

RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

Development of a Reliable Hg-195m → Au-195m Generator for the Production of Au-195m, a Short-lived Nuclide for Vascular Imaging

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A new mercury-195m ($T_{1/2}$: 41 hr) → gold-195m ($T_{1/2}$: 30.6 sec) generator suitable for first-pass as well as steady-state radionuclide angiography studies has been developed. The distribution coefficients, K_D , for mercury (Hg-195m) and gold (Au-196), experimentally evaluated on chelating resin Chelex 100, showed this resin to be suitable as the column packing. Mercury-195m in a Trisma buffer solution at pH 7.40 was loaded on a chelating resin Chelex 100 column, together with gold carrier. Au-195m was eluted with an aqueous solution of 5% glucose in a 0.01M Trisma buffer at pH 7.70 (25°C). Chemical assessment of the eluate has ensured that the eluted carrier-free gold is by no means colloidal: 80% is found in an ionic form, 20% as an uncharged species. Safe clinical use for routine diagnosis in humans is possible.

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So far, the availability of a carrier-free, short-lived, single-photon emitter, in a biologically inert state, has been an attractive but until now unrealized objective for a conventional nuclear medicine department. Furthermore, such a radionuclide if milkable from a medium-lived parent and possessing a half-life ranging from seconds to several minutes, would be considered an indispensable tracer for angiography studies if intravenously injectable as a bolus or by continuous infusion. These dynamic functional studies, especially cerebral blood-flow measurements, require repeated patient investigation, often at short intervals. The only cyclotron-produced generator currently used on a widespread scale is the Rb-81 → Kr-81m generator, applied mainly to ventilation studies. Nevertheless, the krypton-81m gas can also be used in solution, especially for the determination of the right-ventricular ejection fraction (1) and for venoangiographic studies (2). Its main limitation results from its complete elimination by the lungs when it is injected intravenously. Arterial angiography,

therefore, requires the administration of Kr-81m into the arterial supply of the organ; for example, assessing coronary (3) or cerebral blood flow (4) requires arterial infusion or even catheterization. These methods are considered traumatic. The Hg-195m → Au-195m pair was explored as a potential generator (5) for the first time in 1974. The nuclear pair has in fact many pertinent advantages:

1. Hg-195m has a 41-hr half-life and decays to Au-195m, which in turn decays with a 30.6-sec half-life to Au-195 by emission of a 262-keV photon with an internal conversion yield of 33%. A simplified decay scheme is shown in Fig. 1, giving the main gamma emissions for each transition.

2. Au-195m emits predominantly a 262-keV gamma photon and thus provides a clean spectrum for analysis as shown in Fig. 2, which gives the gamma spectrum of Au-195m after isolation from Hg-195m parent.

3. Due to its short physical half-life (30.6 sec) and its biological inertness, Au-195m causes a very low radiation dose, as follows (6):

Heart: 0.78 mrad/mCi (0.21 μ G/MBq).

Kidney: 0.56 mrad/mCi (0.15 μ G/MBq).

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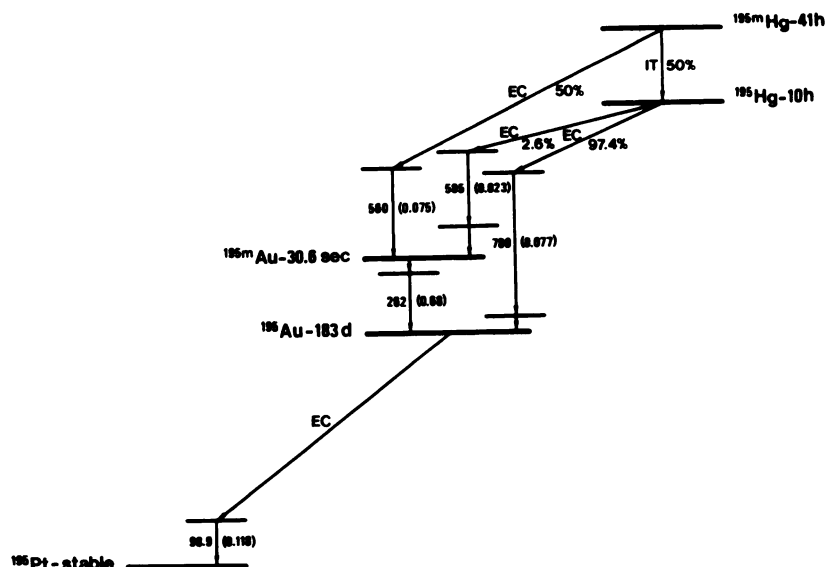


FIG. 1. Simplified decay scheme for Hg-195m, showing main photon emission for each transition.

This permits administration of the large activities often required for repeated single-pass perfusions. These outstandingly favorable characteristics of Au-195m invite an intensive investigation of the production of Hg-195m with a medical cyclotron and the development of a reliable and easy-to-operate Au-195m generator convenient for clinical use. It was only in 1981 that a generator system was proposed by Bett et al. (7). It was found possible to milk Au-195m from a column of vicinal dithiol cellulose with a KCN solution. In such conditions, a typical 20-mCi Hg-195m generator yields about 15% of Au-195m with a 2% Hg-195m breakthrough. This proves the possibility of the chemical separation of Au from Hg, but the column is quite useless for medical applications even if the toxic cyanide could be chemically neutralized before i.v. injection. E. Garcia et al. (6) also proposed a Au-195m generator for hemodynamic studies. The Hg-195m adsorbent is a silica gel column, the eluent a solution of sodium thiosulfate and sodium nitrate.

been made of the external proton beam of the Louvain-la-Neuve cyclotron. A typical high-yield production run from a 1 mm-thick metallic gold target requires the following conditions:

Proton energy:	32 MeV
Operating current:	15 μ A
Production rate at EOB:	5.4 mCi/ μ A-hr (200 MBq/ μ A-hr)
Typical yield:	81 mCi/hr

The separation of Hg from the target is achieved by Parker's method of volatilization (8). Figure 3 shows the experimental setup successfully used for the separation of mercury from the target. The procedure is as follows.

MATERIAL AND METHODS

Production of Hg-195m. Mercury-195m is prepared from a metallic gold target by a (p, 3n) reaction. Use has

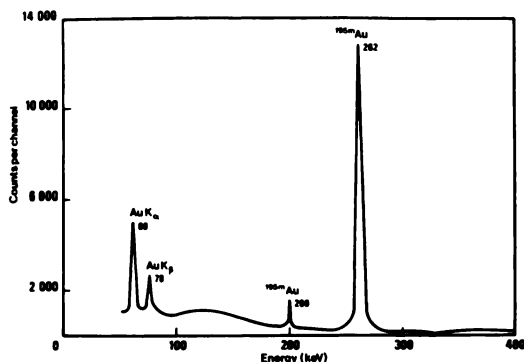


FIG. 2. Ge(Li) pulse-height spectrum from eluted Au-195m.

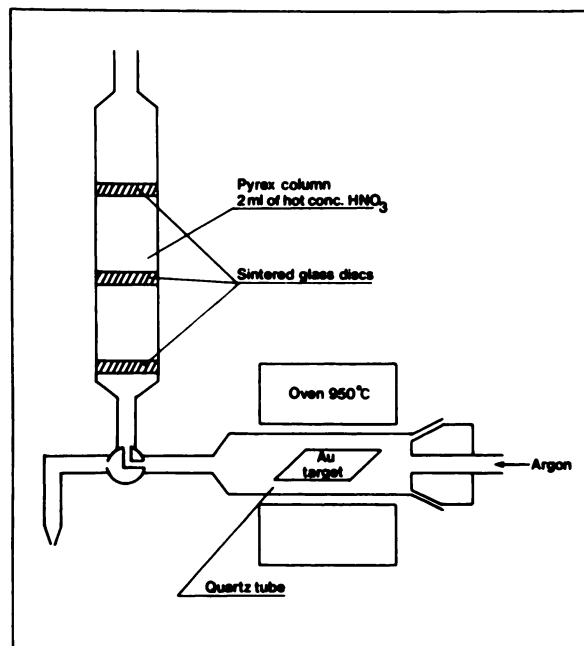


FIG. 3. Experimental setup used for separation of radioactive Hg from gold target.

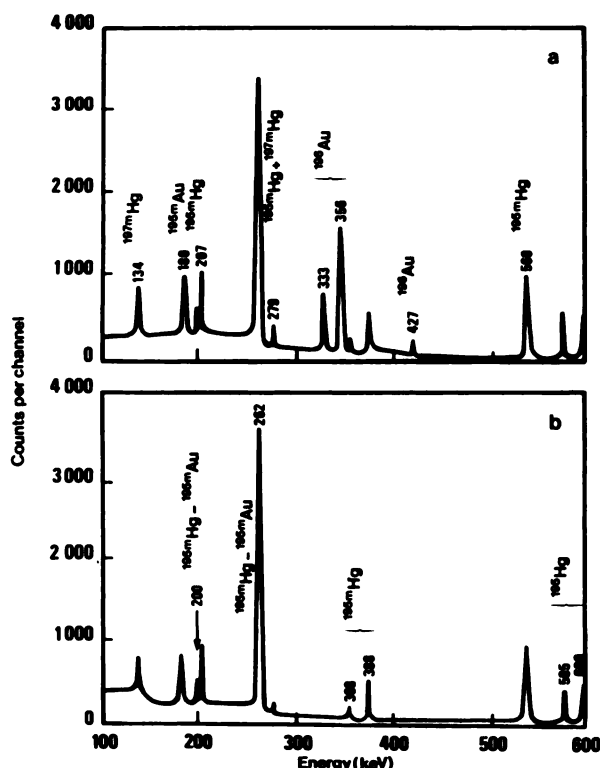


TABLE 1. DISTRIBUTION COEFFICIENTS, K_D , Au^{3+} IN NITRATE MEDIUM (pH 7) ON CHELEX 100, AS A FUNCTION OF EQUILIBRIUM TIME

Equilibrium time (min)	K_D (ml/g)	Log K_D
0.25	27	1.4
0.50	44	1.6
1.0	63	1.8
5.0	420	2.6

shows the very slow absorption rate of Au^{3+} ions on the Chelex resin (Table 1). These slow kinetics of Au^{3+} absorption were confirmed by the high percentage of Au-196 (>80%) that passes through Chelex mini-columns at flow rates higher than 2 ml/min (Fig. 6). The slow absorption of Au^{3+} ions on the Chelex 100 leads us to expect its partial elution.

Typical radioactivity profiles on column and in eluent.

Figure 7 shows the distributions of Hg-195m activity on the column just after loading and after an extensive elution with 5 l of 5% glucose solution buffered at pH 7.7 with $10^{-2}M$ Trisma. A slight shift of the activity profile is seen, showing that Hg breakthrough may be expected to remain constant for an elution volume of 5 l (Table 2).

Figure 8 plots the eluted Au-195m activity as a function of the eluted volume. The activity peak seen in the first seconds of extraction is called the bolus peak. It represents the totality (within the limits set by the extraction yield) of the daughter's activity in equilibrium with the precursor element, available from the beginning of extraction and present in the dead volume (0.1 ml) of the column. The bolus peak is followed by a constant extraction of the daughter's activity, whose level is determined by the size of the volume being measured. The steady-state condition is represented by the horizontal line in Fig 8.

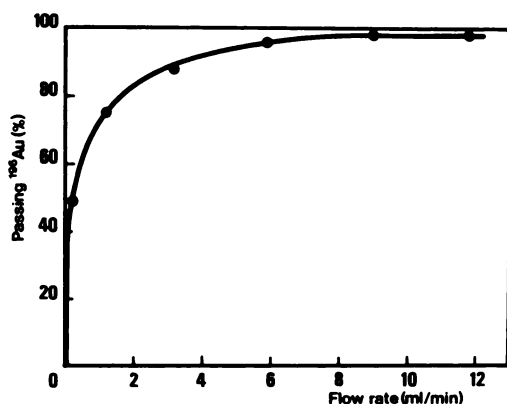


FIG. 6. Percentage of passage of Au-196 through Chelex column 3 cm long and 0.6 cm i.d. as a function of flow rate.

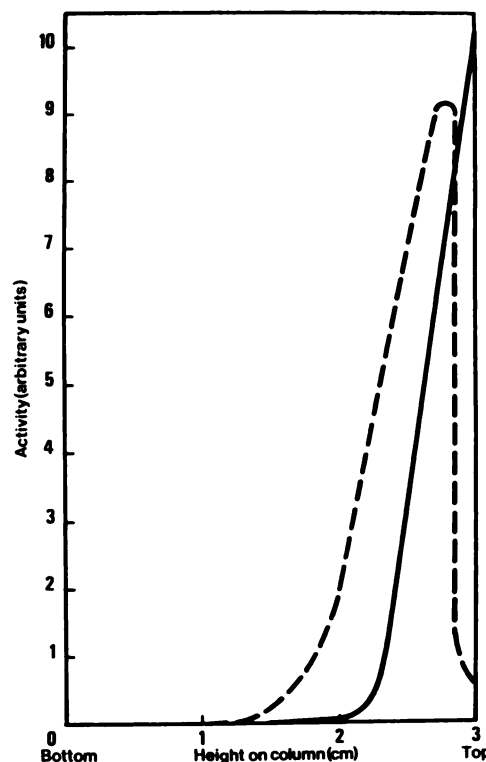


FIG. 7. Activity profile on a column 3 cm high: (—) after loading, (- -) after 5 L of eluent.

Eluted Au-195m characteristics. The Ge(Li) pulse-height spectrum from the eluted solution (Fig. 2) represents the gamma spectrum of pure Au-195m. Figure 9 shows a typical decay curve of the total eluted activity. The calculated half-life is 30.6 ± 0.2 sec. Further investigations on the chemical state of the carrier-free eluted Au-195m have been carried out by using a fast electrophoresis procedure. Two Au-195m radioactivity

TABLE 2. INFLUENCE OF THE ELUENT VOLUME PASSED THROUGH A GENERATOR ON ELUTION YIELD, AND ON Hg-195m BREAKTHROUGH (FLOW RATE 12 ml/min)

Volume (liters)	Au-195m Elution yield (%)	Hg-195m Breakthrough (%/ml)
0.10	20.1	2.30×10^{-3}
1.10	15.3	1.30×10^{-3}
1.24	17.9	1.45×10^{-3}
2.75	16.1	1.63×10^{-3}
2.87	14.7	1.02×10^{-3}
3.03	15.0	1.40×10^{-3}
3.79	12.8	1.20×10^{-3}
3.87	13.4	1.3×10^{-3}
4.50	13.4	1.3×10^{-3}
5.0	14.7	1.53×10^{-3}
5.2	16.2	1.45×10^{-3}
5.4	17.4	1.61×10^{-3}

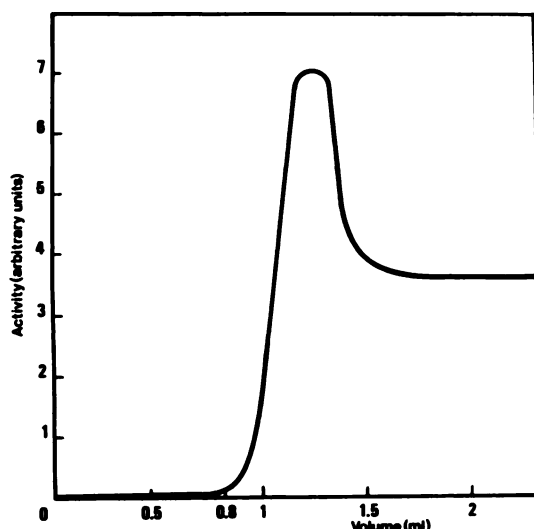


FIG. 8. Eluted Au-195m activity as a function of eluent volume through generator.

spots were identified and assessed following repeated experiments and separate activity measurements on the paper strip:

- first spot: 0 cm unionized form — 20%
- second spot: 5 cm anionic form — 80%

This finding is underlined by the comparable results obtained by chromatography on a column with a strong anionic exchanger such as DOWEX 1 and using 2 *N* HCl as eluent. Only 20% of the overall Au-195m activity can be eluted under these conditions; presumably this fraction represents the 20% of unionized gold identified by electrophoresis.

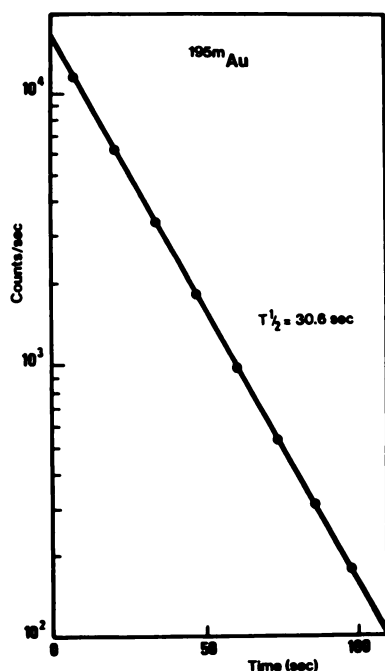


FIG. 9. Decay curve of Au-195m obtained by measurement of 262-keV photon.

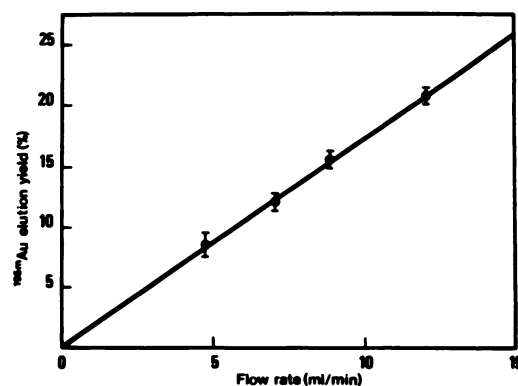


FIG. 10. Influence of eluent flow rate on elution yield in steady-state conditions.

Metallic gold might be formed by the possible reduction of Au^{3+} into Au^0 by the Chelex resin itself (12). The existence of possible colloidal particles was investigated by electron microscopy. No particles larger than 2.5 nm were detected.

Elution yield and breakthrough. Au-195m yields, expressed as percentage of the maximal theoretical value, were calculated as a function of the eluent flow rate, using the relationships proposed by Guillaume in his Rb-81 \rightarrow Kr-81m generator study (11). Both proposed methods used in steady-state conditions yielded the same results. A typical Au-195m elution yield curve is shown in Fig. 10, covering eluent flow rates up to 15 ml/min. For a continuous flow rate of 12 ml/min, an elution yield of $(20 \pm 1)\%$ is reached. On the other hand, a bolus/steady-state yield ratio of less than 1 has been measured. It indicates a time-dependant absorption of Au-195m on the Chelex as previously discussed. We find experimentally that the dependance of the elution yield upon the eluent flow rate was conditioned by the presence of gold carrier (70–280 μg) in the mercury solution before it is loaded on the pre-equilibrated Chelex column.

The finding is plotted in Fig. 11, which shows the obvious influence on the elution yield of the amount of gold carrier added to the parent solution. Indeed, the absence of carrier gold induces a reproducible, constant, low elution yield of $(8 \pm 2)\%$. This experimental finding is now under study for interpretation and for potential improvement of the elution yields in either operational mode of the generator.

The mercury breakthrough received special attention. It is expressed as the percentage of parent activity detected in one ml of the eluate in relation to the total parent activity on the column. The activity profile on the column, after a continuous 5-l elution as given by Fig. 6, anticipated a low breakthrough. Quantitative results of the breakthrough are reported in Table 2, together with the elution yield as a function of eluent volume.

The elution yield tends to decrease slightly from $(20 \pm 1)\%$ to $(16 \pm 1)\%$ after a total eluent volume of more than 5 l, at a flow rate of 12 ml/min. The Hg-195m

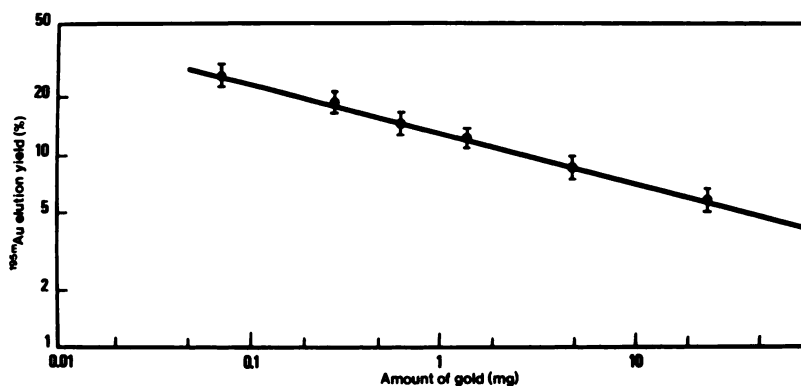


FIG. 11. Influence of amount of inactive gold in loading Hg solution on Au-195m elution yield.

breakthrough was found between $10^{-3}\%$ and $2.3 \times 10^{-3}\%$ per eluted ml. Note that the presence of a sterilizing $0.22 \mu\text{m}$ filter at the outlet of the generator has no effect on the elution yield.

Internal dose calculations for Au-195m. The calculations have been made for intravenous administration. Absorbed dose estimates were made for brain, liver, heart, and kidneys using the absorbed fraction method as proposed in MIRD pamphlet No. 1 (revised) (13).

For liver and kidneys, the S factor was simply taken from the tables in MIRD pamphlet No. 11 (14). For the brain, the S factor was deduced from the ϕ_i factors (15) and the nuclear parameters for Au-195m available in MIRD pamphlet No. 10 (16). For the heart, the S factor was calculated in the same way from the Φ_i factors related to the heart chambers as source organ and to the heart walls as target organ. Data are available in MIRD pamphlet No. 13 (17).

In all our calculations, a homogeneous, exclusive uptake into each organ considered was assumed, the organ being regarded as source as well as target at the same time. This assumption is justified because of the present ignorance of the distribution of carrier-free ionic and uncharged gold between the different human organs.

The cumulated activity \bar{A} in each source organ has therefore been calculated as follows:

$$\bar{A} = 1.443 \times T_{\text{eff}} (\mu\text{Ci-hr}).$$

The physical half-life being considered as the effective one, it follows that the cumulated activity is for 1 mCi of Au-195m:

$$\bar{A} (1 \text{ mCi}) = 12.3 \mu\text{Ci-hr}$$

Table 3 gives a summary of the estimated absorbed doses from Au-195m after a continuous intravenous perfusion of the eluate from a gold generator. Reference (6) does not permit discussion of the large difference from Garcia's values.

Since the biologic parameters describing distribution and retention are not being taken into account, and with the added assumption of instantaneous uptake of the carrier-free gold into the source, the above data must be considered as considerably overestimated. They are

therefore considered only as preliminary indications. Studies of the Au uptake and its time dependence in the different organs, as well as biodistributions in animals, are now in progress. These data are required for the accurate evaluation of the total absorbed doses from the Au-195m/Au-195 pair, taking into account that Au-195 is simultaneously the decay product of Au-195m and of Hg-195. The estimation of the absorbed doses from Hg-195m and Hg-195 is not possible at this time because neither mean absorbed dose per unit cumulated activity nor equilibrium dose constants, Δ_i , are known for these nuclides.

Pharmaceutical controls. The sterility conditions have been systematically checked on the different components before assembly and on the final eluate by innoculating Sabouraux and thioglycollate media to culture respectively fungi and aerobic and anaerobic bacteria. The absence in the eluate of pyrogenic substances has been established using the PYROGENT test (*Limulus amoebocyte lysate*).

Measurement of mercury in the eluate has been done by flameless atomic absorption spectrometry, which shows that the mercury concentration lies between 5 and 12 ppb. Assuming a maximal injection volume of 500 ml, the increase of the mercury concentration in the blood would be of the order of 1 ppb at the time of injection, which can be regarded as nontoxic (18).

Imaging characteristics. The compatibility of Au-195m with a LFOV conventional gamma camera has

TABLE 3. CALCULATED ABSORBED DOSES FROM PERFUSED Au-195m ELUATE FROM AN EXPERIMENTAL GOLD GENERATOR (1 mCi Au-195m)

Organ (source + target)	Doses (mrad)
Brain	1.3
Liver	2.3
Heart	1.5
Kidneys	12.0



FIG. 12. Images of highly perfused organs.

been tested. With the only currently available 300-keV general-purpose parallel-hole collimator, the following results have been obtained:

- FWHM at face: 7 mm.
- sensitivity at face: 650 cps/mCi

The bar-phantom resolution is better than 3 mm.

A 260-keV collimator would obviously provide more adequate imaging characteristics. Nevertheless, rapid buildup of the gold activity into highly vascular organs such as heart, brain, liver, and kidneys has been observed in dogs (Fig. 12). This result apparently shows that the eluted gold might be mainly a blood-pool agent. Further refinements aim to evaluate the time-activity curves for each of the mentioned organs and consequently the suitability of this radionuclide for hemodynamic studies.

Cost evaluation. A typical production run, requiring under present conditions a 2-hr bombardment time, costs a total of ~700 dollars. The potentialities for medical applications will govern the widespread use of this new generator.

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