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by

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May 31, 1967

ABSTRACT

Radioisotopes with very short half lives offer advantages over those with longer lives for visualizing veins, chambers of the heart, and certain organs by means of radioisotope cameras and scanners. Since venograms and angiograms are usually completed within 1 minute after injection of the isotope, the use of very-short-half-life isotopes is feasible and has the advantage that repeat studies can be rapidly performed without a buildup in background level. This allows giving a series of injections while taking several views with a radioisotope camera from different angles or changing the location of the injection site.

When a radioisotope with a half life on the order of a few seconds is injected intravenously, most of the activity dies away during the first complete transit of the circulatory system. The tracer can be administered as a continuous infusion, while a scanner or camera takes a picture of the resulting steady-state condition. This technique also allows the use of slower imaging devices, such as radioisotope scanners and positron cameras, rather than the faster γ -ray cameras presently used.

Radioisotopes with such short half lives are most easily obtained by decay from a long-lived parent radioisotope, the daughter being separated

from the parent by elution from a generator or "cow." Preliminary methods have been developed for obtaining a 4.9-sec iridium-191m and 39-sec silver-109m from long-lived parent radioisotopes. Descriptions are given of the apparatus and chemical procedure for rapid separation and injection of the radioisotope. Preliminary studies show that the lungs of a dog can be effectively imaged with 4.9-sec iridium-191m.

INTRODUCTION

For many years γ -ray counters have been used with radioisotopes to measure the speed and relative volume of blood circulation through the extremities, heart, brain, etc. The use of radioisotope cameras to image the circulation and perfusion of blood is more recent. The first isotope employed for this purpose was 2.6-min barium-137m, which was used in 1963 to image the passage of blood through the heart(1). Although this isotope has a short physical half life, (2.6 min) its high γ -ray energy (0.66 MeV) makes it less satisfactory for imaging purposes than other isotopes.

Most circulation and perfusion studies performed at present employ 6-hour technetium-99m (2). This 0.14 MeV γ -ray emitter is obtained in multimillicurie amounts from a 2.7-day parent isotope. About 10 mCi is injected rapidly into a vein. The radioactive bolus travels through the heart, lungs, and arterial system to various organs, and a series of pictures is taken with a radioisotope camera (3) showing the transit of the isotope through an area of interest. Perfusion through the heart, lungs, kidneys, brain, and placenta has been studied (4-7). Exposure times for each picture vary from a fraction of a second to 10 sec or more.

The moderate γ -ray energy and the large quantity of ^{99m}Tc that can be given without excessive radiation dosage make it very useful for the above studies. However, the 6-hour half life is much longer than necessary. An isotope with a shorter half life would have the advantage that additional studies could be quickly performed, because the radioactivity from a previous injection would rapidly decay away, leaving a low background. In subsequent studies, different projections could be taken with the radioisotope camera, the site of injection could be changed, or other conditions altered. The short half life of the isotope would tend to further reduce the radiation ex-

posure of the patient. Pursuing the reduction in half life to its ultimate goal, isotopes with half lives of a few seconds could be profitably used, either with the bolus-injection technique just described or with the continuous infusion technique described in the next section.

CONTINUOUS INFUSION TECHNIQUE

Veins, arteries, and certain organs can be visualized by continuous infusion of an ultrashort-lived isotope when the half life is short enough that most of it decays during a single complete transit of the circulatory system. A steady-state condition then exists in which the target organ remains radioactive as long as a constant infusion rate is maintained. It can be imaged with either a radioisotope camera or scanner. Ideally, the half life should probably be on the order of 5 to 20 sec. The main arteries, such as the aorta and carotid arteries, should be continuously visible with an intravenous injection of any ultrashort-lived isotope, just as they are visible momentarily after an intravenous injection of ^{99m}Tc pertechnetate.

Organs that take up tracer compounds for very brief times might also be visualized by this method. If the physical half life of the isotope is much shorter than the biological half time of release, the isotope will decay almost completely within the target organ.

The same technique should be useful for visualizing organ tissues with high perfusion rates. These tissues should become relatively radioactive, while tissues with low perfusion rates will remain nonradioactive, since the isotope tends to decay before it fully perfuses the latter tissue. Locating vascular tumors should be possible with this technique.

METHODS OF PRODUCTION AND CHEMICAL PROCEDURE

Radioisotopes with ultrashort half lives can be obtained in large variety and quantity at medical facilities that are located in close proximity to a reactor or cyclotron. Alternatively, a limited number of such isotopes can be obtained by decay from long-lived parent isotopes. Because of the considerably lower cost of parent-produced isotopes, this possibility has been partially explored in this study. To be most useful, the isotopes should:

- (a) Decay by emission of low- to medium-energy γ rays, or by positron emission.
- (b) Have a long-lived parent.
- (c) Be rapidly separable from the parent in sufficiently large quantities with eluting solutions that are physiologically tolerated.
- (d) Be reasonable in cost.

A list of potentially useful ultrashort-lived radioisotopes is given in Table I. All have suitable parent-daughter half lives and γ -ray or positron emissions, but at the time of writing, rapid separation techniques had been worked out for only two of them, iridium-191m and silver-109m. The chemical procedures described here are preliminary.

Iridium-191m

Iridium-191m has a half life of 4.9 sec and is the daughter of osmium-191. The daughter decays by isomeric transition to inactive ^{191}Ir with the emission of 40-keV and 129-keV γ rays. About 70% of the 129-keV γ rays are converted internally to electrons.

The parent radioisotope ^{191}Os , with a 16-day half life, is obtained by neutron irradiation of natural osmium as OsO_4 . Osmium-191 is formed by the (n, γ) reaction from stable ^{190}Os (24.6% abundant). About 7

mCi is obtained by irradiation of 0.5 gm of target material in a flux of 1.5×10^{13} neutrons/cm² sec⁻¹ for 8 hours. About 1/10 as much 95-day ¹⁸⁵Os is produced from ¹⁸⁴Os (0.018% abundant), but this decays to stable rhenium and causes no radioactive contamination in the elution of ^{191m}Ir.

The target material is refluxed for 4 to 5 hours in 30 ml of 8N HCl at 100°C in the presence of ethanol to produce the chloroosmate (8), OsCl₆⁼. This solution of OsCl₆⁼ in hydrochloric acid is then passed through an ion-exchange column consisting of 3 cc of Bio-Rad anion-exchange resin (AG 1X8, minus 400 mesh) in a disposable 5-ml syringe barrel with a glass wool plug at the bottom and a filter cloth at the top. The ion-exchange column is stoppered with a serum vial cap through which a 20-gauge needle is inserted. The needle is connected to an automatic two-way valve (B.D. 470-V), which is in turn connected to a 10-ml syringe used to force the eluent under pressure through the column. A plastic tubing adapter with PE 100 intramedic polyethylene tubing is connected to a male Luer-lock fitting on the ion-exchange column. Column, valve, syringe, and infusion connections for the column are shown in Fig. 1. Sterility of the solution is insured by connecting a millipore filter in a Swinney adapter to the polyethylene tubing. The eluting solution is obtained from the column at flow rates up to 1 ml per second.

In an effort to find a suitable solution for intravenous injection, thiourea, oxalate, and ethylenediaminetetraacetic acid, all of which form complexes or chelates of iridium, were tried as eluting solutions. However, these failed to bring down ^{191m}Ir and the effluent was heavily contaminated with ¹⁹¹Os. An alumina column was tried, but it failed to retain the ¹⁹¹Os. NaCl solutions at different concentrations were also tried; a graph of ^{191m}Ir yield vs NaCl concentration is shown in Fig. 2. A solution of 16 to 18% NaCl gave the best yield of ^{191m}Ir with a minimum of ¹⁹¹Os contamination.

Bio-Rad anion-exchange resin (AG 1X8, minus 400 mesh) is used because of its ability to retain ^{191}Os while permitting the iridium-191m hexachloro-iridate to be eluted carrier-free with relatively good yield. Depending on the flow rate, there is about 10% recovery of $^{191\text{m}}\text{Ir}$ for each 10 ml of eluent. In order to maximize the yield, a minimum volume of resin is used to prevent more than 0.1% ^{191}Os contamination. Particle size of the resin is also important in minimizing contamination of the eluate; resin of 100/200 mesh will increase the contamination by a significant amount over 200/400 mesh resin (9). Continued milking of the column also results in an increase in contamination by the parent isotope.

Although this eluent is satisfactory for animal experiments, its NaCl content is much higher than normal saline, and the search will continue for a more satisfactory eluent for human use.

Silver-109m

Silver-109m has a half life of 39.2 seconds and decays with the emission of 87-keV γ rays, 91% of which are internally converted to electrons. It is the daughter of 1.3-year cadmium-109, which is produced by neutron irradiation of stable ^{108}Cd , and is commercially available from Nuclear Science and Engineering Co.

Chromatographic grade alumina provides a satisfactory ion-exchange material. The alumina column was set up with the same syringe and valving system as shown in Fig. 1. Cadmium-109, as the chloride in 0.5N HCl solution, is passed through 3 cc of Al_2O_3 which has been washed with NaCl solution. The NaCl wash is essential for adsorption of ^{109}Cd by the alumina.

Table II presents a summary of the results obtained in the elution of $^{109\text{m}}\text{Ag}$ from the Al_2O_3 column with various ligands and complexing ions of silver. Satisfactory separation of $^{109\text{m}}\text{Ag}$ from its parent is obtained with

3% NaI solution. The yield is about 34% for a 5-ml elution volume with about 10^{-4} parts ^{109}Cd contamination. Silver-109m comes off carrier-free as AgI or AgI_2^- with a log K of 6.59 and 11.74 respectively, where K is the formation constant of the complex ion (10). Some organic ligands, such as thiourea with a log K of 13.1, ethylenediaminetetraacetic acid with a log K of 7.32, and histidine with a log K of 7.37 (11) all failed to give good separations.

Although the commercial availability and long half life of the parent ^{109}Cd are favorable factors, the high internal conversion of the 87-keV γ rays is a disadvantage in the use of this isotope. Since only 9% of the disintegrations give usable γ rays, and the yield of the ion-exchange column is 34%, about 300 mCi of ^{109}Cd would be necessary to produce counting rates equal to those obtained from 10 mCi of $^{99\text{m}}\text{Tc}$, assuming equal detection efficiency for the two γ rays. Also a more physiologically compatible eluent should be found before this isotope is used in humans.

PRELIMINARY RESULTS AND DISCUSSION

The use of 4.9-sec $^{191\text{m}}\text{Ir}$ to show the patency of veins in a dog is shown in Fig. 3. The ion-exchange column described in the previous section was connected by a short piece of tubing to the right dorsal branch of the lateral sphenous vein, and eluting fluid was forced through the column by means of a syringe into the vein and pictures were obtained by means of the Donner Laboratory Scintillation Camera (7).

The first picture (Fig. 3, left) shows unrestricted circulation of blood through the lateral sphenous femoral vein and inferior vena cava. The second (Fig. 3, center) shows partial blockage of the femoral vein, and the third (Fig. 3, right) shows almost complete blockage of the inferior vena cava by digital pressure applied externally to the dog. Filling of a small collateral vein is also shown in Fig. 3, center. The exposure time for each

picture was 5 sec. The infusion time was slightly longer than the exposure time to allow buildup of the isotope in the veins before the picture was started. It is estimated that about 3 mCi of ^{191m}Ir was within the field of view of the camera during the exposure.

Iridium-191m has also been used to image the pulmonary vasculature of a dog, as shown in Fig. 4. A continuous infusion of ^{191m}Ir was made into the left dorsal branch of the lateral sphenous vein. From there it went through the sphenous femoral vein and the inferior vena cava, then through the heart and into the lung, where it decayed. Radioactivity in the right heart chambers is superimposed on activity in the lung in this projection. A picture of the neck region showed practically no radioactivity in the carotid arteries. Exposure time for each field was about 45 sec.

The reason for the high activity in the lungs of the dog is not known at this time, but presumably it occurred because (a) the passage of blood through the capillary bed of the lungs was slow enough that nearly complete decay of the isotope occurred, or (b) the isotope diffused temporarily into lung tissue and the accompanying fluid space, or (c) colloidal particles, formed by a reaction of the blood with the eluant, were then trapped in the lung.

If temporary trapping by diffusion occurred, the isotope would normally rediffuse out of the lung into the blood in a short time, but the physical half life of the isotope is so short in this case that it would decay almost completely before any rediffusion occurred.

After the above results were obtained, it was thought that this technique might have potential uses in the diagnosis of human lung disease. Advantages over existing techniques include extremely low radiation dose because of the short half life of the isotope, ease of preparation of the tracer compound, and lack of interference with any subsequent isotope procedures. It was tried in

human subjects at San Francisco General Hospital with the cooperation of Dr. Myron Pollycove. However, the lungs were poorly visualized, apparently because the transit time from vein to lungs for humans in the resting state was too long. An isotope with a somewhat longer half life might give a satisfactory result, or, as suggested by Dr. Donald C. VanDyke, the $^{191\text{m}}\text{Ir}$ might be infused through a venous catheter inserted into the pulmonary artery in order to get it through the heart more rapidly.

CONCLUSION

Isotopes with ultrashort half lives should prove to be valuable for clinical diagnostic studies in man. Results with 4.9-sec-half-life $^{191\text{m}}\text{Ir}$ show that it can be used to image veins, the right chambers of the heart, and the lungs in a dog. It is hoped that with further development of the chemical procedures, these isotopes can be applied to human diagnostic problems.

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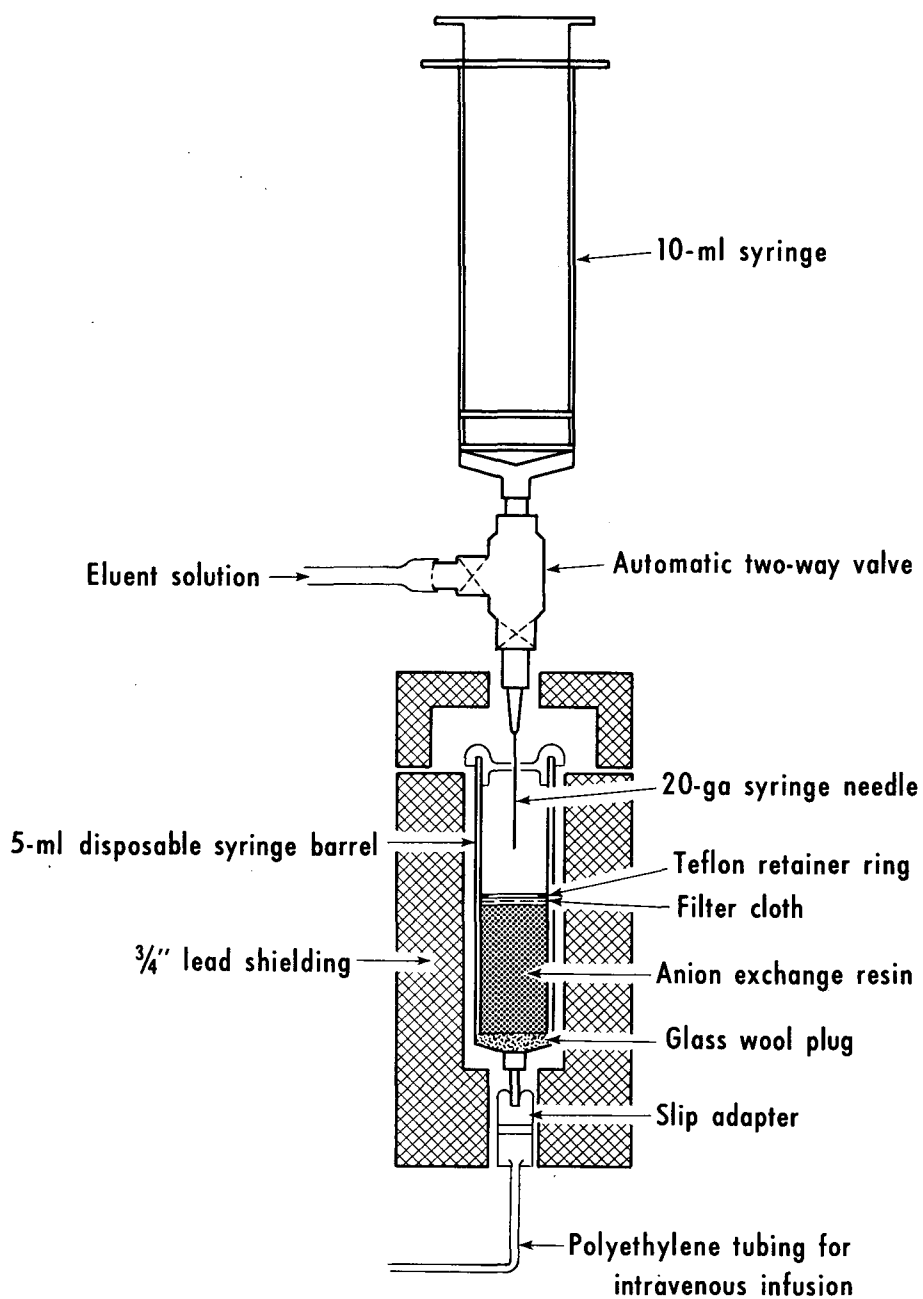
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Table I. Ultrashort-Lived Daughters of Long-Lived Parents.

Isotope	Daughter			Parent				
	Half-life (sec)	Decay modes	Principal γ -ray energy (MeV)	Isotope	Half life	Decay modes	% Abundance	Production method
^{77m}Se	17.5	It, e^-	0.162	^{77}Br	57 hr	ϵ β^+	99 1	$^{75}\text{As}(\alpha, 2n)^{77}\text{Br}$
^{81m}Kr	13	It, e^-	0.193	^{81}Rb	4.7 hr	ϵ β^+, γ	87 13	$^{79}\text{Br}(\alpha, 2n)^{81}\text{Rb}$
^{109m}Ag	39.2	It, 91% e^-	0.087	^{109}Cd	1.3 yr	ϵ		$^{108}\text{Cd}(n, \gamma)^{109}\text{Cd}$
^{167m}Er	2.5	It, e^-	0.208	^{167}Tm	9.6 day	ϵ, e^-, γ		$^{165}\text{Ho}(\alpha, 2n)^{167}\text{Tm}$
^{191m}Ir	4.9	It, $\approx 70\% e^-$	0.04 0.129	^{191}Os	16 day	β^-, γ		$^{190}\text{Os}(n, \gamma)^{191}\text{Os}$
^{82}Rb	80	β^+		^{82}Sr	25.5 day	ϵ		$^{80}\text{Kr}(\alpha, 2n)^{82}\text{Sr}$

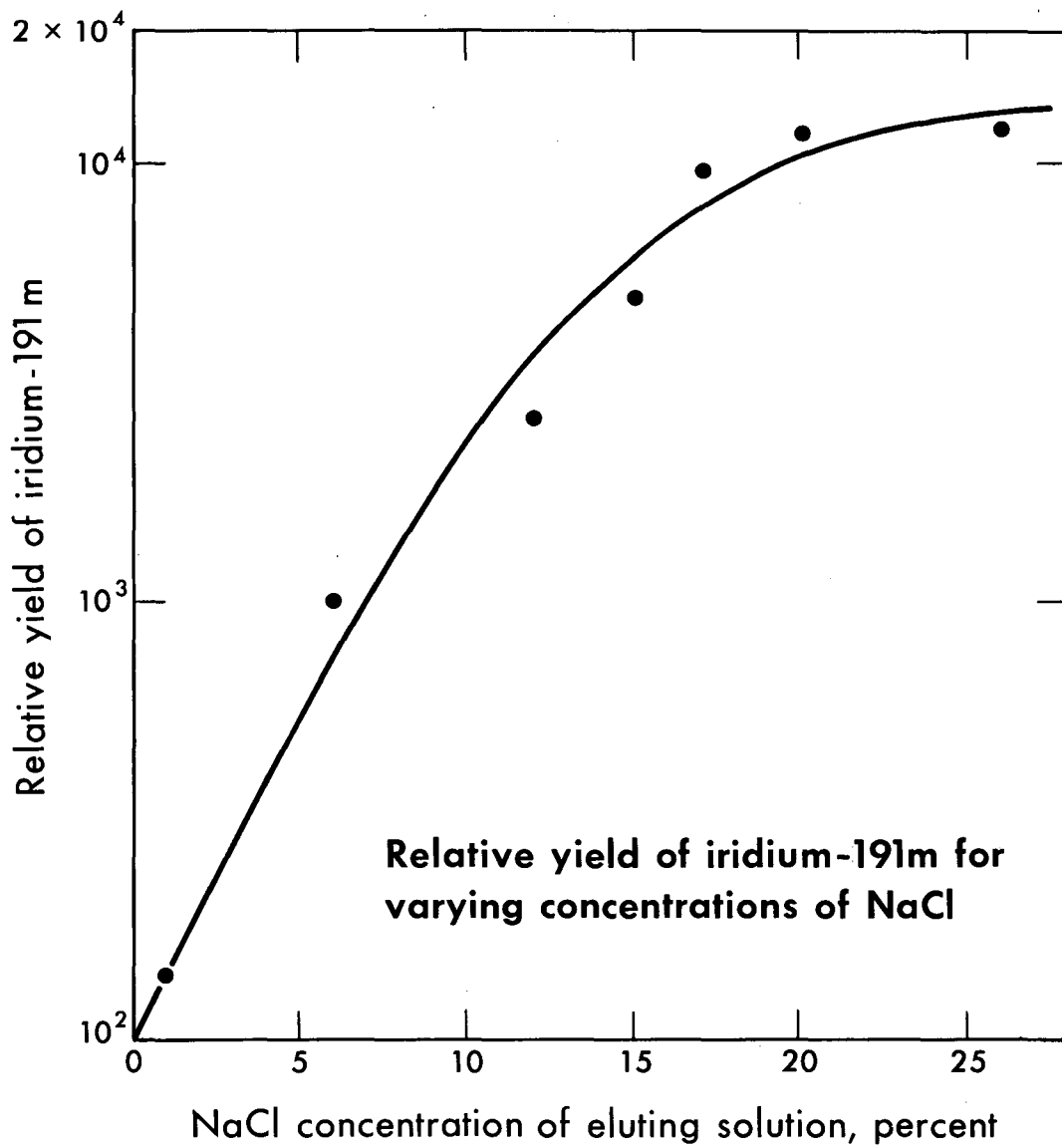
Table II. Effectiveness of Various Eluents in Separating Silver-109m from Cadmium-109 on Alumina.

Eluent solution		^{109}Cd on column (mCi)	$^{109\text{m}}\text{Ag}$ in 5 ml of elluent (mCi)	$^{109\text{m}}\text{Ag}$ from ^{109}Cd (%)	^{109}Cd in 5 ml of elluent (mCi)	^{109}Cd in 5 ml of elluent (%)
Ions	Concentrations					
NaI	2.0%	200	61.0	30.5	7.8×10^{-3}	1.3×10^{-2}
NaI	2.5%	200	64.5	32.2	1.8×10^{-2}	2.8×10^{-2}
NaI	3.0%	200	68.4	34.1	3.7×10^{-2}	5.4×10^{-2}
NaCl	1.0%	200	nil	----	----	----
NaCl	6.0%	200	----	----	High	High
EDTA	0.005M	200	----	----	High	High
S_2O_3^-	0.1N	200	----	----	High	High
NH_2CSNH_2	1.0N	200	----	----	Very high	Very high



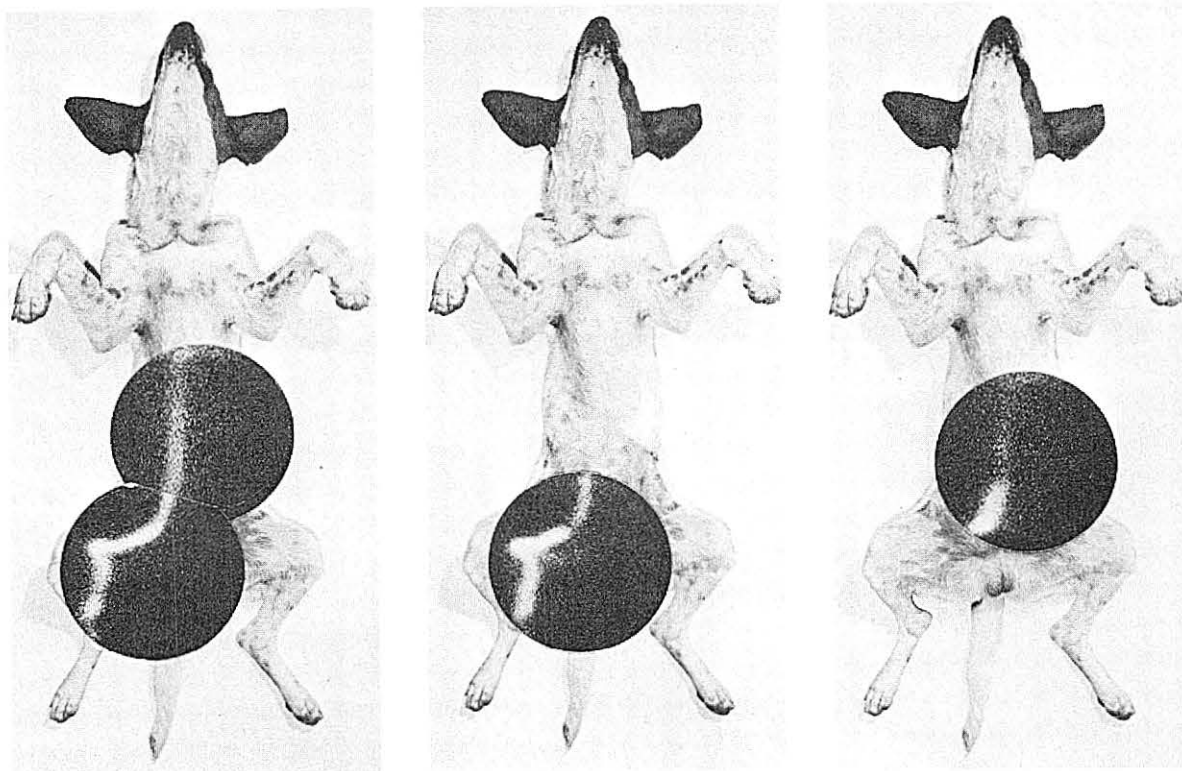
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Fig. 1. Construction of ion-exchange column for rapid elution of ultrashort-lived daughter isotopes.



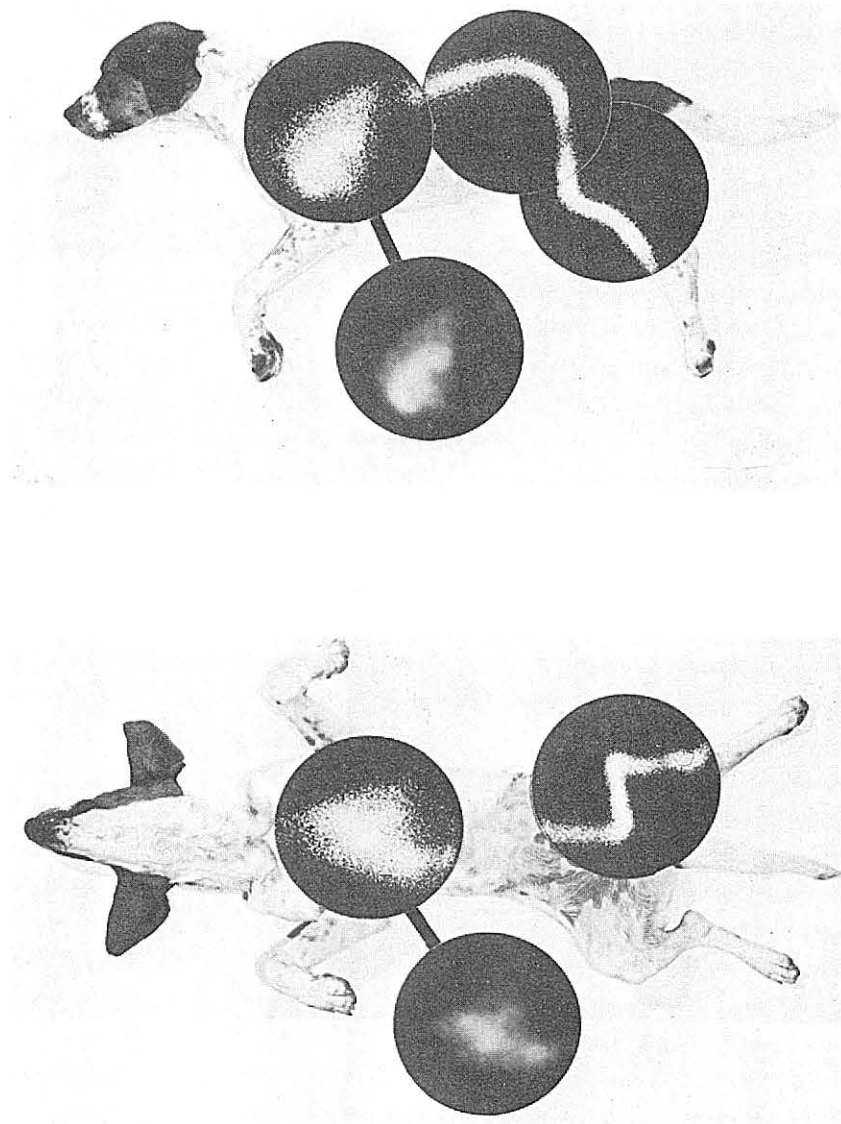
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Fig. 2. Yield of ^{191m}Ir for various concentrations of NaCl eluting solutions.



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Fig. 3. Scintiphotographs of continuous infusion of 4.9-sec $^{191}\text{m}_\text{r}$ into right tibial vein of dog. (left) Normal blood flow. (center) Partial blockage of vein by manual pressure. Collateral vein is also visible. (right) Almost complete blockage.



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Fig. 4. Scintiphotographs of ^{191m}Ir in vein and lung with chambers of heart superimposed. A diffused, darker copy of each lung field is also shown. Each circular field was exposed 45 sec.

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