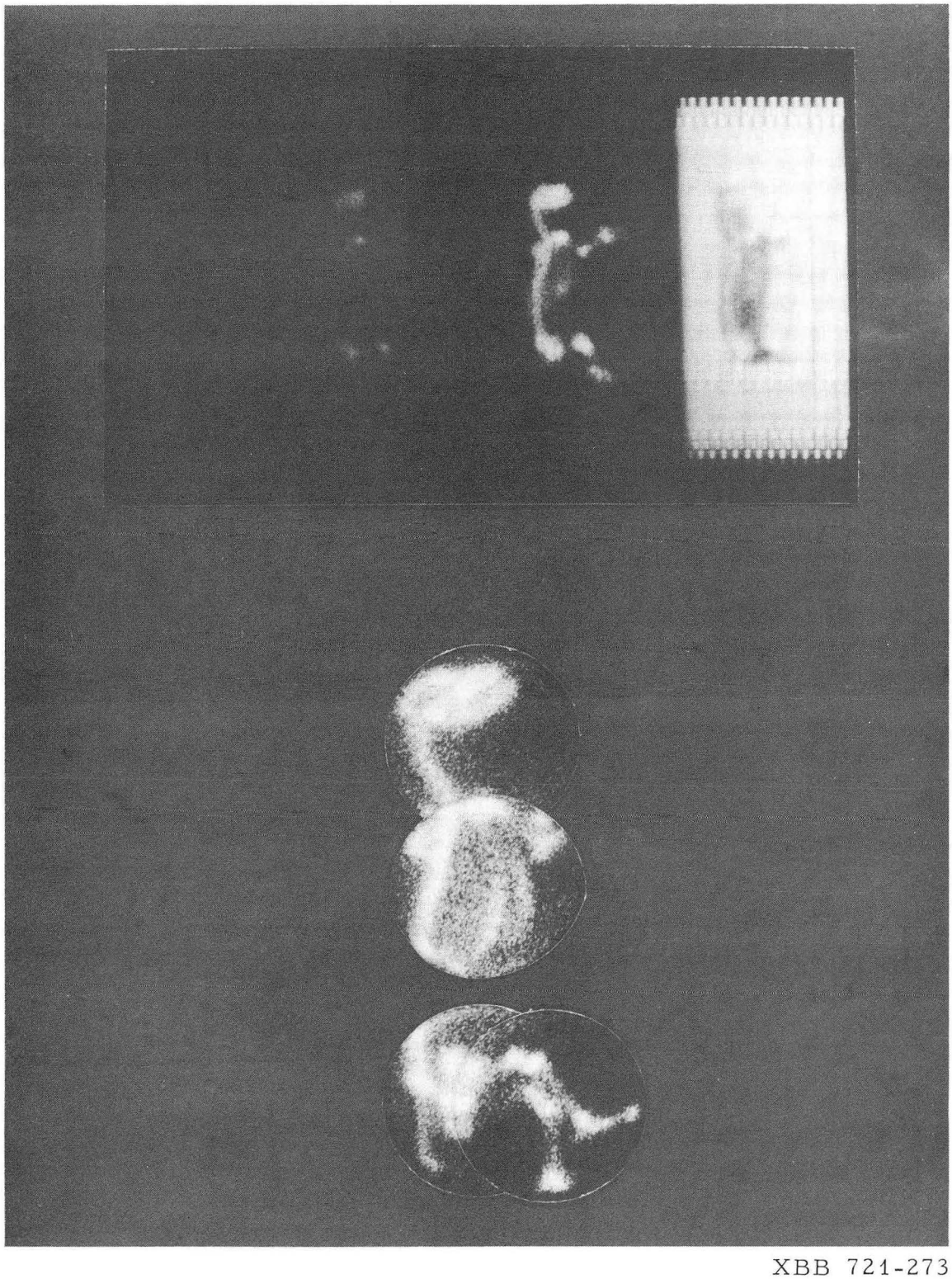

1.0
0.5
0.1
0.05
0.03
Fraction injected dose in blood
^{117}Sn
Tartrate
Citrate
T½ = 9
T½ = 113
0
40
80
120
160
200
Minutes
DBL 727-5399

Fig. 3



XBB 721-273

Fig. 4

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