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FINAL REPORT

DEVELOPMENT OF TUNGSTEN-TANTALUM GENERATOR

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INTRODUCTION:

The purpose of this project was to develop a useable tungsten (W)/tantalum (Ta) generator and came about from a desire to provide state of the art imaging technology for utilization in space. The space environment places a premium on equipment that is lightweight, compact and rugged. The NASA multiwire camera developed originally for high altitude particle physics appears to have these requirements. In addition it was anticipated that the high count-rate capability of this instrument would provide significant improvement in temporal resolution compared to existing imaging instruments. A significant disadvantage of the multiwire gamma camera (MGC) is the low energy efficiency for nearly all commercially available radiopharmaceuticals.

In 1978 -79 a few articles appeared describing a new short-lived radionuclide, Ta-178, for potential use in cardiovascular and pediatric nuclear medicine. This isotope was of interest to us primarily because its energy was low enough to be utilized with the MGC.

Ta-178 is formed following the decay of its parent, W-178 (half-life: 21.7d) and has a half life of 9.3 minutes in turn yielding stable Hf-178. The decay of the parent isotope (W-178) occurs entirely by electron capture to the 9.3 minute Ta-178 state, without feeding the high spin Ta-178 isomer (half life 2.2 hours). In Ta-178 decay, 99.2% of the disintegrations proceed by electron capture and 0.18% by positron emission. Electron capture results in a 61.2% branch to the ground state of Hf-178 and 33.7% to the first excited state at 93.1KeV. The most prominent features of the radionuclide's energy spectrum are the hafnium characteristic radiation peaks with energies between 54.6 and 65.0 KeV.

The optimal radiotracer for in vivo diagnostic use is one which combines the best physical and chemical properties in an effort to yield high quality diagnostic results while minimizing individual organ and total body radiation exposure to the patient. Technetium-99m ($T_{\frac{1}{2}}$ = 6 hr) is an example of such a tracer. Although optimal for many applications, Tc-99m is not optimal for perfusion studies such as venograms and cardiac first-pass studies which take on the order of minutes to complete. For these types of studies, a radionuclide such as Ta-178 with a $T_{\frac{1}{2}}$ on the order of minutes would reduce radiation exposure substantially without degrading image quality. Also, accumulation of radiotracers outside the region of interest of a study (e.g. thyroid and GI buildup in the case of TcO_4^-) results in significantly higher radiation exposure to affected organs. Short lived radionuclides reduce this exposure appreciably since the physical half-time is significantly less than the organ biological half-time. Short lived radionuclides also offer the possibility of repeat studies without buildup of background activity. Using biodistribution data obtained from preliminary animal studies (4) along with the Medical Internal Radiation Dose (MIRD) Committee recommendations and pamphlets (10,11) and Ta-178 output decay data (12) we have calculated the radiation exposure dose to be approximately one-twentieth that of Tc-99m on a per millicurie basis. A twenty-fold reduction in radiation exposure from Ta-178 compared with Tc-99m means that the

usual administered dose can be increased three to four times, greatly increasing the statistical accuracy while reducing radiation exposure by a factor of five. This is very important for improved first pass studies particularly in pediatric radionuclide angiography. The nuclear characteristics of Ta-178 limit its usefulness with the Anger camera. The limiting factors are as follows: (1) The principal photon emissions of Ta-178 are 55 - 65 KeV, an energy range which is not optimal for Anger cameras, and (2) Ta-178 has high energy photons (6% abundance) which penetrate high resolution and medium energy collimators (13). The multiwire proportional camera (MGC), however, is not sensitive to the high energy photons of Ta-178, and the 60 KeV radiation is nearly optimal for imaging with this device. A prototype MGC developed at the NASA/Johnson Space Center is currently undergoing evaluation. The high count rate capability of this instrument allows the use of high Ta-178 activities.

Ta-178 AND W-178 CALIBRATION:

To determine breakthrough at the time of generator elution is difficult because the photon energies of W-178 (56-67 KeV) are close to those of Ta-178 (54-65 KeV). The method employed here was to elute the generator in the morning, allow the Ta-178 to decay 10 - 20 half lives and count the samples for residual activity. Since breakthrough occurs slowly as a function of total elution volume this method detected W-178 breakthrough of less than a fraction of one uCi.

Ta-178 calibration factors were obtained on the Tc-99m setting of two commercial dose calibrators (Capintec, Mediac). Approximately two mCi of Ta-178 were eluted and the activity reading obtained four successive times on both calibrators. The time of each reading was carefully noted so that each reading was decayed back to zero time after elution. The same samples were counted twice for 100 sec near a 3" x 3" NaI (TI) detector connected to a 1024 multichannel analyzer. The NaI (TI) counts were used to determine the actual mCi of Ta-178 present. This was accomplished by comparing the 0.5 MeV and x-ray photon peaks of Ta-178 with the 0.5 MeV and the 60 KeV peaks of Na-22 and Am-241 standards. The Ta-178 windows were 49 - 70 KeV and 477 - 544 KeV. The Am-241 window was 51-71 KeV and the Na-22 window was 477 - 544 KeV. Each peak was corrected for air background and for events resulting from compton scattered photons. The background from compton scattered events was estimated by taking the average count within windows above and below the photopeak. The resultant Ta-178 counts were corrected for radioactive decay during the counting interval and from time zero to the start of the Ta-178 count. The photon abundances employed in the calculations were: Ta-178 x-rays, 88%, Ta-178 0.511 MeV, 2.1%, Am-241 x-rays, 36%, Na-22 0.511 MeV, 180%.

Table 1 gives the results of the Ta-178 calibration measurements. The determination of the mCi of Ta-178 at the time of elution using either Am-241 or Na-22 standards gave essentially identical results, i.e., 1.83 mCi. This value was used to derive a correction factor for Ta-178 using the Tc-99m setting of the two dose calibrators by dividing the mCi of Ta-178 by the dose calibrator reading. For the Searle instrument this value (R) was 1.26 while Capintec was 0.46. The

TABLE 1. TA-178 CALIBRATION (R) USING TC-99M DOSE CALIBRATOR SETTINGS

Searle (mCi)	Capintec mCi	NaI		mCi (NaI) / mCi (dose Cal)
		Am-241 mCi	Na-22 mCi	
1.45	3.95	1.80	1.83	1.26 (Searle)
1.45	3.97	1.85	1.83	0.46 (Capintec)
1.45	3.96			
1.46	3.97			

reason for the large response difference of these instruments is that the Searle instrument is air filled while the Capintec chamber is filled with argon. The absorption coefficient of Ta-178 x-rays relative to the coefficient for 140 KeV photons is higher for argon than for air and therefore the chamber response on the Tc-99m setting is greater for the argon filled device.

BIODISTRIBUTION:

Although the absorbed radiation dose of Ta-178 is one-twentieth that of Tc-99m on a per mCi basis, breakthrough of parent W-178 ($T_{\frac{1}{2}}$ = 21.5 d) could substantially increase the overall absorbed dose. In an effort to ascertain the extent that W-178 contributes to the total body burden we have determined the effective half-life, routes of elimination, and organ distribution of this radionuclide. Also, we have studied the blood clearance of Ta-178 to determine the feasibility of gated cardiac studies with this radionuclide.

A study to determine the effective half-time (Te) of the parent W-178 was performed in rats using decayed generator eluant containing a known quantity of W-178 breakthrough. The solution was buffered to a pH of 7 with phosphate buffer. Two rats were counted (whole body) using a NaI (TL) detector coupled to a multichannel analyzer. This was done over a period of three weeks. The resulting data was graphed and the Te was calculated, Figure 1.

Initially two rats were injected with 10uCi of W-178 and counted, whole body, over a period of three weeks. Whole body counting data demonstrated bi-phasic elimination, 98% eliminated with a effective $T_{\frac{1}{2}}$ (Te) of 8 hours and 2% eliminated with a Te of 10 days. Urine and feces were collected in order to determine the route of excretion. Ninety two percent of the administered dose was in the urine in 72 hours. The biodistribution of W-178 in phosphate buffer was studied in four groups of six animals each (6, 24, 48 and 336 hours) housed in metabolic cages. Each animal was injected with a known quantity of the isotope and appropriate standards were drawn up for each group. Multiple standard dilutions were prepared and counted with each group of samples. The percent dose per organ, percent dose per gram of tissue and route of elimination were determined. Table 2 shows the mean percent administered dose per organ for each time group. Table 3 shows the percent administered dose recovered in the urine. The highest concentration of W-178 was found in bone. This distribution and excretion data were used for calculating the absorbed dose in humans.

Since we have made allowance for a limited amount of W-178 breakthrough in our generator eluant we conducted a study to determine the biological half time and mode of elimination of W-178 in man. Unique facilities at the NASA/ Johnson Space Center's Radiation Counting Laboratory enabled us to perform sensitive whole body counting of W-178.

Six healthy volunteers were injected with a known quantity of W-178 (2-10 uCi). The individuals were counted a minimum of two

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FIGURE 1

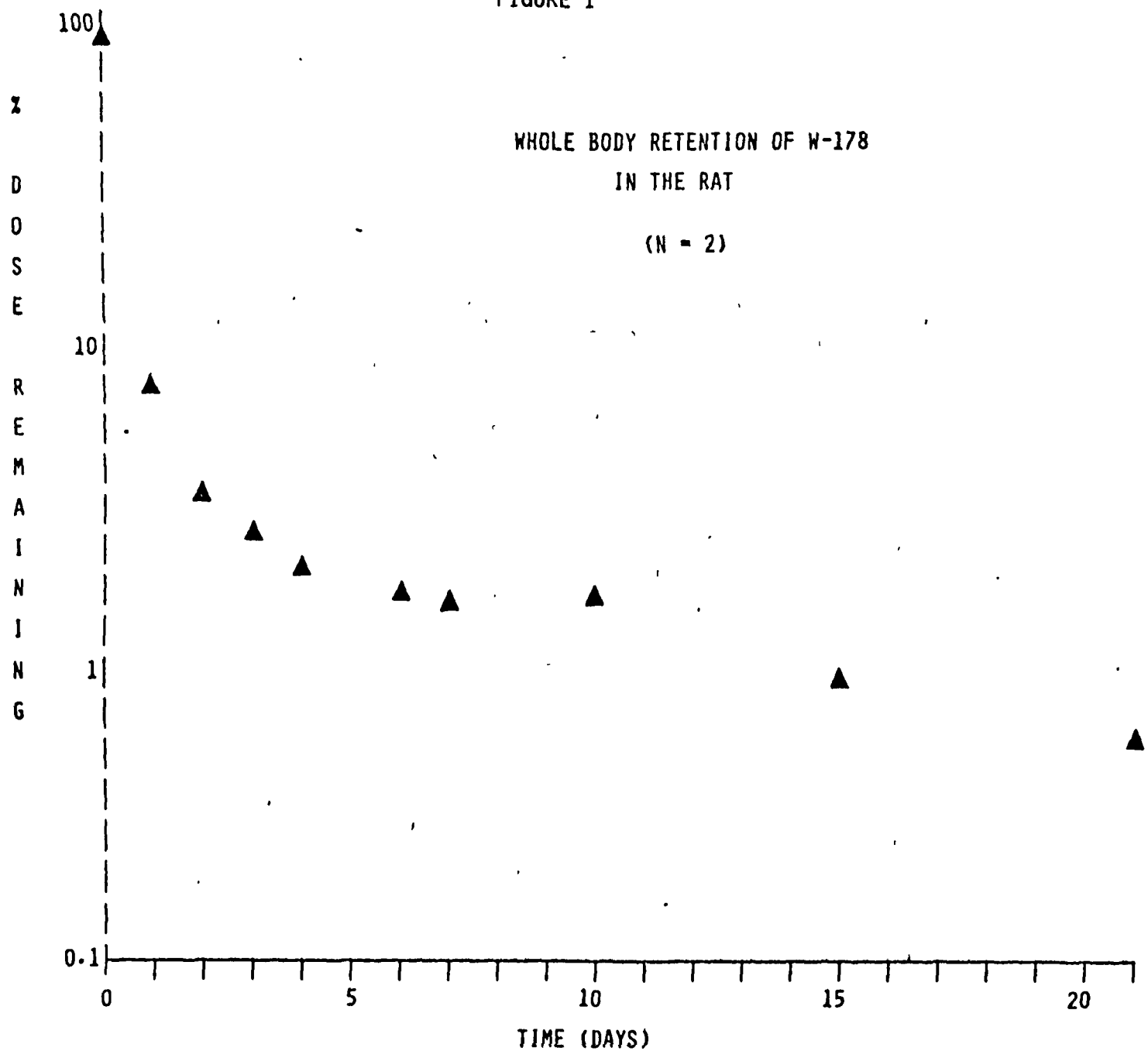


TABLE 2
TUNGSTEN-178 BIODISTRIBUTION IN THE RAT
% ADMINISTERED DOSE PER ORGAN ± S.D.

ORGAN	6 HR. (N=6)	24 HR. (N=6)	48 HR. (N=5)	336 HR. (N=6)
BLOOD	0.82 ± 0.49	0.06 ± 0.04	0.02 ± 0.01	0.005 ± 0.004
SM. INTEST	0.70 ± 0.52	0.05 ± 0.02	0.06 ± 0.04	0.004 ± 0.003
STOMACH	0.62 ± 0.54	0.05 ± 0.04	0.03 ± 0.03	0.004 ± 0.003
LUNG	0.08 ± 0.03	0.01 ± 0.01	0.01 ± 0.003	0.003 ± 0.003
SPLEEN	0.05 ± 0.003	0.02 ± 0.01	0.01 ± 0.01	0.02 ± 0.01
FUR/SKIN	2.20 ± 0.79	0.46 ± 0.21	0.23 ± 0.13	0.19 ± 0.05
BRAIN	0.01 ± 0.003	0.01 ± 0.01	0.004 ± 0.003	0.001 ± 0.001
L. INTEST	0.05 ± 0.02	0.02 ± 0.02	0.01 ± 0.004	0.002 ± 0.003
TESTES	0.12 ± 0.02	0.01 ± 0.003	0.005 ± 0.003	0.001 ± 0.001
BONE	7.04 ± 1.08	5.33 ± 1.63	3.10 ± 0.33	1.53 ± 0.27
LIVER	1.17 ± 0.40	0.13 ± 0.03	0.05 ± 0.01	0.01 ± 0.003
BLADDER	0.03 ± 0.03	0.02 ± 0.01	0.01 ± 0.01	0.004 ± 0.001
CECUM	3.08 ± 4.82	0.75 ± 0.53	1.25 ± 0.48	0.03 ± 0.02
HEART	0.02 ± 0.01	0.003 ± 0.001	0.004 ± 0.003	0.001 ± 0.001
KIDNEYS	1.63 ± 0.44	0.13 ± 0.02	0.05 ± 0.01	0.006 ± 0.002
MUSCLE	1.77 ± 0.65	0.26 ± 0.14	0.18 ± 0.17	0.06 ± 0.10
CARCASS	23.12 ± 4.45	7.26 ± 0.75	3.45 ± 0.33	2.22 ± 0.44

weeks. Urine and blood were collected from two of the six in an effort to determine route of elimination and blood clearance. Whole body counts of W-178 in man demonstrated a three-phase elimination curve, Figure 2. Ninety five percent was eliminated with a Te of 8 hours, 4% with Te of 35 hours and 1.5% with a Te of 11 days. Ninety six percent of W-178 was excreted by 48 hours, Table 4.

Blood levels of W-178 were at background by 24 hours. The effective half times of W-178 in the rat bone closely resembles the long Te components seen in whole body counting of man. We therefore conclude that the long Te fraction (4% and 1.55%) are due to residual bone activity and have calculated our bone dose in man accordingly.

The blood clearance and in vivo organ distribution of Ta-178 was studied in a group of eight healthy volunteers who underwent firstpass radionuclide angiography using the multiwire proportional counter gamma camera (MGC). Blood samples were taken every five minutes beginning at 2 minutes post injection. The samples were counted using a NaI (Tl) detector coupled to a multichannel analyzer. All samples were corrected for decay and compared to a known standard dilution of Ta-178 activity. Blood volumes were determined based on a factor of 71.4 ml/kg body weight and used to determine the percent dose in the blood at equilibrium. Organ distribution was approximated by decay correcting static images obtained over chest and upper and lower abdomen. In man, 88% of the administered Ta-178 dose remains in the blood pool at 5 minutes and decreases an additional 13% in the next twenty minutes, Table 5. No significant organ accumulation was evident other than the blood and minimal bladder activity.

In summary, we have found that W-178 is excreted similarly in the rat and man with 96% eliminated by 48 hours. The effective half-lives (Te) of W-178 in rat bone closely resembles the long Te components seen in whole body counting in man. We therefore conclude that the long Te fractions (4% and 1.5%) are due to residual bone activity.

The critical organ for absorbed radiation from W-178 is the bladder followed by bone and ovaries. The actual increase in absorbed dose to these organs is 15%, 4%, and 2% respectively, assuming 10uCi W-178 breakthrough for a 60mCi Ta-178 study. This level of breakthrough which is maintained throughout the life of the generator does not significantly increase radiation exposure.

In man, 88% of the administered Ta-178 dose remains in the blood pool at five minutes and decreases an additional 13% over the next twenty minutes. It is therefore possible to perform gated cardiac studies following a first-pass study without the need to specifically label a blood component.

ANIMAL IMAGING STUDIES:

Testing in dogs and pigs with various sized generators was conducted. In a number of cases, animals were imaged with the MGC and Ta-178 and with conventional cameras in the Medical Center on the same day. Twenty mCi injections of Ta-178 provided images of quality

FIGURE 2

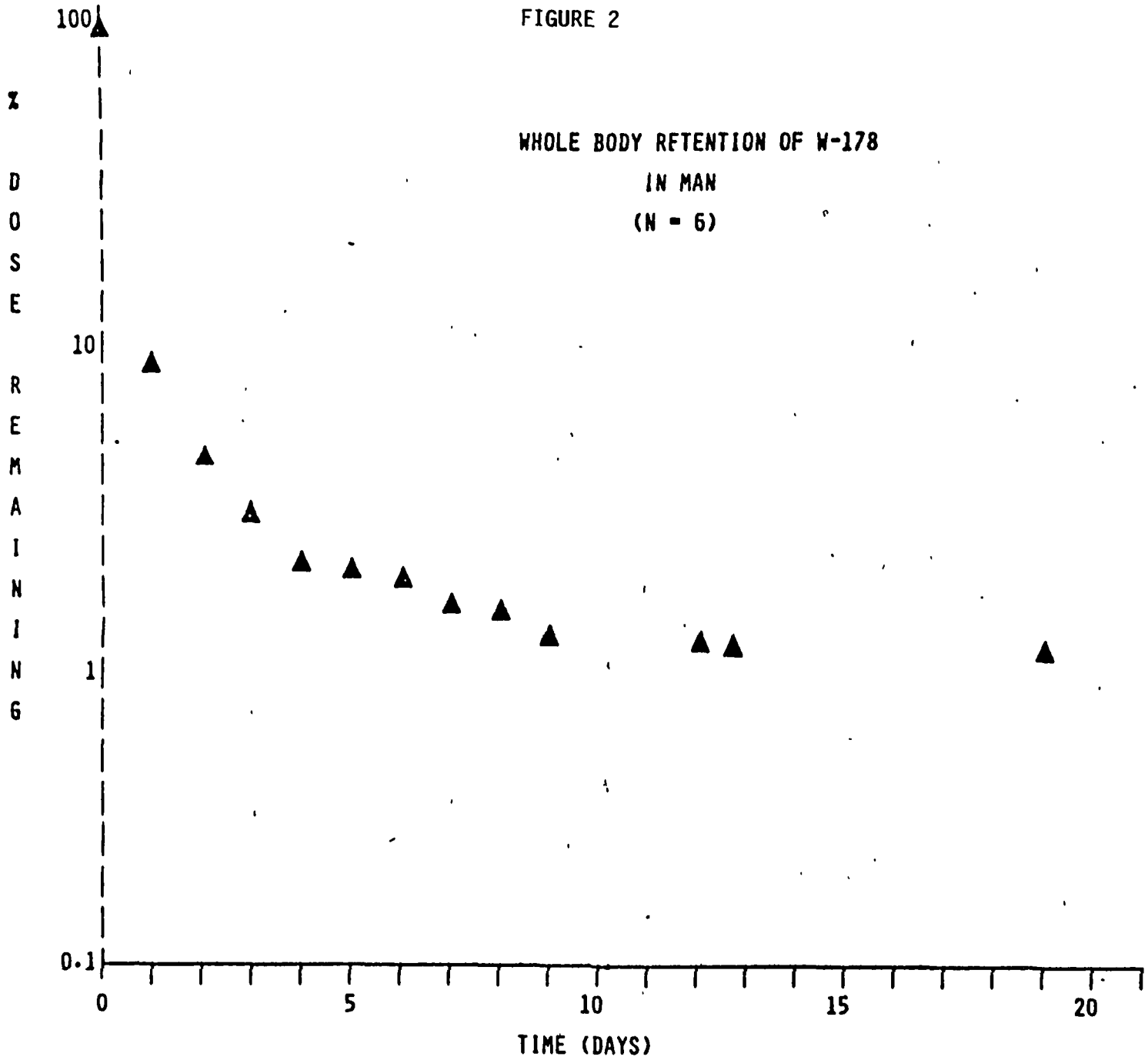

WHOLE BODY RETENTION OF W-178
IN MAN
(N = 6)
% DOSE REMAINING
100
10
1
0.1
0
5
10
15
20
TIME (DAYS)

TABLE 3

TUNGSTEN-178 ELIMINATION IN THE RAT

% ADMINISTERED DOSE RECOVERED ± S.D.

	6 HR. (N=6)	48 HR. (N=6)
URINE	65.43 ± 7.68	93.67 ± 2.28
FECES	1.09 ± 1.80	2.93 ± 1.33

TABLE 4

EFFECTIVE HALF-LIVES OF TUNGSTEN-178

IN MAN

T 1/2	% ADMINISTERED DOSE
8 HRS	95%
35 HRS	4%
11 DAYS	1.5%

IN THE RAT

T 1/2	% ADMINISTERED DOSE
8 HRS	98%
10 DAYS	2%

TABLE 5

TANTALUM-178 BLOOD ACTIVITY VS. TIME IN MAN

TIME	% ACTIVITY NORMALIZED TO 5 MINUTES (N=7)
2 MINUTES	96.79 ± 12.29
5 MINUTES	100.00 ± 0.00
10 MINUTES	94.67 ± 4.64
15 MINUTES	94.75 ± 6.58
20 MINUTES	86.59 ± 7.68
25 MINUTES	85.82 ± 8.29

ACTUAL % ADMINISTERED DOSE IN THE BLOOD AT 5 MINUTES WAS CALCULATED TO BE 87.95 ± 12.66.
BLOOD VOLUMES WERE CALCULATED USING A FACTOR OF 71.4 ML BLOOD PER Kg. OF BODY WEIGHT.

comparable to those obtained from 15mCi of Tc-99m with conventional imaging devices. These studies demonstrated feasibility and demonstrated that improved study quality would result from the ability to use larger dose levels of Ta-178 while reducing radiation exposure to the patient. These results have been published and therefore will not be repeated here, see Appendix II.

HUMAN IMAGING STUDIES:

Pilot first-pass radionuclide angiocardiography studies in nine normal human subjects employing 20-40mCi of Ta-178 have demonstrated excellent image quality with a radiation dose 1/20 that of Tc-99m. Mean LV ejection fraction and peak ejection and filling rates (end diastolic volume/sec) for the nine subjects were 63%, 35%, and 28%. Left ventricular counts, the main determinant of image quality in such studies, were similar to Tc-99m Baird System 77 studies on a per mCi basis although higher resolution collimation was employed for the Ta-178 MGC studies. In comparison with the Baird System 77, superior image quality was demonstrated by the Ta-178 studies as expected from improved pixel size (7.5 mm vs 11mm) and collimator resolution. Further improvement in image quality is expected with larger Ta-178 injections and optimal collimator selection. A portable MGC with Ta-178 offers improved image resolution, lower radiation exposure, and permits repeated rapid studies.

RADIATION EXPOSURE:

The low radiation exposure from the use of Ta-178 is fundamental to the eventual commercial exploitation of this radionuclide. We have considered the radiation exposure both from the parent as well as the daughter fraction. The detailed calculations of organ exposures are contained in the IND application, Appendix I. The accompanying Table 6 summarizes these calculations for a theoretical study involving 60mCi of Ta-178 and 10uCi of W-178 breakthrough. Although the physical half life of W-178 is long (21.5 days), the biological excretion is rapid (both in rats and humans) and therefore this level of breakthrough is not a serious problem. There is residual W-178 activity believed to be located in the bone and therefore this question should be investigated further, especially in a pediatric population with growing bone. It is possible breakthrough contamination could add substantially to the radiation exposure, e.g., if the growth plates concentrate this isotope.

INVESTIGATIONAL NEW DRUG APPLICATION (IND):

The complete IND application is contained in Appendix I. Approval for this IND was obtained in September, 1982. It was clear to us that the current generator system had a number of serious defects, i.e., reliability, early breakthrough, poor yield, unpredictable yield, organic resin. However, without a better system available it was decided to attempt to improve the published version of the generator. It has therefore been our aim to further develop the existing generator system and this section presents the modified method for purification of the parent W-178 (6) and describes the performance

TABLE 6
RADIATION DOSIMETRY

(MILLIRADS)

ORGAN	W-178 BREAKTHROUGH† (10 UCI)	TA-178 STUDY** (60 MCI)
TOTAL BODY	0.5	37.2
OVARIES	0.9	37.2
TESTES	0.5	37.2
BLOOD	0.5	102.6
BONE	1.3	37.2
BLADDER WALL	5.9	37.2

†ASSUMING ORGAN DISTRIBUTION SIMILAR TO THE RAT USING COMBINED W-178 AND TA-178 S FACTORS

**ASSUMING UNIFORM TOTAL BODY UPTAKE

characteristics of the generator system build for human use testing with the multiwire proportional camera.

Production and Separation of W-178

W-178 is produced by the Ta-181 (p,4n) W-178 reaction. The target, a tantalum foil (99.979% Ta-181) weighing approximately 12 grams, is irradiated for 18 hours at a beam current of 15 A, using protons with a maximum incident energy of 43 MeV. The target is significantly larger than the incident proton beam, making the area of impact easily distinguishable. Therefore it is possible to cut away non-activated target and reduce the quantity of stable tantalum. After the excess tantalum has been removed, the W-178 activity is calibrated using the 2.1% annihilation radiation of Ta-178 in equilibrium with W-178 (7,8). To facilitate cooling of the target during irradiation an indium foil is used as a target backplate. The adhesion of indium onto the target necessitates an initial separation step prior to the dissolution of the tantalum target. The indium is removed by mechanical scraping and boiling in concentrated hydrochloric acid (HCl). The tantalum target does not dissolve in concentrated HCl, therefore all tungsten activity is retained. A GE(Li) detector is used to assay for contaminants on the acid boiled foil and in the purified solutions of tungsten fractions. The calibrated foil is dissolved in a teflon beaker using 10 ml of concentrated hydrofluoric acid (HF) and 5 ml of nitric acid (HNO3) added dropwise. The resulting solution is evaporated to almost dryness. Ten milliliters of HF is added and the solution allowed to evaporate to almost dryness. Ten milliliters of 6N HCl and 1.5N HF solution is added and evaporated to almost dryness. This step is repeated twice. Finally, 10ml of the 6N HCL and 1.5N HF solution is added and the solution allowed to cool.

The solution containing the dissolved target is percolated down a pre-equilibrated 200-400 mesh anion exchange column (2.5 cm i.d. x 30 cm high). The column is eluted with a mixture of 6N HCl and 1.5N HF. Ten-milliliter fractions are collected. The fractions are assayed for tungsten activity using a multi-channel analyzer. The tungsten is expected to elute off the column in approximately three column volumes. The collected tungsten fractions are pooled in a teflon beaker and evaporated to approximately 2ml. Ten ml of 6N HCl and 1.5N HF is added and the solution allowed to cool. This tungsten solution is percolated down a second smaller anion exchange column (1.25 cm i.d. x 30cm high) pre-equilibrated with 6N HCL and 1.5N HF. Ten-milliliter fractions are collected and assayed for tungsten activity. The tungsten fractions are pooled in a teflon beaker and evaporated to approximately 1ml. Three ml of concentrated HCl is added to the solution and evaporated to approximately 1ml. This step is repeated. Five ml of 0.1N HCl and 1.0% H_2O_2 is added to the evaporate and brought to a volume of approximately 1ml by evaporation. This procedure is repeated three times and finally allowed to cool. The cooled solution is assayed with a multi-channel analyzer and transferred to a syringe for calibration in an ionization chamber dose calibrator.

The dissolution of the target material and the anion-exchange separation of W0178 from the tantalum target material resulted in an overall recovery yield of W-178 of 85%.

Preparation of the Generator

The generator is comprised of a 2ml resin bed of anion exchange resin AG1-X8 (Bio-Rad Labs) that is fitted with a two-way stopcock and a disposable connecting tube at the bottom. The column and resin are thoroughly cleaned and autoclaved at 250° F for 20 minutes. The resin is then equilibrated with a freshly prepared solution of 0.1N HCL and 0.1% H_2O_2. After the resin is packed in the column, the tungsten solution is added via a syringe in a volume of 1ml or less. The loaded column is washed with 10ml of 0.1N HCl and 0.1% H_2O_2. The wash is collected in a syringe and assayed for tungsten breakthrough. The build-up of the generator column and the loading step for the W-178 onto the anion-exchange resin resulted in more than 99.5% of the W-178 retained by the resin.

Method of Elution

The generator is eluted with 1.5ml of a freshly prepared 0.1N HCl - 0.1% H_2O_2 solution. The Ta-178 eluant is collected in a syringe that is fitted with a 0.22m filter at the bottom of the column. The millipore filter provides a terminal sterilization step similar to commercial generator designs. The generator is kept dry between elutions to reduce the dead volume of eluant and to limit the formation of free radicals in the solution bathing the organic resin, thereby decreasing radiolytic damage to the resin. Also, the dry storage of the unused generator results in a 0.6 ml reduction in Ta-178 bolus size. We feel that dry storage of the resin is a significant improvement of a wet column.

Chemical Purity

Potential impurities are important to identify and quantitate in order to determine the safety and purity of Ta-178 as a radiopharmaceutical. The reagents and resin used in the production of the Ta-178 generator are of analytical reagent grade. Known impurities are identified and quantified in the lot analysis provided with each reagent. Therefore, it is possible to calculate the concentration of known impurities present in the final generator eluant. Another source of potential impurities is the organic ion exchange resin. The resin used in the tantalum generator is comprised of quarternary ammonium exchange groups (tetramethyl ammonium) attached to a styrene divinyl benzene copolymer lattice. Potential degradation of the resin by acids, oxidants, or ionizing radiation could lead to the introduction of organic contaminants. Chromatographic columns identical to the generator columns, but without the radioisotope added, were prepared. They were kept at room temperature for varying lengths of time before elutions were made. In order to identify the organic compounds, mass spectroscopy, gas chromatography and total carbon analysis were performed on the eluant samples. Quantitation of tantalum contamination caused by the original target foil is important

for toxicological reasons, and because tantalum in the oxide form strongly absorbs carrier-free Ta-178 which can significantly lower generator yield. In an effort to determine the effectiveness of the purification process and the final concentration of stable tantalum in the generator eluant, trace metal analysis has been performed. Argon plasma emission spectroscopy was performed on samples eluted immediately after the generator was loaded and flushed with approximately 10ml eluting solution.

The only organic contaminant detectable in the eluant was trimethylamine. Its concentration depends on generator usage and varies from less than 1 to 13.3 ppm per elution usage. The maximum concentration was reached when the generator was left for several days without usage: frequently eluted generators maintained levels below 1.0ppm (See Table 7). Hydrogen peroxide has no significant effect on trimethylamine production at the 0.1% concentration level. Also, levels of trimethylamine in the mock generators were not significantly different from those loaded with up to 40mCi of W-178. Drying both the mock and radioactive generators between elutions had no effect on the trimethylamine concentrations. Spectroscopic analysis revealed tantalum concentrations of 200 parts per billion, indicating that the purification process is effectively trapping greater than 99.999% of stable tantalum. Since tantalum is readily eluted from the column, a decrease in the stable tantalum concentration would be expected with continued successive elutions.

The generator uses 1.5ml of 0.1N HCl and 0.1% H_2O_2 solution as the eluting solution. This solution yields an average of 69% of the theoretically available tantalum except when the generator is left standing for several hours. When initially eluted after prolonged periods without use, the generator yields an average of 40% of the available tantalum. Increased breakthrough is noted on initial elution; the reasons for this have yet to be elucidated, but it is generally observed in chromatographic procedures. The average breakthrough per generator ranged from 0.0024% to 0.0068% W-178 per elution. Breakthrough was determined for each generator until tungsten reached approximately 5uci per elution at which time the generator was rebuilt. Routinely, the generator maintains acceptable levels of tungsten breakthrough for up to 40 elutions. No difference in elution yield was demonstrated in wet versus dry columns. All gamma rays observed in the generator eluant spectrum can be accounted for in the gamma spectrum of Ta-178 and W-178 (8). No other radionuclide was detected.

Radionuclide Purity

Radionuclide identification is performed at a number of stages during the purification process. Using NaI (Tl) and Ge(Li) detectors coupled to multi-channel pulse height analyzers, the tungsten fractions are identified as they are collected from the primary and secondary ion exchange columns. A sample of the final tungsten solution is assayed for radionuclide purity using a solid state GE(Li) detector. After the W-178 is loaded on the generator resin, samples of eluant are collected and gamma spectrum analyses performed using a

TABLE 7

Concentration of trimethylamine (g/ml) in 1.5 ml of 0.1N HCl + 0.1% H_2O_2 eluate as a function of the storage time before elution and as a function of elution volume.

Storage Time (Days)	Average Concentration (g/ml) and range in: 0 - 1.5 ml	1.5 - 3.0 ml	3.0 - 4.5 ml
1	2.4 (0.1 - 3.6)	0.3 (0.2 - 0.3)	0.1 (<1 - 0.3)
2	2.9 (<1 - 4.6)	0.2 (0.1 - 0.3)	0.02 (0.02 - 0.04)
11	2.8 (1.0 - 4.0)	0.3	0.2 (0.1 - 0.4)
38	9.1 (5.7 - 13.3)	0.9 (0.6 -1.5)	0.8 (0.1 - 2.2)

solid state GE(Li) detector. Generators containing between 10 and 60mCi of W-178 were eluted exhaustively until W-178 breathrough rose to unacceptable levels.

Biological Purity

All generators are checked for the presence of pyrogens and bacterial contamination. Samples for testing are taken without passage through the 0.22m filter used during the routine elution. Both the pyrogen test and sterility test are performed in accordance with USPXX protocols (9). The limulus test for pyrogens was performed concurrently with the USP pyrogen test.

Summary

The current generator is based on exchange on a strongly basic anion exchanger. The effect of HCl normality and H_2O_2 concentration on tantalum yield and tungsten breakthrough has previously been studied (4). It has been determined that eluting the generator column with 0.1N to 0.15N HCl produces sufficient yields of Ta-178. Using more concentrated acid solutions shortens the usable life of the generator by lowering the distribution coefficient (K) of tungsten for the resin, thereby increasing parent breakthrough. The presence of 0.1% to 0.1% hydrogen peroxide in the eluting solution has been found effective in reducing tungsten breakthrough. The breakthrough increases with increased usage. This limits the number of elutions to approximately 40 at which time the generator requires rebuilding.

Under controlled conditions, the current generator system can reliably provide diagnostically useful quantities of Ta-178 in physiologically-acceptable solutions. The maximum concentration of stable tantalum detected is 200ppb, an equivalent of 0.0003mg Ta per elution. This is more than 10^6 times lower than the LD_{50} (30mg/kg i.p in the rat) for tantalum as determined by Cochran, et al, (14). At a concentration of 13.3 ppm one elution would contain 0.020 mg of trimethylamine, which is more than 10^6 times lower than the LD_{50} for trimethylamine (325 ng/Kg i.v. in the mouse) (15). Planned clinical trials using the multiwire proportional camera will determine the utility of this short-lived radionuclide in cardiovascular nuclear medicine.

Ta-178 COUNT RATE LIMITATIONS OF GAMMA CAMERAS:

An important consideration for the future commercial development of W/Ta generators is the use of Ta-178 with other cameras as well as the MGC. Good quality images were reported with high energy collimators using Anger and multicrystal collimators. Ta-178 however has a low abundance of high energy photons (0.5 MeV, 2.1%, 1175-1772 MeV, 4%) that can penetrate the collimator thus lowering the count rate response. A study using GE and Baird atomic cameras was undertaken to define this limitation. The methodology and results of this investigation were published in the Journal of Radiology, a copy of which is contained in Appendix II. We found that as the thickness of the multicrystal collimators increased from 1.0inch to 2.5 inches, septal penetration was reduced. However, the sensitivity to 54-65 KeV

photons was also reduced. Therefore, increasing the thickness of the collimator did not improve camera performance. Since the principle use of the multicrystal camera is for producing high count-rate first pass cardiac studies, the significant decrease in the maximum achievable count rate, limits the usefulness of Ta-178 with this device.

As with the multicrystal camera, the Anger camera demonstrates severe count rate degradation at count rates above about 30Kcps. However, since imaging with an Anger camera rarely exceeds 20Kcps the count-rate limitation may not be critical in most cases. The main limitation is the requirement for medium or high energy collimators. In certain situations where the need for repeat studies or low radiation exposure outweighs the disadvantages of these collimators, Ta-178 may be the agent of choice.

ALTERNATE GENERATOR COLUMN STUDIES:

Background

The tungsten-178/tantalum-178 radionuclide generator has been used by our laboratory for initial clinical trials in humans. It has proven useful for clinical research and testing. However, the current limitations of this system will probably preclude its widespread use particularly where applications require larger generators with, for example, 300-500 mCi. This problem has prompted us to investigate a number of alternatives to the current column, including the use of an inorganic adsorbent.

Neirinckx et al. have studied the behavior of W-178 and Ta-178 on various inorganic adsorbers without succeeding in developing a pharmaceutically acceptable system (16). We have continued the search for such a system, beginning by defining the functional parameters of the so-called "working" system (Bio-Rad's AG1-X8 and 0.15N HCl, 0.1% H_2O_2), to provide a means of evaluating other potential systems. We also studied the behavior of W-178 with similar organic resins under identical conditions and tried to modify it by changing the halide complex of tungsten. Our final objective was to study the behavior of tungsten on potential inorganic adsorbers.

The following solid phases were tested: AG1-X8, AG1-X4, AG2-X8, AGMP-1, AMP-1, BIOGEL HTP (Bio-Rad Laboratories); controlled pore glass beads (CPG) CPG/THIOL, CPG/DAE Glycophase, CPG/Aminopropyl Aminoethyl (Pierce Chemical Co.); barium sulfate, bismuth oxide, lanthanum oxide, lead oxide, zinc oxide, zinc sulfide (Aldrich Chemical Co.); and zirconium tungstate (Alfa Chemical Co.)

The following liquid phases were tested: 0.15N HCl, 0.1% H_2O_2; 0.1M sodium thiosulfate; 0.1M sodium nitrate; 0.9% sodium chloride; distilled water; 0.1M dibasic sodium phosphate; 0.1M citric acid; and sodium fluoride solutions of varying concentrations.

Determination of the Distribution Coefficient (K_d)

We intended to determine by batch equilibration the distribution coefficient of tungsten for a solid/liquid system under controlled conditions. This would give us an index of affinity, or how strongly tungsten is held by the solid phase. This was done by equilibrating approximately 100 mg of solid phase with 5 g of liquid phase for approximately 0.5 h. In most cases 100 mg of material was placed in a 15 ml Falcon tube and equilibrated 3 times with 5 g of liquid phase. The final system was therefore 100 mg of solid phase and 5 g of liquid phase. To this system, 100 µl of a W-178 solution (10-30 µCi) was added. Each system was done in triplicate. The W-178 was carrier-free in a solution of 0.15N HCl, 0.1% H_2O_2. The tungsten solution used in these experiments was purified from a tantalum target as described elsewhere (17).

After the W-178 was added, the system was closed and mixed for 0.5 h on a Nutator mixer. The tubes were then centrifuged at 1500 rpm for 10 min in an IEC/Damon UV centrifuge. Immediately after centrifugation an aliquot of the liquid phase was counted for 0.1-1 min in a 2 inch NaI(Tl) well crystal coupled to a multichannel analyzer. The early counts were used to check the affinity of Ta-178 for the solid phase in question but were not used for determination of Ta-178 K_d's. From the difference between the early counts and the later counts taken after all the Ta-178 unassociated with W-178/Ta-178 equilibrium had decayed, we were able to estimate reasonably well the affinity of Ta-178 for a given solid phase. Tungsten K_d's were calculated using the x-ray emissions of W-178 and Ta-178 in equilibrium, allowing 2 h or more for decay of unassociated Ta-178 before counting. The percent W-178 per gram of solid and liquid phase was determined and the distribution coefficient calculated as

$$\frac{\text{concentration of W-178 in solid phase}}{\text{concentration of W-178 in liquid phase}}, \text{ or}$$

$$K_d = \frac{\text{percent W-178 in solid phase}}{\text{percent W-178 in liquid phase}} \times \frac{\text{volume of liquid phase}}{\text{mass of solid phase}}$$

Organic Resins

We first studied the behavior of W-178 on organic resins. The generator system we use in our laboratory is comprised of Bio-Rad's AG1-X8 (a divinyl benzene copolymer resin with quaternary ammonium functional groups covalently bound to the matrix) as the solid phase and 0.15N HCl, 0.1% H_2O_2 as the mobile or liquid phase. We performed K_d experiments with this system to determine its "working behavior" and to try to reproduce K_d values for W and Ta affinities in the literature (18). We studied the behavior of W-178 on several related solid phases in order to understand the binding mechanisms. We also investigated different functional groups and complexes of tungsten in an effort to improve the properties of the system.

Table 8 summarizes the W-178 K_d's obtained with 5 organic resins using 0.15N HCl, 0.1% H_2O_2 as the liquid phase. There is a pattern of decreasing K_d with increasing crosslinkage. Since the active group for AG1 and Dowex1 is the same, $R\text{-}CH_2N(CH_3)_3$, as is the ionic form (chloride), the difference in behavior is probably due to the variation in percent crosslinking. Crosslinkage affects a number of resin characteristics. Highly crosslinked resins have higher wet volume capacities and are more resistant to shrinking or swelling. They are also less permeable to large molecules, exhibit slower equilibration rates and have smaller hydrated diameters. Low crosslinkage resins demonstrate the opposite characteristics. It is possible that the increased permeability and faster equilibrium rates account for the greater affinity W-178 displays for lower crosslinked resins. The wet volume capacity is probably of negligible importance at the tracer level and therefore a resin's ability to swell would be relatively unimportant. The effect of hydrated diameter on the K_d value is unclear.

TABLE 8--Behavior of W-178 in 0.15N HCl, 0.1% H_2O_2 on various organic anion exchangers.

Solid phase	Characteristics	K_d
AG1-X4	Strongly basic (AG1), with quaternary ammonium group, 4% crosslinkage	161
AG1-X8	Same as above, 8% crosslinkage	100
DOWEX1-X10	Same as above, 10% crosslinkage, greater variation in particle size	88
AGMP-1	A macroporous exchanger chemically equivalent to AG1, more rigid structure, 20% crosslinkage	71
AG2-X8	Slightly less basic than AG1, 8% cross-linkage	213

The behavior of W-178 on AG2-X8 compared to its behavior on AG1-X8 is interesting. Tungsten displays a K_d value twofold greater for AG2-X8 than for AG1-X8, using 0.15N HCl, 0.1% H_2O_2 as the liquid phase. The functional groups for these resins are

AG1-X8 $R-CH_2-N^+-(CH_3)_3Cl^-$
AG2-X8 $R-CH_2-N^+-(CH_3)_2(C_2H_4OH)Cl^-$

The polystyrene resin matrix (R) is the same for both as is the percent crosslinkage. AG2 is slightly less basic than AG1 and is excellent for removing hydroxide ions from aqueous solutions (19). The increased affinity of W-178 for AG2 relative to its affinity for AG1 may be due to the softness of the functional group and the corresponding stability of the ionic bond formed. The ability of AG2 to remove hydroxide ions from solution may be a factor in the increasing K_d if the chemical formula for tungsten in solution, which Neirinckx et al. proposed [$W(OH)_3Cl$], does in fact exist (18). The ability of the hydroxyl groups to interact (i.e., form ionic bonds) with the functional group of AG2 may therefore enhance the affinity of tungsten for AG2 over AG1.

Effect of Iodide Complex Formation on K_d

It is known that I^- has a relative selectivity of 175 for AG1-X8, using OH^- as a standard of 1.0. Chloride ion (Cl^-) has a relative affinity of 22 (19). With this in mind we prepared an iodide complex of W-178 in an effort to determine the effect of this halide on the distribution coefficient of tungsten for AG1-X8. It has been demonstrated by Ehrhardt et al. that forming an iodide complex of cadmium ($CdCl_4^-$) increased the K_d of this radionuclide for AG1-X8 (20).

To prepare an iodide complex of tungsten, we combined equal volumes of W-178 in 0.15N HCl, 0.1% H_2O_2; and a saturated solution of potassium iodide in a plastic tube and heated at 100° for 15 min and then let the mixture stand, well capped, for 24 h. For K_d determination we used 100 ul of the W-I mixture and added it directly to dry AG1-X8 resin (~100 mg). This was mixed by hand for 10 min to wet as much of the resin as possible. We then added 5 g of liquid phase (HCl/H_2O_2) and mixed for 30 min. A control containing the same amounts of W-I solution and liquid phase was prepared. The tube containing the resin was centrifuged to sediment the resin particles from the liquid phase, and an aliquot of the liquid phase was counted against the control.

Our results show a significant increase in the affinity of the tungsten iodide complex for the AG1-X8 resin (Table 9), although they are not indicative of a great increase in practical generator performance.

TABLE 9--Behavior of tungsten-iodide complex on AG1-X8.

Complex	Liquid phase	K_d	S.D.
Chloride	HCl/H_2O_2	100	± 1.63
Iodide	HCl/H_2O_2	112	± 2.16

We also examined how the order of addition of chemicals would affect K_d values when using iodide complexes. All systems contained 100 µl of W-I complex, 5 ml of 0.15N HCl, 0.1% H_2O_2 and approximately 100 mg of AG1-X8, in the final stage. Appropriate controls were prepared for each solution of tungsten. For this experiment all solid phases were pre-equilibrated with the liquid phase three times before the addition of the tungsten solutions or the final liquid phase. Five ml of liquid phase (0.15N HCl, 0.1% H_2O_2) were added to two tubes containing ~ 100 mg of AG1-X8 and the phases were mixed well for 5 min before adding 100 µl of W-178 solution in 0.15N HCl, 0.1% H_2O_2 and as iodide complex. A third tube, containing 100 mg of AG1-X8, was drained of excess liquid phase after equilibration, and 100 µl of the tungsten-iodide complex were added. All three tubes were allowed to equilibrate for 0.5 h. Table 10 summarizes the results of this experiment.

TABLE 10--Effect of order of addition of liquid phase (0.15N HCl/0.1% H_2O_2) and W-halide complex on K_d of the complex on AG1-X8.

Order of addition of W-178	W-complex	~K_d	Actual K_d
After liquid phase	Chloride	100	80
After liquid phase	Iodide	106	85
Before liquid phase	Iodide	113	113

Whether the tungsten-iodide complex was added before or after the liquid phase, it had a greater affinity for AG1-X8 than did tungsten-chloride. These results are not conclusive, however, because concentration may enhance binding of tungsten.

Reproducibility and Stability of W-178

During the course of our work we have noted that the affinity of W-178 for most solid phases decreases with time. We have used AG1-X8 as a reference to follow the change in K_d with time. Our initial determinations gave us a value of 100 as the K_d of W-178 for AG1-X8 in 0.15N HCl, 0.1% H_2O_2. This agrees with the value reported by Neirinckx et al. (18) Twelve days later, under similar conditions (liquid phase, solid phase, equilibration times), W-178 displayed a K_d of 80 for AG1-X8.

In an effort to "rejuvenate" the solution of W-178, we "reprocessed" it according to a protocol described previously. Briefly, the W-178 solution was evaporated almost to dryness in a Teflon beaker. To this, 5 ml of concentrated HCl was added and evaporated almost to dryness, and the procedure was repeated. Then 5 ml of 0.15N HCl was added and again evaporated almost to dryness, and this step was repeated twice. Finally the W-178 activity was taken up in 0.15N HCl, 0.1% H_2O_2, giving rise to a clear solution of W-178.

Using the "reprocessed" W-178 solution, we repeated the K_d experiments, using 0.15N HCl, 0.10 H_2O_2, and AG1-X8. The experiment was run in triplicate with two controls. We obtained K_d values of 97, 93 and 95 ($x = 95 \pm 2$). Although these values were lower than those determined initially, we have shown that the W-178 solution can be "rejuvenated" to increase its affinity for AG1-X8. The K_d of W-178 with other adsorbers and resins also decreased on standing.

Behavior of W-178 on Various Inorganic Adsorbers

One of our major objectives was to investigate a number of inorganic adsorbers which might be desirable as generator column components because of their radioresistance and lack of potential organic contaminants.

Neirinckx et al. (16) studied the behavor of tungsten on a variety of inorganic adsorbers including alumina, silica gels, numerous hydrous oxides, oxides and insoluble salts of heteropolyacids. We tested oxides, sulfides, precipitated phosphates and insoluble salts of heteropolyacids not included in Neirinckx's work. These included hydroxyapatite, ammonium molybdophosphate (Bio-Rad), zirconium tungstate (Alfa Products), zinc sulfide, zirconium oxide, zinc oxide, lead oxide, lanthanum oxide, bismuth oxide, barium sulfate (Aldrich Chemical Co.), and controlled pore glass beads with covalently bonded functional groups: CPG-THIOL, CPG-DAE Glycophase and CPG-Aminopropyl Aminoethyl (Pierce Chemical Co.)

Insoluble oxides and hydrous oxides were of interest because of their properties of high capacity anion exchange. Anion or cation exchange by oxides and hydrous oxides is known to occur predominantly by displacement of hydrogen and hydroxide ions from the sorbents, provided that these have been washed free of impurity ions. The amphoteric reactions of hydroxyl groups are responsible for the adsorbers' ion exchange characteristics; predominant functional groups are probably metal hydroxide bonds (21).

Except for ZrO, none of these metal oxides showed a substantial affinity for tungsten in this liquid phase (Table 11). In most cases these solid phases demonstrated greater or similar affinity for Ta-178. Zirconium oxide bound tantalum strongly in HCl/H_2O_2. Because of its high affinity for W-178, it was tested with other liquid phases. Maeck et al. studied the adsorption of metals on inorganic ion exchangers in nitrate media (22). Their data show strong retention of W on ZrO at a pH more acidic than 3 ($K_d > 10^4$). Tantalum at pH 3 exhibits a $K_d \sim 10^2$ and at pH 1 a K_d of $\sim 10^{1.5}$. We investigated the behavior of W-178 on ZrO in $NaNO_3$ solution at pH 1. In this system, W-178 displayed a K_d greater than 6,000. Unfortunately, Ta was also strongly bound. In an attempt to separate W from Ta (i.e., reduce the K_d of Ta), small quantities of NaF were added. Fig. 3 shows the effect of increasing amounts of NaF on the K_d of W-178. Tantalum behaved similarly.

TABLE 11.--Affinity of W-178 for metal oxides in 0.15N HCl, 0.1% H_2O_2.

Solid phase	K_d	Affinity for Ta
Zirconium oxide	1800	Yes >>
Zinc oxide	2	Yes >>
Bismuth oxide	20	Yes
Lead oxide	< 1	No
Lanthanum oxide	15	Yes

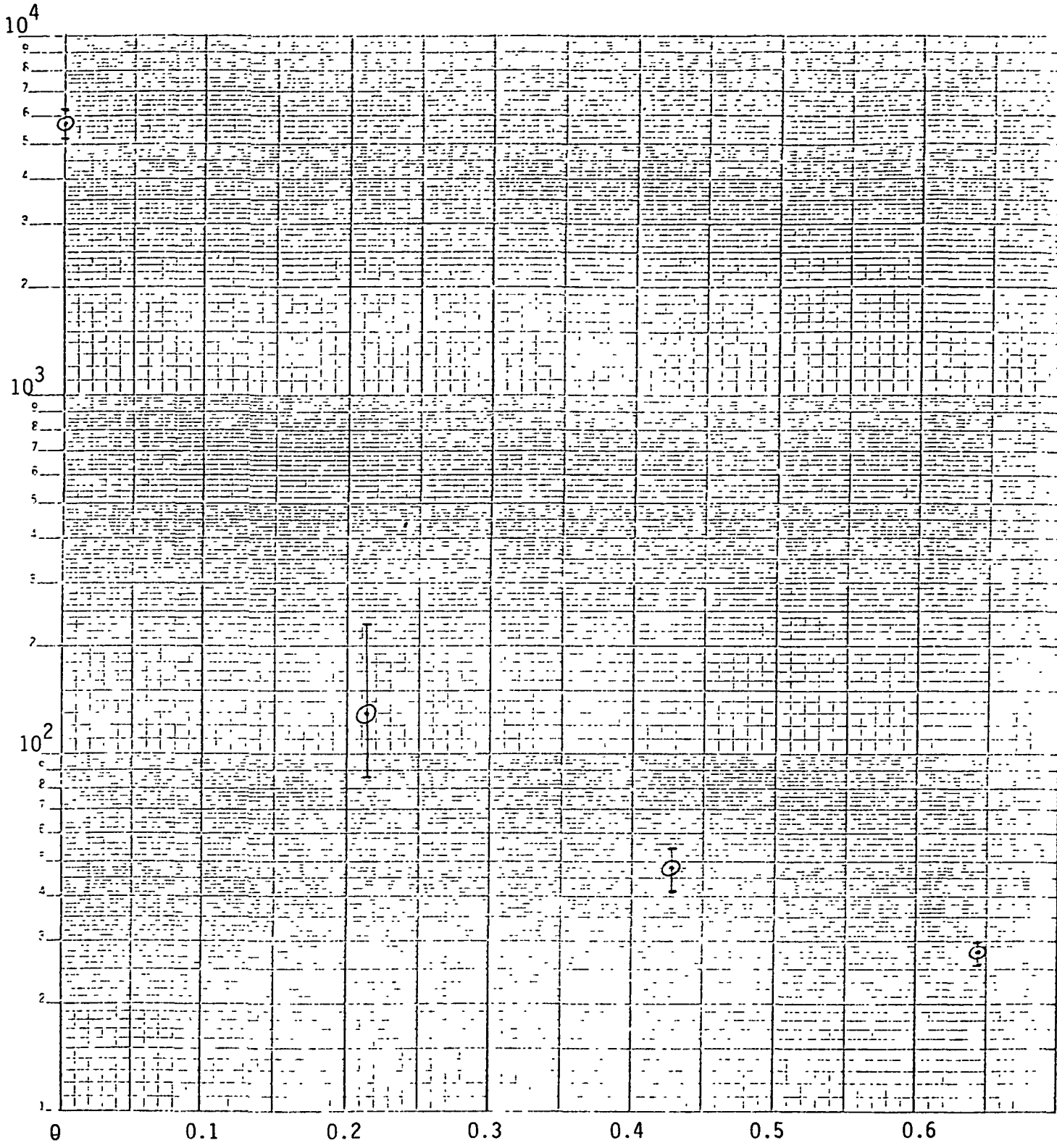


Figure 3.

K_D of Tungsten - 178 for Zirconium Oxide in 0.1 M Na Nitrate pH 1 ; with varying concentrations of NaF, n = 3.

We continued our search for suitable inorganic adsorbers by examining the behavior of W-178 on the heteropolyacid salt ammonium molybdophosphate, zirconium tungstate (a combination of an acid oxide of a tetravalent metal with a polyvalent anion), zinc sulfide and barium sulfate (Table 12).

TABLE 12--The behavior of W-178 on various inorganic adsorbers with HCl/H_2O_2 as the liquid phase.

Solid phase	K_d
Ammonium molybdophosphate	1100
Zirconium tungstate	24
Zinc sulfide	< 2
Barium sulfate	< 1

Of this group only ammonium molybdophosphate (AMP-1) displayed a high affinity for W-178. This material also showed a relatively low affinity for Ta-178. We estimated that approximately 18% of the available tantalum was found in the liquid phase (as we had no pure, long-lived isotopes of tantalum, we could not perform K_d calculations for Ta with this system). This looked quite promising, as the available tantalum which was in the liquid phase of AG1-X8 and related resins was about 20%.

Not having a suitable Ta isotope for determining a K_d, we constructed a generator column with AMP-1. Unfortunately, the material is microcrystalline and when packed in a column effectively blocks supporting frits and displays poor flow characteristics. There is a way of increasing the flow, but it requires a covalent attachment to silica gel that is not feasible. Further work in this area may prove fruitful if the characteristics of AMP-1 are unchanged when it is bound to a second solid phase.

Behavior of W-178 on Hydroxylapatite

W-178 is selectively retained in the bones of animals we have studied (23). Therefore we hypothesized that a material which is chemically similar to bone may in fact show this selective binding. We used Bio-Rad's Biogel HTP (hydroxylapatite) as the solid phase and a non-chelating buffer at pH 8.5. This system had a K_d for W of ~28, with a much greater affinity for Ta than for W.

Controlled Pore Glass Beads with Various Functional Groups

All of the previously described inorganic systems failed to give us a suitable replacement for the organic resin based system (Bio-Rad's AG type). We therefore sought functional groups similar to those of the organic resin but with inorganic solid support. Leyden et al. reported that W, as tungstate at the nanogram level, may be recovered from saline solution using controlled pore glass beads (CPG) treated with N-β-aminoethyl-γ-aminopropyl trimethoxysilane (24). Maximum adsorption occurred in a pH range between 4 and 5 (100%). Our efforts to reproduce this work with carrier-free tungsten as a heteropolyanion gave a K_d value of about 9. This corresponds to approximately 90% of the W being bound to the adsorber (gram:gram basis).

We studied CPG supports with other functional groups in hopes of achieving greater W-178 binding. The second CPG studied was CPG/QAE (quaternary trimethylammonium chloride). (AG1 has a trimethylammonium functional group). We performed K_d experiments using CPG/QAE and 0.15N HCl, 0.1% H_2O_2. The K_d was approximately 18, significantly lower than those with AG1 or AG2.

The last CPG exchanger to be studied was CPG/THIOL. CPG/THIOL contains a covalently attached hydrocarbon extension arm, terminating in a free reactive thiol group. These free thiol groups have been used to remove heavy metals from solution (25). We studied CPG/THIOL in various liquid phases with interesting results. Table 13 summarizes the behavior of W-178 on CPG/THIOL in various liquid phases.

TABLE 13--Behavior of W-178 on CPG/THIOL in various liquid phases.

Liquid phase	K_d
0.15N HCl, 0.1% H_2O_2	158
0.1M $NaNO_3$	638
0.1M $Na_2S_2O_3$	937
0.9% NaCl	2,558
Distilled water	8,639

CPG/THIOL shows great potential as an inorganic adsorber for W-178. All liquid phases tested demonstrate higher K_d values than the "working system" based on AG1-X8. From our estimations it seems all combinations tested have a higher affinity for W than Ta, and except for distilled H_2O, all have significantly less affinity for Ta.

Summary

We have reproduced the K_d values found in the literature for the "working" W-178/Ta-178 generator column. We have found that the W-178 solution purified from a Ta foil irradiated with protons shows a decreasing affinity for the AG1-X8 resin over time, when it is allowed to stand in dilute HCl. We were able to "rejuvenate" this solution by reprocessing to attain K_d values similar to those found with freshly processed material.

Our study of W-178 behavior on the AG1 and AG2 type resins (Bio-Rad) showed the effects of crosslinkage and degree of basicity on K_d. The AG1 type resins demonstrated greater K_d values (AG1-X4: 161, AG1-X8: 100) with lower crosslinkage. The AG2 type resin, with a weaker basic functional group, had a greater K_d (213) than AG1-X8 with similar crosslinkage, probably because of the ability of this resin to scavenge hydroxyl ions. From these results one could conclude that the optimal organic system would in fact be AG2-X8 or AG2-X4 in 0.15N HCl, 0.1% H_2O_2.

The limited experimentation with iodide complexes of W-178 and the uncertainty of the chemical species does not allow us to form strong conclusions about the usefulness of this halide complex. It does, however, warrant further investigation with particular emphasis on long-term stability of the complex.

Of the inorganic materials studied, excluding the CPG's, only zirconium oxide and ammonium molybdophosphate (AMP) showed high affinity for W-178. Zirconium oxide may be suitable as an adsorber if a liquid phase can be found which forms stable complexes with Ta-178, thereby allowing it to come into solution and pass through the column; oxine (8-hydroxyquinoline) may be useful as such an agent. Ammonium molybdophosphate also showed great potential, strongly binding W-178 without a strong affinity for Ta-178. Unfortunately, the flow characteristics of AMP when it is packed in a column are poor. Changing the AMP by covalently attaching it to a larger diameter inert support may severely alter the adsorption characteristics by greatly reducing the surface area. Further work in this area is warranted.

The testing of hydroxylapatite as an adsorber because of the long-term retention of W-178 in bone was a long shot which did not pay off in the liquid phase used (buffer pH 8.5) because of the high affinity of hydroxylapatite for Ta-178. The factors involved with in vivo localization are complex and not altogether understood, but our results (K_d ~28) showed that on a gram per gram basis (liquid to solid phase), ~96-97% of the W-178 was bound to hydroxylapatite. Further work with various liquid phases may show interesting results.

Controlled pore glass beads gave the most interesting results. Although the amino based functional groups were the most chemically similar to the AG1 and AG2 type resins, neither displayed affinity for W-178 to a great degree. Our study of W-178 on CPG/THIOL with various liquid phases was most promising. In all the liquid phases studied, W-178 showed a high affinity for the solid phase and when our initial counts were compared to later counts, Ta-178 seemed to display a substantially

lower affinity for these solid phases. Further work is warranted with various liquid phases and long lived isotopes of tantalum, as well as freshly processed W-178 solutions for the construction of trial generators.

SUMMARY:

Extensive research of different absorbents and eluents by both E.R. Squibb and Sons and by Baylor College of Medicine failed to demonstrate an exchange column superior to the Bio-Rad AG1-X8 resin eluted with dilute hydrochloric acid and hydrogen peroxide. Significant improvement in the original processing and column preparation were achieved resulting in an approved IND for human use after extensive safety and efficacy testing in animals. The first testing of Ta-178 in humans was conducted using the NASA developed multiwire gamma camera. These studies documented the theoretical advantages of Ta-178 and the MGC for radionuclide angiography including reduced patient radiation exposure. This latter point is extremely important to NASA because of additional exposure received during spaceflight. These basic studies have been sufficiently successful that Mallinckrodt's Diagnostic Products Division has agreed to supply processed columns to continue the research at Baylor College of Medicine.

REFERENCES

1. Neirinckx RD, Holman BL, Davis MA, et al: Tantalum-178 Labeled Agents for Lung and Liver Imaging. J. Nucl. Med. 20:1176-1180, 1979.

2. Holman BL, Neirinckx RD, Treves S, et al: Cardiac Imaging with Tantalum-178. Radiology 137:525-526, 1979.

3. Holman BL, Harris GL, Neirinckx RD, et al: Tantalum-178. A Short-lived Nuclide for Nuclear Medicine: Production of the Parent W-178. J. Nucl. Med. 19:510-513, 1978.

4. Neirinckx RD, Jones AG, Davis MA, et al: Tantalum-178 - A New Short-Lived Nuclide for Nuclear Medicine: Development of Potential Generator System. J. Nucl. Med. 19:514-519, 1978.

5. Neirinckx RD, LeBlanc A, Vogel M, et al: W-178 - Ta-178 Generator: A Study of Chromatographic Behavior of Tungsten and Tantalum on Inorganic Adsorbents. Presented at the 3rd International Symposium on Radiopharmaceuticals, Julich, Germany, 1982.

6. Neirinckx RD, Ku TH, Holman BL, et al: Production and Purification of Tungsten-178. Int. J., Appl. Radiat. Isot.: 30:341-343, 1979.

7. Nuclear Data Sheets, National Academy of Sciences, National Research Council, Academic Press, New York and London.

8. Lederer CM, Shirley VS, eds. Table of Isotopes John Wiley & Sons, Inc. New York, 1978.

9. The Pharmacopeia of the United States of America, 20th Revision. Mack Publishing Co, Easton, PA 1980. pp. 902-903, 878-882.

10. Loevinger R, Berman M: A Revised Schema for Calculating the Absorbed Dose from Biologically Distributed Radionuclides. MIRD pamphlet No. 1, Revised. New York, Society of Nuclear Medicine, March, 1976.

11. Snyder WS, Ford MR, Warner GG: Estimates of Specific Absorbed Fractions For Photon Sources Uniformly Distributed in Various Organs of a Heterogenous Phantom. MIRD pamphlet No. 5, Revised. J. Nucl. Med., 1978.

12. Tantalum-178 ($T_{\frac{1}{2}}$ 9.3m) "Output" decay data, courtesy of Mary R. Ford, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

13. LeBlanc AD, Lacy J, Johnson P, et al: Ta-178 Count Rate Limitations of Anger and Multcrystal Cameras. Radiology 146:242-243, January 1983.

14. Cochran KW, Doull J, Mazor M, et al: Acute Toxicity of Zirconium, Colubium, Strontium, Lanthanum, Cesium, Tantalum and Yttrium. Arch. Ind. Hyg. Ocup. Med. 1, 637-650, 1950.

15. Fairchild EJ, Lewis RJ, Tatken RL: Eds. Registry of Toxic Effects of Chemical Substances. Vol. I & II, 1977 Edition DHEW Publ. No. (NIOSH) 78-104-B.

16. Neirinckx RD, et al: In Proceedings of the American Chemical Society Symposium on Ultra Short-Lived Radionuclide Generators, 1983.

17. Neirinckx RD, et al: Int. J. Appl. Rad. Isot. 30:341-343, 1979.

18. Neirinckx RD, et al: J. Nucl. Med. 19:514-519, 1978.

19. Bio Rad Laboratories, Catalog K, 6-14, 1985.

20. Erhard GJ, et al: J. Nucl. Med. 24:349-352, 1983.

21. Fuller MJ, Chromatography Rev. 14:45, 1971.

22. Maeck WJ, et al: Anal. Chem. 35:13, 2086-90.

23. Babich JW, et al: J. Nucl. Med. 24:122, 1983.

24. Leyden DE, et al: Anal. Chem. 48:1, 67-70.

25. Pierce Chemical Co., Handbook 211, March 1983.

APPENDIX I

I N D

APPENDIX: 1

Notice of Claimed Investigational Exemption

for a New Drug (IND)

Submitted to Food and Drug Administration

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Use of this form is prohibited after [illegible]

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

NOTE No drug may be shipped or study initiated unless a complete statement has been received (21 CFR 312.1(a)(2))

Name of Sponsor Technology Inc., Life Science Division

Address 17625 El Camino Real Suite 311 Houston, Tx. 77058

Date July 1, 1982

Name of Investigational Drug Tantalum-178 as a sterile, pyrogen-free, buffered solution for intravenous injection.

To the Secretary of Health, Education and Welfare
For the Commissioner of Food and Drugs
Bureau of Drugs (HFD-106)
5600 Fishers Lane
Rockville, Maryland 20857

Dear Sir

The sponsor, Technology Incorporated, Life Science Division, submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and §312.1 of Title 21 of the Code of Federal Regulations.

Attached hereto in triplicate are

1 The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered (If the drug has only a code name, enough information should be supplied to identify the drug.)

2 Complete list of components of the drug including any reasonable alternates for inactive components

3 Complete statement of quantitative composition of drug including reasonable variations that may be expected during the investigational stage

4 Description of source and preparation of, any new-drug substances used as components, including the name and address of each supplier or processor other than the sponsor, or each new-drug substance

5 A statement of the methods, facilities, and controls used for the manufacturing processing and packing of the new drug to establish and maintain appropriate standards of identity strength quality, and purity as needed for safety and to give significance to clinical investigations made with the drug

6 A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows

a Adequate information about the preclinical investigations including studies made on laboratory animals on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug Such information should include identification of the person who conducted each investigation identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection Enough details about the investigations to permit scientific review The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing When this information the outline of the plan clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified The Food and Drug Administration will be prepared to confer with the sponsor concerning this action

b If the drug has been marketed commercially or investigated (e.g. outside the United States) complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug

c If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigations and experience with its components including all reports available to the sponsor suggesting side-effects contraindications and ineffectiveness in use of such components Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration Include a statement of the expected pharmacological effects of the combination

d If the drug is a radioactive drug, sufficient data must be available from animal studies or previous human studies to allow a reasonable calculation of radiation absorbed dose upon administration to a human being

7 A total (one in each of the three copies of the notice) of all informational material, including label and labeling which is to be supplied to each investigator This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications side-effects and precautions suggested by prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators

8 The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken

9 The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and effectiveness of the drug as it is received from the investigators together with a statement that the sponsor has obtained from each investigator a completed and signed form as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to undertake the phase of the investigation outlined in section 10 of the "Notice of Claimed Investigational Exemption for a New Drug." (In crucial situations phase 1 investigators may be added and this form supplemented by rapid communication methods and the signed form FD-1571 shall be obtained promptly thereafter.)

10 An outline of any phase or phases of the planned investigations and a description of the institutional review committee as follows:

a Clinical pharmacology. This is ordinarily divided into two phases. Phase 1 starts when the new drug is first introduced into man; only animal and in vitro data are available; with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range. phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. A general outline of these phases shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will be undertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience gained need be reported only in the progress reports on these early phases, or in the development of the plan for the clinical trial phase 3. The first two phases may overlap and, when indicated, may require additional animal data before these phases can be completed or phase 3 can be undertaken. Such animal tests shall be designed to take into account the expected duration of administration of the drug to human beings, the age groups and physical status, as for example, infants, pregnant women, premenopausal women, of those human beings to whom the drug may be administered, unless this has already been done in the original animal studies. If a drug is a radioactive drug, the clinical pharmacology phase must include studies which will obtain sufficient data for dosimetry calculations. These studies should evaluate the excretion, whole body retention, and organ distribution of the radioactive material.

b. Clinical trial. This phase 3 provides the assessment of the drug's safety and effectiveness and optimum dosage schedules in the diagnosis, treatment or prophylaxis of groups of subjects involving a given disease or condition. A reasonable protocol is developed on the basis of the facts accumulated in the earlier phases, including completed and submitted animal studies. This phase is conducted by separate groups following the same protocol (with reasonable variations and alternatives permitted by the plan) to produce well-controlled clinical data. For this phase, the following data shall be submitted:

i. The names and addresses of the investigators. (Additional investigators may be added.)

ii. The specific nature of the investigations to be conducted, together with information or case report forms to show the scope and detail of the planned clinical observations and the clinical laboratory tests to be made and reported.

iii. The approximate number of subjects (a reasonable range of subjects is permissible and additions may be made) and criteria proposed for subject selection by age, sex, and condition.

iv. The estimated duration of the clinical trial and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration.

c. Institutional review committee. If the phases of clinical study as described under 10a and b above are conducted on institutionalized subjects or are conducted by an individual affiliated with an institution which agrees to assume responsibility for the study, assurance must be given that an institutional review committee is responsible for initial and continuing review and approval of the proposed clinical study. The membership must be comprised of sufficient members of varying background, that is, lawyers, clergymen, or laymen as well as scientists, to assure complete and adequate review of the research project. The membership must possess not only broad competence to comprehend the nature of the project, but also other competencies necessary to judge the acceptability of the project or activity in terms of institutional regulations, relevant law, standards of professional practice, and community acceptance. Assurance must be presented that neither the sponsor nor the investigator has participated in selection of committee members, that the review committee does not allow participation in its review and conclusions by any individual involved in the conduct of the research activity under review (except to provide information to the committee), that the investigator will report to the committee for review any emergent problems, serious adverse reactions, or proposed procedural changes which may affect the status of the investigation and that no such change will be made without committee approval except where necessary to eliminate apparent immediate hazards, the reviews of the study will be conducted by the review committee at intervals appropriate to the degree of risk, but not exceeding 1 year, to assure that the research project is being conducted in compliance with the committee's understanding and recommendations, that the review committee is provided all the information on the research project necessary for its complete review of the project, and that the review committee maintains adequate documentation of its activities and develops adequate procedures for reporting its findings to the institution. The documents maintained by the committee are to include the names and qualifications of committee members, records of information provided to subjects in obtaining informed consent, committee discussion on substantive issues and their resolution, committee recommendations, and dated reports of successive reviews as they are performed. Copies of all documents are to be retained for a period of 3 years past the completion or discontinuance of the study and are to be made available upon request to duly authorized representatives of the Food and Drug Administration. (Favorable recommendations by the committee are subject to further appropriate review and rejection by institution officials. Unfavorable recommendations, restrictions, or conditions may not be overruled by the institution officials.) Procedures for the organization and operation of institutional review committees are contained in guidelines issued pursuant to Chapter 1-40 of the Grants Administration Manual of the U.S. Department of Health, Education, and Welfare, available from the U.S. Government Printing Office. It is recommended that these guidelines be followed in establishing institutional review committees and that the committees function according to the procedures described therein. A signing of the Form FD-1571 will be regarded as providing the above necessary assurances. If the institution, however, has on file with the Department of Health, Education, and Welfare, Division of Research Grants, National Institutes of Health, an "accepted general assurance" and the same committee is to review the proposed study using the same procedures, this is acceptable in lieu of the above assurances, and a statement to this effect should be provided with the signed FD-1571. (In addition to sponsor's continuing responsibility to monitor the study, the Food and Drug Administration will undertake investigations in institutions periodically to determine whether the committees are operating in accord with the assurances given by the sponsor.)

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the additional phase or phases is submitted before such additional phases begin. This does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records for each subject maintained to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given, and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation.

11 A statement that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor.

12 A statement that the sponsor will notify each investigator if a new drug application is approved, or if the investigation is discontinued.

13 If the drug is to be sold, a full explanation why sale is required and

should not be represented as the commercialization of a new drug for which an application is not approved.

14. A statement that the sponsor assures that clinical studies in humans will not be initiated prior to 30 days after the date of receipt of the notice by the Food and Drug Administration and that he will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days. If such request is made, the sponsor will be provided specific information as to the deficiencies and will be afforded a conference on request. The 30-day delay may be waived by the Food and Drug Administration upon a showing of good reason for such waiver, and for investigations subject to institutional review committee approval as described in item 10c above, and additional statement assuring that the investigation will not be initiated prior to approval of the study by such committee.

15. When requested by the agency, an environmental impact analysis report pursuant to §25.1 of this chapter.

16. A statement that all nonclinical laboratory studies have been, or will be, conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if such studies have not been conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in conducting the study and those required in the regulations.

Very truly yours,

SPONSOR	PER
Technology Inc., Life Science Division 17625 El Camino Real Suite 311 Houston, Tx. 77058	INDICATE AUTHORITY BRANCH MANAGER LIFE SCIENCES DIVISION

(This notice may be amended or supplemented from time to time on the basis of the experience gained with the new drug. Progress reports may be used to update the notice.)

ALL NOTICES AND CORRESPONDENCE SHOULD BE SUBMITTED IN TRIPLICATE.

1. Best Descriptive Name:

Tantalum-178 (T 1/2 = 9.3 min.) as a sterile, pyrogen-free, buffered solution for intravenous injection (pH 6.5). The chemical form of Tantalum in this preparation is most likely $Ta(OH)^{+}_{4}$ (1).

2. Complete List of Components

1. Tantalum Ta-178 as $Ta(OH)^{+}_{4}$
2. 0.1N HCL and 0.1% H_2O_2 solution as eluant
3. Sterile water for injection
4. Dibasic sodium phosphate

3. Quantitative Composition of Drug

1. Tantalum: The quantity of tantalum will vary depending on the activity of the parent Tungsten-178 and the amount of stable tantalum remaining after purification of the tantalum cyclotron target.

Stable Tantalum: Tracer analysis using Argon Emission Plasma Spectroscopy has been used to determine the amount of stable tantalum present in the generator eluant. Results of this test determined the concentration of tantalum to be 198 parts per billion ppb (see Appendix 3).

198 ppb = 1.98×10^{-4} mg/ml

1.98×10^{-4} mg/ml x 1.5 ml per dose =

2.97×10^{-4} mg per dose

0.000297 mg per dose

Contribution of Tantalum-178 to total tantalum:

mCi x dps/mCi x T 1/2 (min) x 60 sec x Avg. Life Factor

1mCi x 3.7×10^{7} x 9.3 min x 60 sec x 1.443 =
2.979×10^{10} disintergrations to complete decay/mCi.

$\frac{2.979 \times 10^{10} \times 178}{6.023 \times 10^{23}} = 8.8 \times 10^{-12}$ grams Ta-178 per mCi.

Stable Hafnium-178

Since Ta-178 decays 100% to Stable Hf-178 the concentration of hafnium will be equal to that of Ta-178 after complete decay thereby yielding: 8.8×10^{-12} grams Hafnium-178.

2. 1.5 ml of a 0.1N HCL, 0.1% H_2O_2 solution

5.469 mg HCL in 1.5 ml 0.1N HCL
1.5 mg H_2O_2 in 1.5 ml 0.1% H_2O_2

3. / 0.5 ml of phosphate buffer pH 9.2

31.9 mg of Na_2HPO_4 in 0.5 ml solution

4. Sources and Purity

1. Tantalum Metal (as a cyclotron target)
Purity 99.979% Reactor Experiments, Inc., 963 Terminal way, San Carlos, California 94070

2. Hydrochloric Acid, AR, (ACS), HCL approximately 37%, Mallinkrodt, Inc., Paris, Kentucky

3. Hydrogen Peroxide 30% (Stabilized), Baker Analyzed Reagent, J.T. Baker Chemical Company, Phillipsburg, New Jersey.

4. Sodium Phosphate Dibasic, AR, (ACS), Anhydrous, Mallinkrodt, Inc. Paris, Kentucky or J.T. Baker Chemical Company Phillipsburg, New Jersey.

5. Sterile Water for Injection, USP, Abott Laboratories, North Chicago, Ill. 60064.

5A. Production and Purification of Tungsten-178 (T 1/2 = 21.5 days)

1. The high purity previously cleaned Tantalum foil is irradiated with protons at Nasa's Lewis Research Center in Ohio. The reaction involved for the production of the parent is Ta-181 (p,4n) W-178 (2). The foil is received in one piece and the process begins with the counting and calibration of the foil activity as well as the spectral identification of the foil activity using a Multichannel Analyzer connected to a NaI(Tl) detector. The foil is cut so that the center most section of the foil containing the greatest concentration of activity is used for the production of the generator. This section of foil is then transfered to a teflon beaker previously sterilized in an autoclave and rinsed with sterile water for injection (SWFI), USP.

2. The Tantalum foil is dissolved in approximately 10 ml of concentrated Hydroflouric Acid (Mallinkrodt, Paris, Kentucky) with approximately 5 ml of HNO_3 added dropwise to the solution while heated at a constant temperature of 150°C.

3. When the metal has totally dissolved the solution is allowed to evaporate to a volume of approximately 2 ml. At this time 10 ml of conc. HF is again added to the evaporate and this solution is again allowed to evaporate down to approximately 2 ml (not quite dryness).

4. Again 10 ml of conc. HF is added to the evaporate and again it is allowed to come down to a volume of 2 ml while on the hot plate.

5. At this time 10 ml of concentrated Hydrochloric Acid is added and again allowed to evaporate down to approximately 2 ml or less.

6. At this time 10 ml of a solution containing 6N HCL and 1.5N HF is added to the evaporate. This is allowed to evaporate to approximately a 2 ml volume. This step is repeated twice.

7. At this time 10 ml of a solution of 6N HCL and 1.5N HF is added to the teflon beaker containing the evaporate and allowed to cool.

8. An ion exchange column is prepared using Anion Exchange Resin AG 1-X8 (BioRad Labs., Richmond, CA). The total capacity of the resin is 3.2 meq/dry gram and 1.4 meq/ml resin bed. An excess of resin is added to a teflon beaker where it is prewashed with distilled water. The water is decanted after the resin has settled and an excess of 6N HCL and 1.5N HF is then added to the resin for equilibration. This HCL + HF solution is decanted and an excess of the HF + HCL solution is again added, mixed gently and allowed to settle. The resin is then loaded on a column 30 cm high x 2.5 cm inside diameter which has been fitted with a teflon wool plug. The total quantity of resin added to the column is 150 ml. The capacity of the resin is therefore 150 ml x 1.4 meq/ml = 210 meq. The weight of the fraction of irradiated target to be processed is less than 10 grams.

$$\frac{181}{2} = \frac{90.5 \text{ mg}}{\text{meq}} \qquad \frac{90.5 \text{ mg}}{\text{meq}} \times 210 \text{ meq} = 19.005 \text{ g}$$

19.005 g is then the capacity of 150 ml of resin for tantalum. This is at least a two fold excess of resin, and more likely three fold with our average foil fraction weighing 6-7 g. After the column is loaded 30 ml of HF + HCL solution is passed through it to insure that none of the resin is leaking from the column.

9. The column is finally eluted so that the level of eluant is just above the resin surface.

10. Now the evaporate from step 7 is added to the column. At this time we begin to collect 15 ml fractions of eluant. The evaporate is allowed to come down to the surface of the column before more solution is added to insure that all the evaporate has entered the resin. At this time two, 15 ml portions of the eluting solution are added to the column and brought down to just above the resin surface.

11. The eluting solution is now added to the top of the column and the fraction collecting continues. We expect the Tungsten to elute from the column in approximately 3 column volumes or 450 ml.

12. The Tungsten fractions are identified using a multichannel analyzer. All the fractions are pooled, and the total volume is approximately 100 ml.

13. The pooled fractions are then added to a teflon beaker and evaporated to bring the volume down to not quite dryness (approximately 1 ml).

14. 10 ml of the HCL + HF solution is then added to the evaporate and allowed to cool.

15. This evaporate is added to a second anion exchange column 30 cm high x 1.25 cm i.d. containing 40 ml of AG 1-X8 anion exchange resin, pre equilibrated with 6N HCL a 1.5N HF solution as was the Primary column (see step 8), capacity of resin is 5.068 g Tantalum.

16. The primary column eluant which has been evaporated and brought to a volume of approximately 10 ml with 6N HCL and 1.5N HF is now added to the secondary column. It is allowed to come down to just above the surface of the resin and then 15 ml of the HF and HCL solution is added and brought down to the surface. This is repeated once again before the column is filled with the HCL and HF eluting solution. Fractions are collected in 10 ml portions. The tungsten is seen at approximately 65 - 75 ml.

17. The tungsten fractions are collected (approximately 60 ml) and pooled in a teflon beaker.

18. The secondary column eluant is then evaporated down to a volume of approximately 1 ml.

19. 3 ml of concentrated hydrochloric acid is added to the evaporate and evaporated to not quite dryness ($\leq$ 1 ml). This is repeated once.

20. 5 ml of a 0.1N HCL and 1.0% H_2O_2 solution is added to the evaporate and brought down to volume ($\leq$ 1 ml). This is repeated once.

21. 2 ml of 0.1N HCL and 1.0% H_2O_2 solution is then added and allowed to cool.

5B. Preparation of Tungsten 178/Tantalum 178 Generator

1. An excess of anion exchange resin AG1-X8 (Bio Rad Labs, Richmond, California) is added to a prewashed, prerinsed teflon beaker. The Resin is then washed with an excess of SWFI. The excess liquid is decanted and the washing repeated twice before the beaker is covered with alumnium foil, and wrapped in autoclave paper.

2. The generator column is comprised of a 4 ml borosilicate glass barrell econo-column (Bio-Rad Laboratories, Richmond, CA.) with a two-way stopcock (Pharmaseal, Inc. Glendale, CA.) at the bottom. This column is washed with detergent, rinse with tap water vigorously and then rinsed 5-10 times with pyrogen-free water. The column, with stopcock attached, is then wrapped in bio-shield sterilization wrap (American Hospital Supply Corp., Evanston, Illinois).

3. Both the resin in the teflon beaker and the column contained in the sterilization wrap are autoclaved for 20 min at 250°F (15 psi), (American Sterilizer Company, Erie, Pa. Type QDS 2036).

4. After sterilization is completed the resin is equilibrated with 0.1N HCL and 0.1% H_2O_2. The excess solution is decanted and the equilibration step is repeated twice.

5.1 At this time a sterile disposable connecting tube (Cook, Inc. Bloomington, IN.) is attached to the stopcock. The equilabrated resin is brought up into a sterile disposable 5 cc syringe and loaded onto the column. The final volume of the resin bed is approximately 1.5 ml.

6. Now the evaporate (step 5. A, (21)) is introduced onto the column via a sterile disposable plastic syringe. The evaporate is passed through the column and the eluant is collected at the bottom by a 10 cc disposable plastic syringe. The beaker containing the evaporate is rinsed with a solution of 0.1N HCL and 1.0% H_2O_2 and passed through the column.

7. The column is now flushed with 5 ml of the 0.1N HCL and 0.1% H_2O_2 solution, which is passed through a Millex-GS filter (0.22 um) (Millipore Corp., Bedford, Ma). The flush which passes through the column is assayed for activity. Gamma spectrum analysis, and mass spectrometry are performed for identification of any radionuclide or mn.

8. The column is now fitted with a Millex-GS filter at the top of the column and each syringe is fitted with a Millex-GS 0.22 um filter before being attached to the connecting tube, for terminal sterilization.

5C. Preparation of Buffer Solution (pH 9.2)

1. The buffer solution is prepared using glassware prepared as described in Appendix 1. To a 100 ml volumetric flask 6.388 g of dibasic sodium phosphate is added. This is brought to volume with sterile water for injection, USP (Abbott Labs, North Chicago, IL). The pH of this solution is checked using a pH meter (Beckman Model 76 Century SS, Beckman, Inds., Fullerton, CA).

2. This buffer solution is then transfered asceptically into sterile, pyrogen-free, 30 ml, empty multi-injection vials (Elkins-Sinn, Inc., Cherry Hill, New Jersey 08034). This is done by attaching a Millex-GS filter to a 10 cc sterile disposable syringe (Pharmaseal, Inc., Glendale, California) with the plunger removed. The filter is then fitted with a sterile 21g needle (Beckton, Dickinson and Co., Rutherford, New Jersey). The top of the vial is swabbed with isopropyl alcohol 70% and then the needle is introduced into the vial. The buffer is then poured into the barrel of the syringe and delivered into the vial. This is done for 3 vials using separate needles, syringes, and filters for each one. All lot numbers of reagents and vials used in the preparation of the buffer are recorded. Each batch of newly prepared buffer is also given a lot number. Work sheets for the preparation of the buffer can be found in Appendix 4. Sample from each lot of buffer are tested for sterility and pyrogencity.

5D. Elution of the generator

1. 0.5 cc of the phosphate buffer is asceptically drawn up into a 3 cc syringe.

2. The syringe is then fitted with a Millex-GS filter and attached to the connecting tube at the bottom of the generator.

3. Freshly (daily) prepared eluting solution (0.1N HCL and 0.1% H_2O_2) is passed through the column and into the syringe. A volume of approximately 1.5 cc is drawn into the syringe.

4. The pH of the resulting solution is 6.5.

5E. Quality Assurance Testing

1. Sterility and pyrogenicity testing are performed on samples taken from each newly constructed generator and each newly prepared lot at phosphate buffer (according to USPXX). Samples taken from both the generator (as eluant) and the phosphate buffer are sent to outside laboratories for determination of pyrogenicity. Both generator eluant and phosphate buffer are tested for sterility by the Microbiology laboratory at NASA/Johnson Space Center. Routine pyrogen testing will be conducted by our laboratory using the Limulus Lysate Pyrogent Test. Routine Sterility testing will be done by the Microbiology laboratory at NASA/JSC. All results will be kept on file in our laboratory. (See Appendix 2 for results).

2. Radionuclidic purity of the generator eluant is determined for each newly constructed generator. A germanium (lithium) solid state detector-coupled to a multichannel analyzer is used for acquisition of emission data. The data is analyzed by computer and a copy of this data is kept on file.

3. Determination of residual (carrier) tantalum metal is done using argon plasma emission spectroscopy. This is done to insure that our processing is effectively trapping all the tantalum metal. In this manner we are able to determine the specific activity of the radionuclide and assure carrier free concentrations. (See Appendix 3 for results).

4. Chemical purity of the generator eluant is checked via mass spectroscopy and total organic carbon analysis. In order to identify and quantify possible organic contaminants mass spectroscopy and total organic carbon analysis (TOC) is run on samples of each newly constructed generator. TOC is repeated periodically to determine changes in the quantity of organic contaminants (i.e. trimethylamine) present. (See Appendix 3 for results).

5F. Labeling

1. The label of the administered radiopharmaceutical will have on it the following:
   a. Subject's name and file number.
   b. Name of drug, concentration, lot number.
   c. Calibration date and time with noted activity.
   d. Caution - New Drug limited to investigational Use.
   e. Caution - Radioactive material with standard emblem.

6A. Toxicity of Components

1. Cochran et. al. have studied the toxicity of tantalum in animals (rats). They found the LD_{50} for tantalum chloride, administered via intraperitoneal injection, to be 38 milligrams per Kg and for tantalum flouride 173 mg per kilograms (i.p.) (3).

   The amount of tantalum injected per dose of the tantalum-178 radiopharmaceutical has been calculated to be 2.97×10^{-4} mg (the contribution of the radioactive Ta-178 is assumed negligible at 8.8×10^{-9} mg/mCi). Assuming the normal subject is 70 kilograms we would calculate our dose to be 4.24×10^{-6} mg/Kg stable tantalum. This is more than $.8 \times 10^{6}$ times less than the LD50 for tantalum in the rat.

2. The daughter of tantalum-178 is stable hafnium-178. Haley et al.(4) have studied the toxicity of hafnyl chloride in mice and determined the LD_{50} to be 112 mg/Kg with a range of 93.3 to 134.4 mg/Kg. Since tantalum-178 decays 100% to Hf-178 we can say there are an equal number of hafnium atoms present at the end of decay. This amount 3.5×10^{-7} mg per 40 mCi is more than 10^{6} times below the LD_{50} for hafnium.

3. Studies (5) on the toxicity of Dibasic Sodium Phosphate (Na_2HPO_4) have yielded data on the lowest lethal dose in three different species:

   1000 mg/Kg i.p. in the rat.
   1000 mg/Kg subcutaneous in the rat.
   1000 mg/Kg I.M. in the rat.
   298 mg/Kg I.V. in the dog.
   1075 mg/Kg I.V. in the rabbit.

   Assuming that the toxicity in man mimicks that found in the dog (298 mg/Kg) and calculating our dose to be 0.456 mg/kg we calculate a measure of safety to be 654. That is our dose in 654 times below the LD_{50} for intravenously injected Dibasic Sodium Phosphate in the dog.

4. Preliminary organic analysis on the generator eluant indicates the presence of trimethylamine. Trimethylamine is believed to be a breakdown product of the quarternary ammonium exchange site. This quarternary ammonium is the active site for exchange on the anion exchange resin used for the generator column. Gas chromotography and total organic analysis indicates the amine to be present at a maximum concentration of 24 parts per million (ppm). This concentration being equal to 0.024 mg/ml or 0.036 mg/injection. The LD_{50} for trimethylamine is 325 mg/Kg (I.V. in the mouse) (5). Basing our dose and calculations on a 70 Kg subject, the administration of 0.036 mg/injection is more than 10^{6} times below the LD_{50} (I.V. in the mouse).

5. A subacute toxicity study was performed in our laboratory using female Sprague-Dawley rats. Each rat (approx. weight 300 gm.) was injected daily for eight days with a dose 117 times the normal human dose on a per kilogram basis. Weights of each animal were recorded daily prior to injection (I.P.), and three days after the last injec-

tion prior to necropsy. No significant changes in body weight were noted. Gross anatomical examination performed by Craig Fisher, M.D. of the Johnson Space Center, Houston, Texas showed no pathology. Histological examination performed by David Judge, M.D. of the Methodist Hospital, Baylor College of Medicine, Department of Pathology, Houston, Texas showed no pathology.

An acute toxicity study using rats injected once with 234 times the normal human dose showed no gross antomical or histological pathology (D. Judge, M.D.).

Preclinical studies of Ta-178 have been done on a number of animals at the Johnson Space Center, and at Harvard University. No pathologies or anomalies were noted in reference to the use of the Tantalum-178 radiopharmaceutical.

6B. Radiation Dosimetry

1. Using biodistribution data obtained from preliminary animal studies (1) along with the MIRD committee recommendations and pamphlets (6,7), we have calculated the dose to significant organs from Ta-178. Absorbed fractions were obtained from MIRD pamphlet No. 5 (7), and equilibrium dose constants, Δi, were calculated from decay data (8,9).

2. General Assumptions:
   a. All assumptions made here are those found in the MIRD system (6,7).
   b. There is instantaneous uptake of the radiopharmaceutical in all organs.
   c. Tissue distribution is uniform in all organs except when calculating liver and blood dose.
   d. The effective life of the radiopharmaceutical is 9.3m, assuming infinite retention in all organs.
   e. There is homogeneous uptake of the radiopharmaceutical in each organ.
   f. Dose calculations will be based on an injected dose of one millicurie.

$\tilde{A}_h$ = Cumulated activity (uCi-hr) in source organ.

$\tilde{A}_h$ = 1.44 x T 1/2 effective x Injected dose (uCi) x % uptake.

$S_{(rk \leftarrow rh)}$ = absorbed dose per unit cumulated activity.

$S_{(rk \leftarrow rh)} = \Sigma \ \Delta_i \ \Phi (r_k \leftarrow r_h)$

Δ_i = equilibrium dose contant (gm-rad/uCi-hr)

$\Phi i_{(rk \leftarrow rh)}$ = specific absorbed fraction of energy for target organ rk for particles i emitted from source organ r_h.

$\bar{D}_{(rk \leftarrow rh)}$ = mean absorbed dose (in rads) to a target organ r_k from a radionuclide distributed uniformly in a source organ r_h.

$$\bar{D}_{(rk \leftarrow rh)} = \tilde{A}_h \; S_{(rk \leftarrow r_h)}$$

2. Total Body

Assuming 100% uniform distribution, instantaneous uptake and infinite retention of the radiopharmaceutical throughout the total body we calculate the dose to the total body as follows:

$\bar{D}_{(rk \leftarrow rh)} = \tilde{A}_h \; S_{(rk \leftarrow rh)}$

$\tilde{A}_h$ = (1.44 x 0.155h x 1000 uCi x 100%)

$S(rk \leftarrow rh)$ = 2.7768×10^{-6}

$\bar{D}_{(rk \leftarrow rh)}$ = 6.198×10^{-4} rads per millicurie

$\bar{D}_{TB}$ = 0.6198 millirad per millicurie

3. Testes, Ovaries, Red Marrow

Assuming there is uniform uptake of the radiopharmaceutical throughout the total body, we estimate the dose to the testes, ovaries, and red marrow as being equivalent to the calculated total body dose.

$\bar{D}$ = 0.6198 millirad per millicurie

4. Liver

Preliminary studies of the biodistribution of tantalum-178 in phosphate buffer (pH 7.0) in rats shows 13% uptake in the liver (1). This is in excess of the uniform uptake of the liver by 10.43%. The following equation (10) was used to determine the absorbed dose to the liver:

$$\bar{D} = \frac{\tilde{A}}{M_L} \Sigma \Delta np \; \emptyset \; np + \left[\frac{\tilde{A}_L}{M_L} - \frac{\tilde{A}_{TB}}{M_{TB}} \right] \Sigma \Delta \emptyset \; (L \leftarrow L)$$

$$+ \left[\frac{\tilde{A}_{TB} - \tilde{A}_L}{M} \right] \Sigma \Delta \emptyset \; (L \leftarrow TB)$$

$\bar{D}_L$ = absorbed dose to the liver for all radiations (rads).

$\tilde{A}_L$ = cumulative activity in the liver (uCi-hr).

$\tilde{A}_{TB}$ = cumulative activity in the total body (uCi-hr).

M_L = mass of the liver.

M_{TB} = mass of total body.

Δ_{np} = equilbrium dose constant for non-penetrating radiations.

$\emptyset_{np}$ = absorbed fraction for non-penetrating radiations.

$\bar{D}_L$ = 2.28 millirads per millicurie

5. Blood

Preliminary studies (1) report radiopharmaceutical distribution in the blood to be 37%. We have therefore calculated the absorbed dose from non-penetrating and penetrating radiations.

For non-penetrating radiations we have used the following equation:

$$\bar{D}_{Bnp} = \frac{\tilde{A}}{M_B} \quad \Sigma \quad \Delta np \quad \emptyset \quad np$$

where $\bar{D}_{Bnp}$ = absorbed dose to the blood from the blood, for non-penetrating radiation.

$\tilde{A}_B$ = cumulative activity in the blood (uCi-hr)

M_B = mass of blood

Δnp = equilibrium dose constant for non-pentrating radiation

$\emptyset np$ = absorbed fraction for non-penetrating radiation

$\bar{D}_{Bnp}$ = 1.375 millirads per millicurie

For calculating the absorbed dose to the blood from penetrating radiation we consider the blood to be uniformly distributed throughout the whole body and calculate the absorbed dose using the specific absorbed fractions for total body (11).

Using the equation below for penetrating radiation only, we have calculated the absorbed dose for photons.

$$\bar{D} = \tilde{A}S$$

$$\bar{D}_{Blood\ p} = \tilde{A}\, S_{(TB \leftarrow TB)}$$

$$\tilde{A}_{TB} = 1000\ uCi \times 1.44 \times 0.155 \times 100\%$$

$$S_{(TB \leftarrow TB)} = \Sigma\ \Delta\ \emptyset_{(TB \leftarrow TB)}$$

$$= 1.492 \times 10^{-6}$$

$$\bar{D}_{Blood\ p} = (223.2\ uCi\text{-}hr)\ (1.492 \times 10^{-6}\ rads/uCi\text{-}hr)$$

$$= 0.333\ millirad\ per\ millicurie$$

Total Dose to the Blood

$$\bar{D} = \bar{D}_{Bnp} + \bar{D}_{Bp}$$

$$= 1.375 + 0.333 = 1.708 \text{ millirads per millicurie}$$

6C. Radiation Dosimetry Summary

Organ	millirad per millicurie	millirads per 40 mCi dose
Total Body*	0.62	24.8
Ovaries*	0.62	24.8
Testes*	0.62	24.8
Red Marrow*	0.62	24.8
Liver+	2.28	91.2
Blood°	1.71	68.4

* assuming uniform Total Body Uptake
\+ assuming 13% Uptake
° assuming 37% Retention

7. There have been no prior clinical investigations using Tantalum-178 in humans. All informational material acquired in phase I of this investigation will be recorded and supplied to the investigators in phase II. No relevant hazards are known for the radiopharmaceutical under investigation. The LD_{50}'s for all components have been cited and the dosages of each and their relative margins of safety have been calculated. It is suggested that women be excluded from preliminary testing due to the uncertainty of determining pregnancy and the unneccessary chance of possible exposure to the fetus.

8. Investigators should be qualified Nuclear Medicine physicians with expertise in the safe handling of radioisotope and clinical experience with cardiovascular imaging. Other investigators should be experienced in cardiology and/or internal medicine.

9. The names and summary of the training and experience of each investigator and the individuals in charge of monitoring the progress of the investigation can be found in Appendix 5. Clinical Pharmacology forms (FDA 1572) have been received from the investigators named below (Sec. 10.2, 10.3) and are on file with the sponsor.

10. Planned Investigations

1. Test Hypothesis

Tantalum-178 is a short-lived nuclide whose inclusion into the current arsenal of medical radionuclides would allow a significant reduction of radiation exposure for the patient population. Animal studies using tantalum-178 labeled liver and lung imaging agents show good agreement with images obtained using technetium-99m labeled agents (12). Other studies with animals comparing Ta-178 and Tc-99m first-pass radionuclide angiocardiography have demonstrated that

Ta-178 can be used in this manner with conventional imaging systems (13). The physical characteristics of tantalum-178 make it an attractive diagnostic tool. Its production via decay of the long-lived parent tungsten-178 allows for the construction of a generator system which supplies the short-lived nuclide over a long period of time. The short half-life of Ta-178 provides it with a relatively low radiation dose, estimated to be one twentieth that of technetium99m. The low energy photon emissions of Ta-178 allow the use of the Multiwire Proportional Camera for Nuclear Medicine imaging. The energies of Ta-178 are better suited for detection by the MWPC than by conventional NaI(Tl) Crystal Cameras (Anger and Baird Cameras), (14,15). The MWPC is capable of higher count rates than either the Anger or Baird cameras, thereby providing increased spatial resolution of the images obtained. The camera itself is lightweight and portable allowing it to be useful in the intensive care unit setting. Production of the camera is rather inexpensive in comparison to those used at this time in Nuclear Medicine Clinics. These factors concerning the MWPC make it an attractive instrument for study and development.

It is therefore our objective to evaluate Tantalum-178 and the MWPC as a system for first-pass radionuclide angiocardiography. First-pass radionuclide angiocardiography using Technetium-99m and the Baird Multicrystal Camera is an accepted technique for the measurement of cardiac parameters as is the Tc99m multiple gated cardiac study using the Anger Camera (16,17). Our evaluation will be based on the comparative results of these tests as explained below in 10.3.

2. Phase I

Phase I of the clinical investigation will be conducted using normal, healthy volunteers who are employees at the Johnson Space Center, Houston, Texas. The subjects will be males over the age of 21. The number of subjects in phase I will be limited to ten.

This phase of the planned investigation will be conducted at the Life Science Research Facility, Johnson Space Center, Houston, Texas. The investigators include P.C. Johnson, M.D. and M. Bungo, M.D.

Prior to any testing all informational material concerning Ta-178 and the MWPC will be reviewed by the JSC Human Research Review Committee, the JSC Radiation Safety Committee (RSC), and the Medical Isotopes Operations Subcommittee of the RSC. No testing will begin without approval from the above mentioned committees.

This phase of the investigation is intended to provide the investigators with information on the distribution, metabolism and excretion of the radiopharmaceutical. Each subject will be given a dose of the radiopharmaceutical in the range of 10 to 40 mCi. Blood clearance will be determined and organ distribution will be studied. Blood clearance will be determined by taking sequential blood samples from the subject and plotting blood activity verus time. Organ distribution will be done by taking multiple spot images of major organs.

Data acquired from these preliminary investigations should lead to a more accurate calculation of the absorbed radiation dose as well as an optimum dose of the radiopharmaceutical (mCi).

3. Phase II

Phase II of the investigation will be conducted at the Methodist Hospital, Baylor college of Medicine, Houston, Texas. The additional investigators include L. Polinar, M.D., Director Nuclear Cardiology, Methodist Hospital and S. Jhingran, M.D., Director of Nuclear Medicine, Methodist Hospital. Prior to the implementation of any part of phase II all information will be reviewed and approved by these institutions' Radiation Safety and Institutional Review Committee. The maximum number of (patients) subjects to be involved is one-hundred. The duration of the study will be one year. Subjects included in phase II of the planned investigation will be volunteers selected from the patient population of the Nuclear Cardiology Department. Criteria for selection of subjects is that they have been referred to Nuclear Cardiology for a first-pass or multiple gated angiocardiography study. In addition to this requirement the subject must also be male and 21 years of age or older. Once a subject has been selected and consents to participate in the study he will be briefed as to the purpose and procedures of the test. The benefits and hazards will be explained. Prior to the first-pass or multiple gated radionuclide scan which the patient has been scheduled, the patient will undergo a first-pass radionuclide scan using tantalum-178 imaged with the multiwire proportional camera. This will be done one-half hour prior to the Technetium-99m radionuclide angiocardiograph.

Data obtained with the Tantalum-178 angiocardiogram will be evaluated in relation to data obtained with the Technetium-99m/Baird and Anger Camera Systems.

Further evaluation of Tantalum-178 angiocardiograms will include comparative studies with contrast angiography. Patients referred to Cardiology for contrast angiography will be screened for inclusion in this study. The criteria for subject selection is that they be male and over the age of 21.

Parameters considered for evaluation and comparison for both nuclear medicine and radiological procedures are: (1) ventricular ejection fractions, (2) ventricular volumes, (3) ventricular wall motion, and (4) cardiac output.

3. Written consent will be required of all subjects involved in both phase I and phase II of this investigation (see appendix 6 for copies of consent forms).

4. The sponsor will monitor the progress of the study and keep updated reports of all findings. Observations of any and all adverse reactions associated with this investigation will be reported to the FDA and kept on file by the sponsor.

11. Statement of discontinued investigation

I, the sponsor, will notify the Food and Drug Administration if the investigation is discontinued, and in so doing state the reasons therefore.

12. I, the sponsor, will notify each investigator if a new drug application is approved, or if the investigation is discontinued.

13. Not Applicable.

14. I, the sponsor, testify that clinical studies in Humans will not be initiated prior to 30 days after the receipt of the notice by the Food and Drug Administration and that I will continue to withhold or rebrief clinical studies if requested to do so by the FDA prior to the expiration of such 30 days.

15. Not Applicable.

16. All non-laboratory studies have been or will be conducted in compliance with good laboratory regulations as set forth in Part 58.

References

1. Neirinckx RD, Jones AG, Davis MA, et al: Tantalum-178 - A New Short-lived Nuclide for Nuclear Medicine: Development of a Potential Generator System. J. Nucl. Med. 19:514-519, 1978.

2. Neirinckx RD, Ku TH,Holman BL, et al: Production and Purification of Tungsten-178. Int. J. Appl. Rad. Isot. Vol. 30, p 341-343,1979.

3. Cochran KW, Doull J, Mazor M et al: Acute Toxicity of Zirconium, Columbium, Strontium, Lanthanum, Cesium, Tantalum and Yttrium. Arch. Ind. Hyg. Occup. Med. 1, 637-650, 1950.

4. Haley TJ, Raymond K, Komesu N, et al: The Toxicological and Pharmacological effects of hafnium salts. Toxicol. Appl. Pharmacol. 4, 238-246, 1962(b).

5. Fairchild EJ, Lewis RJ, Tatken RL; Eds. Registry of Toxic Effects of Chemical Substances. Vol. I and II, 1977 Edition, DHEW publ. No. (NIOSH) 78-104-B.

6. Loevinger R, Berman M,: A Revised Schema for calculating the absorbed dose from biologically distributed radionulcides MIRD pamphlet No. 1, Revised. New York, Society of Nuclear Medicine, March 1976.

7. Snyder WS, Ford MR, Warner GG: Estimates of specific absorbed fractions for photon sources uniformly distributed in various organs of a heterogenous phantom MIRD pamphlet No. 5, Revised, J. Nucl. Med. 1978.

8. Tantalum-178 (T 1/2 9.3m) "Output" decay data, courtesy of Mary R. Ford Oak Ridge National Laboratory, Oak Ridge, Tennessee.

9. Nuclear Data Sheets, National Academy of Sciences, National Research Councit, Academic Press, New York and London.

10. Cloutier RJ, Watson EE, Rohrer RH, et al: Calculating the radiation dose to an organ. J. Nucl Med. No. 1, Vol. 14, 53-55, 1973.

11. Smith EM, Brownell GL, Ellett WH: Radiation Dosimetry in Principles of Nuclear Medicine, Wagner H.N. Jr. Ed. W.B. Saunders Co. Philadelphia, PA. 1968.

12. Neirinckx RD, Holman BL, Davis MA, et al: Tantalum-178 labeled Agents for Lung and Liver Imaging. J. Nucl. Med. 20:1176-1180, 1979.

13. Holman BL, Neirinckx RD, Treves S et al: Cardiac imaging with Tantalum-178. Radiology 137: 525-526, 1979.

14. Lacy J, LeBlanc A, Bungo M, et al: Multiwire Proportional Counter Imaging Camera and Ta-178 Isotope-New Technology in Cardiac Imaging. Presented at Am. Heart Assoc. November 16-19, 1981, Dallas, Tx.

15. LeBlanc A, Lacy J, Johnson P, et al: Ta-178 Count Rate Response of Anger and Multicrystal Cameras. Radiology 1982 (in Press).

16. Marshall RC, Berger HJ, Costin JC et al: Assessment of cardiac performance with quantitative radionuclide angiocardiography. Sequential left ventricular ejection fraction, normalized left ventricular ejection rate, and regional wall motion. Circulation 56: 820-829 Nov 1977.

17. Ashburn WL, Schelbert HR, Verba JW: Left Ventricular ejection fraction - a review of several radionuclide angiographic approaches using the scintillation camera. Prog. Cardiovasc. Dis. 20: 267-284 Jan-Feb 1978.

Appendix 1: Reagents, equipment, and glassware preparation.

Procedure and Available Facilities

Reagents

1. Nitric Acid 70% AR
2. Hydrofluoric Acid 48% AR
3. Hydrochloric Acid 37% AR
4. Hydrogen Peroxide 30% AR
5. High Purity Tantalum Foil 99.979%
6. Dibasic Sodium Phosphate
7. Sterile water for injection, USP

Apparatus

1. 2 - 250 ml and 1 - 150 ml Teflon Beakers 2. 1 - 30 cm x 2.5 cm I.D. Chromotography Column
3. 1 - 30 cm x 1.25 cm I.d. Chromotography Column
4. Hot plate
5. Balance
6. Chemical Fume Hood
7. Nalgene graduated cylinders 1 - 100 ml, 1 - 50 ml, 1 - 25 ml
8. 4 ml econo-columns
9. Anion Exchange Resin AG 1-X8
10. Teflon wool
11. Sterile disposable tubing connector
12. Sterile disposable syringes 3 cc, 5 cc, 10 cc.
13. 2 ml Pyrex disposable pipets with bulbs
14. 1 - 100 ml volmetric flask
15. 30 ml sterile injection vials
16. Millipore 0.22 um filter disposable

Preparation of Sterile Glassware

1. Wash all glassware well in detergent solution (Alconox, Alconox Inc. New York, NY)
2. Rinse glassware with rapid tap water.
3. Soak for 4 hours in strong solution g chemsolv (Mallinkrodt) diluted fourfold in hot water.
4. Rinse thoroughly with distilled water and then with pyrogen-free water.
5. Wrap in aluminum foil and autoclave at 15 psi for 1 hour.
6. Finally bake in hot air oven at 180^{o}C for 2 hours.

Appendix 2: Results of sterility and pyrogenicity testing.

Sample: Genentech Exact M-1

Test requested: Sterility

Requested by: J Babish Bon • Muscle Lab

Date Received: July 7, 1982

RESULTS:

No growth in 14 days on TSB or Thio

Date reported July 7, 1982

Initial

Sample: PHOSPHATE BUFFER 0.45M pH 7.2

Test requested: STERILITY

Requested by: _____

Date Received: 7 June 1982

RESULTS:

TSB
thio
SAB
} No growth on 7 days

Date reported 15 June 1982

Initial ICK

M. B. A. LABS

MICROBIOLOGICAL AND BIOCHEMICAL ASSAY LABORATORIES

P O BOX 9461, 340 S 66TH ST HOUSTON TEXAS 77011

TEL 713 928 2701

PYROGEN TEST REPORT

Sample submitted by:	TECHNOLOGY INC.
Date received:	6-7-82
Date completed:	6-18-82
Sample:	PHOSPHATE BUFFER
Lot number:	060382
Laboratory report number:	H-2466

RESULTS

The sample was found to be NON-PYROGENIC

Amount of sample injected intravenously: .07 ML/KG

	Animal # 4	Animal #5	Animal#
Weight (kg)	2.2	2.3	2.3
Control temperature °C.	39.5	39.0	39.3
Temp. 1 hr. after injection °C.	39.8	38.7	40.0
Temp. 2 hrs. after injection °C.	39.9	38.9	39.7
Temp. 3 hrs. after injection °C.	39.5	39.1	39.3
Temperature rise °C.	0^0	$+.1^0$	0^0

The sample was tested for pyrogens according to the procedure outlined in U.S.P. X X.

M. B. A. LABS

MICROBIOLOGICAL AND BIOCHEMICAL ASSAY LABORATORIES

P O BOX 9461, 340 S 66TH ST HOUSTON TEXAS 77011

TEL 713'928 7701

PYROGEN TEST REPORT

Sample submitted by: TECHNOLOGY INC

Date received: 6-7-82

Date completed: 6-18-82

Sample: GENERATOR ELUANT M-1

Lot number:

Laboratory report number: H-2466

RESULTS

The sample was found to be NON PYROGENIC

Amount of sample injected intravenously: 0.28 ML/KG

	Animal # 1	Animal # 2	Animal #
Weight (kg)	2.6	2.3	2.0
Control temperature °C.	39.2	39.5	39.7
Temp. 1 hr. after injection °C.	38.7	39.3	39.4
Temp. 2 hrs. after injection °C.	38.8	39.3	39.7
Temp. 3 hrs. after injection °C.	38.8	39.3	39.7
Temperature rise °C.	-.4°	-.2°	0°

The sample was tested for pyrogens according to the procedure outlined in U.S.P. X X.

M. B. A. LABS

MICROBIOLOGICAL AND BIOCHEMICAL ASSAY LABORATORIES

P O BOX 9461, 340 S 66TH ST HOUSTON, TEXAS 77011

TEL 713 928 2701

Sample submitted by: TECHNOLOGY INC.

Date received: 3-16-82

Date completed: 3-24-82

Laboratory report number: H-1986

Sample identification: GENERATOR ELUENT (L-1) FROM 2-10-82

RESULTS

THE SAMPLE WAS FOUND TO BE NON- PYROGENIC

AMOUNT OF SAMPLE INJECTED INTRAVENOUSLY: 0.28 ML/KG

	ANIMAL #1	ANIMAL #2	ANIMAL #3
WEIGHT (KG)	2.15	2.38	2.27
CONTROL TEMPERATURE ^{O}C.	38.3	38.4	38.8
TEMP. 1 HR. AFTER INJECTION ^{O}C.	38.3	38.1	38.6
TEMP. 2 HRS. AFTER INJECTION ^{O}C.	38.6	38.1	38.9
TEMP. 3 HRS. AFTER INJECTION ^{O}C.	38.8	38.2	38.9
TEMPERATURE RISE ^{O}C.	+0.5	-0.2	+0.1
TOTAL TEMPERATURE RISE	+0.6^{O}C		

THE SAMPLE WAS TESTED FOR PYROGENS ACCORDING TO THE PROCEDURE OUTLINED IN U.S.P. XX, 1980, PG. 903, RADIOACTIVE PHARMACEUTICALS.

XX

Reported by Dennis R Smith

M. B. A. LABS

MICROBIOLOGICAL AND BIOCHEMICAL ASSAY LABORATORIES

P O BOX 9461 340 S 66TH ST HOUSTON, TEXAS 77011

TEL 713 928 2701

Sample submitted by: TECHNOLOGY INC.

Date received: 3-16-82

Date completed: 3-24-82

Laboratory report number: H-1986

Sample identification: PHOSPHATE BUFFER
PREPARED 3-8-83
FILTERED AND PACKAGED 3-9-82

RESULTS

THE SAMPLE WAS FOUND TO BE NON-PYROGENIC

AMOUNT OF SAMPLE INJECTED INTRAVENOUSLY: 0.07 ML/KG

	ANIMAL #4	ANIMAL #5	ANIMAL #6
WEIGHT (KG)	1.98	2.04	2.27
CONTROL TEMPERATURE ^{O}C.	38.9	38.3	38.4
TEMP. 1 HR. AFTER INJECTION ^{O}C.	38.8	37.9	37.8
TEMP. 2 HRS. AFTER INJECTION ^{O}C.	38.7	38.0	37.9
TEMP. 3 HRS. AFTER INJECTION ^{O}C.	38.6	37.8	37.8
TENPERATURE RISE ^{O}C.	-0.3	-0.5	-0.6
TOTAL TEMPERATURE RISE	0.0^{O}C		

THE SAMPLE WAS TESTED FOR PYROGENS ACCORDING TO THE PROCEDURE OUTLINED IN U.S.P. XX, 1980, PG. 903, RADIOACTIVE PHARMACEUTICALS.

Reported by Donald R. Smith

SCIENTIFIC ASSOCIATES, INC.
6200 S LINDBERGH ST. LOUIS MO 63123 • TELEPHONE 314 487 6776

REPORT OF ANALYSIS

SUBMITTED BY Technology, Inc.
P. O. Box 58827
Houston, Texas 77058

DATE September 15, 1981

MARKS. 8/26/81

YOUR P O NUMBER 6197

SAMPLE TESTED Decayed Generator Eluent (Tungsten 178 + Tantalum 178) in 0.1NHCl + 0.1% H_2O_2

DATE RECEIVED 9/1/81

TESTED FOR PRESENCE OF PYROGENS

S A NUMBER 299661

According to the procedure outlined in the U S P XX, we have

tested sample marked Decayed Generator Eluent (Tungsten 178 + Tantalum 178) in 0.1NHCl + 0.1% H_2O_2 *

and found it to be PYROGEN FREE

when injected 1.6 ml. (1/3 of total sample volume) per animal, undiluted.

ntravenously into healthy animals None of the

animals displayed signs of ill effect during the performance of this test

mal No	Weight	Control Temperature °C	Temperature 1 hr. after Injection °C.	Temperature 2 hrs after Injection °C.	Temperature 3 hrs after Injection °C	Temperature Rise °C
L	3.4 kg.	39.3	39.2	39.3	39.3	0.0
!	2.9 kg.	39.0	38.9	38.9	39.2	0.2
!	3.4 kg.	39.2	39.6	39.6	39.5	0.4

pH of test sample as received = 2.0. Sample adjusted to pH of 7.0 with sodium hydroxide immediately prior to injection.

m

SCIENTIFIC ASSOCIATES, INC.

BY Robert H. Monteith

SCIENTIFIC ASSOCIATES, INC.
6200 S LINDBERGH ST LOUIS MO 63123 • TELEPHONE 314.487 6776

COPY

STERILITY TEST REPORT

SUBMITTED BY: Technology Incorporated
P. O. Box 58827
Houston, TX 77058

DATE COMPLETED: September 9, 1981

LOT NUMBER: 8/26/81

YOUR P.O. NUMBER: 6197

DATE RECEIVED: September 1, 1981

SAMPLE ANALYZED: DECAYED GENERATOR ELUENT (Tungsten 178 & Tantalum 178)

S.A. SAMPLE NUMBER: 299663

NUMBER OF UNITS TESTED: 1

METHOD OF TESTING: U.S.P. XX, pg. 878-882, testing 0.1 ml of 1 x 6 ml unit by membrane filtration.

RESULTS: MICROBIAL GROWTH IN STERILITY TESTING MEDIA

Aerobic Bacteria	Anaerobic Bacteria	Yeasts	Molds
0	0	0	0

0 Denotes no growth + Denotes growth

CONTROLS

Atmospheric Controls:	no growth
Media Controls:	no growth
Dilution Fluid Controls:	no growth
Inhibition Controls:	growth

Organisms used for Inhibition Controls: Cl. sporogenes & B.subtilis

CONCLUSIONS: Under the test conditions, the samples examined meet U.S.P. XX requirements for sterility.
The sample cultures did not show inhibitory activity when inoculated with microorganisms, and all negative controls conform to specifications, thus indicating that the test results are valid.

SCIENTIFIC ASSOCIATES, INC.

By: L.N.Mattson, Vice-President

Viexed:
Mailed: 9/9/81

SCIENTIFIC ASSOCIATES, INC.
6200 S LINDBERGH ST LOUIS MO 63123 • TELEPHONE 314-487 6776

REPORT OF ANALYSIS

Gen "G"

CORRECTED REPORT

SUBMITTED BY Technology, Inc.
Bldg. 37, Department SD-3
Lyndon B. Johnson Space Center
Houston, Texas 77058

DATE April 3, 1981

MARKS GRI-3 3/19/81

YOUR P.O NUMBER 0517

SAMPLE TESTED ^{178}Ta + ^{178}W Isotope

DATE RECEIVED 3/26/81

TESTED FOR PRESENCE OF PYROGENS

S A NUMBER 293122

According to the procedure outlined in the U S P. XX, we have

tested sample marked ^{178}Ta + ^{178}W Isotope*

and found it to be PYROGEN FREE

when injected 1.1 ml./animal undiluted

intravenously into healthy animals None of the

animals displayed signs of ill effect during the performance of this test

Rabbit No	Weight	Control Temperature °C	Temperature 1 hr. after Injection °C.	Temperature 2 hrs after Injection °C	Temperature 3 hrs after Injection °C.	Temperature Rise °C
1	2.8 kg.	38.5	38.5	38.5	38.6	0.1
2	2.8 kg.	39.4	39.3	39.5	39.4	0.1
3	2.7 kg.	39.4	39.3	39.3	39.4	0.0

*pH of test sample as received = 2.0. Sample adjusted to pH of 6.5 with sodium hydroxide immediately prior to injection.

SCIENTIFIC ASSOCIATES, INC.

BY Robert H. Mueller

Appendix 3: Results of Analytical testing.

ANALYTICAL CONSULTING SERVICES, INC.
6251 Corporate Drive • Houston Texas 77036 • 713/995-8080
ACS LABS

June 4, 1982

John Babich
Technology, Inc.
P.O. Box 58827
SD 3
Building 37
Houston, Texas 77058

Subject: One Sample for Tantalum

Re: Lab No. 3967

P.O. No. 0964

Analytical Data:

Tantalum..... 198 ppb

Sincerely,

ANALYTICAL CONSULTING SERVICES, INC.

Paul S. Watson
Lab Manager

PSW/rm

Appendix 4: Reagent Work Sheet
Sample

oduct: Phosphate Buffer

Date: 3June82

Ingredients	Amount	MFGR	Lot No.	Initials
Sodium Phosphate Dibasic (AR)	12.776gm	Mall.	KMSA	
SWFI	qs 200ml	Abbott	27-525-DK	
30ml Sterile Empty Multi Injection Vials		Elkins-Sinn	012047	

cedure Used:

1) 200ml volumetric flask was prepared as described in glassware preparation protocol.
2) 12.776gm of reagent grade (ACS) dibasic sodium phosphate anhydrous is added to the volumetric flask.
3) The flask is brought to volume with sterile water for injection ,USP
4) The resulting solution is transfered to 30ml multiinjection vials using 20cc syringes and 0.22um sterile dispoible filters .

hod of Sterilization: 0.22u m Sterile Filters (Gelman)

No. 060382 Amount Produced: 200ml

e Released:

t Results: pH 9.2

ility: Steris GSC/Microbiology Ok 6/7/82 reject 6/15/82

genicity: Non-pyrogenic MBS Rabbit H2766 6/18/82

APPENDIX II

PUBLICATIONS

Tantalum-178 Count-Rate Limitations of Anger and Multicrystal Cameras[1]

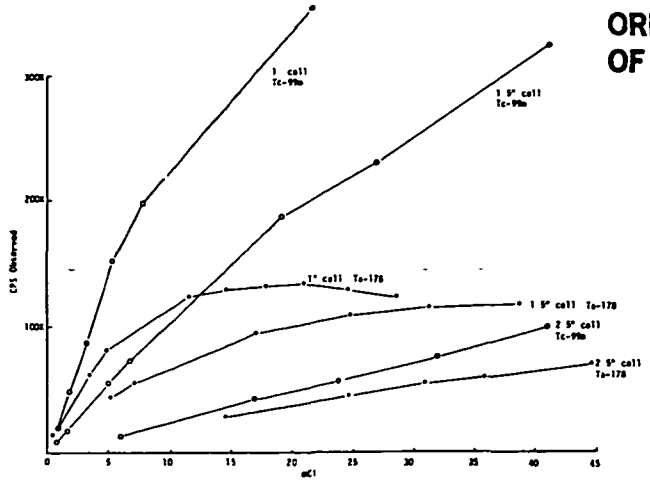
Adrian D LeBlanc, Ph D.
Jeff L Lacy, M D
Philip C Johnson, M.D
Larry R Poliner, M D
Satish G Jhingran, M D

Tantalum-178 (^{178}Ta) is compared with technetium-99m (^{99m}Tc) as an imaging agent to be used with Anger and multicrystal cameras in first-pass cardiac studies.

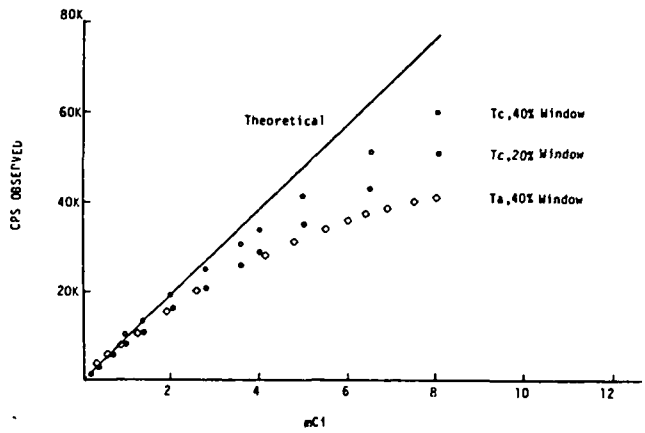
Index terms Heart, radionuclide studies
5(1) 1299 • Radionuclide imaging, comparative studies

Radiology 146. 242–243, January 1983

Figures 1 and 2



1. ^{178}Ta and ^{99m}Tc count-rate response curves of the multicrystal camera using the 1.0-, 1.5-, and 2.5-inch collimators



2. ^{178}Ta and ^{99m}Tc count-rate response curves of an Anger camera using the medium energy collimator A 40% ^{178}Ta window normally used for scanning is compared to ^{99m}Tc curves that were obtained with a 20% and 40% window

TANTALUM-178 (^{178}Ta) is a generator-produced radionuclide with a half-life of 9.3 minutes and primary photon emissions of between 54 and 65 keV. Compared with ^{99m}Tc, the very low radiation exposure and short half-life of ^{178}Ta make ^{178}Ta an attractive potential imaging agent. Good quality images have been reported using high energy collimators with Anger and multicrystal cameras (1, 2). ^{178}Ta, however, has a low abundance of high energy photons (0.5 MeV, 2.1%, 1175–1772 MeV, 4%) that penetrate medium and high energy collimators of Anger and multicrystal cameras, significantly lowering the maximum count-rate response of these instruments.

METHODS

The count rate response of a multicrystal camera (Baird Atomic, System 77) was determined for ^{178}Ta and ^{99m}Tc using standard 1.0-, 1.5- and 2.5-inch collimators by placing calibrated amounts of ^{178}Ta or ^{99m}Tc approximately two inches above the detector. The source for ^{178}Ta was allowed to decay over approximately 45 minutes while the observed count rate was recorded at various time intervals. The count-rate response curve was plotted against mCi (1 mCi = 37 MBq) of ^{178}Ta after correcting for decay. The ^{99m}Tc curves were obtained by successively adding calibrated amounts of activity to the same beaker after complete decay of the ^{178}Ta. The camera settings for ^{178}Ta were: bias, 4%, threshold, 4%, window, 30%. For ^{99m}Tc, the usual settings were used: bias, 6%, threshold, 10%, window, 30%.

The count-rate response curve of an Anger camera (G.E. Maxi II) using a medium-energy parallel-hole (MEP) collimator was obtained in a manner similar to that stated above. A 40% window (24 keV) was used for ^{178}Ta and compared with the ^{99m}Tc response curves that were obtained with 20% (28 keV) and 40% (56 keV) windows.

RESULTS

Figure 1 shows the multicrystal response curves for ^{99m}Tc and ^{178}Ta. For all three collimators, significant differences between the ^{99m}Tc and ^{178}Ta response curves are evident above counts rates of about 60 Kcps. The number of mCi at which this occurs is a function of the collimator that is used, and it ranges from 3–4 mCi (111–148 MBq) for the 1-inch collimator, to 30 mCi (1110 MBq) for the 2.5-inch collimator. Figure 2 compares the count rate response of ^{99m}Tc and ^{178}Ta using an Anger camera and an MEP collimator. For equal size windows (40%) the response curves appear to diverge at

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around 20 Kcps For equal energy window widths, this divergence occurs around 30–40 Kcps. Saturation for ^{178}Ta occurs at a count rate of about 45 Kcps The shape of the gamma spectrum from a point source of ^{178}Ta was observed to vary with the source-to-collimator distance As the source was moved away from the collimator the shape of the spectrum approached that obtained without a collimator (no septal penetration)

DISCUSSION

As the thickness of the multicrystal collimators increased from 1 0 inch to 2.5 inches, septal penetration was reduced, however, the sensitivity to 54–65 keV photons was also reduced Therefore, increasing the thickness of the collimator did not improve camera performance Since the principle use of the multicrystal camera is for producing high count-rate first-pass cardiac studies, the significant decrease in the maximum achievable count rate limits the usefulness of ^{178}Ta with this device.

As expected, the relative contribution of the high energy photons to the observed count rate is a function of the window-size setting of the Anger camera The instrument response was also seen to be a function of the source-to-collimator distance This was observed by collecting ^{178}Ta spectra at various distances from the collimator It is speculated that whereas the sensitivity of the 54–65 keV photons is independent of the source-to-collimator distance, the number of high energy photons penetrating and interacting with the crystal will decrease approximately in proportion to the inverse square of the source-to-collimator distance

As with the multicrystal camera, the Anger camera demonstrates severe count-rate degradation at count rates above about 30 Kcps However, since imaging with an Anger camera rarely exceeds 20 Kcps, the count-rate limitation may not be critical in most cases The main limitation is the requirement for medium or high energy collimators In certain situations where the need for repeat studies or low radiation exposure outweighs the disadvantages of these collimators, ^{178}Ta may be the agent of choice

References

1 Holman BL, Neirinckx RD, Treves S, Tow DE Cardiac imaging with Tantalum-178 Radiology 1979, 131 525–526

2 Holman BL, Zimmerman RE, Bifolck LV, Neirinckx RD Scintigraphic imaging with Tantalum-178 and the Anger scintillation camera concise communication J Nucl Med 1979, 20 538–542

INSTRUMENTATION

A Gamma Camera for Medical Applications, using a Multiwire Proportional Counter

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A multiwire proportional counter gamma camera, specifically designed for nuclear medicine applications, is portable and weighs less than 50 lb including shielding and collimator. The basic operating characteristics have been investigated with various radioactive sealed sources. The camera demonstrates a peak count rate of 850,000 cps, an intrinsic spatial resolution of 2.5 mm, and excellent image uniformity when used with x-ray sources in the range of 22–81 keV. Tests of the device with Ta-178—a very promising, short half-life (9.3 min), low-energy radionuclide—using 20 mCi injections provided images of quality comparable to those obtained from 15 mCi Tc-99m studies with conventional imaging devices. The camera used with Ta-178 offers particular promise in first-pass nuclear cardiology studies. Considerably improved study quality will likely result in this area because of the increased injectable dose levels offered by Ta-178 combined with the high-count rate capability and improved resolution.

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The multiwire proportional counter (MWPC) was developed in the late 1960s for applications in high-energy physics (*1*,*2*). Since that time, MWPC technology has developed rapidly and is currently heavily utilized in this field for position determination of particles and gamma rays. Although widespread use of the MWPC as a medical imaging device has not yet emerged, the potential is well recognized (*3*).

A number of groups have developed and reported MWPC single-photon imaging detectors (*4–6*) Reported devices using moderate pressurization (<5 atmospheres) have shown good resolution, simplicity of construction, and generally good results for detection of radiation in the energy range 20–80 keV One group has described a 10-atmosphere device and its use with Tc-99m (*5*). Significant difficulties were reported, including problems with fluorescence emission, rapid gas contamination, and signal rise-time fluctuations.

A deficiency of all reported devices is the inability of their basic electronic systems to form images at the high counting rates that are made possible by the basic MWPC detector. The potential high-count-rate capability is a feature that should be used to advantage in dynamic radionuclide studies.

We report a MWPC camera of moderate pressurization that allows nearly full realization of the device's basic advantages. The camera exceeds the state of the art in nuclear medicine imaging in both count-rate capability and spatial resolution Furthermore, its images are almost totally free of the distortions often present in Anger camera images, particularly at high count rates. The camera is also very compact, lightweight, and capable of portable operation.

Detection efficiency limits the application of the device to energies below 100 keV. Although the most commonly used radionuclide, Tc-99m, cannot be ade-

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TABLE 1. CAMERA PHYSICAL CHARACTERISTICS

Sensitive area	25 cm diameter
Sensitive depth	5 cm
Gas mixture	90% xenon, 10% methane
Gas pressure	3–5 atmospheres
Wire spacing	2 mm anode and cathode
Anode-cathode spacing	6 mm
Entrance window	0 51 mm aluminum
Total camera weight	23 kg
External dimensions	40 × 40 × 12 cm

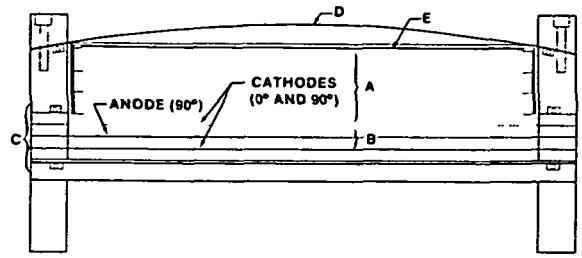

FIG. 1. Longitudinal diagram of MWPC detector showing drift region (A), detection region (B), aluminum pressure vessel (C), aluminum entrance window (D), and negative high-voltage collection electrode (E)

quately imaged, there are significant areas of application of the camera. The commercially available emitters Tl-201 and Xe-133 both should be excellently imaged by the MWPC. A newly reported radionuclide, Ta-178, (*7–9,11*) has very promising potential as a cardiac imaging agent (*9*). Its short half-life offers significant advantages over Tc-99m, and its energy (55–65 keV) is ideally suited to the MWPC A suitable generator system has been developed (*8*) and is used extensively in our laboratory. Full development of Ta-178 into a routinely available radionuclide, along with the commercial nuclides mentioned, would provide a powerful radionuclide inventory for use with the MWPC.

We present here detailed tests of the camera system, covering many of the characteristics important to application in nuclear medicine. In this paper we limit ourselves to results with the radionuclides Ta-178, Am-241, I-125, Xe-133, and Cd-109 Detailed performance with Tl-201 and Xe-133 is being explored and will be reported in the future. In addition, we present initial physiological testing of the camera with Ta-178 in animals. In this testing we have concentrated on the first-pass radionuclide ventriculography technique. Samples of these studies carried out in the dog and pig are presented.

INSTRUMENT DESCRIPTION

The MWPC detector produces a signal whose duration is one-tenth that of NaI(Tl) All commercially available instrumentation for radionuclide imaging is based on NaI(Tl), and its slow pulses significantly limit the rate at which position information can be collected. We have developed a detector and electronics that take almost full advantage of the intrinsic speed of the MWPC while maintaining a simple physical and electronic design that is compatible with low cost

The basic physical characteristics of the detector are summarized in Table 1. A longitudinal section is shown in Fig 1. The detector consists of a drift region (A) and a detection region (B), contained within an aluminum pressure vessel (C) having a thin aluminum entrance window of spherical shape (D).

X-rays entering through the aluminum window interact with the pressurized gas (xenon) in region A. The resulting ions are impelled to the detection region by a drift field of 1000 volts/cm In the detection region are mounted three parallel wire planes two outer planes being operated at ground potential (cathodes), with the inner plane at high positive potential (anode). The drifted ionization is collected at the anode, where the charge is amplified by gas avalanche

Position determination of the anode avalanche is obtained by detection of the signals induced in the two cathode grids, which are oriented orthogonally to each other. Each wire of each cathode grid is attached to a tap of a discrete delay line, and position is sensed by measurement of the delay time between occurrence of the avalanche on the anode grid and arrival of the signals at the ends of the cathode delay lines Unlike previously reported delay-line readout systems for medical applications (*4*), we use very high-speed delay lines (delay = 10 nsec/cm) (*10*) This provides a maximum delay-line clearance time of less than 250 nsec and a typical mean clearance time of 150 nsec Therefore, rate performance is improved with this system.

The encoding of the position of an event is accomplished through high-speed digital circuitry The electronic block diagram is shown in Fig. 2. The four time delays obtained from the delay lines are digitized by high-speed counters (600 MHz), which are gated by the anode signal and gated off by the delay-line outputs. These four digital values are passed on to a high-speed processing unit that forms the digital sum of the coordinates obtained from a given delay line This sum value is compared with a constant value equal to the total delay of the delay line. This test rejects any confused events that result from pile-up or scatter within the detector gas. Energy selection is accomplished by application of a pulse-height window test to the prompt anode signal If this test is failed, the digital counters are not started and the circuits are immediately ready to process a new event.

Simultaneously with the sum test, the processor also computes a difference between the delays on each axis

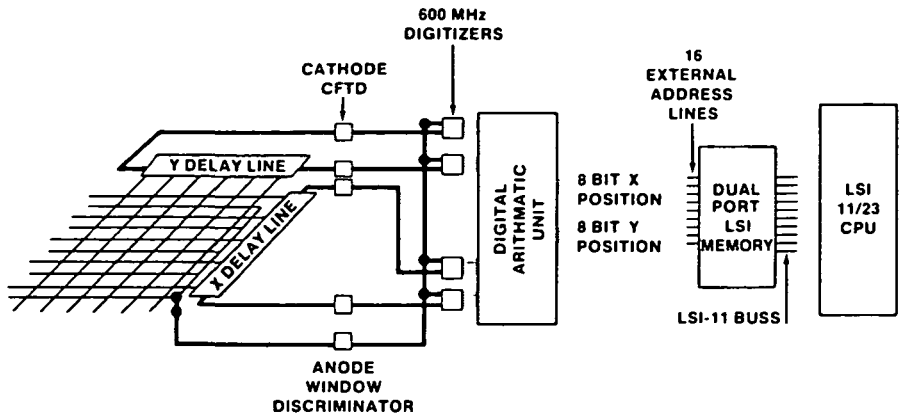

FIG. 2. Block diagram of readout electronics.

and adds a digital offset value This value for each axis (8-bit words) is used as the event position (for zero offset it is the position relative to the center of the chamber). The digital sum and difference logic is implemented with high-speed, Motorola emitter coupled logic (MECL) circuits that require less than 300 nsec to perform the sum test and to provide the difference position value.

The offset difference values (8 bits X and 8 bits Y) are passed through a formatting circuit that sets the desired frame format. Four frame sizes are facilitated—16 × 16, 32 × 32, 64 × 64, and 128 × 128. In each of these formats the cell size can be zoomed by factors of 2 and 4. A continuous zoom capability is also provided by variation of oscillator frequency, which can range from 100–600 mHz, providing a continuous zoom by a factor of 6.

The formatted digital position coordinates are transferred through a first in, first out (FIFO) memory into an LSI-11/23 computer by means of a unique dual-ported memory. This memory can respond on the LSI-11 buss as a standard RAM memory, or under software control can be set to respond on an external buss to the digital coordinates from the arithmetic processor The memory can accept events on the external buss at a rate of 3 MHz

The LSI-11 computer controls data acquisition, display, and storage Data can be stored either on a flexible disk (RX02) or hard disk (RK05). A color display system is used for image display of both processed and real-time images Static image data can be collected and stored to disk. Dynamic study data can be collected and written to RK05 disk in film-strip fashion. Frames of 64 × 64 pixels can be collected at 10 fps, 32 × 32 frames at 40 fps, and 16 × 16 frames at 160 fps. The image memory of the display system can be used as a high-speed image buffer memory. The 256 × 256 pixel memory allows storage of up to 64k bytes of acquired image data. Dynamic image data can be collected in this buffer at approximately four times the rate allowed by the RK05 disk. The LSI-11/23 also provides a powerful postdata-collection processing system.

BASIC PERFORMANCE CHARACTERISTICS

Efficiency and sensitivity. The absolute detection efficiency of the detector operated at 3 and 5 atmospheres (absolute) is plotted in Fig. 3 The efficiencies at the energies of the potentially useful nuclides I-125, Ta-178, Tl-201, and Xe-133 are indicated. Thorough pressure testing of the camera indicates that it can be operated safely at pressures up to 5 atm (safety factor of 4). Although operation at this pressure would significantly increase detection efficiencies, particularly for Tl-201 and Xe-133, we have chosen to explore thoroughly the capabilities of the device at 3 atm before going to higher pressures. All results reported here were obtained at 3 atm (absolute).

Energy resolution. The energy deposition mechanism in a MWPC is dependent on the energy of the incident photon. For energies below the K-shell excitation energy of xenon (35 keV), L-shell interactions occur and most of the photon energy is deposited entirely at the interaction site. For energies above 35 keV, the excess energy above 35 keV is deposited at the interaction site and a 30-keV fluorescence photon is emitted 88% of the time

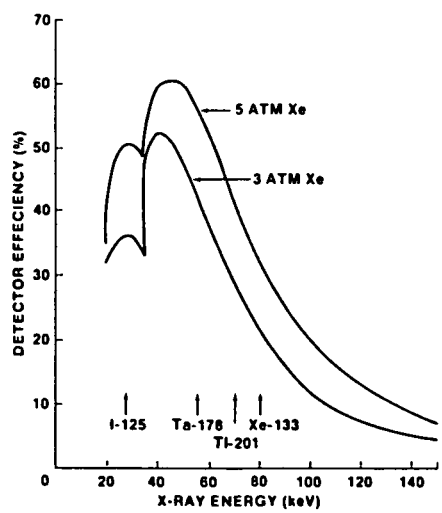

FIG. 3. Detector efficiency against x-ray energy for operating pressures of 3 and 5 atmospheres absolute

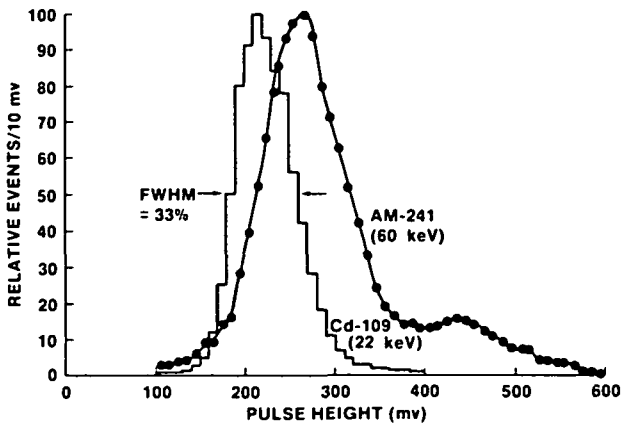

FIG. 4. Pulse-height spectra of Cd-109 (22 keV) and Am-241 (60 keV) Deposited energies in these cases are 22 and 25 keV respectively

(12% of the fluorescence emissions are internally converted, leading to total energy deposition at the interaction site).

To demonstrate the energy resolution characteristics of the MWPC, we display in Fig 4 the energy spectrum of Cd-109 and Am-241. Cd-109 emits dominantly 22 keV x-rays (Ag K x-rays) and a very low abundance (3%) 88 keV photon, whereas Am-241 emits only a 60 keV photon Thus, these two nuclides produce 22-keV and 25-keV deposited energy (with 30-keV fluorescence escape in the case of Am-241). Due to the dominance of fluorescence escape in our detector design, the intrinsic energy resolution for 60-keV x-rays from Fig. 4 is 33% of 25 keV, or 14% (FWHM) of the total incident energy This is the energy-resolution figure that should be used for comparisons with NaI devices which have negligible fluorescence escape Although this value is roughly equivalent to NaI devices, we expect significant improvement in the future through modifications in the pulse-height measurement circuitry. The current circuits use only the leading edge (first 30 nsec) of the proportional charge collected, which probably does not contain an adequate portion of the charge delivered The likely enhanced energy resolving power in the 50- to 80-keV range could be significant in rejection of Compton scatter at these low energies.

An idiosyncrasy resulting from flourescence escape should be discussed An x-ray, such as that from Ta-178, which is 25 keV above the xenon K-shell energy, is indistinguishable from x-rays of 25 keV total incident energy, since the latter are below the xenon K shell Thus, an energy window set to accept 50–70 keV x-rays, as might be done for Ta-178 imaging, will also accept Compton degraded x-rays in the energy range 15–35 keV This is of little practical consequence, since very little of the Compton radiation is able to scatter down from 60 keV to 35 keV and penetrate intervening tissue. What little flux may be present in this energy range can be very effectively removed with a copper filter This effect would be a problem only for nuclides with emissions much closer to the K-shell energy

Gas contamination is a well-known phenomenon in long-term sealed operation of MWPC detectors Electronegative gas contaminants, which can result from outgassing of detector interior structure, cause loss of primary ionization produced by x-ray interactions. Effects of such contaminants show up as a spreading of the detector's energy resolution. To evaluate this potential problem, the Cd-109 pulse-height spectrum was carefully monitored for loss of resolution over a period of 90 days No discernible deterioration occurred over this period. Thus, gas contamination is not expected to be a significant operational problem. Contamination tests of longer duration are in progress.

Rate performance. The event-rate performance of the camera was investigated by irradiation of the uncollimated camera with a 40-mCi Am-241 source In Fig. 5 various rates are plotted against the distance of this source from the camera The image rate curve (C) shows the paralyzing behavior typical of both Anger and multicrystal cameras, with a peak count rate of 850,000 cps. At this peak count rate approximately 50% of the

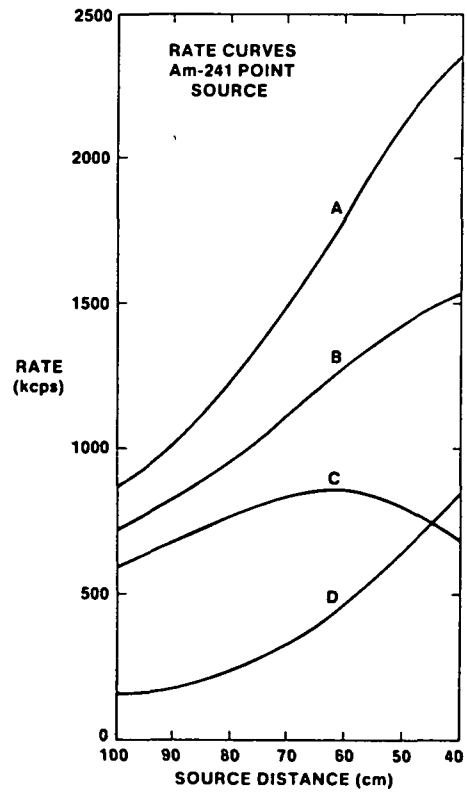

FIG. 5. Detector rates for uncollimated detector irradiated by Am-241 source, against distance of source from face of detector. A = threshold discriminator count rate B = window discriminator count rate (30% window) C = count rate passing energy window and ambiguity rejection circuitry D = rate of rejection by ambiguity circuitry

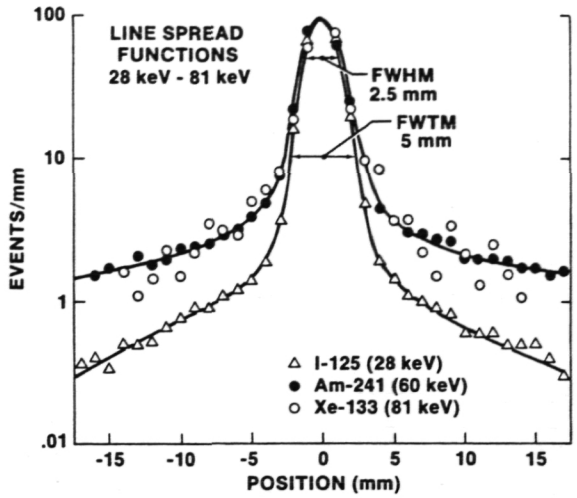

FIG. 6. Line spread functions for Am-241 (60 keV), I-125 (28 keV), and Xe-133 (81 keV). For Xe-133 a 1-mm Cu absorber was used to remove abundant xenon fluorescence x-rays.

events interacting in the detector make it through the digitizing circuitry into the image. Curve A is the anode discriminator rate; curve B the rate at which events pass the energy window; and curve D is the rate of event rejection by the sum test logic.

Intrinsic detector resolution and image uniformity. The intrinsic detector resolution was determined by irradiation of the detector along a narrow line (<1 mm width). Figure 6 shows the line spread functions measured in this way for x-ray energies of 28, 60, and 81 keV. The resolution at 28 keV determined by this technique is 2.5 mm full width half maximum (FWHM) and 5 mm full width tenth maximum (FWTM). These values are degraded by less than 5 percent for 60-keV and 81-keV x-rays.

As previously indicated, most of the detected events in the MWPC are events for which fluorescence escape has occurred. Fluorescence photons have a large mean range in the gas (11 cm). Thus, in the small percentage of cases that these x-rays interact, they can significantly alter the measured x-ray position. The effect of fluorescence on resolution can be quantified by comparing the 60-keV and 81-keV line spread functions with that for 28-keV x-rays from I-125 (Fig. 6). The latter do not excite fluorescence. The FWHM and FWTM values are only very slightly degraded by the presence of this radiation; however, the effect of fluorescence shows up in two subtle ways. First, there is a low-level halo effect, which appears as a small tail in Fig. 6. It results from clean detection of a fluorescence photon, usually many cm from the interaction site. Second, a higher sum-test rejection rate is observed for the 60-keV radiation. At low event rates, a rejection rate of 13% is observed for 60 keV whereas 3% is observed for 22 keV. These measurements show that very small effects on image quality result from the fluorescence. The effect is limited to a slight reduction in sensitivity (10%) and a very low-level, diffuse halo. Most of the events with associated fluorescence interactions are rejected by the sum-test logic.

Image uniformity was investigated by irradiation of the uncollimated detector with an Am-241 source at a distance of 1.5 meters. The resulting flood image is shown in Fig. 7A for a pixel resolution of 2 × 2 mm. Uniformity fluctuations of at most ±5% are present.

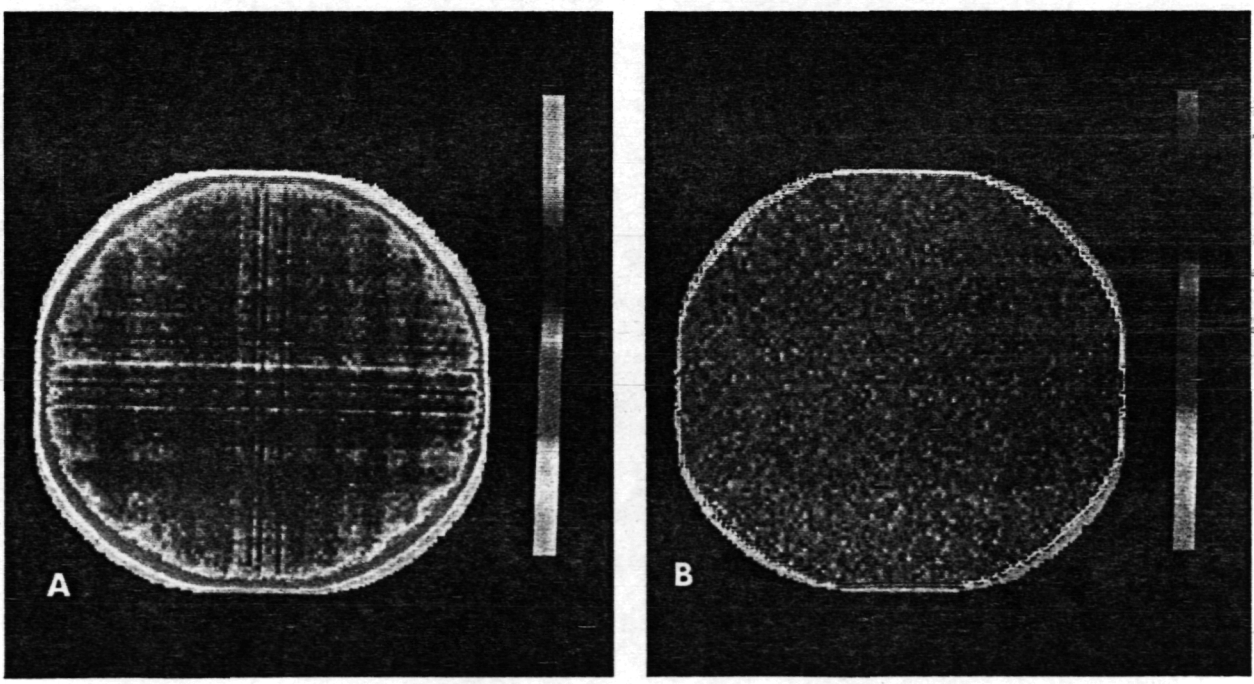

FIG. 7. A: Am-241 flood image obtained by irradiation of uncollimated detector at 1.5 m distance; 128 × 128 format with 2 × 2 mm cell size. B: corresponding flood-corrected image.

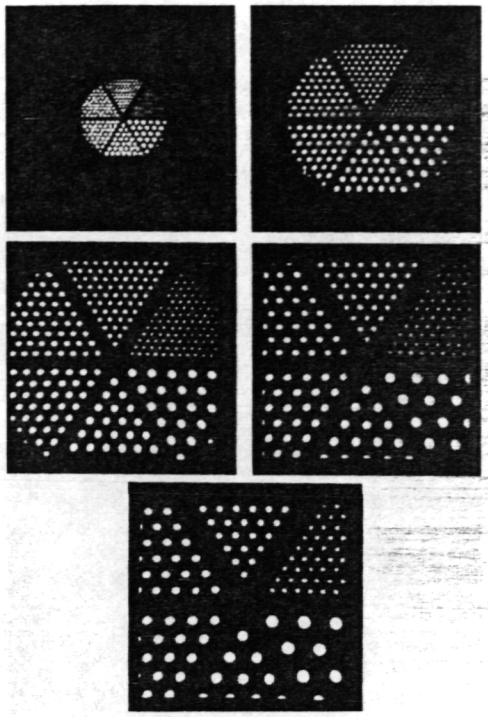

FIG. 8. Anger pie-phantom images for oscillator frequencies of 100, 200, 300, 400, and 500 MHz.

Most of the nonuniformity is confined to very-high-frequency fluctuations within a spatial scale of less than 3 mm. These likely result from differential nonuniformities of the delay lines used for readout and from slight variations in detector wire spacing. The nonuniformities have been shown to be both stable and correctable. Figure 7B is a "flood corrected" flood image in which the nonuniformities have been reduced to less than ±1% by flood correction. In many applications such as cardiac imaging, in which high spatial resolution (<5 mm FWHM) is not required, such correction is not necessary.

In order to compare the overall image quality of the MWPC with that of the Anger camera, we have performed standard phantom testing. Figure 8 shows a series of images obtained by irradiation of the uncollimated detector through a standard Anger pie phantom. An Am-241 source was used at a distance of 1.5 m. The zoom effect in these images was obtained by varying the digitizer oscillator frequency from 100 to 500 MHz in 100-MHz steps. The images were collected in 128 × 128 format, with the cell size ranging from 1 × 1 mm for the 500-MHz image to 5 × 5 mm for the 100-MHz image.

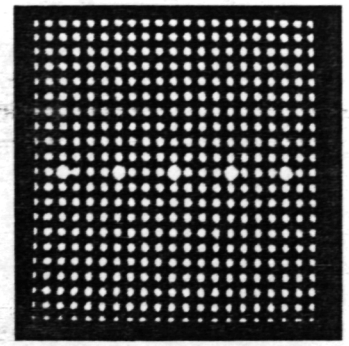

FIG. 9. Image of Smith orthogonal hole phantom obtained with Am-241 source at 1.5 m distance and detector event rate of 100,000 cps.

Image distortions were investigated by irradiation of the detector through a standard Smith orthogonal hole phantom (0.63-cm spaced grid of holes 0.16 cm in diameter). An Am-241 source was used at a distance of 1.5 m. Figure 9 shows the resulting image, obtained in 128 × 128 format, 1 × 1 mm cell size, with a detector count rate of 100,000 cps.

Imaging with parallel-hole collimators. Two conventional parallel square-hole collimators have been used with the MWPC camera. Their characteristics are shown in Table 2. Most of the studies reported used the high-sensitivity (HS) collimator, which was chosen to provide adequate resolution and high sensitivity for dynamic cardiac studies. This collimator has an intrinsic sensitivity more than twice that of the Baird 1.5″ collimator and smaller angular acceptance by a factor of 0.77. This collimator's higher sensitivity more than offsets the lower efficiency of the MWPC relative to NaI(Tl). This is a result of the much lower packing fraction of the conventional collimator optimized for low energies, as compared with the Baird collimator, which has very thick septa (*12*).

The sensitivity of the detector operated at 3 atm, measured for the high-sensitivity and high-resolution (HR) collimators, is shown in Table 3 for I-125 and Ta-178 emitters. The calculated sensitivities for Tl-201 and Xe-133 are also included.

The image count rate relative to the Ta-178 dose has

TABLE 2. COLLIMATOR CHARACTERISTICS—CONVENTIONAL SQUARE HOLE

Collimator	Hole length (cm)	Hole size (cm)	Septal thickness (cm)	Sensitivity
High resolution (HR)	2.2	0.14	0.018	9050 cps/mCi
High sensitivity (HS)	1.1	0.14	0.018	36200 cps/mCi

TABLE 3. INSTRUMENT SENSITIVITY IN cps/mCi FOR VARIOUS EMITTERS

Collimator	I-125	Ta-178	Tl-201	Xe-133
High resolution (HR)	3700	3710	2830	2125
High sensitivity (HS)	15000	14900	11351	8513

been determined. A 3-in.-diam beaker containing 70 mCi of Ta-178 in water solution was placed 3 in. above the face of the camera with the HS collimator in place, and the event rate in the detector recorded for a 30-minute period (>3 half-lives). The resulting dose-response curve is plotted in Fig. 10.

The resolution performance of the MWPC camera, using the HS and HR collimators, has been investigated using an Am-241 source 2 mm in diameter. The point spread functions were obtained for various distances between source and collimator in air and in a water bath 15 cm deep. The FWHMs from these point spread functions are plotted in Fig. 11. Note that although much of the Compton-scattered radiation is detected due to the small energy loss in a single Compton interaction at 60 keV, it has very little effect on FWHM. This is doubtless because the Compton angular distribution at 60 keV is nearly isotropic. Thus, much of the scatter entering the collimator is relatively far from the source, resulting in a diffuse halo.

Increased attenuation losses is a concern often expressed with regard to application of low-energy emitters. It is important to realize, however, that the differences between 140 keV and 60 keV is of minimal significance in many applications. The mass attenuation coefficients of soft tissue at these two energies are 0.154 cm^2/g and 0.204 cm^2/g, respectively. At tissue depths

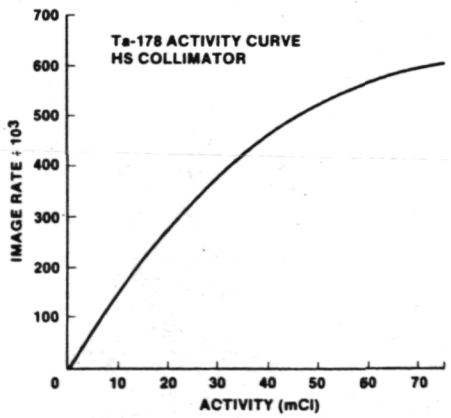

FIG. 10. Detector image rate produced by decaying Ta-178 solution in 7.5 cm beaker, placed 7.5 cm above MWPC camera with HS collimator.

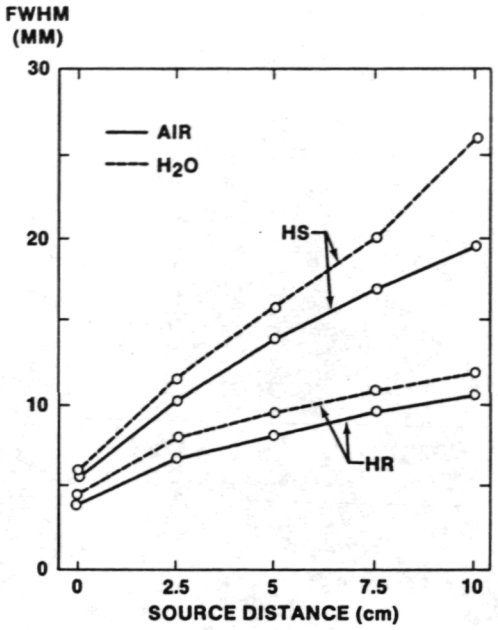

FIG. 11. FWHM plotted against distance to Am-241 point source, in air and H_2O, with HR and HS collimators.

typically encountered in cardiac imaging (5–10 cm), 60 keV produces a transmitted flux of 73% of that produced by an equal 140-keV dose. Only for deep-organ imaging (>10 cm depth) are image statistics significantly affected by 60-keV x-ray energy compared with Tc-99m. For example, at a 15-cm depth, 60-keV radiation is attenuated to 47% of that of 140-keV radiation. Bone attenuation is another potential concern. To evaluate the effect of sternum and rib attenuation upon cardiac images, we have measured the total attenuation of 60-keV radiation in human cadaver dry specimens. In the anterior and left anterior oblique projections, the total sternal attenuation in an average subject was found to be less than 4%, and the rib attenuation less than 3%. These values are below the statistical noise level in typical cardiac images, and therefore should be of little consequence.

ANIMAL CARDIAC STUDIES

First-pass radionuclide ventriculography studies have been carried out in animal subjects in order to determine the effectiveness of the MWPC camera and Ta-178 combination in a common dynamic study. We used a 32-kg dog and a 68-kg pig. Several studies were performed in each subject at short repeat intervals to determine the reproducibility of ejection fraction and wall-motion measurements. Images were evaluated for overall quality. For comparison, a study was carried out in a pig using Tc-99m and a multicrystal camera*. All MWPC studies used the high-sensitivity collimator, whereas a standard 1″ collimator was used with the camera.

TABLE 4. SUBJECT DATA

Subject number	Species	Weight	Anesthesia	Ta dose	or	Tc dose
1	dog	32 Kg	nembutal	20 mCi		—
2	pig	68 Kg	sodium thiamylal	12 mCi		15 mCi

METHODS

A jugular venous catheter was implanted in each subject to provide for reproducible bolus injection and for convenience in handling the subjects. The catheter was inserted to the junction of the superior vena cava and right atrium. All subjects were anesthetized for the duration of the studies—pentobarbital for the dog and sodium thiamylal for the pig—in titrated amounts to produce sedation but not respiratory arrest. Tantalum-178 was injected in all cases as a 1.5-ml bolus followed by a 10-ml rapid saline flush (<0.5 sec injection time). Technetium-99m was injected as a 0.5-ml bolus followed by a 10-ml flush.

Detailed subject data are shown in Table 4. MWPC image data were collected in a 16 × 16 cell format and 1 cm^2 pixel area. Frame collection was begun just before injection and continued for 20 sec. The frame rate was varied from study to study so that ~16 frames per cardiac cycle were collected. The multicrystal camera study used the standard procedure with 50 fps.

All studies were analyzed to obtain left-ventricular volume curves, ejection fraction, and representative cycle images. Data analysis of the MWPC studies was identical to that of the Baird study with two exceptions. A first-order spatial smoothing was applied to the raw data rather than the temporal smooth, and the left-ventricular phase background subtraction was applied without temporal variation.

Three studies were performed on Subject 1 (Table 4) at 30-min intervals, the first two in the anterior position and the third in left lateral. Subject 2 was studied once in left lateral and once, 1 hr later, in the anterior position. The multicrystal camera comparison studies were performed on this subject 2 hr later, with light anesthesia maintained in the interim. A left lateral study was performed first (15 mCi of Tc-99m) followed 15 minutes later by an anterior study (15 mCi of Tc-99m). A static background was collected between studies and used to subtract background from the second study.

RESULTS

The analyzed left-ventricular images for one anterior and one left-lateral canine study are shown in Fig. 12. The diastolic image border, defined as the point at which the background-subtracted image is 30% of the highest pixel, is shown in white. The color-encoded systolic image is superposed on this border. A second anterior study (not shown) was virtually indistinguishable from the one shown. The calculated ejection fractions for the three studies were 49 and 46% for the two anterior studies and 54% for the left-lateral.

Analyzed left-ventricular images from the pig (Subject 2) are shown in Fig. 13. Ejection fractions of 62% and 68% were found for the anterior and left-lateral views, respectively. A comparison of the left-lateral MWPC study and a similar one on the multicrystal camera is shown in Fig. 14. For ease of comparison, both studies were analyzed on the multicrystal system using identical procedures. The injected doses were 12 mCi (Ta-178) and 15 mCi (Tc-99m). The measured ejection fractions were 62% and 64%.

DISCUSSION

It is evident that the left ventricle is well visualized by this technique. Wall motion is easily determinable. Measurements are repeatable to the extent that the physiologic specimen can be expected to remain stable from study to study.

The MWPC/Ta-178 study compares well with the multicrystal/Tc-99m study. Qualitatively, the images are very similar. Two differences were noted in the data. The total-image statistics for the Ta-178 study were ~30% lower for the same administered dose, and the ventricular cross-sectional area, as determined by standard Baird software, was somewhat increased (25%). The former effect is doubtless a result of the slightly higher attenuation of 60-keV radiation relative to 140 keV. The latter effect probably results from the presence of more background in the Ta-178 study, which is not handled correctly by the standard Baird background subtraction. A separate background technique for Ta-178 will likely be needed for absolute volume measurements.

CONCLUSIONS

The much improved count rate, resolution, and portability of the MWPC detector should lead to significant enhanced capabilities in clinical nuclear medicine applications. The MWPC, however, will have certain optimal areas of application, but in others it will have little

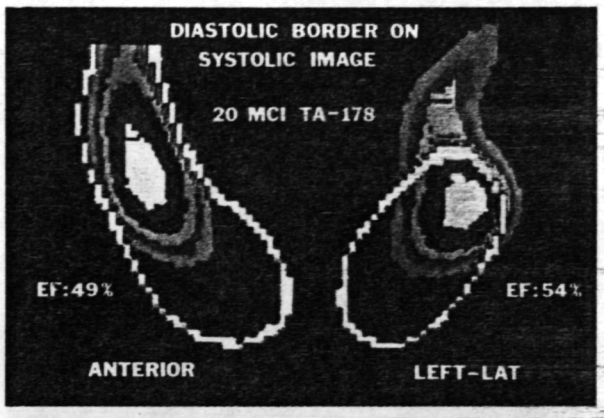

FIG. 12. Representative first-pass study in 32-kg dog, with 20-mCi Ta-178 injection.

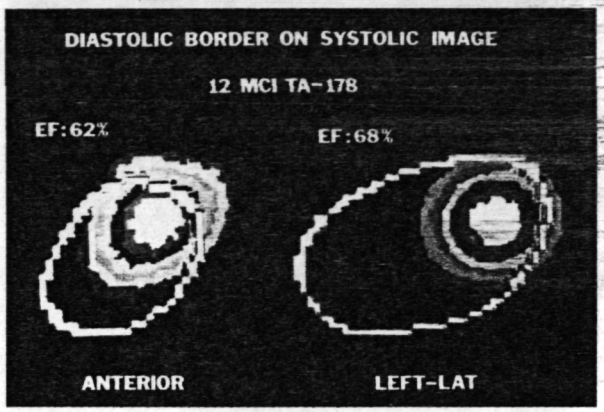

FIG. 13. Representative first-pass study in 68-kg pig, with 12 mCi Ta-178 injection.

or no advantage over existing NaI imaging devices. The limitation of the MWPC to energies below 100 keV makes the imaging of deep organs (>10 cm) difficult due to greater attenuation losses. The concomitant problem with the low-energy limitation, suboptimal scatter rejection, makes it unlikely that the MWPC will compete in photon-deficient applications such as liver imaging. The MWPC should excell, however, in imaging of shallow organs with foci of increased activity, benefiting from high count capability combined with good spatial resolution. Thus, cardiac imaging is a most promising area of application. Many of the limitations in this field currently result from poor counting statistics in first-pass studies and long acquisition times in gated studies. Significant improvement in both of these areas should result from use of the MWPC and Ta-178. They offer whole-body doses a factor of 20 below those with Tc-99m, and critical-organ doses a factor of 65 below those of Tc-99m (*8*). Therefore, much larger doses are possible and multiple studies can also be performed. This, combined with the high count capability of the MWPC, will provide greatly improved image statistics in first-pass studies and lower acquisition times in gated studies. Additional benefits in this field will likely accrue from the compactness of the MWPC, which will allow multiple-head cameras providing simultaneous multiple-view imaging. Single or multiple-head devices with high portability are also possible for application in coronary care units and mobile clinic settings.

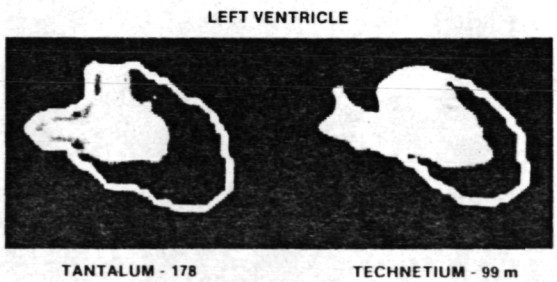

FIG. 14. Comparative study in 68-kg pig. Left: LV image from 12-mCi Ta-178 MWPC first-pass study of Fig. 13, processed by multicrystal camera software. Right: LV image from 15-mCi Tc-99m first-past study carried out and processed on multicrystal system.

Pediatric cardiac applications in particular should benefit greatly from the low radiation exposure of Ta-178. The higher resolution of the MWPC should offer an important enhancement as well in this area, where very high count rates can be achieved over very small spatial dimensions. One can envisage sueh applications as serial shunt quantitation in which a patient could be studied repeatedly to evaluate shunt status, without catheterization. Also, many forms of anomalous cardiac structure could be assessed with Ta-178 first-pass studies. Yet another application is serial evaluation of the effects of corrective surgery.

Although some of the advantages of Ta-178 could be achieved with NaI devices, cameras currently on the market have significantly compromised performance

with Ta-178 due to high-energy emissions at 0.5 and 1 MeV (*7–8*). These photons penetrate even very-high-energy collimators and are picked up by the NaI crystal with enough efficiency to produce significant deadtime losses (*11*). Although these high-energy gammas penetrate the MGC collimator, they are picked up by the gas detector with far lower efficiency and therefore have little or no effect on deadtime.

Radiology is another field of application for which the MWPC is well suited. Bone densitometry can be carried out by transmission imaging in a fraction of the time required for the scanning techniques, the use of which is increasing. The MWPC has excellent detection characteristics for x-ray energies appropriate for this work (30–80 keV). The high rate capability of the device reported here allows very rapid single-image acquisition, which may be of importance for such applications as osteoporosis screening and diagnosis. This may allow multiple views to be acquired or even tomographic image formation in the same or less time than is required for single-view images using current technology.

Finally, lower instrumentation cost is another potential advantage of the MWPC camera. If mass produced, this device should be cheaper and easier to maintain than sodium iodide devices, and considerably more rugged. The MWPC readout system reported here, being digital in nature, is entirely free from adjustment problems such as those caused by photomultiplier gain drift in crystal cameras.

FOOTNOTE

* Baird System 77.

ACKNOWLEDGMENTS

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REFERENCES

1. CHARPAK G, et al: The use of multiwire proportional counters to select and localize charged particles. *Nucl Inst Methods* 62:235–240, 1968
2. CHARPAK G, BOUCLIER R, BRESSANI T, et al: Some readout systems for proportional multiwire chambers. *Nucl Inst Methods* 65:217–220, 1968
3. ZIMMERMAN RE: Advances in nuclear medicine imaging instrumentation. In *Medical Radioisotope Scanning.* Vol. 1, pp 121–125, 1976
4. PEREZ-MENDEZ V, KAUFMAN L, LIM CB, et al: Multiwire proportional chambers in nuclear medicine: Present status and perspectives. *J Nucl Med Biol* 3:29–33, 1976
5. BOLON C, et al: Pressurized xenon-filled multiwire proportional chamber for radionuclide imaging. *IEEE Trans Nucl Sci*, NS-25(1):661–664, 1978
6. BORKOWSKI CJ, KOPP MK: Electronic discrimination of the effective thickness of proportional counters. *IEEE Trans Nucl Sci*, NS-24(1):287–292, 1978
7. HOLMAN BL, HARRIS GL, NEIRINCKX RD: Tantalum-178—a short lived nuclide for nuclear medicine: Production of the parent W-178. *J Nucl Med* 19:510–513, 1978
8. NEIRINCKX RD, JONES AG, DARUS MA, et al: Tantalum-178—a-short lived nuclide for nuclear medicine: Development of a potential generator system. *J Nucl Med* 19: 514–519, 1978
9. HOLMAN BL, NEIRINCKX RD, TREVES S, et al: Cardiac imaging with tantalum-178. *Radiology* 131:525–526, 1979
10. LACY JL, LINDSEY RS: High resolution readout of multiwire proportional counters using the cathode coupled delay line technique. *Nucl Inst Methods* 119:483–498, 1974
11. LEBLANC AD, LACY JL, JOHNSON PC, et al: Tantalum-178 count-rate limitations of Anger and multicrystal cameras. *Radiology* 146:242–243, 1983
12. JONES RH, GRENIER RP, SABISTON DC JR: Description of a new high count rate gamma camera system. In *Medical Radioisotopes Scintigraphy*, International Atomic Energy Agency, SM-164/122:299–312, 1973

Nuclear Medicine's Role in NASA

RADIONUCLIDE STUDIES IN ASTRONAUTS PROVIDE DATA ON MICROGRAVITY EFFECTS

The Lyndon B. Johnson Space Center will provide a special tour covering medical and technical research for attendees of the Society's 32nd Annual Meeting in Houston, TX, this month.

The U.S. National Aeronautic and Space Administration (NASA) began using nuclear medicine techniques during the Gemini program in the early 1960s to determine the effects of weightlessness on plasma volume and red cell mass, explained Philip Johnson, MD, a researcher in NASA's Medical Sciences Division.

Dr. Johnson will give a presentation on the nuclear medicine aspects of the space program, which is now exploring a new gamma camera and radionuclide for use in the Space Lab and Shuttle missions, during the Society's tour.

Bed rest simulates space flight

Bed rest is used to simulate space flight, explained Dr. Johnson. Since plasma volume decreases during bed rest, NASA scientists were not surprised to find that it also decreased in Gemini IV astronauts, who underwent iodine-131 human serum albumin studies.

"What was totally unexpected," said Dr. Johnson, "was that when we calculated the volume of the red cell mass from the determined blood plasma volume, we found a decrease in red cell mass."

Subsequently, the crews of the Gemini V and Gemini VII missions underwent, after splashdown, chromium-51 red cell mass studies which showed a significant decrease in erythrocytes.

"I think we had the only NRC license that stated we could do studies at sea and in international waters," said Dr. Johnson.

NASA scientists are still trying to discover the cause of the decrease in red cell mass. After iron kinetics studies during Spacelab I in late 1983, the NASA team found a fairly normal rate of iron incorporation, and discounted the theory of inhibited erythropoiesis.

With Spacelab IV, scheduled to fly in early 1988, NASA plans to run plasma volume, red cell mass, red cell survival, and iron turnover determinations in space, said Dr. Johnson, in both humans and rats.

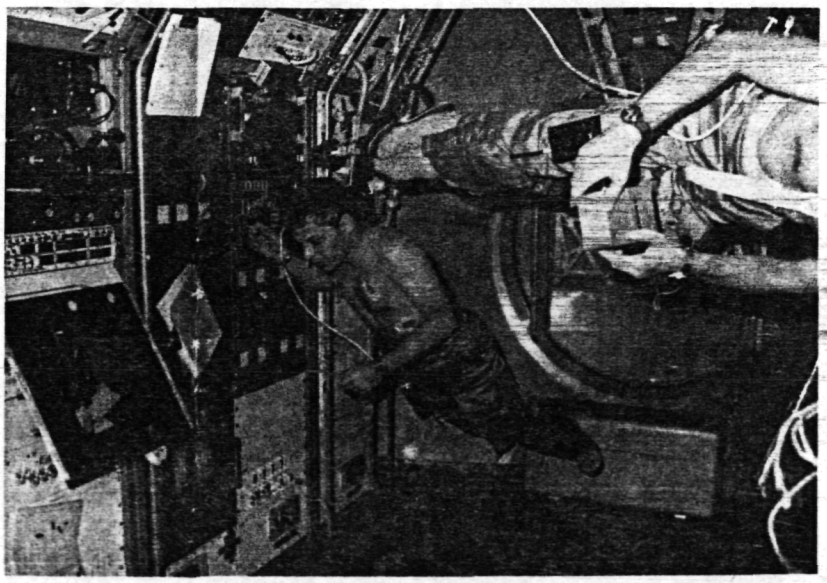
Spacelab IV passengers will also be injected with radioactive aldosterone to measure secretory rates.

"I think NASA has lead the way in radioassays," said Dr. Johnson. "Our methods of determining red cell mass and plasma volume are more accurate than methods used elsewhere in clinical settings."

Bone loss in weightlessness

Immobilization and space flight entail considerable losses of trabecular bone, averaging about one percent per week, although the

(continued on page 560)



NASA astronaut Robert A.R. Parker (left), mission specialist aboard Spacelab I, monitors biomedical testing with fellow crewman Ulf Merbold, a payload specialist with the European Space Agency. The mission was in orbit from November 28 to December 8, 1983. **(Courtesy of NASA)**

(continued from page 559)

degree of loss may vary greatly among individuals, reported Richard B. Mazess, PhD, associate professor of medical physics at the University of Wisconsin.

Dr. Mazess participated in a NASA program to study bone loss in bed rest subjects, Skylab astronauts, and patients with spinal cord injuries. "The major advances of the past several years in bone measurement have direct applications for manned space missions, paraplegics, patients confined to bed by disease, and the large population of relatively hypodynamic elderly individuals," he said in an editorial in *Calcified Tissue International* (*1*).

These advances in bone measurement include dual-photon absorptiometry and x-ray computed tomography. NASA conducted bone densitometry studies during the Apollo program (which included the first moon landing in 1968) and in Skylab missions.

Slow-twitch muscles atrophy

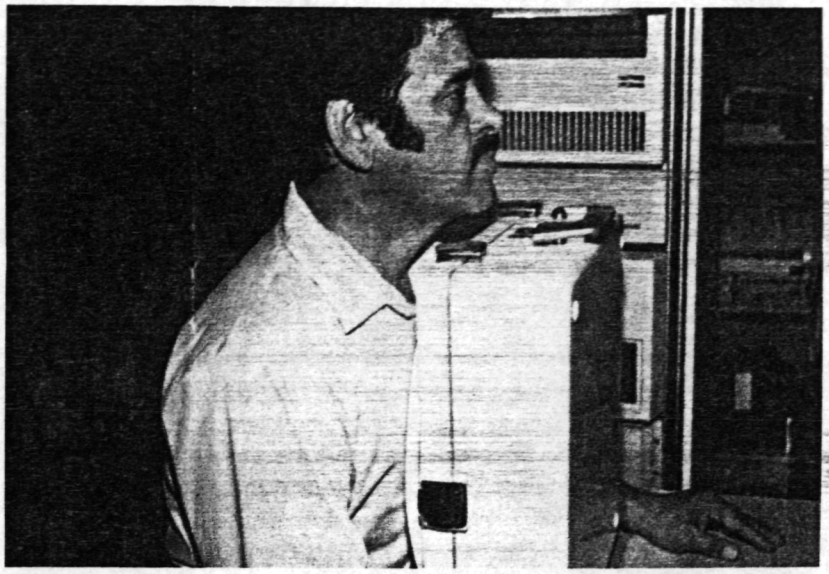
NASA is now actively pursuing the use of nuclear magnetic resonance (NMR) procedures to measure muscle atrophy in legs, said Dr. Johnson. "We see quite a bit of atrophy with bed rest," he said, "but we haven't tested spaceship crews yet."

The slow-twitch muscles, which maintain a body's upright position, "show quite dramatic changes in the amount of water absorbed when a subject stands after a period of bed rest," he explained. (Fast-twitch muscles are used in running.)

Tantalum-178 shows promise

A new low-energy radionuclide, tantalum-178, shows promise in potential clinical applications in pediatric nuclear cardiology and in patient settings that require a lightweight portable imaging system.

Mallinckrodt's Diagnostic Products Division will be supplying tantalum processed columns to Methodist Hospital in Houston for research purposes. The radionuclide is generated there for use in clinical trials with a multi-wire proportional camera, also created through NASA research.



Subject undergoing a study with a multi-wire proportional gamma camera, developed through the NASA space program. **(Courtesy of NASA)**

Jeffrey Lacy, PhD, assistant professor of medicine at Baylor College of Medicine, played a key role in designing the camera, and is now comparing the device to other imaging systems.

Unlike the Anger camera, the multi-wire proportional camera does not use a crystal. A gas-filled component with a grid serves as the detector, which is highly sensitive to low-energy (under 100 keV) gamma rays.

"With a prototype system, we're working at around 900,000 counts per second, which is roughly a five-fold improvement over the single crystal," said Dr. Lacy. "I also believe that the imaging capabilities with regard to uniformity and spatial resolution are quite superior," he added.

Dr. Lacy said that the camera weighs 50 pounds (as opposed to several hundred pounds for a typical Anger camera) and occupies a volume of approximately 15 by 15 by 5 inches, lending itself to "bedside imaging" capabilities.

"We think it would be very practical for maneuvering around in the coronary care unit or the post-surgical unit—to get in and do a study and get out without major inconveniences to the patient," said Dr. Lacy.

The camera loses sensitivity and resolution with high-energy radionuclides such as technetium-99m. Although tantalum-178 is years away from possible commercial use, it shows potential as a valuable diagnostic tool.

In cardiovascular applications, for example, "if it can be used for a multiple-gated acquisition and first-pass studies with the same isotope within a relatively short time, and aid the physician in better patient management, then the multi-wire proportional camera/tantalum-178 combination have an excellent chance to succeed in the market," said Dennis C. Wolfe, product manager of in vivo radiopharmaceuticals at Mallinckrodt.

References

1 Mazess RB, Whedon GD: Immobilization and Bone. *Calcified Tiss Intl* 35:265-267, 1983

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Radionuclide Generators

New Systems for Nuclear Medicine Applications

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Oak Ridge National Laboratory

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Evaluation of Adsorbents for the Ta-178 Generator

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The currently used Ta-178 generator is based on a radiation sensitive adsorbent and can be eluted about 50 times before W-178 breakthrough becomes unacceptable. We evaluated a series of inorganic and organic adsorbents as support for this generator. Hydrated inorganic materials adsorb tantalum very strongly from most aqueous solutions and none was found useful for the W-178/Ta-178 generator. Tantalum complexing agents are not able to desorb tantalum without dissolving the adsorbents to an appreciable extent. Chelating resins with a high affinity for W were investigated because they could reduce the W-178 breakthrough. They also adsorb tantalum too strongly to be suitable as substrates for the Ta-178 generator.The Bio-Rad AG1x8 system was found to be superior to the other tested systems. The effects of autoclaving, complexant additives and prolonged elution on the Ta-178 yield were measured and the chemical breakdown products quantitated.

The usefulness of generator-derived short-lived radionuclides is well established. The principal advantages are the opportunity to perform rapid repeat studies after various interventions and the use of high levels of activity without subjecting the patient to an unacceptable radiation dose. Special detectors are necessary for the detection of these high activities of radionuclides since the standard Anger-camera is not able to handle such high count rates. One is practically limited to multi-crystal cameras or gas cameras like the multi-wire proportional (MWPC) or the gas scintillation counters. This implies that the electromagnetic radiation of the radionuclide should preferably be of low energy, as these are most suitable

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for efficient detection with gas detectors. Such low-energy electromagnetic radiation can be found in the characteristic x-rays of heavy elements.

Tantalum-178 (Ta-178) is a short-lived radionuclide ($T_{1/2}$ = 9.3 min) that decays with emission of characteristic hafnium x-rays which are efficiently detected by the MWPC. The usefulness of Ta-178 lies mainly in the low patient radiation-dose per mCi injected. The high activities that can be injected generate the high photon fluxes that allow an accurate evaluation of fast physiologic processes. The principal use of Ta-178 has been in the assessment of the left ventricular ejection fraction (1,2).

A generator for the production of Ta-178 has been described earlier (1). It is based on an organic anion-exchange resin which is sensitive to radiolysis. The distribution coefficient for tungsten (W) under the separation conditions is low (2), which results in increased W-178 breakthrough after approximately 50 collections. Furthermore, the eluate has not previously been evaluated for organic resin breakdown products. This paper summarizes the results of a thorough evaluation of the existing Ta-178 generator and an evaluation of alternative adsorbents, most of them inorganic, as generator support media.

Experimental

Radionuclide Properties of Ta-178. Tantalum-178 is formed from the decay of its parent W-178 ($T_{1/2}$ = 21.7 d), and has a half-life of 9.3 minutes yielding stable Hf-178. The decay of the parent isotope (W-178) occurs entirely by electron capture to the 9.3 minute Ta-178 state, without feeding the high spin Ta-178 isomer (half-life 2.4 hrs). In Ta-178 decay, 99.2% of the disintegrations proceed by electron capture and 0.8% by positron emission. Electron capture results in a 61.2% branch to the ground state of Hf-178 and 33.7% to the first excited state at 93.1 keV. The balance, 4.3%, feeds hafnium levels between 1175 and 1772 keV. The most prominent features of the energy spectrum of this radionuclide are the hafnium characteristic x-rays with energies between 54.6 and 65.0 keV.

Materials. A number of inorganic and organic adsorbents were evaluated. All the inorganic materials are hydrates and were evaluated in combination with injectable aqueous solutions. Complexing agents were added to some eluents in order to reduce tantalum adsorption. Chelating resins, such as the pyrogallol-formaldehyde copolymer, were tested for their adsorption of tungsten. The adsorption of tantalum onto non-hydrated adsorbents such as the organic adsorbent Bio-Rad AG1x8 and silylated silica were evaluated.

The following chromatographic inorganic adsorbents were donated by Applied Research SPRL (Belgium): hydrous titanium oxide, titanium oxide-hydrogen peroxide hydrate, hydrous zirconium oxide, hydrous ferric oxide, hydrous stannic oxide, polyantimonic acid, silicic acid, hydrous chromium oxide, hydrous manganese dioxide, zirconium phosphate, tin phosphate, Phomix (20% ammonium phosphotungstate in zirconium phosphate), Siphozir (zirconium phosphate-silicate), chromium phosphate, titanium phosphate, molybdenyl ferrocyanide, zirconium ferrocyanide, ferric ferrocyanide and K-Co ferrocyanide. Alumina was obtained from Woelm (Eschwege, Germany). Tungsten carbide, non-chromatographic, was obtained from Pfaltz and Bauer (Stamford, Conn.). Tungsten disulfide was obtained from Alfa-Ventron (Danvers, Mass.). Bio-Rad AG1x4A was obtained from Bio-Rad (Richmond, Ca.). Some inorganic materials were synthesized in our laboratory. This group included tungstic acid, CaF_2 and SrF_2-coated Al_2O_3, anhydrous SnO_2, TiO_2, SiO_2, CrO_3, MnO_2, tin phosphate, zirconium phosphate, titantium phosphate, molybdenyl ferrocyanide, zirconium ferrocyanide and ferric ferrocyanide. Tungstic acid was produced by heating WO_3 with a B_2O_3 flux to 1,200°C, cooling the melt to 800°C at a rate of 2°C/hour and then to room temperature. The CaF_2- or SrF_2-coated Al_2O_3 were prepared by treatment of an Al_2O_3 adsorbent, saturated with Ca^{2+} or Sr^{2+} with a NaF solution. Controlled pore glass beads (237 A mean diameter) were obtained from Electronucleonics, Inc. (Fairfield, NJ). Silane Z-6020 was obtained from Dow-Corning. Two kinds of chelate resin were synthesized and evaluated: A pyrogallol-formaldehyde copolymer (3,4) and a copolymer of alphabenzoin oxime with formaldehyde. Bio-Rad AG1x8 200-400 mesh was used as adsorbent to evaluate the published generator method (1). Silylated silicagel was prepared according to the procedure of Leyden, et al (5). Fine grains of controlled-pore glass beads (CPG) were heated for three hours with 100 ml of a 10% solution of Z-6020 silane in toluene. The filtered and toluene-washed product was dried overnight at 80°C and used as a tungsten-adsorbent.

Determination of Partition Coefficients (K_D). The K_D values of W and Ta between the adsorbents and various mobile phases of interest were measured by batch equilibration. The first adsorbent was pre-equilibrated three times with the liquid phase, and the supernate decanted. The batch equilibration was performed using 100 mg of adsorbent and 5 grams of mobile phase, to which a W-178-Ta-178 mixture was added. The two phases were then shaken for 10 minutes by means of a Hematec Aliquot mixer.

After centrifugation, samples from each phase were analyzed for W-178 and Ta-178 using a Ge (Li) detector coupled to a Nuclear Data ND60 γ-spectrophotometer. Tantalum-178 was quantitated using its 93 keV gamma-ray. After correction for physical decay, the K_D values are calculated as the ratio of the concentrations of the element in the static and the mobile phase (2). Since the concentrations are proportional to the radioactivity level

$$K_D = \frac{\text{activity of radionuclide/g adsorbent}}{\text{activity of radionuclide/g mobile phase}}$$

where the adsorbent is always weighed as an air-dried powder. Tungsten-178 was quantitated after both fractions were allowed to decay for 90 minutes and by counting the equilibrium activity of Ta-178 associated with the W-178. The K_D-values were calculated as for tantalum.

Adsorption Studies. The inorganic adsorbents listed above wei evaluated with the following non-complexing eluents: 10^{-3}N HCl, 0.1N NaOH, 0.25% $Na_2HPO_4.7H_2O$, 0.9% NaCl and 0.1% $NaHSO_3$. The adsorption of W and Ta onto organic adsorbents was also evaluated. The W and Ta adsorption onto the pyrogallol-formaldehyde resin was evaluated with aqueous mobile phases as a function of pH. The K_D of W and Ta between silica or silylated silica and mobile phases containing dilute HCl or 1% NaF were determined. An attempt to improve the adsorption of W onto Dowex 1x8 was made by converting the loaded W-178 activity to phosphotungstate, either by recrystallizing the phosphotungstate and using its HCl solutions or by forming it in situ by means of H_3PO_4 and direct evaluation of this solution. The K_D values for W and Ta between Bio-Rad AG1x4 and HCl solutions of differing normality were also determined. The effect of the addition of 10^{-2} M or 10^{-1} M H_3PO_4 to the 0.1 N HCl mobile phases was measured. The K_D values for W and Ta between either HCl or NaF solutions and the chelating resin Chelex 100 were determined as a function of the pH of the mobile phase.

The adsorption of W and Ta onto inorganic adsorbents from mobile phases containing fluoride was also studied. The K_D values of W and Ta between fluoride containing aqueous phases and MnO_2, Ti-phosphate, SiO_2, silylated SiO_2 and SrF_2 were determined as a function of the pH of the mobile phase. A study was made of the rate of adsorption of W and Ta onto ZrO_2 from a 0.1%

Na-oxalate solution and onto MnO_2 from 1% NaF solutions. A study of the rates of desorption of W and Ta from MnO_2 by means of 1% NaF solutions was made.

Distillation Generator. Irradiated tantalum foils were dissolved in HF + HNO_3, the solution converted to 29N HF and heated to boiling in an all-Teflon distillation apparatus. Nitrogen was used as a carrier-gas to distil (W-178) WF_6 which could be used to generate the non-volatile (Ta-178)TaF_5. This would then be isolated by vacuum manipulation of the WF_6.

Further Evaluation of the Existing Ta-178 Generator. Shielded Ta-178 generators of 2 cc bed size that can be eluted in a short time by means of vacuum aspiration were prepared in the Squibb Minitec configuration. Generators were built using Bio-Rad AG1x8 as the adsorbent. The effects of eluent acidity and hydrogen peroxide concentration, autoclaving, column bed size variation, total eluent volume used and eluent additives on the breakthrough of W-178 and the yield of Ta-178 were evaluated. The eluate was analyzed for possible organic resin-degradation products by means of gas-chromatography. In order to quantitatively evaluate the presence and magnitude of the impurity in successive elutions, twelve "cold" standard columns were loaded with Bio-Rad AG1x8 resin and subjected to a standard W-178-loading procedure, except that no W-178 was present in solution. The elutions were performed with 0.15 N HCl + 0.01% H_2O_2. At 1, 3, 11, and 38 days after preparation, three elutions of 1 ml each were collected from each column. The pH of the samples were adjusted to 12 as required for the gas chromatography procedure. Quantitation was by flame ionization after the gas chromatographic separation.

Results

The results of the K_D determinations are shown in Tables I-IV. In Table I the data for systems that strongly adsorbed both W and Ta are summarized. Table II contains data on those systems which strongly adsorb only Ta. In Table III the systems that poorly adsorbed W are described. The effect of acidity on the adsorption of W and Ta onto a pyrogallol-formaldehyde chelate resin is summarized in Table IV. The K_D values of W and Ta between silica or silylated silica and 1% NaF solutions of different pH values are summarized in Figure 1 (lines 3 and 3A). The K_D values for the same adsorbents but using different concentrations of HCl in the eluent are summarized in Table V.

Table I. K_D Values for W and Ta Between Various Eluents and Inorganic Adsorbents with a High Affinity for Both Elements

Adsorbent/ Eluent	10^{-3}N HCl	H_2O	0.1N NaOH	0.25% PO_4^{3-}	0.9% NaCl	0.1% $NaHSO_3$
$TiO_2.H_2O_2$						
K_{DW}	>2500	>500	59	>1300	>1300	>1000
K_{DTa}	>200	>400	>140	>300	>350	>300
Fe_2O_3/ K_{DW}	>2400	>1000		>125	>800	>800
K_{DTa}	>500	>250		>125	>200	>170
Sb_2O_5/K_{DW}	>250			>600	>900	>800
K_{DTa}	>100			>200	>200	>200
MnO_2/K_{DW}	2100		95	800	5600	
K_{DTa}	>350		>200	>300	>800	
Ti-phosph/						
K_{DW}	275		140	380	1100	
K_{DTa}	>150		>110	>200	>200	
Fe(111)/ ferrocy/						
K_{DW}	1500		125	470	800	
K_{DTa}	>140		>140	>90	>60	
ZrO_2/K_{DW}	>100	>400			>250	>250
K_{DTa}	>200	>100			>50	>50

Table II. K_D of Tantalum Between Various Eluents and Inorganic Adsorbents with a High Affinity for Tantalum

Absorbent/ Mobile Phase	10^{-3}N HCl	0.1N NaOH	0.25% $PO_4$3-	0.9% NaCl	0.1% $NaHSO_3$
TiO_2	>200	>30	>60	>150	>300
$SnO_2(CaCl_2)$	>200	>40	>200	>250	
Zr(ferrocy)	>250	>50			
Ni(ferrocy)	>200	>70			
Ti(ferrocy)	>300	>90			
K-Co(ferrocy)	>300	>180	>60	>70	
WS_3	>100				>100

Table III. K_D Values of W Between Various Eluents and Inorganic Adsorbents with Low Affinity for Tungsten

Adsorbent/ Mobile Phase	10^{-3}N HCl	H_2O	0.1N NaOH	0.25% $PO_4$3-	0.7% NaCl +0.2% $NaHCO_3$	0.9% NaCl	0.1% $NaHSO_3$
SnO_2	30	68	41	6	5	120	18
SiO_2	27		7			3	
Neutral Al_2O_3	30		6	8			
CrO_3	2		2	3		3	
Zr-phosph	15	44	16	89	55	96	55
Sn-phosph	4	14	8	51	28	78	35
Tungsten Carbide	5		1	36	6	12	24
Phomix		34	17				
Siphozir		53	12				
Cr-phosph	3		4				
Cu-ferrocy	8		10				
MoO_2(ferrocy)	7						
TiO_2	95	110	10	17	21		
Al_2O_3/CaF_2	3		3	6		28	
Al_2O_3/SrF_2	6		8	15		20	
WS_3			2	24	2		6

Table IV. K_D of W and Ta Between P-F Resin and HCl Solutions

- log N(HCl)	K_D, W		K_D, Ta	
	Adsorption	Desorption	Adsorption	Desorption
1	285	2,500	210	2,000
2	420	3,250	310	2,000
3	490	3,900	200	2,000
4	350	2,850	220	2,000

Table V. K_D of W and Ta Between Silica or Silylated Silica and Aqueous Dilute HCl

- log N(HCl)	K_D, W		K_D, Ta	
	Adsorption	Desorption	Adsorption	Desorption
	Silylated silica			
1	650	>5,000	>500	>500
2	19	130	>500	>100
3	28	16	>20	>10
	Silica			
1	26	450	>20	>200
2	30	850	>20	>500
3	56	>5,000	>20	>1,000

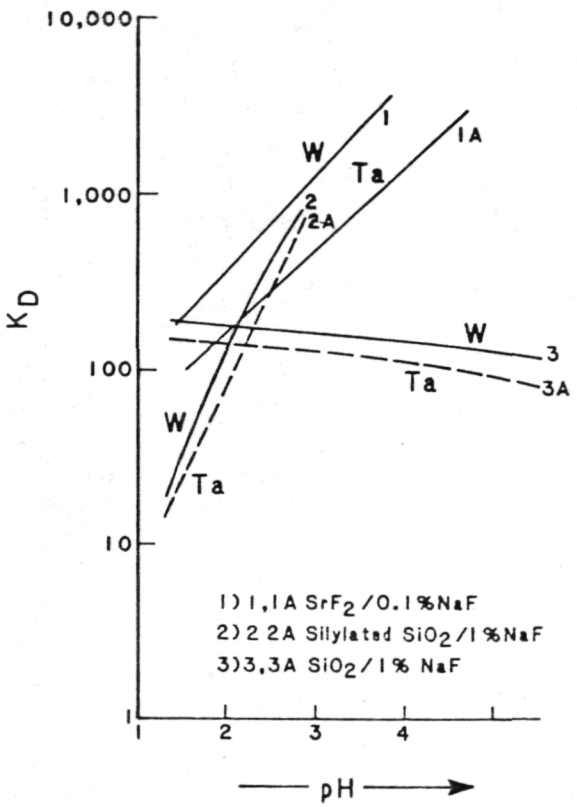

Figure 1. Distribution coefficients (K_D) of W and Ta between SrF_2, silylated SiO_2 or SiO_2 and aqueous NaF solutions as a function of the pH of the mobile phase.

C-2

The results of the adsorption experiments using Bio-Rad AG1x8 with the W-phosphotungstate were negative because stronger Ta-adsorption occurred with these phosphate-containing solutions. The results of the K_D determination for W and Ta between Bio-Rad AG1-x4 and HCl solutions of different normality are summarized in Figure 2. The effect of the addition of H_3PO_4 to the 0.1 N HCl mobile phase is also indicated. The results of the K_D determinations for W and Ta between Chelex 100 and dilute HCl solutions are shown in Table VI. The results for Chelex 100 using 1% NaF solutions of varying pH are summarized in Table VII. The K_D of W and Ta between MnO_2 and aqueous solutions of differing NaF concentrations and pH are summarized in Figure 3. The K_D values for W and Ta between Titanium phosphate and either 1% NaF or 0.1% NaF solutions as a function of pH are shown in Table VIII. The K_D values as a function of pH for W and Ta between SrF_2 and 0.1% NaF solutions are summarized in Figure 1 (lines 1 and 1A). In Figure 1 the K_D values of W and Ta between SiO_2 (lines 2 and 3A) or silylated SiO_2 (lines 2 and 2A) and 1% NaF solutions as a function of pH are summarized.

The results of the determination of the adsorption rates of W and Ta onto ZrO_2 and MnO_2 are shown in Figure 4. Lines 1 and 2 show the adsorption of W and Ta onto MnO_2 from 1% NaF solutions. Lines 3 and 4 depict the adsorption of W and Ta by ZrO_2 from a 0.1% sodium oxalate solution. Lines 5 and 6 of Figure 4 show the desorption of W and Ta from MnO_2 by 1% NaF solutions. Using the Minitec configuration, a full bolus of Ta-178 was eluted from the 2 cc Bio-Rad AG1-x8 columns by means of 1.5 ml of HCl 0.15 N + 0.01% H_2O_2. The elution is performed with an evacuated vial and takes only 15 seconds. The adsorbent bed can be left dry between elutions.

In the distillation experiment, (W-178)WF_6 could not be distilled from the 29 N HF solutions, using the all-Teflon distillation apparatus.

The elution yield for Ta-178 from Bio-Rad AG1-x8 by means of 1.5 ml of 0.10 N HCl + 0.01% H_2O_2 or 1.5 ml of 0.15 N HCl + 0.01% H_2O_2 was 33% and 52%, respectively. The Ta-178 yields and W-178 breakthrough values obtained with 2 ml of 0.15 N HCl containing variable amounts of H_2O_2 are shown in Table IX. Table X shows

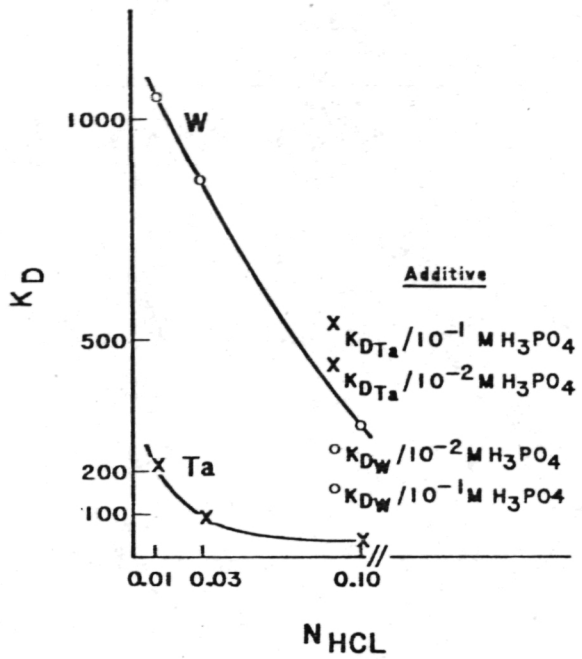

Figure 2. Distribution coefficients (K_D) of W and Ta between Bio-Rad AG1x4 and aqueous HCl solutions as a function of HCl concentration.

Table VI. K_D of W and Ta Between Chelex 100 and Mobile Phases of Varying HCl Concentration (10' Desorption)

	K_D	
pH	W	Ta
0.6	950	100
0.8	1,250	150
1.0	3,000	400
1.1	3,000	-
1.3	4,000	500
4.8	75	40
9.0	10	10
	10	20

Table VII. K_D of W and Ta Between Chelex 100 and 1% NaF Aqueous Solutions as a function of pH (10' desorption)

pH	K_D	
	W	Ta
1.8	1,600	85
2.0	300	100
3.1	350	80
3.9	-	90
5.1	130	40
6.0	170	50
7.4	30	25
8.3	20	20
8.7	10	10
9.9	1	2

Table VIII. K_D of W and Ta Between Ti-phosphate and fluoride solutions as a function of pH

pH	1% NaF K_D		pH	0.1% NaF K_D	
	W	Ta		W	Ta
0.4	42	22	1.1	230	>250
0.8	150	50	1.5	890	410
1.3	90	70	2.0	360	175
1.6	270	150	3.0	420	160
2.1	320	200	3.4	450	160
4.0	760	140	4.3	780	200
5.4	920	120	4.7	1,250	340
6.0	1,900	170	5.0	1,450	340
6.4	530	370	5.1	1,100	320
6.6	460	>500	5.2	1,100	330

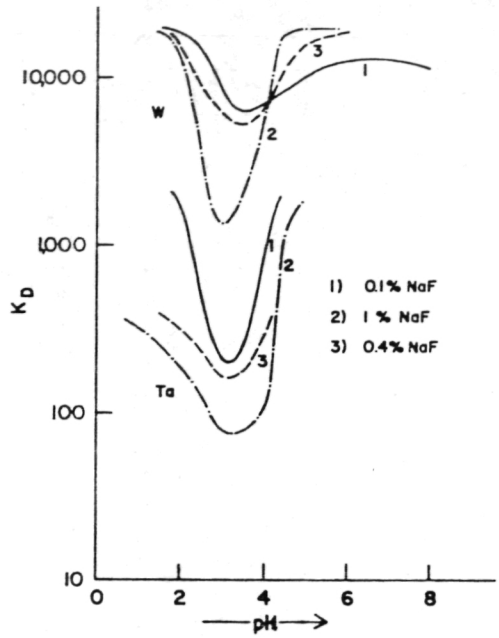

Figure 3. Distribution coefficients (K_D) of W and Ta between MnO_2 and aqueous NaF solutions of different concentration as a function of the pH of the mobile phase.

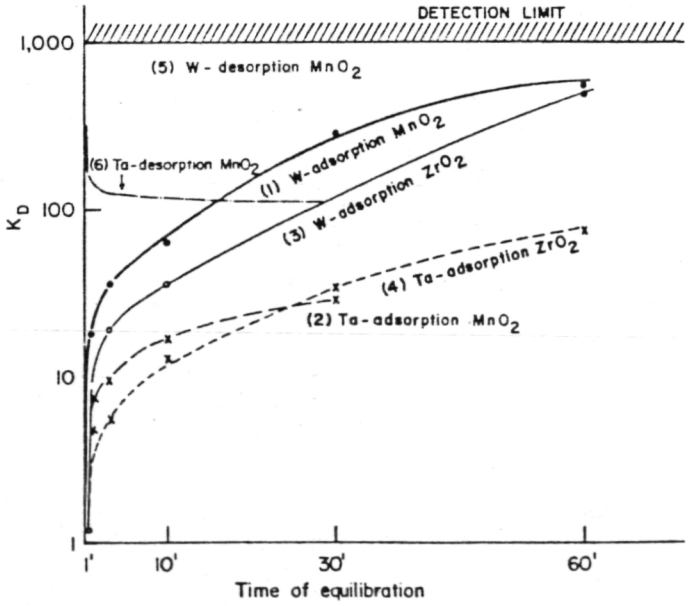

Figure 4. Adsorption rate of W and Ta onto MnO_2 and ZrO_2 from aqueous 1% NaF solutions and desorption of these elements from MnO_2.

the influence of autoclaving of the loaded AG1-x8 generator on the Ta-178 yield and radiochemical purity (RCP). To inhibit the migration of particles during the autoclaving, an intermediary filter was added 5 mm under the top filter of the column. The effect of autoclaving on the Ta-178 yield and RCP for this type of column is summarized in Table XI. The results of an exhaustive elution of a 1 cc Ta-178 generator based on Bio-Rad AG1x8 is shown in Table XII. Each elution was performed with 1 ml of HCl 0.15N + 0.01% H_2O_2. Several mixtures of 0.15 N HCl with other components were evaluated as eluents for a 2 cc Ta-178 generator. The results are summarized in Table XIII. Trimethylamine was identified as a product of the decomposition of the Bio-Rad AG1-x8 anion-exchange resin. The quantitative results obtained by gas-chromatography and FID are summarized in Table XIV.

Discussion

Using a 0.10 N HCl + 0.01% H_2O_2 as eluent, the Life Sciences Division of the National Aeronautics and Space Administration (NASA) has successfully operated a large number of Ta-178 generators based on Bio-Rad AG1x8 and has successfully tested them in human subjects (5). Ultimately, their intention is to use these for evaluation of cardiac function of astronauts in space. The only published Ta-178 generator is based on adsorption of W-178 on an organic anion-exchanger and elution of the daughter isotope by means of a dilute HCl eluent, containing a small amount of H_2O_2. The eluate can easily be converted to an injectable solution and the Ta-178 yields in 1 ml eluent volume are higher than 50%. However, the W-breakthrough increases to more than 0.1% after about 50 collections. The early breakthrough and the radiolytic instability of organic adsorbents are the main drawbacks of this system. An attempt to correct these shortcomings by using a more radiation-resistant inorganic adsorber or with any other adsorbent that would adsorb W more strongly than Bio-Rad AG1x8 did not lead to a procedure that was superior to the original system. Many inorganic adsorbents have a high affinity for tungsten but typically also adsorb tantalum very strongly. It was noted that Ta-178 which had grown in from W-178 while the latter was adsorbed was very strongly retained by all the inorganic adsorbents. The reason for this strong Ta binding may result from isoelectronic transition of the W-178 which probably does cleave any chemical bonds between the daughter isotope Ta-178 and the atoms or groups of the molecule. Since most of the experiments have been performed with WO_4^{2-}, the resultant Ta species may be expected to remain oxygenated because Ta 5d-orbitals overlap strongly with oxygen 2p-orbitals to give substantial π-bonding.

Table IX. Ta-178 Yield and W-178 Breakthrough from *Bio-Rad AG1x8 as a Function of the* H_2O_2-Concentration

% H_2O_2	Ta-178 Yield (%)	W-178 Breakthrough ($x10^3$)
0	17	5
0.01	48	0.2
0.05	54	N.A.
0.10	38	<0.2
0.20	55	N.A.
0.50	51	N.A.

N.A. = Not Available

Table X. Ta-178 Yield and RCP Before and After Autoclaving of the Loaded Generator

Eluent Volume (ml)	Ta-178 Yield (%)		W-178 Breakthrough	
	Before	After	Before	After
1	48 (n=5)	42	<0.1(n=5)	5(n=5)
1.5	45 (n=5)	N.A.	<0.1(n=5)	N.A.

Table XI. Effect of Autoclaving on Ta-178 Yield and RCP for the Modified Column

	Ta-178 Yield		W-178 Breakthrough ($x10^3$)	
Eluent	Before	After	Before	After
HCl 0.15N + 0.1% H_2O_2	48(n=5)	47(n=5)	0.5	0.3
HCl 0.15N + 0.01% H_2O_2	N.A.	37(n=5)	N.A.	0.5

Table XII. Ta-178 Yield and W-178 Breakthrough from a 1 cc Bio-Rad AG1x8 Column as a Function of the Total Eluted Volume

Volume Eluted (ml)	Ta-178 Yield (%)	W-178 Breakthrough ($x10^{-3}$)
1 - 10	40	0.07
11 - 20	37	0.05
21 - 30	49	0.05
31 - 40	46	0.24
41 - 50	72	1.7
51 - 60	67	4.6
61 - 70	47	6.1
71 - 80	44	5.1
81 - 90	54	5.0
91 -100	45	5.0

Table XIII. Effect of Eluent Additives on Ta-178 Yield from Bio-Rad AG1x8

Eluent	Ta-178 Yield (%)
HCl 0.15N + 10^{-2} N NaF	0.3
HCl 0.15N + 0.03 N HNO3	10
HCl 0.05N + 0.1% Na_3-citrate	0.6

Table XIV. Trimethylamine Concentration in Generator Eluent as a Function of Time Between Elutions

Time after Preparation (days)	Trimethylamine (ppm)		
	1st Eluate	2nd Eluate	3rd Eluate
38	9	0.9	0.2
11	3	0.3	0.2
3	3	0.2	0.02
1	2	0.3	0.03

The initial protonated species of the resultant Ta oxides can expand their coordination sphere by coordinating water molecules. Since most of the evaluated adsorbents are hydrates, this could explain the strong tantalum binding. Tantalum-complexing agents, such as fluoride, hydrogen peroxide, oxalate, citrate and tartrate, did not succeed in desorbing tantalum from the inorganic adsorbents. A good chemical separation was obtained with MnO_2 as as adsorbent and a solution of 1% NaF as an eluent. However, the solubility of the hydrated MnO_2 in these eluents makes this process pharmacologically unacceptable. Synthetic chelating resins, such as Chelex 100 and the copolymer of pyrogallol and formaldehyde, in combination with pharmacologically acceptable eluents, were unable to separate W and Ta better than Bio-Rad AG1x8.

Our more detailed study of the Ta-178 generator based on Bio-Rad AG1x8 has confirmed that higher acidity eluents result in higher yields of Ta-178. A minimum of 0.01% H_2O_2 is necessary to ensure a good (>50%) Ta-178 yield and low (<0.02%) W-178 breakthrough. We have also found that the yields and breakthrough characteristics are unaffected by autoclaving of the generator. About 50 collections of Ta-178 can be made from a 1 cc-bed-size column before the W-breakthrough becomes larger than 0.1%. Addition of complexants such as fluoride , ascorbate or citrate has a negative effect on Ta-178 yield. The generators can be stored dry between elutions without any effect on yield or breakthrough. The only organic breakdown product that can be detected in the generator eluent is trimethylamine. We have also shown that the resin-breakdown was caused by the acidic eluent rather than by radiolysis. The contaminant increases in concentration with the duration of the exposure to the eluent but is almost quantitatively removed by the first elution. The highest levels observed were 9 ppm trimethylamine after 6 weeks of exposing the generator to the acid without any elution being performed. After one elution, the concentration drops to 1 ppm. The problem is effectively eliminated by dry-storage of the generator between elutions.

Literature Cited

1. Neirinckx, R. D.; Jones, A. G.; Davis, M. A.; Harris, G. I.; Holman, B.L. J. Nucl. Med. 1978, 19, 514-519.
2. Neirinckx, R. D.; Davis, M. A.; Holman, B. L. Int. J. Appl. Radiat. Isot. 1981, 32, 85-89.
3. Neirinckx, R. D.; Davis, M. A. J. Nucl. Med. 1979, 20, 681.
4. Neirinckx, R. D.; Davis, M. A. In "Radiopharmaceutical II"; Society of Nuclear Medicine: New York, N.Y. 1979; pp. 791-799.
5. Babich, J. W., personal communication.

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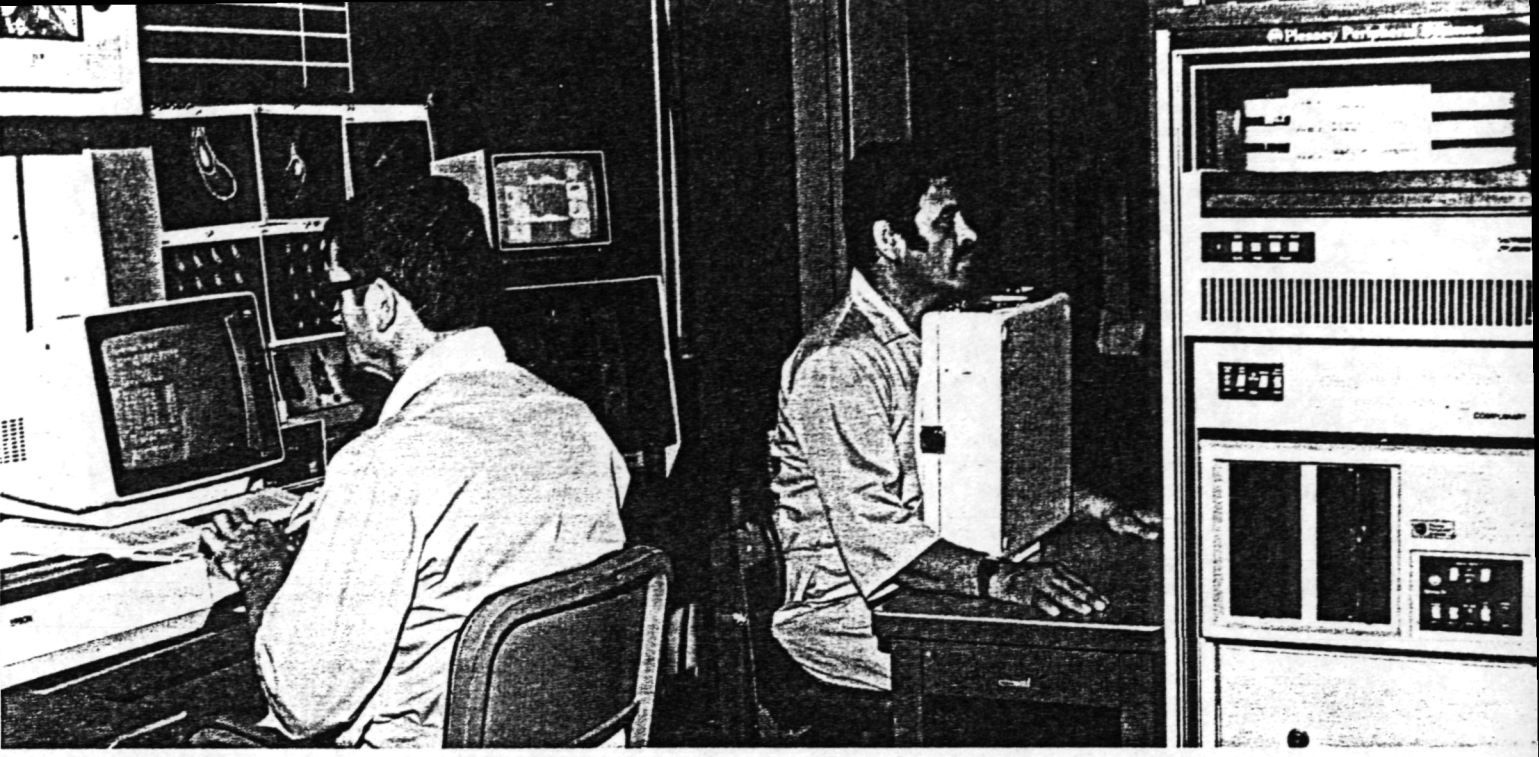

Figure 1: Multiwire gamma camera (center) operating in the Johnson Space Center Gamma Ray Imaging Laboratory.

Multiwire gamma camera for radionuclide and radiographic imaging in space and on earth

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Johnson Space Center
Houston, Texas

A portable multiwire gamma camera (MGC) has been developed by NASA for cardiovascular studies in space.[1,2] The same characteristics that make this device suitable for space research may provide substantial benefits in earthbound clinical work.

The device employs a gas mixture (xenon-methane) and wire grid structures rather than a sodium iodide crystal and photomultiplier tubes for detection of radiation. The elimination of photomultiplier tubes and reduction of lead shielding required makes possible a very compact portable device (Figure 1) which is intrinsically very rugged. In addition, the camera is capable of high resolution limited only by the grid wire spacing and is very fast, producing signals with a duration one-tenth that of sodium iodide signals. A refined high-speed delay line readout system has been developed which provides an event rate of 850,000 cps[3,4] (Figure 5).

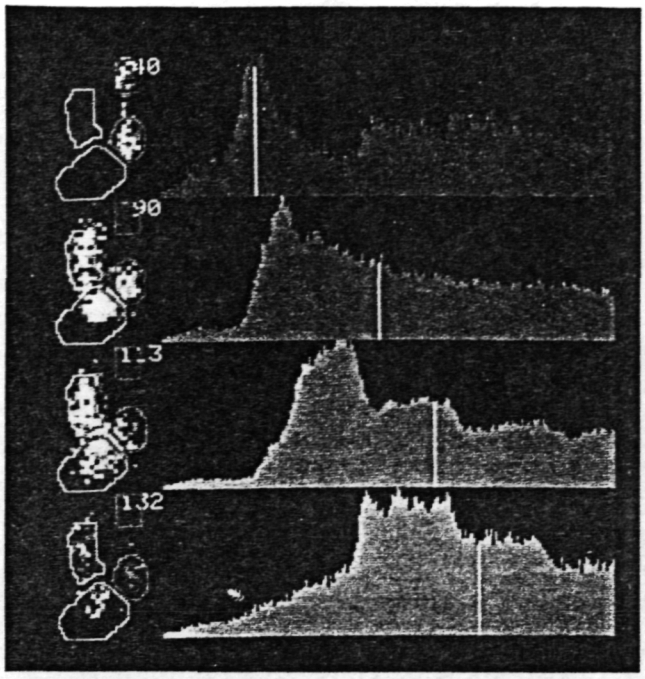
The prototype devices being tested have an active area of 10 inches diameter, a wire grid spacing of 2 mm and exhibit a spatial resolution of 2.5 mm FWHM for 30-80 KeV radiation (Figure 6). Good sensitivity is exhibited in this same energy range, making practical nuclear medicine applications with the standard isotopes thallium-201 and xenon-133. Although sensitivity is not adequate for technetium (Tc-99m), a new low-energy, short half-life isotope is being refined for application with the MGC. It will provide many of the diagnostic capabilities of Tc-99m with vastly reduced radiation exposure even with increased isotope dose, with improved image statistical quality. This new isotope is being tested with the MGC at the Johnson Space Center and is showing great promise for cardiac studies.

The MGC also has potential as a digital radiography device. It has excellent imaging characteristics in the standard radiographic energy range and is capable of producing directly digitized images at relatively low cost. This application may be particularly useful in space where the MGC could provide the detector for a general radiographic facility. Both planar and tomographic imaging could be relatively easily implemented in zero-gravity situations, and radiographic data conveniently relayed to the ground for diagnosis.

Tantalum-178

Tantalum-178 (Ta-178) is a radionuclide with exceptional characteristics for use with the MGC. It has a very short but convenient half-life of 9.3 minutes. A practical generator system reported by Neirinckx, et al.[5]

About the author
Jeffrey L. Lacy, Ph.D., currently directs the Gamma Ray Imaging Laboratory at the Johnson Space Center, Houston, Texas. The principal activity of this laboratory is application of the multiwire gamma camera imaging to medical areas of interest to NASA. Dr. Lacy has had a long history of fundamental development of this technology at the Johnson Space Center including development of sophisticated instruments for high energy astrophysics research. ***For more information, circle no. 599 on the Reader Service Card on page 21.***



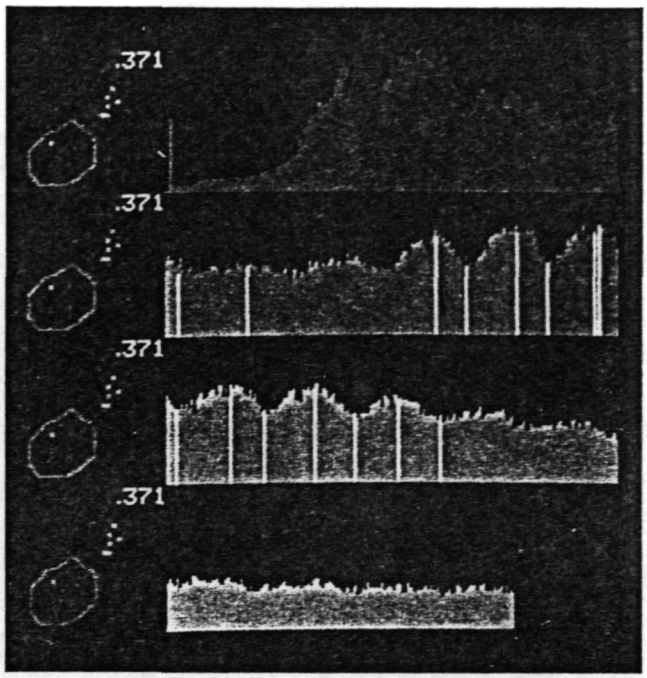


Figure 2 (left): Time activity curves corresponding to the structure of the superior vena cava, right atrium, right ventricle and pulmonary artery during the first four seconds after injection of a 20-mCi bolus of Ta-178. **Figure 3 (right):** Left ventricular time activity curve during an 18-second period following injection of a 20-mCi bolus of Ta-178.

exists based on the 22-day cyclotron-produced parent, tungsten-178 (W-178). Furthermore, the dominant emission energy of 55-65 KeV is practically ideal for the MGC. Detailed human and animal biologic distribution studies, performed in our laboratory by Babich and LeBlanc[6], have demonstrated no significant target organ concentration of either Ta-178 or the parent W-178 breakthrough. In addition, the parent W-178 is rapidly excreted from the body (biologic halflife of six hours), making exposure from the low levels of W-178 breakthrough negligible. Thus, wholebody dose levels a factor of 20 below, and target organ doses a factor of 65 below those of Tc-99m pertechnitate are achieved. In addition to substantial radiation dose advantages, Ta-178 offers the possibility of multiple repeat studies without build-up within the subject. The economics and operational convenience of the generator are excellent due to the long W-178 half-life. The generators have a useful life of at least one month and 50-100 elutions can be performed over this period.[6]

Less waste

In addition to the basic advantages of Ta-178 for physiologic investigation in general, the Ta-178/W-178 system has major advantages for space flight nuclear medicine applications. The generator parent half-life is convenient for shuttle space missions, which range in duration from 5 to 30 days in the near future and could even be practically employed for 60 to 90-day space station tours of duty. The short half-life of Ta-178 would prevent build-up of activity within the shuttle waste system that would result from multiple studies with longer half-life isotopes.

More than 20 W-178/Ta-178 generators of activity from 20-100 mCi have been produced at the Johnson Space Center over the past two years. These generators have shown good yield, low breakthrough, and excellent reliability. The W-178 for these generators has been produced at the Lewis Research Center cyclotron and supplied by Dr. James Blue, the director of the facility.

Trial MGC/Ta-178 studies

Pilot human studies of the MGC employing Ta-178 have begun at the Johnson Space Center. Eight human volunteer subjects have been studied by first-pass technique with Ta-178 bolus injections ranging from 20-60 mCi. To investigate reproducibility,

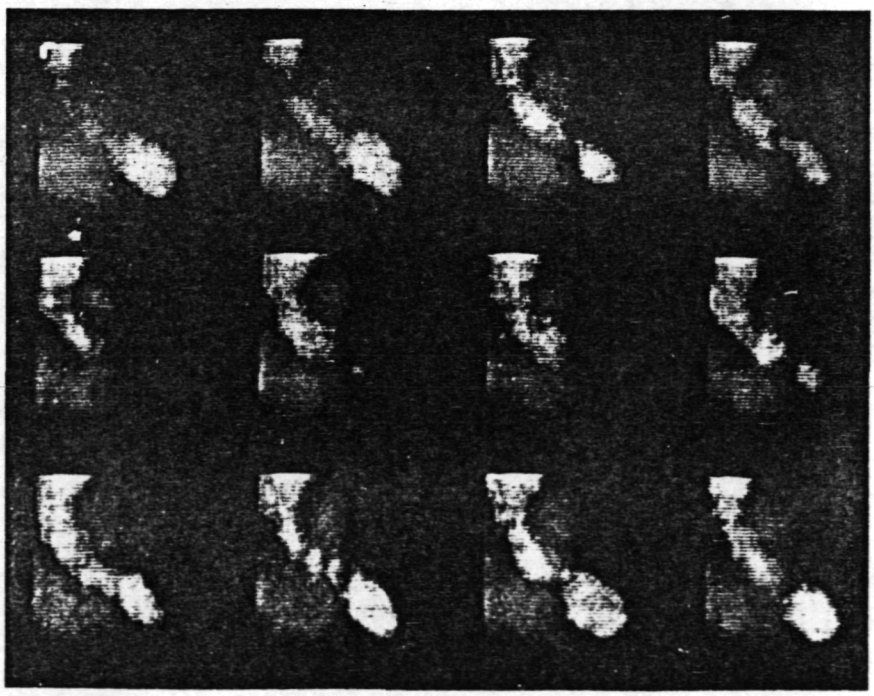


Figure 4: Cardiac representative cycle obtained from a 20-mCi Ta-178 first-pass study. Left and right ventricular images are separately obtained and superimposed with red and blue coding, respectively.

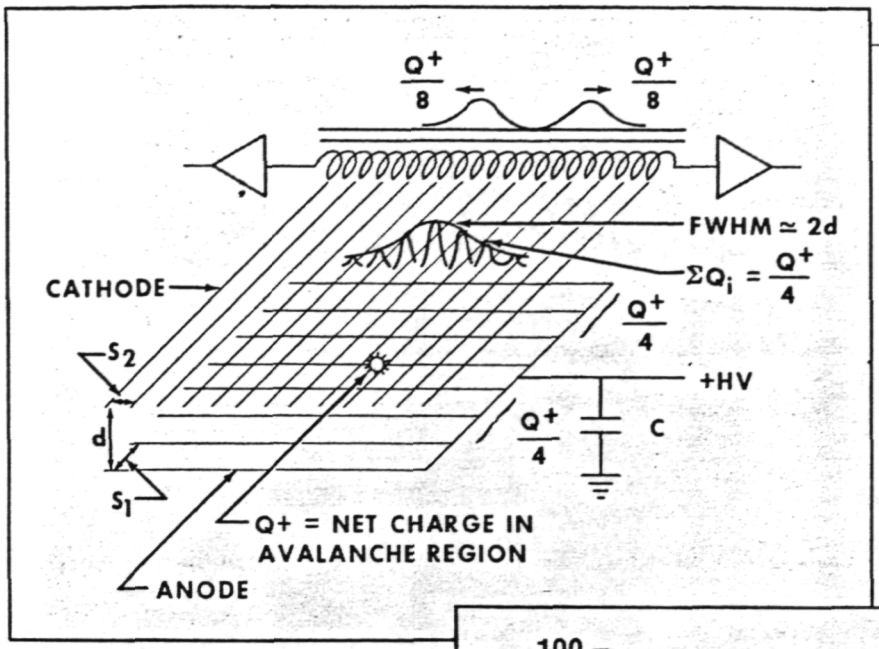
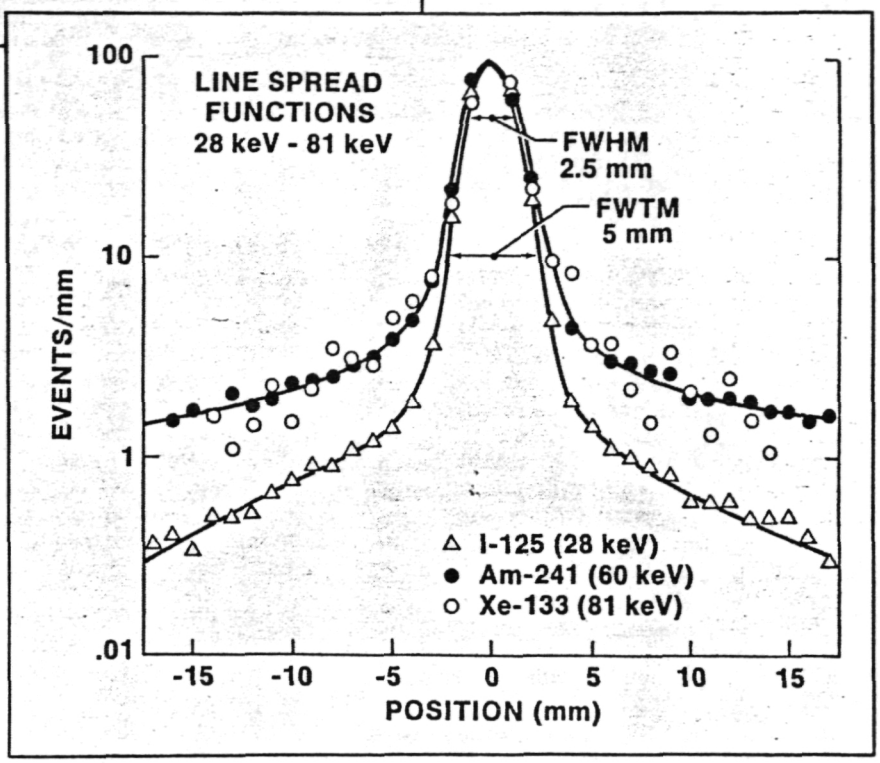


Figure 5 (left): High-speed delay line readout system. **Figure 6 (below):** Line-spread resolution measurements for x-ray energies ranging from 30 to 80 KeV.



repeat studies were performed in some of the subjects with 30-minute spacing. The MGC collected these studies at a frame rate of 40 fps in 32 x 32 format and a pixel size of 0.5 x 0.5 cm.

Figure 2 (page 45) shows time activity curves from one of these studies corresponding to the first four seconds post injection. Time activity curves of the four regions outlined in the left margin are displayed from top to bottom delineating superior vena cava, right atrium, right ventricle, and pulmonary artery. In Figure 3 the left ventricular time activity curve from the same study is displayed for the entire 18-second data acquisition period.

Representative cycle images of the right and left ventricles have been obtained from these studies by standard software procedures. One of the studies is displayed in Figure 4 (page 45), with the right ventricle coded in blue and left ventricle in red. Figure 7 (page 47) displays left ventricular volume curves obtained from two 20 mCi studies repeated in the same subject at 30-minute spacing. Currently, these studies are quantitatively similar to Tc-99m multi-crystal camera studies in terms of spatial resolution, image statistics, and temporal resolution. Substantial improvements are expected through optimization of isotope dose, collimator characteristics, and data analysis techniques.

Radiographic studies

The uncollimated MGC detector has undergone limited testing as a radiographic device. Exceptional data collection rate combined with high resolution offers unique potential in this area. Figure 8 (page 48) shows digital radiographs with the device. All of these were obtained by transmission imaging with a sealed-point I-125 (30 KeV) source. Other sources such as americium-241 (60 KeV) and gadolinium-153 (44 and 100 KeV) can be employed with equal efficacy in cases where higher x-ray energy is desired. Great flexibility in this technique is achieved by varying the source, specimen and detector separation to obtain an image on the detector that fills its active area independent of the specimen size. This is clearly demonstrated in Figure 8b and 8c in which specimen size ranges from a few millimeters to 8 cm. In each case the image size has been adjusted to match the 10-inch active area of the MGC. Radiation dose from this type of study is very low. All the studies of Figure 8 were performed with a dose of less than 1 mRad.

Ground-based applications

Clinical testing of the MGC and Ta-178 isotope is proceeding at two different sites. A complete MGC camera has recently been delivered to Duke University, where Dr. Robert Jones will apply the device with emphasis on long-range pediatric applications. Another camera will be tested in the near future at The Methodist Hospital, Houston. Cardiology applications will be investigated by Dr. Larry Poliner and Dr. Mario Verani within the cardiology

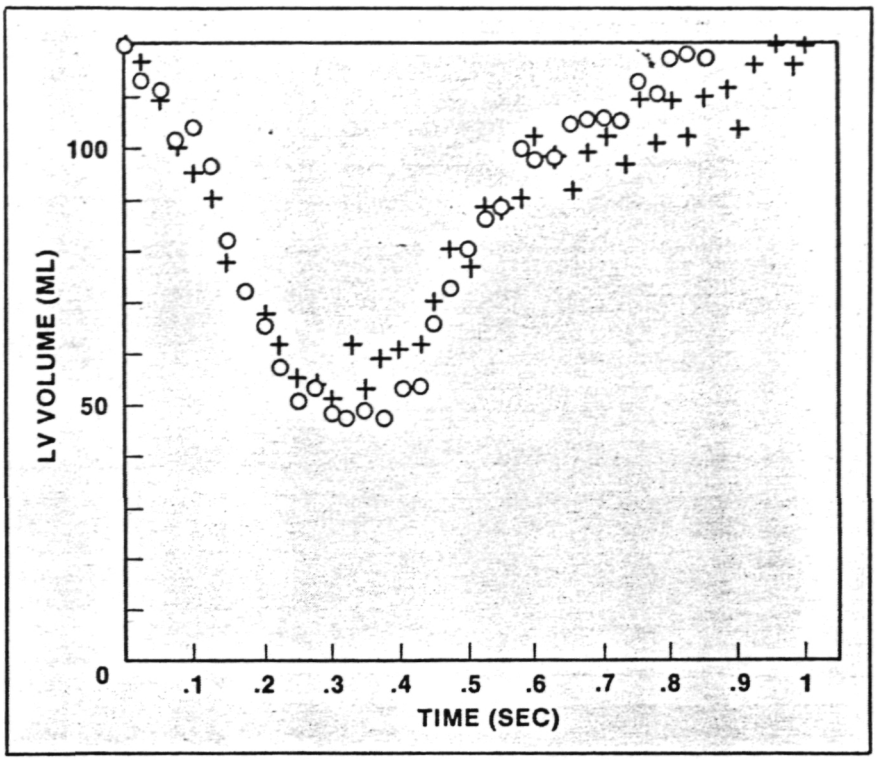


Figure 7: Left ventricular volume curves obtained from 20-mCi Ta-178 first-pass studies performed 30 minutes apart in the same subject as in Figure 4 on page 45.

department at Baylor College of Medicine, headed by Dr. Robert Roberts. Other nuclear medicine applications will be explored by Dr. Adrian LeBlanc of the Baylor nuclear medicine department. This testing will concentrate on validation of the technique for disease diagnosis and detection. In addition, a highly portable camera will be applied at Baylor for study of acute myocardial infarction in the coronary care unit. Pediatric applications with this same camera will be investigated by the pediatric cardiology group at the Texas Childrens Hospital, Houston, headed by Dr. Dan McNamara.

The MGC/Ta-178 technique possesses many advantages for coronary disease applications. Much larger isotope doses can be administered allowing first-pass studies of superior statistical and spatial resolution to be obtained with the MGC. Multiple studies can be performed either for frequent assessment such as following acute myocardial infarction or for long-term follow-up. Highly portable single and multiple-head cameras, which can be constructed at relatively low cost, could provide easy access to patients in intensive care and ease of use in remote locations. Multiple-view cameras would provide the capability of three-dimensional reconstruction of intracardiac structures by first-pass technique. Such reconstruction providing dynamic cross-sectional images of all cardiac structures will likely improve assessment of regional function. This is of great importance both in following acute myocardial infarction and in the early detection of coronary diseases by exercise studies. These techniques of three-dimensional reconstruction are currently being developed at the Johnson Space Center. If they provide significantly improved sensitivity as expected for exercise-induced dysfunction, the MGC/Ta-178 modality could provide a means of early coronary disease detection applicable at low cost to large populations at risk for development of disease.

Pediatric applications

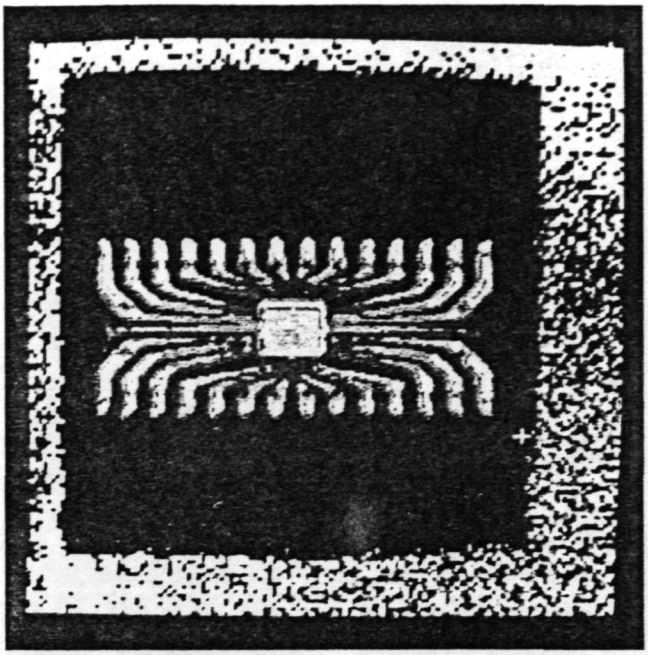
Pediatric medicine could potentially benefit greatly from this new technology as well. Ta-178 doses as high as 40 mCi can be given to newborn infants with acceptable radiation exposure levels. Thus, high-quality shunt quantitation and other cardiac measurements with serial follow-up should be possible. The high portability of the MGC should provide easy application in the pediatric intensive care unit. Multi-view MGC devices with pinhole collimators could provide three-dimensional reconstruction of cardiac structures in these patients as well. Such instruments offer great potential for multi-faceted diagnosis of the many newborn infants with cardiopulmonary difficulties of unknown origin. For example, differentiation could be obtained between primary pulmonary dysfunction and cardiac shunts, which produce the same outward symptoms in many cases.

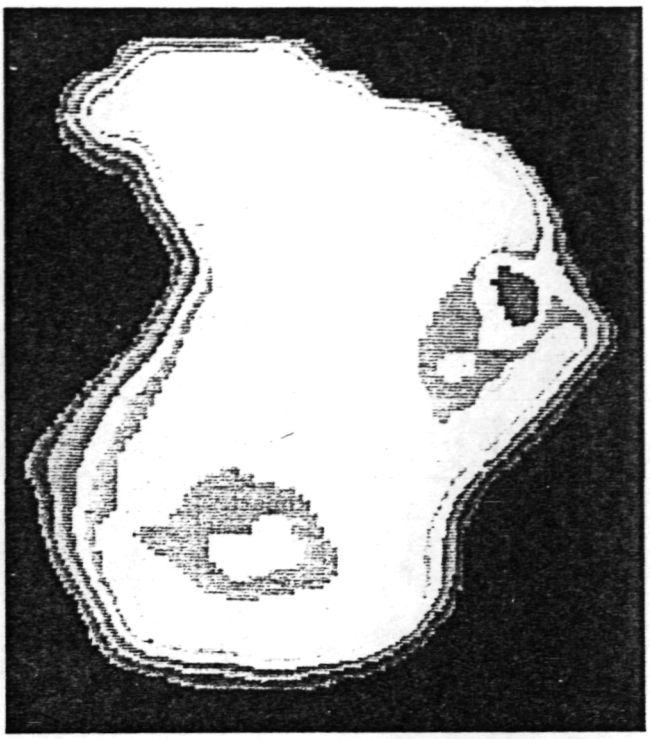
Potential applications in the radiology area also look promising. Osteoporosis, a disease with high prevalence in post-menopausal women, could likely be significantly controlled if quick, inexpensive bone measurements could be performed to screen for accelerated bone density losses in this population. The MGC may provide the necessary technology. Bone density measurements in areas such as the heel or lower arm can be performed with the MGC and I-125 source in a matter of seconds by simple transmission imaging (Figure 8) and result in a radiation exposure of less than 1 mRad. Thus, the technology provides the possibility of quick, inexpensive screening for low bone densities that could be applied even in remote locations.

Space application

Significant vascular and non-vascular fluid shifts result from exposure to a zero-gravity environment. These shifts are expected to have significant effects on cardiac chamber, pulmonary and central vessel volumes and potentially on cardiac function. Although the effects are relatively benign in short-duration flights, fundamental understanding of these alterations is of great importance particularly as longer-duration missions become necessary in the space station era. In-flight measurement of the volumes of individual cardiopulmonary structures and the functional parameters of the cardiac chambers is central to this understanding.

Individual cardiac chamber vis-





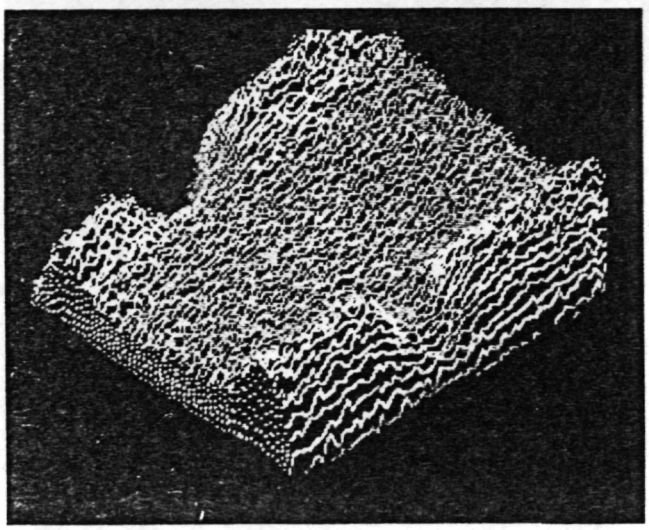


Figure 8: Radiographic images produced with the uncollimated MGC camera and a 100 mCi sealed I-125 source. **Top left (A):** Integrated circuit 2 cm in length. **Left (B):** Three-dimensional bone density presentation from an MGC radiograph of a rat femur with 2mm hole perpendicular to bone shaft. **Above (C):** Human heel (calcaneus) radiograph obtained with radiation exposure less than 1 mRad.

ualization is difficult with current technology due to the overlap of the different cardiac structures in any given viewing plane. The first-pass technique offers the greatest potential for separation of these structures due to the discrete nature of the radionuclide transit through the cardiopulmonary system. The right and left ventricles are well separated temporally by the significant transit time through the lungs. Even serial chambers such as the right atrium and the right ventricle can be separated by this technique by means of radionuclide dilution differences present even in these nearby structures. Techniques for such separation are being developed at Duke University and the Johnson Space Center and will likely represent the best technology available for imaging individual cardiac structures. The much higher statistics and multiple-view imaging permitted by the MGC/Ta-178 technology should greatly enhance these capabilities.

In addition to determination of the cardiopulmonary effects of zero gravity, the MGC/Ta-178 technique can be employed also to directly measure the vascular fluid shift. Babich and LeBlanc have shown that Ta-178 is bound in the blood with high efficiency.[6] Therefore, the blood volume distribution through the entire subject anatomy can be determined by scanning. Additional information relating to fluid redistribution, in particular the non-vascular component of this redistribution, can be obtained by transmission imaging. The MGC, combined with Ta-178 and sealed radiography sources, thus represents a powerful technology for near-term research work aboard the space shuttle.

Space station facility

As duration of space missions increases, and particularly with the advent of space station activities, the need for sophisticated medical diagnostic equipment in space will emerge. The MGC has the potential to supply the technology for both nuclear medicine and general radiographic diagnostic imaging in space. A proposal is currently being prepared for a space diagnostic imaging facility shown in Figure 9. It incorporates a single 10-inch MGC detector and x-ray source into a structure which allows both planar radiography and transmission tomography. In this facility a subject is strapped to

a rigid x-ray transparent platform. For planar radiography studies, the x-ray source and MGC are moved along tracks parallel to the subject until the appropriate anatomical region is viewed. The subject is then moved parallel to the x-ray beam direction to obtain the magnification factor appropriate for the anatomy being studied.

The mechanics of tomographic imaging are easily implemented in zero gravity. Such imaging is facilitated by rotation of the patient about his long axis. The bed of the device can be adjusted vertically (Figure 9) so that the position of the rotation axis above the bed can be varied. Thus, any anatomical region can be imaged tomographically, from wrist to a torso, by appropriate subject positioning and image magnification.

This general purpose facility would provide a multitude of diagnostic radiographic capabilities including lung and other organ imaging to aid diagnosis of various ailments; skeletal radiographs for diagnosis of fractures; and tomographic bone density measurements for serial determination of bone density changes induced by zero gravity. The same MGC could be employed either mounted in the facility or separately for nuclear medicine applications with Ta-178 and other injectable isotopes including those used in ECT and exercise studies.

In conclusion, the multiwire camera offers great potential in clinical and space medicine for both nuclear medicine and radiology applications. Many of these applications will be explored and validated in coming years through collaborative research projects between NASA and clinical institutions. It is expected that applications of great benefit to both space and clinical medicine will emerge in the near future.

REFERENCES

1. Lacy JL, LeBlanc AD, et al: A multiwire proportional counter gamma camera for medical applications. *J Nucl Med.* Submitted.
2. Lacy JL, LeBlanc AD, Babich JW, Bungo MW, Johnson PC: Multiwire proportional counter gamma camera and tantalum-178 radionuclide—new technology. *J Nucl Med* 24:24, 1983.
3. Lacy JL, Lindsey RS: High resolution readout of multiwire proportional counters using a cathode coupled delay line readout technique. *Nucl Inst Methods* 148:119, 1973.
4. Perez-Mendez, et al: Multiwire proportional chambers in nuclear medicine: Present status and perspectives. *J Nucl Med Biol* 3:29, 1976.
5. Neirinckx RD, et al: Tantalum-178—a short-lived nuclide for nuclear medicine: Development of a potential generator system. *J Nucl Med* 19:514, 1978.
6. Babich JW, LeBlanc AD, Lacy JL, Johnson PC, Jhingran: Biological fate of tungsten-178 and tantalum-178. *J Nucl Med* 24:122, 1983.

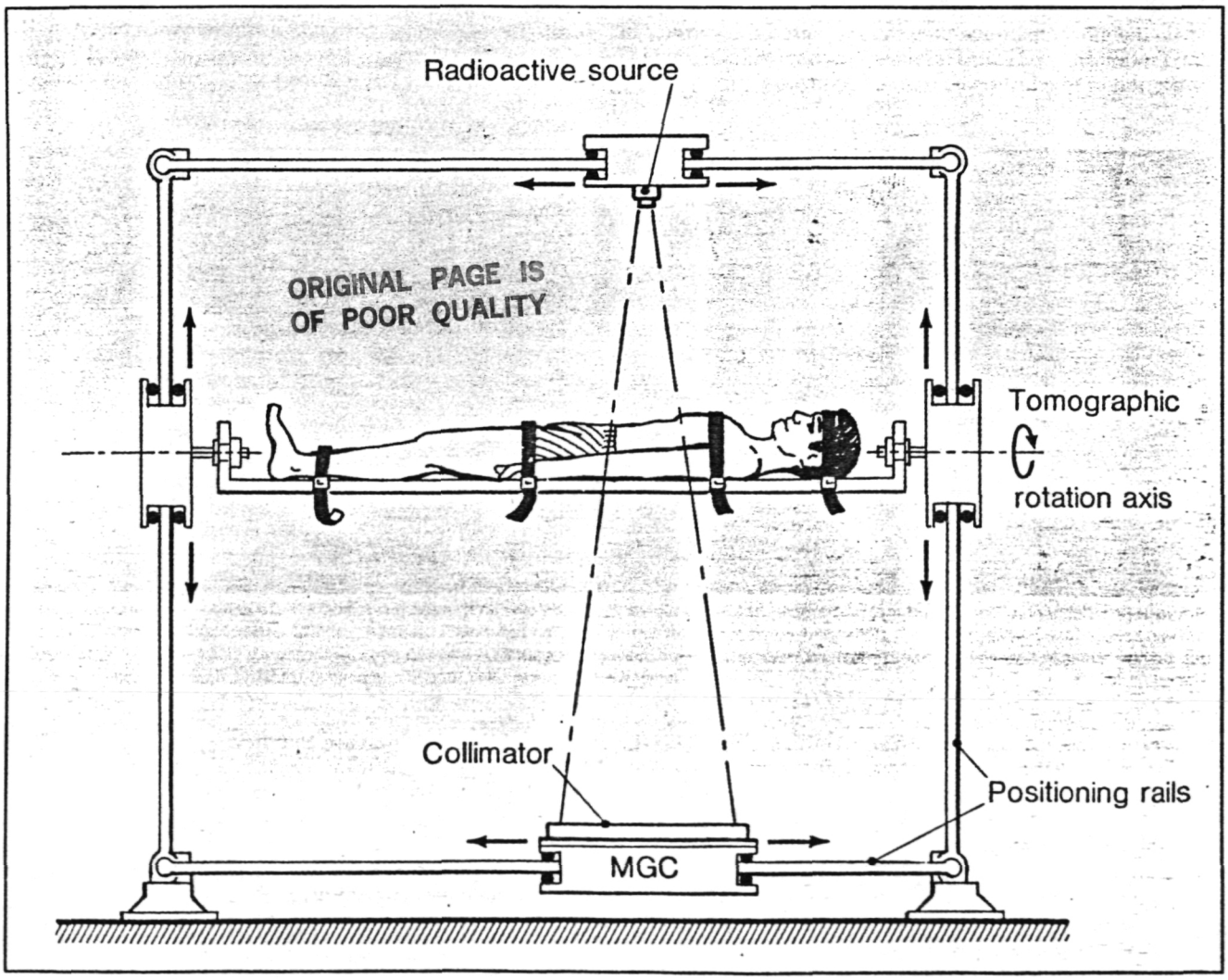


Figure 9: Space radiography facility providing planar radiographs and tomographic images of all anatomical areas. Flexibility is included in the system by providing for translation parallel and perpendicular to the subject's long axis, and positioning the bed perpendicular to the tomographic rotation axis.

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TA-178 AS AN IMAGING AGENT FOR ANGER AND MULTICRYSTAL CAMERAS. A.D. LeBlanc, J.L. Lacy, P.C. Johnson, L. Poliner, and S. Jhingran. Baylor College of Medicine and Johnson Space Center, NASA, Houston, TX.

The purpose of this study was to extend previous work with Ta-178 with particular attention to the requirements for cardiovascular studies.

Irradiated Tantalum foils were dissolved and purified using published techniques to obtain Tungsten-178. A W-178→Ta-178 generator was constructed and tested. We investigated different collimators on both a multicrystal and an Anger camera by comparing Ta-178 and Tc-99m images and calculated ejection fractions obtained using a cardiac phantom. In addition, pulse height spectra were obtained with and without collimators to investigate septal penetration. Scatter and septal penetration of low and medium energy Anger camera collimators were evaluated by imaging point sources of Ta-178, Am-241 and Tc-99m. It is concluded that Ta-178 can be used for first pass studies with the multicrystal camera taking advantage of the high count rate capability of this device. The 1" high sensitivity collimator reduces septal penetration to acceptable levels. The Tc-99m and Ta-178 processed images were judged to be very close in quality. Imaging Ta-178 with an Anger camera and a medium energy collimator reduced septal penetration to acceptable levels, but produced poorer images compared to those using Tc-99m and a high resolution collimator because of poorer inherent and collimator resolution and because a greater fraction of compton scattered photons are accepted by the pulse height analyzer. However, for calculating ejection fractions and displaying wall motion, Ta-178 and a medium energy collimator gave satisfactory results.

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BIOLOGICAL FATE OF TUNGSTEN-178 AND TANTALUM-178. J.W. Babich, A.D. LeBlanc,, J. Lacy, P. Johnson, and S. Jhingran. Medical Research Branch, NASA/JSC and Baylor College of Medicine, Houston, TX.

Ta-178 (from W-178/Ta-178 generator) imaging with the multiwire proportional camera (MWPC) is under evaluation for first-pass cardiac studies in humans. The purpose of this work is to define the biodistribution and metabolic fate of Ta-178 and W-178 as a generator breakthrough product.

Two rats injected with 10uCi of W-178 were counted (WBC) daily for 21 days, sacrificed and the organ distribution of residual W-178 determined. The WBC demonstrated two effective half-lives (Te), 8hrs (98%) and 10 days (2%) with 93% of the activity recovered in the urine. At 21 days the greatest concentration of activity was in bone followed by spleen and liver. Three human volunteers injected with 2uCi of W-178 were counted in a whole body counter (NASA/JSC) from 0-450hrs. Blood and urine collections were obtained up to 4 days. The WBC demonstrated multiple components with approximately 95% excreted with a Te of 8hrs, 4% with Te of 30-40hrs, and 1.5% with Te of 11 days. At 4 days 84-93% of activity was found in the urine. Blood levels rapidly decreased to bkg by 24hrs. Both human and animal data indicate rapid elimination of the potential W-178 breakthrough product. Five additional volunteers were injected with 20mCi of Ta-178 to evaluate the MWPC, blood clearance and organ distribution. Blood samples were taken at 2,5,10,15, 20,25min post injection. Decay corrected static images of the thoracic, upper and lower abdomen obtained at 2,10,30 min post injection showed no significant organ concentration. Blood activity at 25min ranged from 79-95% of the 5min samples suggesting gated as well as first-pass studies may be feasible.

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ABSTRACT REPRODUCTION SPACE

NEW MULTIWIRE GAMMA CAMERA WITH A UNIQUE SHORT-LIVED ISOTOPE TANTALUM-178

Jeffrey L. Lacy, PhD, Mario S. Verani, MD, FACC, Mark E. Ball, John W. Babich, Adrian LeBlanc, PhD, Michael Bungo, MD, Philip Johnson, MD, Robert Roberts, MD, FACC Baylor College of Medicine, Houston Texas

Conventional gamma cameras utilize NaI detectors which are limited in either count-rate (< 200,000 cps) or resolution (> 1 cm). The long $T\frac{1}{2}$ of isotopes such as Tl-201 or Tc-99m provide prolonged radiation exposure and also prevent frequent repetitive imaging in the acute setting. Short-lived positron emitting isotopes require a cyclotron for production and extensive imaging facilities. Accordingly, to overcome these problems a compact portable xenon multiwire gamma camera (MGC) and short-lived isotope Ta-178 have been developed. Camera count-rate and resolution measured with phantoms are 850,000 cps and 2.5 mm respectively. Pilot first-pass radionuclide angiocardiography studies in 9 normal human subjects employing 20-40 mCi Ta-178 injections have demonstrated excellent image quality with a radiation dose 1/20 that of Tc-99m. Mean LV ejection fraction and peak ejection and filling rates (end diastolic volumes/sec) for the 9 subjects were 63%, 3.5, 2.8. . Left ventricular counts, the main determinant of image quality in such studies, were similar to Tc-99m/Baird System 77 Studies on a per mCi basis although higher resolution collimation was employed for the Ta-178/MGC studies. In comparison with the Baird System 77 superior image quality was demonstrated by the Ta-178 studies as expected from improved pixcel size (7.5 mm versus 11mm) and collimator resolution. Further improvement in image quality is expected with larger Ta-178 injections and optimal collimator selection. In conclusion, the portable MGC with Ta-178 offers a system with improved image resolution lower radiation exposure, and permits repeated rapid studies in even critically ill patients.

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MULTIWIRE PROPORTIONAL COUNTER GAMMA CAMERA AND TANTALUM-178 RADIONUCLIDE--NEW IMAGING TECHNOLOGY. J.L. Lacy, A.D. LeBlanc, J.W. Babich, M.W. Bungo, P.C. Johnson. Johnson Space Center, Baylor College of Medicine, Methodist Hospital, Houston, TX

A pressurized Xenon multiwire proportional counter (MWPC) specifically designed for nuclear medicine applications has been developed. The device employs a high speed readout system which provides very high count rates (>800,000 cps), excellent image resolution (2.5mm FWHM), and distortion free performance at the highest rates. The device is a light weight compact unit which is well suited to portable operation. It has a high sensitivity for x-ray energies up to 80 KeV. It can be employed effectively with Xe-133 and Tl-201 radionuclides. A newly developed radionuclide, Ta-178, is an excellent imaging agent for use with the camera having both optimal energy (60 KeV) and a short half life (9.3 min). High quality first pass cardiac studies employing 20 mCi Ta-178 have been performed in five volunteer subjects. Studies have been analyzed to obtain right and left heart images, ventricular wall location determinations, ejection fraction values, and region of interest histograms. These results demonstrate the feasibility of performing first pass studies with higher spatial resolution and image statistics and with far less radiation exposure than is currently possible employing Tc-99m and current imaging technology.

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MULTIWIRE PROPORTIONAL COUNTER IMAGING CAMERA AND TANTALUM 178 ISOTOPE -- NEW TECHNOLOGY IN CARDIAC IMAGING

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A pressurized Xenon multiwire proportional counter (MWPC) specifically designed for cardiac imaging applications has been developed. The device employs a high speed delay line readout system which provides very high count rates (>500,000 counts/sec) and excellent image resolution (2mm). The device is a light weight compact unit which is well suited to portable operation. The MWPC has a high sensitivity for x-ray energies below 65 kev (>20,000 counts/sec/mCi) and can be employed (with somewhat reduced sensitivity) for energies up to 80 kev. Tantalum-178 is an ideal imaging agent for use with the camera having both optimal energy (55-65kev) and a short half life (9.3min). A successful Ta-178 generator (parent half life = 22 days) has been constructed and used to provide samples of radiopharmaceutical. Tests employing a dynamic cardiac phantom have been performed in which ejection fraction and stroke volume are mechanically set. Good image quality and accurate determination of ejection fraction were demonstrated. A series of canine studies have been performed and compared with similar studies using a commercial scintillation camera (Baird System 77) with both Ta-178 and Tc99m.

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AUTHOR'S SIGNATURE _____

"The author affirms that the material herein will not have been previously published as a manuscript or presented at any national meeting, that any animal studies conform with the "Guiding Principles in the Care and Use of Animals" of the American Physiological Society and that any human experimentation has been conducted according to a protocol approved by the institutional committee on ethics of human investigation or — if no such committee exists — that it conforms with the principles of the Declaration of Helsinki of the World Medical Association (CLINICAL RESEARCH 14:193, 1966).

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^{178}W-^{178}Ta GENERATOR: A STUDY OF THE CHROMATOGRAPHIC BEHAVIOUR OF TUNGSTEN AND TANTALUM ON INORGANIC ADSORBENTS.

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Because of potential in-space utilization of a ^{178}W-^{178}Ta generator on board the Space Lab. an effort has been made to extend the useful life of the ^{178}Ta generator as well as to substitute a more radiation resistant inorganic adsorber for the organic anion-exchanger presently used (1). Therefore, a study of the chromatographic behaviour of tungsten and tantalum was carried out by batch equilibration studies of a ^{178}W-^{178}Ta mixture or ^{182}Ta between inorganic adsorbents and various complexing and non-complexing eluents. The inorganic adsorbents that were evaluated are SnO_2, Al_2O_3, ZrO_2, TiO_2, $TiO_2 \cdot H_2O_2$, Fe_2O_3, polyantimonic acid, CrO_3, MnO_2, chromium phosphate, titanium phosphate, zirconium phosphate, tin phosphate, molybdenyl ferrocyanide, zirconium ferrocyanide, ferric ferrocyanide.

The complexants that were evaluated are fluoride, citrate, tartrate and oxalate. The most promising results were obtained with fluoride containing eluents. A summary of the K_D values of W and Ta between MnO_2 and a 1% NaF solution as a function of pH is shown in Fig. 1. The observed minimum in the adsorption of both tantalum and tungsten is just above the point of zero charge (PZC pH 2.8) of MnO_2. This indicates the desorption of anionic complexes from a cation exchanger. In 1% NaF solutions the tantalum species present are TaF_6^-, TaF_7^{2-} and hydroxo fluoride compounds of complex structure (2,3,4). At higher pH values the stability of the complexes decreases rapidly in favor of hydrolyzed species, which could explain the increasing tantalum adsorption at increasing pH above the PZC.

The K_D values obtained with the inorganic adsorbents, eluted with a pH 6 1% NaF solutions are summarized in Table 1. The $K_{D_W}/K_{D_{Ta}}$ ratio for these systems do not lend themselves to the development of a suitable ^{178}Ta generator.

Most other adsorbent/complexing eluent combination adsorbed tantalum more strongly than tungsten, with K_D values for both tungsten and tantalum declining with increasing pH.

The following conclusions can be drawn from these experiments:

1. The kinetics of adsorption and desorption of tantalum and tungsten are very slow, leading to large discrepancies in K_D values obtained by adsorption or desorption procedures.

2. In the absence of complexing agents the earth acid tantalum forms very stable hydrolyzed compounds (5) that strongly absorb to almost all inorganic exchangers over a wide pH range. Hydrolysis with the hydration water of the adsorbent may be the reason for the strong tantalum binding.

3. Complexing agents are effective at desorbing tantalum from inorganic exchangers. However, solubility of the adsorbents and desorption of tungsten are obstacles that must be overcome on the way to a ^{178}W-^{178}Ta generator based on inorganic adsorbents.

Fig. 1

K_D Values of W and Ta between MnO_2 and 1% NaF solutions as a f(pH)

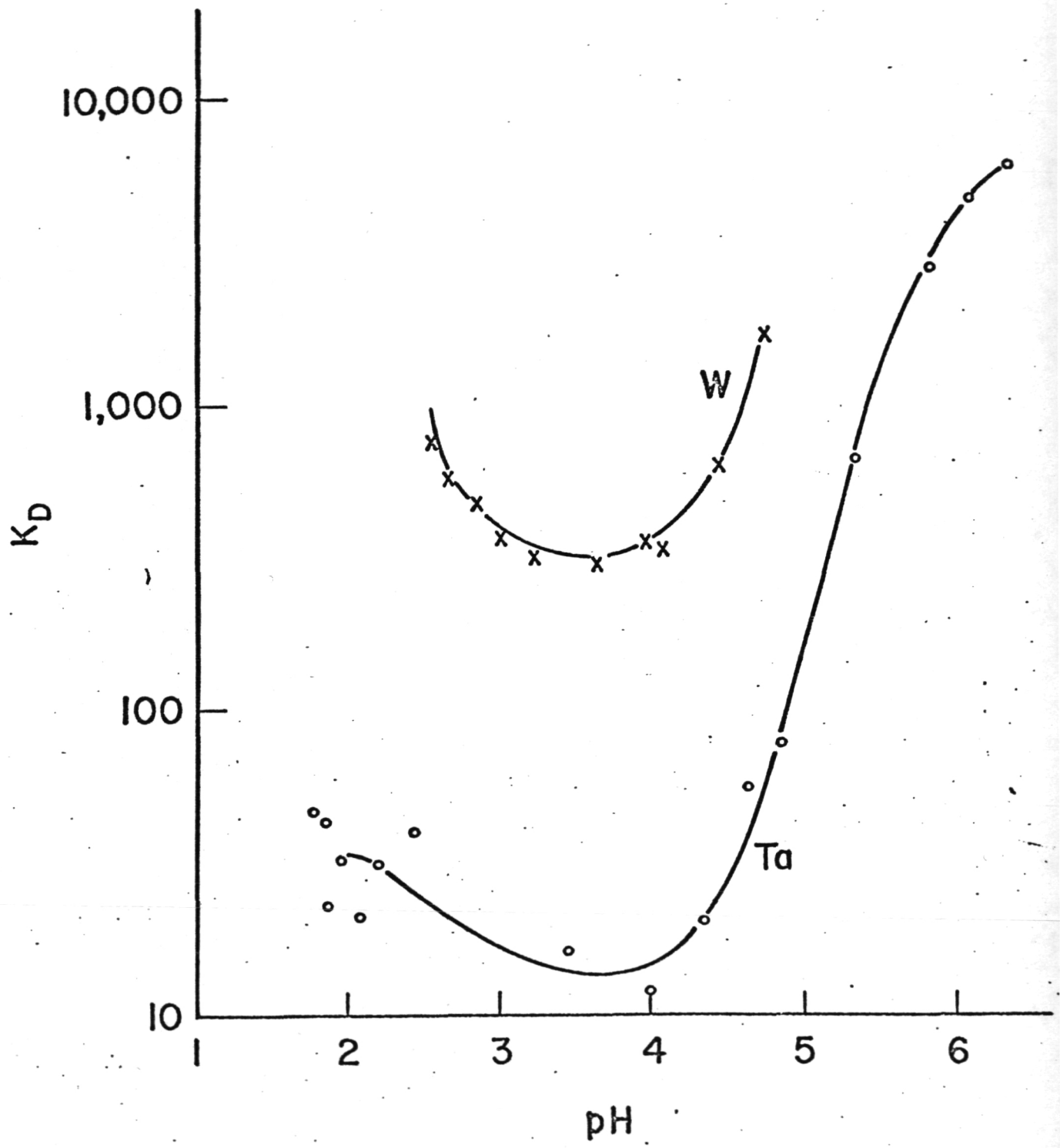

Table 1

K_D values for W and Ta between inorganic adsorbents and aqueous solutions, containing 1% NaF (equil. time = 10')

Adsorbent	K_D			
	W		Ta	
	adsorption	desorption	adsorption	desorption
stannic oxide	260	1,600	73	800
Tin-phosphate	7	85	7	50
titanium oxide	60	450	90	700
zirconium oxide	10	410	13	1,500
zirconium phosphate	7	140	4	100
copper ferrocyanide	8	27	20	60

References:

(1) Neirinckx R.D., Jones A.G., Davis M.A., Harris G.I., and Holman, B.L., J. Nucl. Med., 19, 514 (1978).

(2) Pakholkov, V.S., and Suntsov A.S., Zh. Prikl. Khi., 49, 737 (1976).

(3) Pakholkov V.S., and Suntsov A.S., Zh. Prikl. Khim., 52, 1484 (1978).

(4) Laskorin B.N., Vodolazov L.S., Fedulov Y.N., Schishkina E.G. and Petrenko V.I., Zh. Neorg. Khim., 24, 3082 (1979).

(5) Strelow F.W.E., and Van der Walt T.N., Anal. Chem., 47, 2272 (1975).