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THE TECHNETIUM-99m GENERATOR*

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THE TECHNETIUM-99m GENERATOR

ABSTRACT

A combination of useful nuclear properties of 6-hour ^{99m}Tc of interest in nuclear medicine has led to the development of a simple, rugged, and compact generator which makes the short-lived isotope available for use at locations far removed from sources of production.

Parent ^{99}Mo is produced as a separated carrier-free fission product or by neutron bombardment of molybdenum. Each method has advantages and disadvantages. The separated fission product, because it yields higher product concentrations, is the most widely used material in the nuclide generator.

The daughter ^{99m}Tc is "milked" by elution with physiological saline solution. The process separates ^{99m}Tc from the parent ^{99}Mo in a form requiring little further processing for clinical use. The ^{99}Mo remaining in the generator continues to decay forming fresh ^{99m}Tc of which the activity reaches a maximum every 23 hours, permitting several milkings per day.

THE TECHNETIUM-99m GENERATOR

INTRODUCTION

The interest in and use of ^{99m}Tc as a tracer in nuclear medicine has rapidly increased during the last year or two. A rare combination of nuclear properties provides this radionuclide with considerable advantages over other agents in applications such as organ visualization and tumor localization. The development at Brookhaven National Laboratory of a simple generator whereby 6-hour ^{99m}Tc can be milked from its parent, 2.7-day ^{99}Mo, has made it possible to use the isotope at great distances from the production site.

Technetium-99m was initially suggested for potential medical applications because of its favorable nuclear characteristics[1]. Figure 1 shows the decay scheme of ^{99}Mo-^{99m}Tc[2,3]. The 6-hour half-life, although short, is sufficiently long for many applications and for chemical manipulations when desired. The energy of the gamma

radiation (140 keV) has satisfactory tissue penetration and yet is readily collimated. The combination of short half-life and absence of beta radiation make feasible the administration of millicurie amounts of the nuclide with tolerable radiation dosage to the patient[4]. The high counting rates resulting from such large amounts produce improved statistics and, when used with high-efficiency high-resolution collimators, can yield information not previously available. The decay of ^{99}Mo-^{99m}Tc to the ^{99}Tc ground state is of no consequence due to the long (2×10^5 year) half-life of ^{99}Tc; (i. e. $\sim 3.3 \times 10^{-9}$ mC and $\sim 3.0 \times 10^{-8}$ mC of ^{99}Tc are produced by the decay of 1 mC of ^{99m}Tc and 1 mC of ^{99}Mo, respectively).

Chemical and physiological studies of ^{99m}Tc by Harper and associates have resulted in several clinical applications[5,6,7,8]. Chemically technetium belongs to group VII-A and behaves like manganese and rhenium, the resemblance to the latter being particularly close

in the higher oxidation states. As the pertechnetate, (TcO_4^-), the most stable form in aqueous solutions, technetium resembles iodide very closely in its biological distribution thereby making it feasible to use this isotope for short-term thyroid studies and scanning. Technetium-99m, as the pertechnetate ion, has found its most useful application to date in brain scanning. This is due, however, not to any increased tumor specificity but primarily to reduced scanning times and improved statistics resulting from the ability to use large amounts of activity relative to other isotopes previously used.

The excellent nuclear properties of ^{99m}Tc have led to a search for other chemical compounds and complexes of technetium with different biological behavior. The ability of technetium to combine with other materials when reduced to lower oxidation states[9] has been investigated by Harper, et al[8] in Chicago and Stern and McAfee[10] in Baltimore. This work has resulted in compounds

useful for several additional applications which will be described in later papers.

A procedure has been developed at Brookhaven for preparing a ^{99m}Tc-labeled colloid by coprecipitation with elemental sulfur, which has proved to be extremely useful for visualization of the reticuloendothelial system[11] and for studies of bone marrow distribution[12]. As the chemical characteristics of technetium are explored further, there is little doubt that additional applications for ^{99m}Tc will be developed.

PRODUCTION

Technetium-99m, if it is to find widespread use for clinical applications, must be available in large quantities at a reasonable cost and in a readily usable form of high purity. The isotope can be supplied to the user by two methods; either as separated ^{99m}Tc, in which case the supplier would store the parent ^{99}Mo and perform the separation, or in the form of a generator

from which the user would milk the ^{99m}Tc as desired. The latter has been the most widely used method to date, particularly by the larger institutions which have the necessary facilities and sufficient work load to use the generator efficiently. Shipment of separated ^{99m}Tc presents formidable problems due to the short half-life but may be practical for users located near a supplier and for smaller hospitals requiring irregular supplies.

Parent ^{99}Mo, in Curie quantities, can be produced in a nuclear reactor as a fission product from the neutron irradiation of uranium or by the thermal neutron bombardment of molybdenum. A long reactor irradiation (to saturation activity) of 100 mg of ^{235}U will yield approximately 2.2 Curies of fission product ^{99}Mo at a neutron flux of 10^{13} neutrons/(cm^2 sec); the same irradiation of 1 g of molybdenum will produce about 200 mC of activity. The fission product process for the production of ^{99}Mo has the advantage of a carrier-

free product, thereby allowing the adsorption of large amounts of the radioisotope on an ion exchange generator system without danger of leakage of the parent molybdenum activity. The same general production procedure and equipment can also be used for the production of other useful isotopes, thereby reducing the cost. On the other hand, ^{99}Mo produced by the neutron irradiation of molybdenum requires less elaborate equipment for processing and entails substantially fewer problems of waste disposal. However, the production of high-specific activity ^{99}Mo by this method requires the use of expensive high-flux reactors to produce a product suitable for the preparation of high-activity ^{99m}Tc generators.

High-purity, carrier-free fission product ^{99}Mo is produced at Brookhaven National Laboratory from neutron irradiated ^{235}U. Figure 2 shows the hot cell used for the production of multicurie amounts of ^{99}Mo per run, with sufficient shielding for handling several

hundred Curies of total fission products. Figure 3 is a view of the remotely operated processing equipment removed from the cell. Irradiated uranium samples are transported from the reactor and are transferred into the equipment through the top of the cell. Figure 4 illustrates the simple procedure that has been developed for the separation of carrier-free ^{99}Mo and ^{132}Te from other fission products. (Tellurium-132 is frequently produced from the same production run as the molybdenum.) The procedure involves the dissolution of the irradiated uranium sample in HNO_3 and the adsorption of the molybdate and tellurite ions on an alumina (Al_2O_3) column[1, 13,14]. After washing to remove uranium and other fission product cations from the column, the molybdenum is eluted with NH_4OH. (The tellurium activity can be recovered by elution with NaOH.)

The ^{99}Mo solution is transferred to the facility shown in Figure 5 for final purification, sampling and generator preparation. Purification is accomplished

by adsorption of the basic molybdate on Dowex-1 anion exchange resin, washing to remove trace radioimpurities, and elution of the final product with 1.2 N HCl. After sampling for ^{99}Mo assay, the product solution is loaded onto the ^{99m}Tc generator which is then washed with NaCl for injection and packaged for shipment. The present facility can prepare several generators simultaneously; approximately twenty generators can be loaded, washed and packaged for shipment in two hours.

Molybdenum-99 is also produced by the thermal neutron irradiation of molybdenum usually in the form of MoO_3. Specific activities of 200 mC to several Curies of ^{99}Mo per gram of molybdenum can be achieved by this method depending on the neutron flux of the reactor. The irradiated MoO_3 is dissolved in NH_4OH and adjusted to a pH of 3-3.5 with acid for adsorption on generators. Precautions must be taken to see that the adsorption capacity of the generator is not exceeded due to the relatively large amounts of stable molybdenum present;

otherwise leakage of molybdenum from the generator can occur.

^{99m}Tc GENERATOR

The ^{99m}Tc generator was developed at Brookhaven in 1957 and is based on the adsorption of carrier-free ^{99}Mo on an alumina column. Originally the molybdenum activity was a by-product of ^{132}Te production, and the ^{99m}Tc was milked or eluted from the column with dilute HNO_3. However, the eluant was later changed to HCl (0.1 N) to be more suitable for medical applications. Traces of aluminum were removed from the eluted ^{99m}Tc solution either by neutralization and filtration or adsorption on Dowex-50 cation exchange resin followed by neutralization. An alternative method of purification consisted of adjusting the eluted pertechnetate solution to 5 N NaOH, and extracting the technetium into methyl ethyl ketone[15,16]. After the ketone is evaporated, the ^{99m}Tc is taken up in any desired volume of saline

solution or other solvent. The technetium solution can be sterilized prior to administration by autoclaving or microfiltration.

Figure 6 shows the present Brookhaven ^{99m}Tc generator, which utilizes carrier-free ^{99}Mo. The device is simple, rugged, and compact with overall dimensions of 1.5 x 4 inches. The small amount (5 g) of Al_2O_3 necessary to retain the molybdenum requires small volumes for elution, thereby yielding the technetium in high concentration. The generator is now milked by pouring physiological saline solution through the column; 90-95% of the ^{99m}Tc activity is eluted in the first 10 ml free of Al^{+++}, and in a form requiring little further processing for clinical use. The milking yield of ^{99m}Tc relative to the ^{99}Mo activity on the generator when they are at equilibrium is 70-80%. This is due to the fact that all of the Mo does not decay through the ^{99m}Tc isomer (~84%). Generators of this type can be routinely prepared con-

taining over 500 mC molybdenum with a technetium product having less than 0.1 μC of total radioactive contaminants per mC of ^{99m}Tc.

Figure 7 shows a simple equipment setup for eluting the generator and filtering and collecting the product with a minimum amount of handling and manipulation. The product, ready for use, is eluted with sterile NaCl solution into a plastic syringe to which is attached a pre-sterilized micro-filter holder. The solution is filtered by drawing it into a sterile pre-evacuated bottle. If the solution is to be autoclaved, the filter can be omitted, allowing the product to flow directly from the syringe through the needle into the bottle. A second needle can be used for venting the bottle. This type of equipment is also useful as a final step in the labeling of albumin, colloid, etc. with ^{99m}Tc.

Radioassay can be carried out routinely and quickly using a commercially available well-type ionization

chamber and electrometer* that has been calibrated against a ^{57}Co standard[17,18]. This method avoids the necessity of diluting the sample for counting samples in a well-type scintillation counter.

Following separation from the parent ^{99}Mo, ^{99m}Tc grows back and reaches a maximum in approximately 23 hours. Thus daily milkings yield large batches of product. However, more frequent milkings yield still more total activity within a given period of time, although the amount per milking is reduced. The growth of technetium reaches 50% of maximum in approximately 6 hours, making it feasible to elute several times a day.

SEPARATED TECHNETIUM-99m

Technetium-99m can be supplied directly to the user separated from the parent ^{99}Mo, which is retained

*NE014 standard ionization chamber and NE503A electrometer, produced by Rand Nucleonics and Controls, Welwyn Garden City, Hertfordshire, England.

by the supplier. However, due to the relatively short half-life of ^{99m}Tc, the problems of scheduling and shipping are great, limiting the usefulness to short distances. The advantages of receiving the isotope precalibrated, in a form ready for use and when needed, can make this the method of choice for some users near a supplier. The conversion of pertechnetate to other chemical forms may be carried out more easily by the supplier than by small hospitals lacking the proper facilities.

Technetium-99m can be separated in quantity for distribution by eluting a generator loaded with large amounts of ^{99}Mo or by repeated extraction from ^{99}Mo solution. The use of carrier-free ^{99}Mo is ideal for the preparation of multi-hundred millicurie generators of small physical size, which allow rapid elution with small volumes. Low specific activity ^{99}Mo requires the use of larger columns resulting in more difficult shielding problems, slower milking, and lower concen-

trations of product activity. There might be some advantage in milking this type of generator with methyl ethyl ketone[19] (MEK) followed by evaporation to reduce volumes.

Solvent extraction separation of ^{99m}Tc from aqueous solutions of ^{99}Mo can be used with both carrier-free and low-specific activity material. This procedure is the method of choice for specific activities too low to be feasible for adsorption on alumina columns. An extraction process has been developed at Brookhaven[20], whereby separated ^{99}Tc can be supplied to nearby hospitals, in areas where only low-flux reactors are available and processing facilities are limited. The procedure consists of dissolving reactor-irradiated MoO_3 in NaOH and extracting ^{99m}Tc from the basic solution (5 N NaOH) with MEK[15,16]. Traces of the aqueous solution are removed from the MEK by passing it through a small column of Al_2O_3 (acid type). The MEK is evaporated to dryness, and the carrier-free ^{99m}Tc activity can then be

taken up in an appropriate solvent, e. g. saline solution, and assayed. The ability to process multi-gram amounts of MoO_3 eliminates the problem of low neutron flux and erratic operating schedules of the reactor.

SUMMARY

The technetium-99m generator makes practical the widespread use of 6-hour ^{99m}Tc in nuclear medicine and at locations remote from the production site.

^{99}Mo is produced as a fission product during neutron irradiation of uranium or by neutron capture during neutron bombardment of stable molybdenum. The fission product process has the advantage of producing a carrier-free product of which large amounts can be loaded onto a generator. The neutron irradiation of molybdenum requires a simpler process which presents fewer waste disposal problems, but only limited amounts of the product can be loaded onto a generator successfully.

The technetium-99m generator has evolved into a simple, rugged, and compact device, 1.5 inches diameter x 4 inches high. The ^{99}Mo parent is firmly fixed on a small amount of Al_2O_3. The daughter ^{99m}Tc, milked by elution with physiological saline solution, requires little further processing for clinical use. The process can be repeated several times daily.

A simple setup for elution, filtering, and collecting the ^{99m}Tc ready for use, requires a minimum amount of handling and manipulation.

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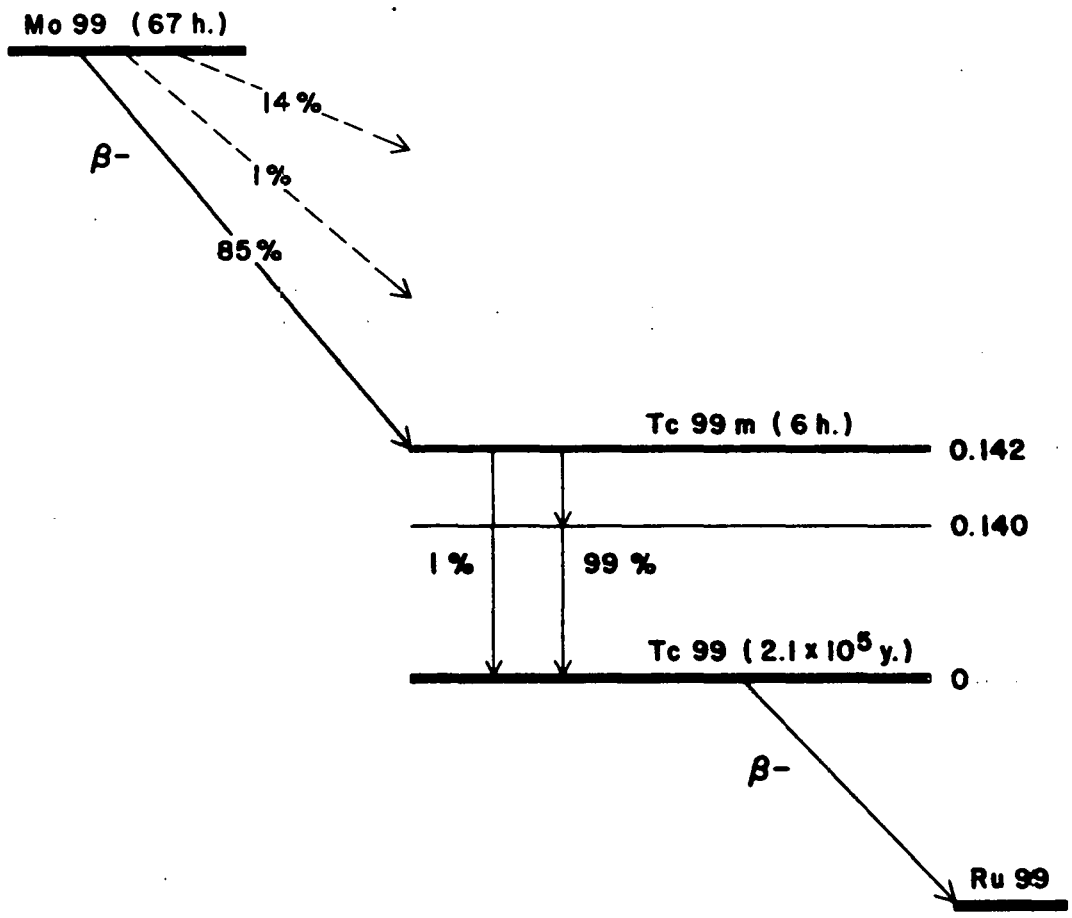


FIGURE 1

^{99}Mo-^{99m}Tc DECAY SCHEME

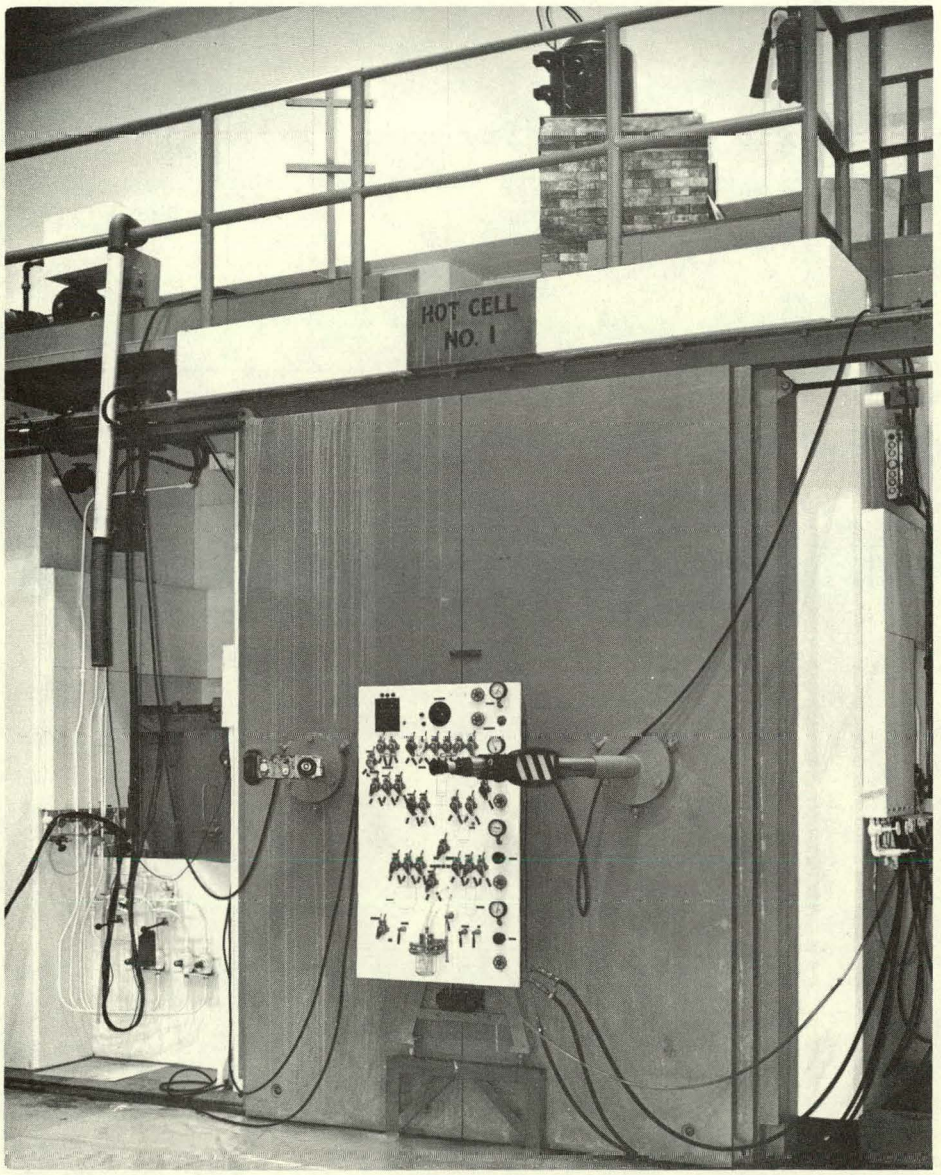


FIGURE 2

SHIELDED CELL FOR PROCESSING

CARRIER-FREE ^{99}Mo

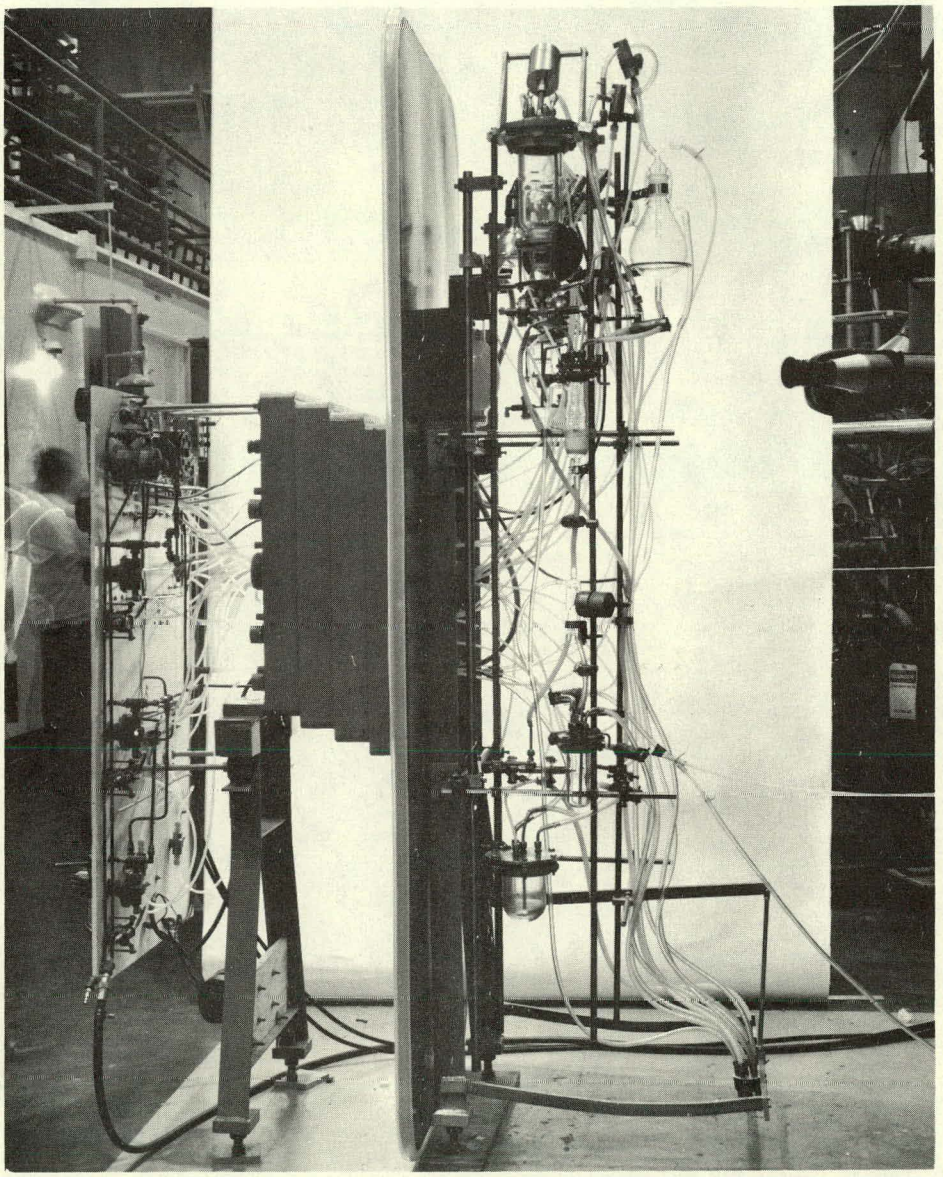
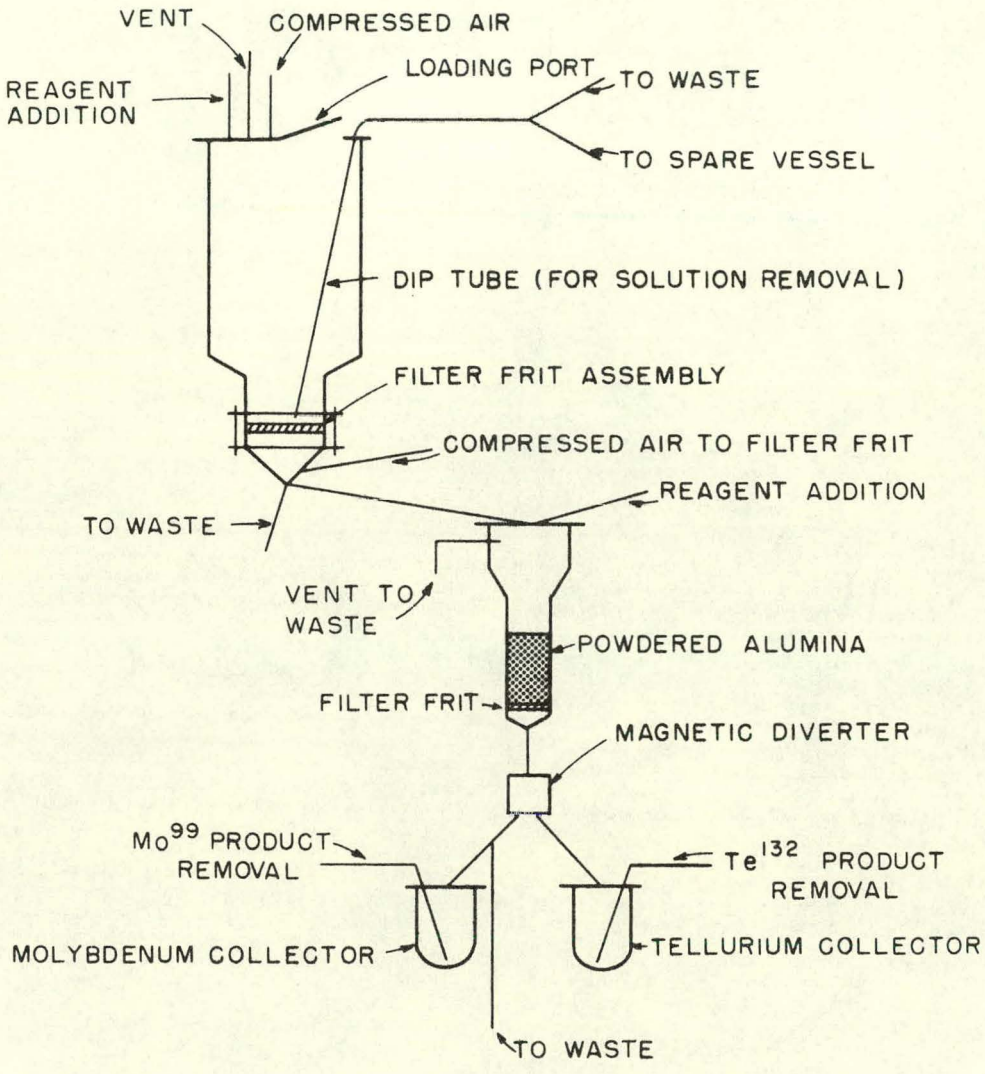


FIGURE 3

PROCESSING EQUIPMENT REMOVED FROM CELL



FISSION PRODUCT SEPARATION EQUIPMENT

FIGURE 4

FISSION PRODUCT SEPARATION EQUIPMENT

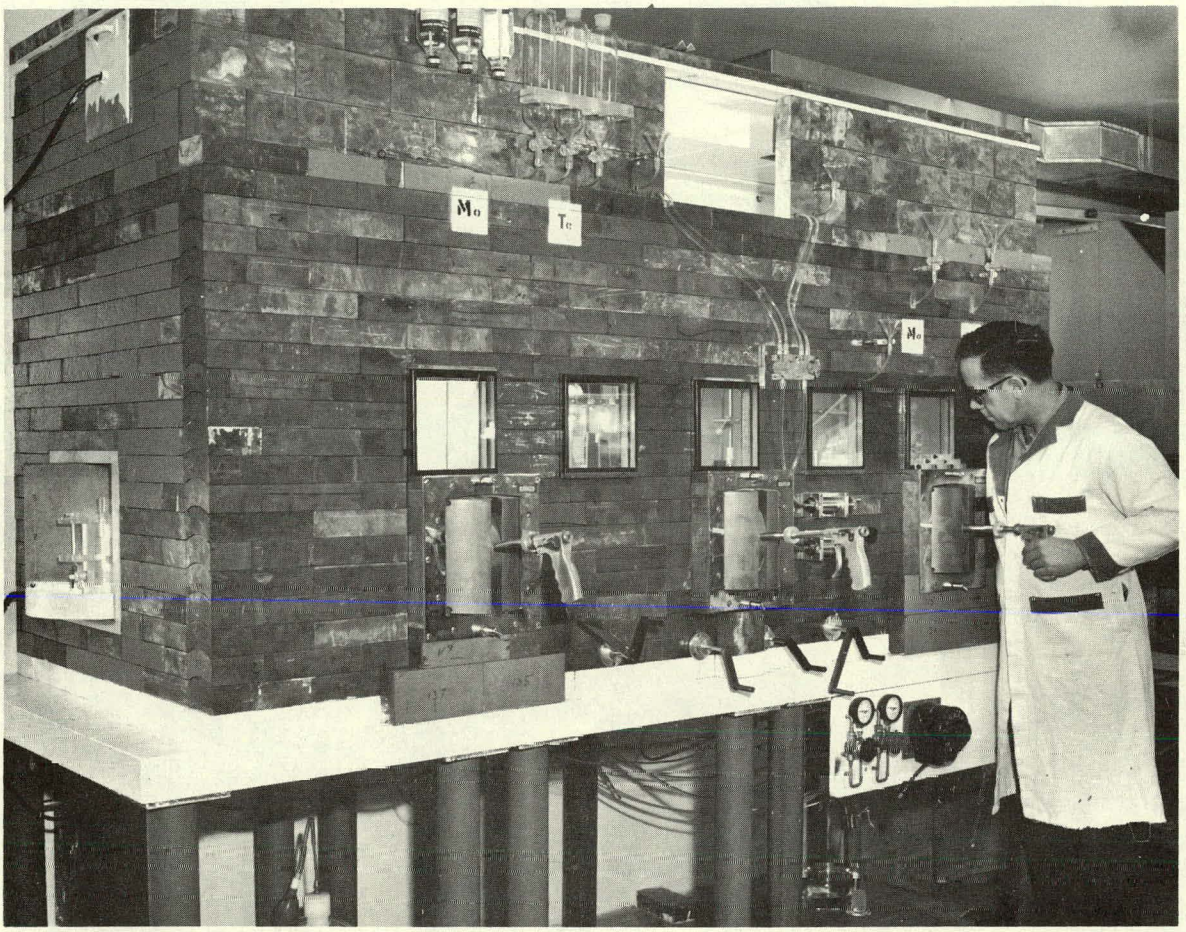
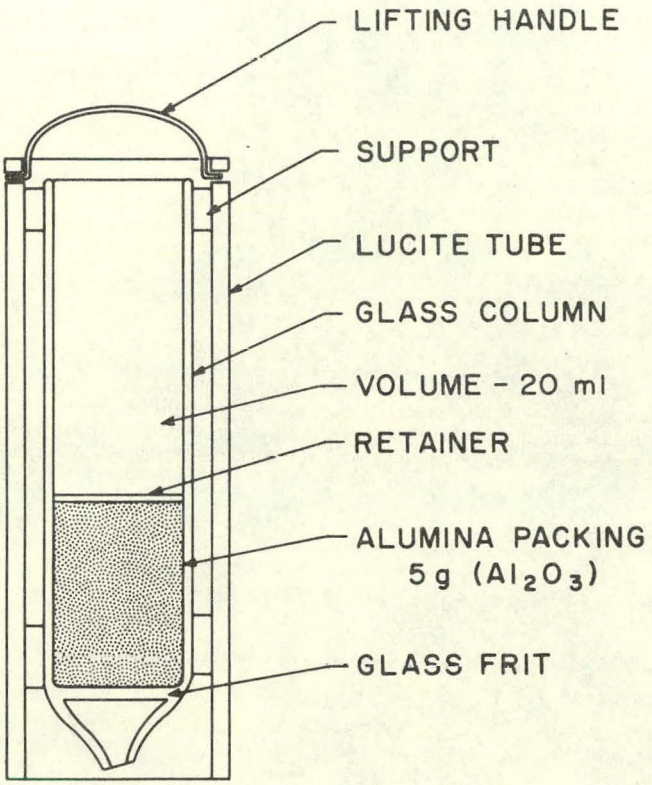


FIGURE 5

SHIELDED FACILITY FOR ^{99}Mo PURIFICATION

AND ^{99m}Tc GENERATOR LOADING



Tc^{99m} GENERATOR

FIGURE 6

^{99m}Tc GENERATOR

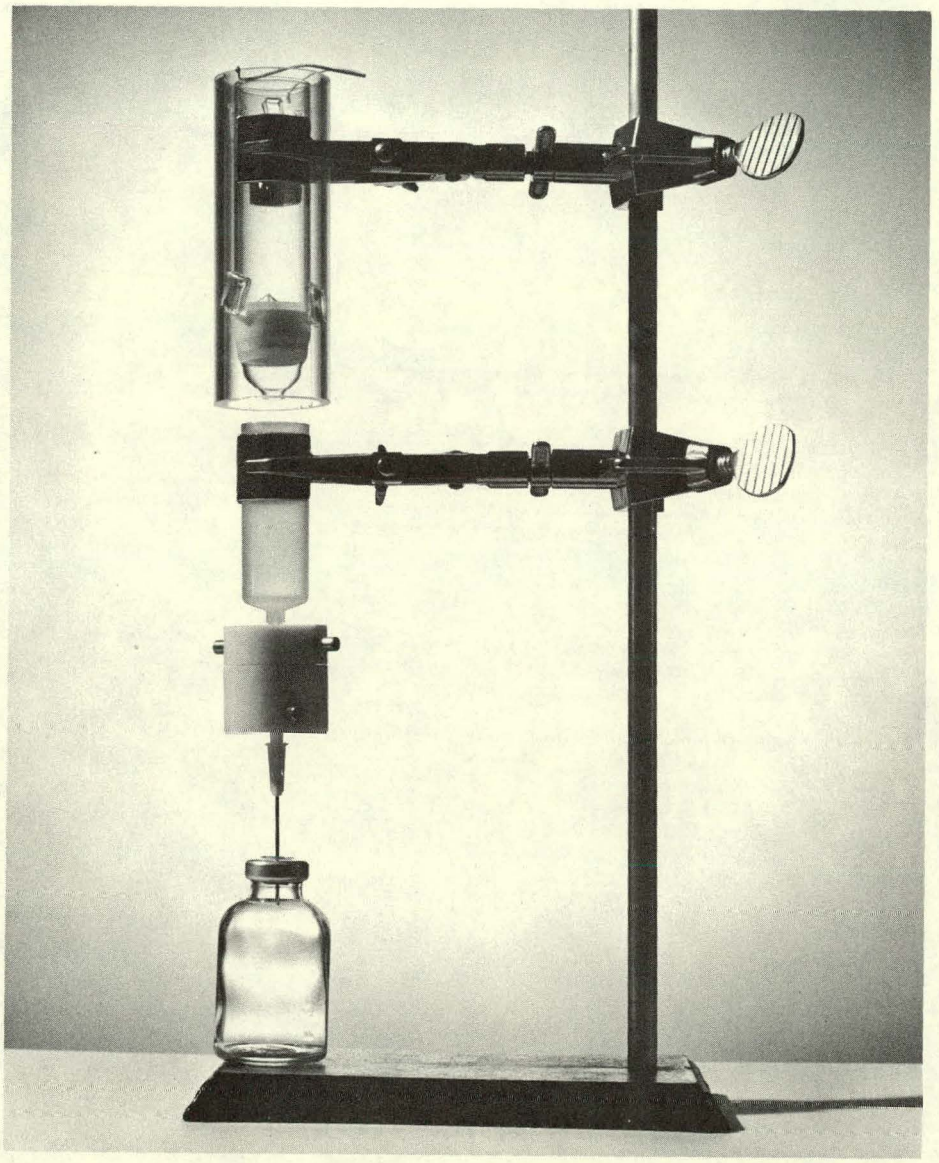


FIGURE 7

SETUP FOR ELUTING GENERATOR

AND PREPARING PRODUCT FOR USE