

[54] GENERATION OF A SUPPLY OF
RADIONUCLIDE

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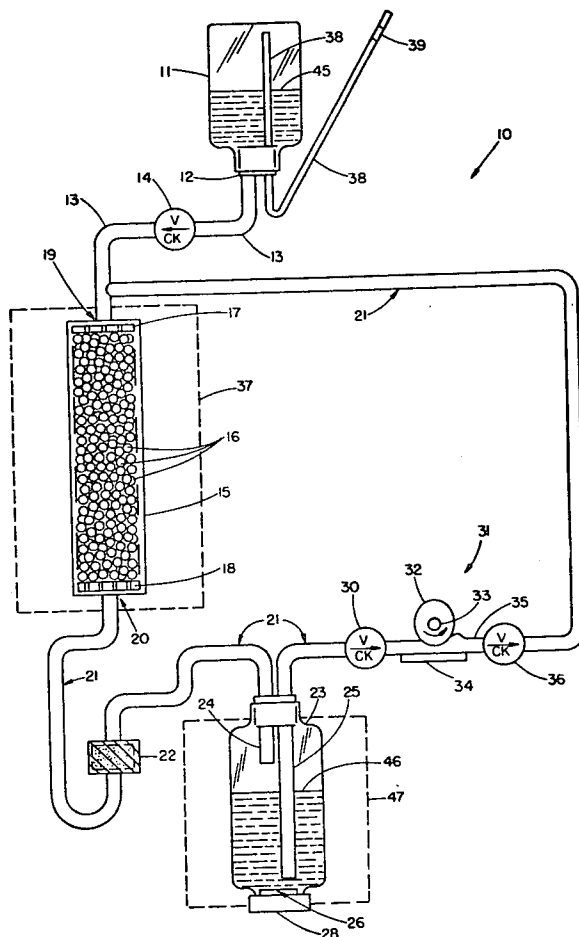
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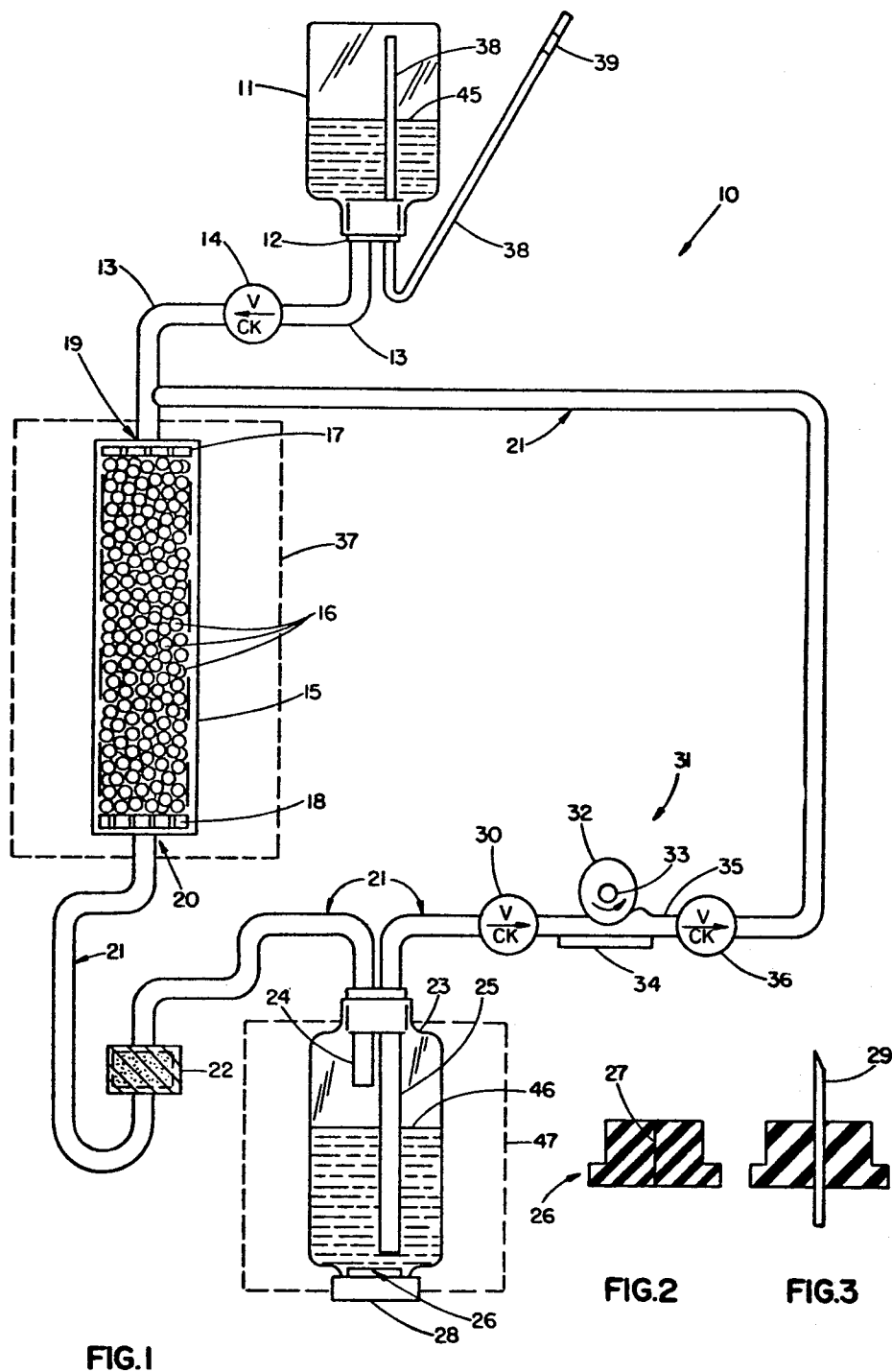
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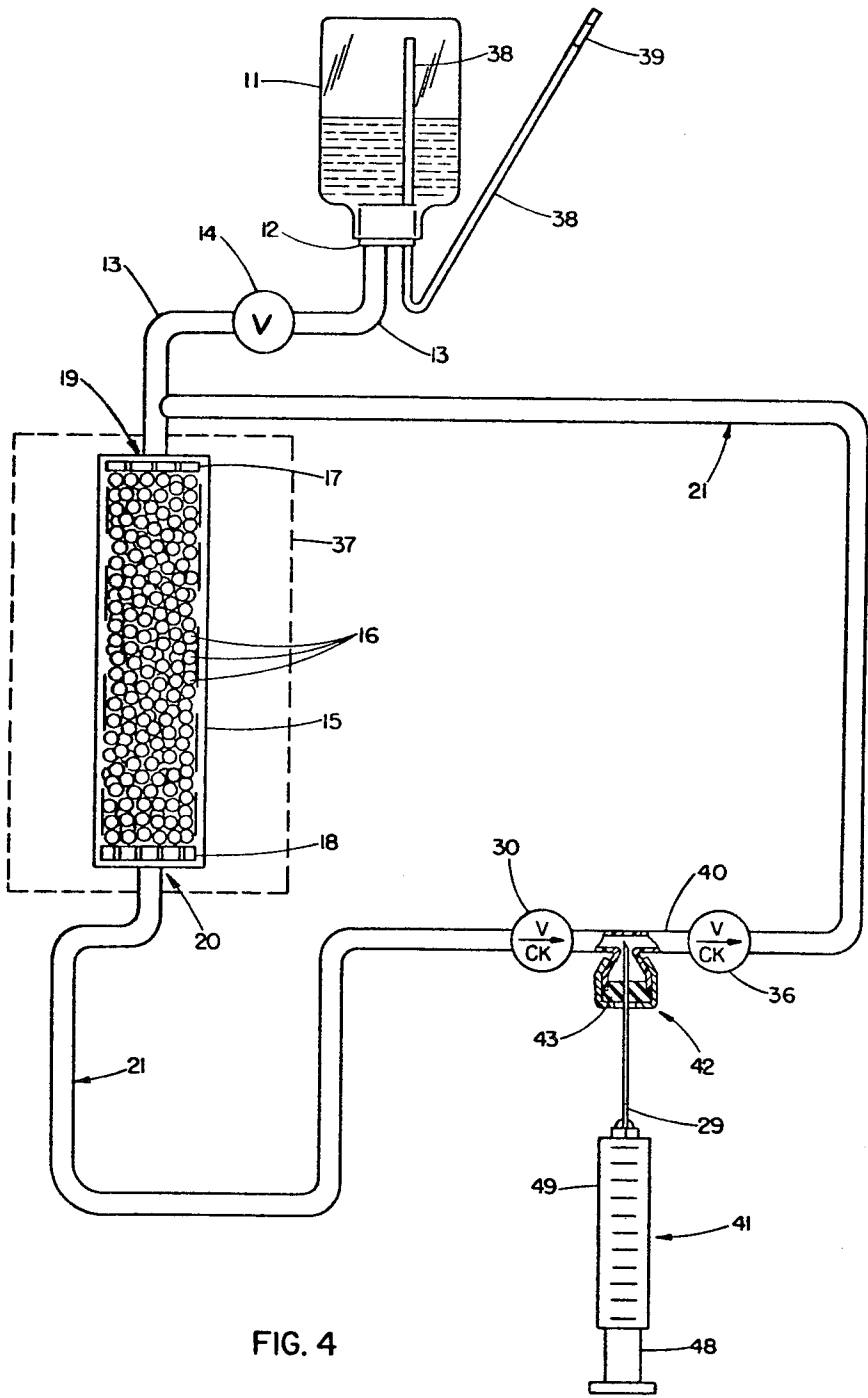
ABSTRACT

A method and apparatus for generating and maintaining an available supply of a radioactive eluate with at least a minimum level of activity. A relatively short-lived daughter radionuclide is produced by the radioactive decay of a relatively longer-lived radionuclide in a radionuclide generating chamber. The daughter radionuclide is separated from the parent radionuclide by use of an eluting solution. The resultant solution is recycled through the generator chamber to replenish and concentrate the amount of daughter radionuclide contained therein. Because a relatively large amount of eluate is produced and maintained at at least a minimum level of radioactivity, it is possible to easily meet fluctuating demands for the daughter radionuclide.

18 Claims, 4 Drawing Figures







GENERATION OF A SUPPLY OF RADIONUCLIDE

This application is a continuation-in-part of application, Ser. No. 195,734, filed Nov. 4, 1971.

This invention relates to a method and apparatus for generating and maintaining a continuous supply of a radioactive eluate with at least a minimum level of radioactivity. This invention has particular application to the field of nuclear medicine, where individual dosages or aliquots of a short-lived radionuclide are required.

BACKGROUND OF THE INVENTION

While a wide variety of radionuclides may be produced utilizing the apparatus and techniques of the invention disclosed herein, the invention has particular applicability to the production of technetium-99m, a short-lived daughter radionuclide, from molybdenum-99, the longer-lived parent. Technetium-99m is used in nuclear medicine for injection into a patient as a radioactive tracer. Technetium-99m, in its usual form (per-technetate ion) as produced from molybdenum-99, when injected into a patient, enters the blood stream and tends to concentrate in brain lesions. Alternatively, technetium-99m can be processed subsequent to its generation, so that it will tend to concentrate in other organs of the body. Thus used, technetium-99m is a valuable diagnostic tool for physicians in determining the nature and extent of physical, physiological, and circulatory irregularities in the organs of the body.

This invention is not limited to the generation of technetium-99m, however. Table I below lists other exemplary parent and daughter radionuclides along with their customary uses in nuclear medicine. Any one or more of these radionuclides may be utilized to form the subject matter of the present invention.

TABLE I

Parent Radionuclide	Daughter Radionuclide	Use
Cesium-137	Barium-137m	Dynamic Studies
Germanium-68	Gallium-68	Positron Scanning
Yttrium-87	Strontium-87m	Bone Scanning
Tin-113	Indium-113m	Scanning

All of the radionuclides injected into patients preferably share the characteristic of being short-lived. For example, the half-life of technetium-99m is 6 hours. This is considerably shorter than the half-life of 2.7 days of its parent, molybdenum-99. A short half-life is an important property of radioactive materials to be injected into a living patient in nuclear medicine because excessive exposure to radioactivity is in this way avoided. This lessens any health hazard posed to the patient and also makes possible a fairly rapid sequence of tests utilizing radioactive substances without traces of radionuclides injected earlier interfering with subsequent studies.

In the production of radionuclides to be administered to patients, separation of the daughter radionuclide is effected by eluting or "milking" the desired daughter radionuclide from the parent radionuclide. In the usual case the parent radionuclide is firmly affixed to an inert substrate. The daughter is separated from the parent by passing a liquid solvent through a bed containing the parent radionuclide so that there is maximum contact between the solvent and the parent. The parent radionuclide spontaneously decays or disintegrates to form the daughter radionuclide. The solvent used selectively

removes the desired daughter radionuclide in preference to the parent radionuclide. The solvent is termed an eluant while the solution passed from the generator chamber containing the desired daughter radionuclide is termed an eluate.

STATE OF THE ART

In conventional radionuclide generating systems, several problems currently exist. The quantity of the required dosage of eluate varies widely, depending upon the initial level of radioactivity and the half-life of the parent nuclide. That is, a highly radioactive quantity of parent nuclide will yield the daughter radionuclide in a concentration sufficient so that only a few milliliters of eluant are required to produce the eluate being administered to the patient. Conversely, a large quantity of eluate must be administered to a patient when it is produced from a quantity of parent radionuclide having a low level of radioactivity.

Moreover, the desired daughter radionuclide will decay to an unsuitably low radioactive concentration within a short period of time with the radionuclide generating systems now available. This defect in the conventional systems is particularly serious where the time required to re-establish radioactive equilibrium within the generator is relatively long.

In conventional systems it is necessary for the parent and the desired daughter radionuclide to be assayed subsequent to the production of the desired daughter radionuclide. For example, in conventional systems, the molybdenum breakthrough test must be performed on each dosage of technetium-99m generated to insure that the parent radionuclide, molybdenum-99, is not present in any significant amount in the dosage to be administered to the patient. In preferred embodiments of the present invention, a subsequent assay is unnecessary since the parent and daughter radionuclides may be continuously monitored within the system.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the invention to provide a radionuclide generating system in which a supply of the desired daughter radionuclide is available in a high concentration. In conventional generators, the radioactive concentration of the eluate decays according to the half-life of the daughter radionuclide. In the system described herein, the daughter radionuclide is constantly being replenished by radioactive decay of the parent radionuclide and the radioactive concentration is always higher than from conventional generators. At equilibrium the radioactive concentration of the eluate decays according to the half-life of the parent radionuclide. For example, using the present invention in the production of technetium-99m from molybdenum-99, the half-life of the eluate is 67 hours, the half-life of molybdenum-99, rather than 6 hours, the half-life of technetium-99m.

Another object of this invention is to increase the concentration of a daughter radionuclide obtainable per unit of eluate. The improvement in the concentration obtainable varies somewhat with the total radioactivity of the parent radionuclide, the eluant, and the form in which the parent radionuclide is provided in the generator chamber, but the improvement in concentration is generally by about a factor of 3, when compared with conventional systems.

Another object of this invention is to further reduce the time required in the preparation of dosages of a daughter radionuclide by continuously assaying the supply of eluate prior to withdrawing the specific dosage for a particular patient. This object is achieved in the preferred embodiments of the invention by providing the generating system with a reservoir within which the eluate collects and resides for a time prior to recirculation through the generator chamber. While in the reservoir, the radiation level therein is monitored utilizing a radiation detecting device.

A further object of the invention is to minimize the time required in processing a dosage of a desired daughter radionuclide by eliminating the requirement for a parent radionuclide breakthrough test subsequent to the preparation of each individual dosage. This is made possible by the continuous performance of the breakthrough test while the eluate is present in the reservoir.

In a broad aspect of this invention is a method of generating an eluate containing a desired daughter radionuclide in a closed generating system comprising passing an eluant from a source of said eluant through a generator chamber containing a parent radionuclide which spontaneously decays into a daughter radionuclide, selectively removing the daughter radionuclide in preference to said parent radionuclide to form an eluate, and recirculating the eluate produced thereby through said generator chamber in order to maintain a supply of eluate at a desired level of radioactivity in said generating system.

In another broad aspect this invention is a radionuclide generating system comprising a generator chamber having an inlet and an outlet and containing a parent radionuclide that undergoes spontaneous radioactive decay to produce a daughter radionuclide, a source of eluant which selectively removes the daughter radionuclide in preference to the parent radionuclide connected to the inlet of said generator chamber, a recirculation line conducting the solution containing the dissolved daughter radionuclide from the outlet of said generator chamber for recycling to the inlet of said generator chamber, pumping means for forcing the aforesaid solution through the recirculation line, and a withdrawal port for withdrawing solution from the radionuclide generating system.

The invention may be more adequately depicted in the accompanying drawings in which:

FIG. 1 schematically depicts a preferred embodiment of this invention.

FIG. 2 is an enlarged cross-sectional view of the withdrawal port of FIG. 1 in a closed position.

FIG. 3 is an enlarged cross-sectional view of the withdrawal port of FIG. 1 in an open position.

FIG. 4 schematically depicts the operation of an alternative form of the invention.

Referring now to FIG. 1 there is illustrated a radionuclide generating system 10 comprised of a clear plastic generator chamber 15 having opposing ends 19 and 20. End 19 has an inlet connected to a flexible plastic supply line 13 and end 20 has an outlet connected to recirculation line 21. Retainers 17 and 18 are interiorly positioned in the generator chamber 15 adjacent to ends 19 and 20 respectively. The retainers 17 and 18 provide a means for holding the contents of the generator chamber 15 in place, and retainer 17 also assists in distributing the fluid flow uniformly throughout the cross-

section of generator chamber 15. The generator chamber 15 contains a charge of a granular material containing a parent radionuclide that undergoes radioactive disintegration to form a daughter radionuclide. This charge is packed into the generator chamber 15, and as illustrated, is comprised of granular particles 16 supporting quantities of the parent radionuclide on the surface thereof. Lead shielding, indicated at 37, prevent excessive radiation from escaping from generator chamber 15 and thereby endangering personnel in the immediate vicinity. A source of solvent or eluant such as the bottle 11, contains a quantity of a solvent or eluant 45 that selectively elutes the daughter radionuclide produced from the parent radionuclide in preference to all other material in the generator chamber 15. The eluant source bottle 11 is closed by a rubber stopper 12 through which the supply line 13 and air vent 38 extend. The supply line 13 and air vent 38 are sealed to the stopper 12 and stopper 12 is sealed to bottle 11 so that there is no leakage in the eluant supply system. The eluant 45 flows through supply line 13 and through the check valve 14 located therein to the fluid access inlet connection at end 19 of generator chamber 15. The solvent or eluant 45 flows through the generator chamber 15 where it removes the daughter radionuclide produced by the disintegration of the parent radionuclide adsorbed on the supporting substrate. The solution, or eluate formed by the eluant and dissolved daughter radionuclide passes through the retainer 18 and the fluid access outlet connection to the recirculation line 21.

Recirculation line 21 is connected in communication between the outlet at end 20 of the generator chamber 15 and the inlet at the end 19 of the generator chamber 15 to recirculate to the generator chamber 15 the solution containing the daughter radionuclide. A microporous filter 22 for removing particulate matter from the solution is positioned in the recirculation line 21. Likewise, a fluid reservoir bottle 23 is also located in the recirculation line 21. Recirculation line 21 is constructed of flexible plastic tubing which is severed in the reservoir bottle 23. The eluate flows from the recirculation line section 24 into the reservoir bottle 23. The eluate 46 resides in reservoir bottle 23 longer than at any other place in the system, but eventually is passed through the tube section 25 to the pumping means 31.

The pumping means 31 is comprised of a peristaltic pump exteriorly positioned with respect to the recirculation line 21 and acting upon section 35 of line 21. The peristaltic pump is comprised of a fixed, flat surface 34 and an eccentric cam 32 rotating about shaft 33. As the cam 32 rotates, eluate enters section 35 through check valve 30, which checks the solution flow in one direction thereby limiting flow in recirculation line 21 to the counterclockwise direction indicated. When the cam 32 rotates so that the section 35 is not compressed, eluate flows through the check valve 30 into the section 35. As the cam 32 progresses in its counterclockwise motion, it compresses the section 35 from left to right, as illustrated in FIG. 1, thereby forcing the eluate 46 through check valve 36 and through the remainder of recirculation line 21 for recycling to generator chamber 15.

A withdrawal port 27 is located in the rubber stopper 26 in reservoir bottle 23 in the recirculation line 21. The rubber stopper 26 is held in place against bottle 23 by a metal collar 28 and has an aperture forming the

withdrawal port 27 and extending axially through stopper 26. Because stopper 26 is formed of rubber, the rubber expands radially inward, thereby closing the withdrawal port 27 unless the withdrawal port is somehow held open. The withdrawal port 27 may be forced open by the insertion of a liquid withdrawing tube, such as the hypodermic needle 29 depicted in FIG. 3. Eluate may be extracted from the reservoir 23 through the use of a hypodermic syringe, by means of which eluate 46 is withdrawn from reservoir chamber 23 through hypodermic needle 29 to the barrel of the syringe for injection into a patient. It should be mentioned that the withdrawal port may not exist until a needle initially punctures the rubber stopper 26 for the first time. Such a system is commonly termed a puncturable septum.

Because the eluate is to be injected into a living subject, it is extremely important that all parts of the system with which the liquid solvent or solution comes in contact are sterilized prior to use. In addition, certain other precautionary sterilizing features are included in the invention embodiment as depicted. For example, the rubber stopper 26 is swabbed with germicide prior to inserting therein any means for withdrawing eluate. Also, the microporous filter 22 is a microporous sieve having a pore size no greater than 0.4 microns in diameter. Preferably, the pore size of the microporous filter 22 is even smaller, 0.2 microns or less. While a microporous sieve is not necessary where prior sterilizing techniques are carefully practiced, a microporous sieve is sometimes advisable as an added precaution to insure continuing sterility should inadvertent contamination exist. Bacteria which might otherwise survive prior sterilization techniques are thereby prevented from passing through the recirculation line 21 to the withdrawal port 27. One further antiseptic precaution is a wad of cotton or a microporous filter 39 positioned in the air vent 38 so as to render harmless any biological particles carried in the air entering the source bottle 11 to displace eluant 45 withdrawn from source bottle 11.

In order to continuously monitor the level of radioactivity within the eluate 46, a radioactivity detecting means, such as a conventional ionization chamber-electrometer 47, is positioned proximate to the fluid reservoir bottle 23. The ionization chamber-electrometer measures the change in electric potential difference between a pair of charged electrodes in the chamber. This difference results from the ionization produced by incident radiation. It is important, therefore, that the ionization chamber 47 be shielded from exterior radioactivity, so that the only radiation measured is that of materials within the reservoir bottle 23. For this reason the ionization chamber-electrometer may be clad in lead shielding. The electric potential difference between the electrodes in the ionization chamber is transformed to a current, which is the output of the electrometer. The magnitude of the current varies with the degree of ionization in the gaseous material between the pair of electrodes in the ionization chamber. The electrometer does not distinguish individual pulses caused by individual disintegration, but rather gives a readout of the ionization resulting from a large volume of disintegrations produced in the vicinity of the ionization chamber. The level of radioactivity in the reservoir bottle 23 is thereby continuously monitored. The proper amount of eluate to be withdrawn for a dose to be administered to a patient is thereby readily ascertainable.

The generator of this invention finds greatest utility in separating a relatively short-lived daughter radionuclide from a longer-lived parent radionuclide where the half-life of the parent radionuclide is at least two times as great as the radioactive half-life of the desired daughter radionuclide. As a specific example, in the operation of the invention as a technetium-99m generator, the eluant, or solvent 45 is a saline solution, and molybdenum-99 is deposited on granular particles of alumina, which collectively serve as a supporting substrate in the generator chamber 15. The molybdenum-99 is adsorbed onto the alumina in the form of a molybdate compound, as in the conventional manner of technetium-99m production. The radioactivity of the molybdenum-99 is usually at a level of between 600 and 100 millicuries. The saline solvent 45 is passed through the generator chamber 15 and selectively removes or elutes the pertechnetate-Tc 99m ions produced by the disintegrating molybdenum-99. The desired daughter product, the pertechnetate-Tc 99m ions, are carried from the generator chamber 15 as a solution and this eluate is recirculated to generator chamber 15 by pumping through the closed generating system. In passing through the system, the eluate passes through the microporous filter 22 prior to recirculation through the generator chamber 15. Microporous filter 22 is located upstream from the fluid reservoir bottle 23 in the recirculation line. As desired, dosages of the eluate containing technetium-99m are withdrawn from the recirculation line through the withdrawal port 27, as previously described. The amount of eluate withdrawn will normally be a quantity in which the radioactivity level is about 10 millicuries, if the dose is to be administered directly to a patient.

While the solution of technetium-99m ions in solvent is present within the reservoir bottle 23, the radioactivity of the eluate is continuously monitored. The eluate is passed up the tube section 25 of recirculation line 21, through the pump 31 for recirculation to the generator chamber 15.

An alternative embodiment of the invention is depicted in FIG. 4. FIG. 4 illustrates a simpler form of the invention in which a pair of check valves 30 and 36 are located in the recirculation line 21 closely adjacent to and on either side of the eluate withdrawal port 42. The withdrawal port 42 is formed by a rubber stopper 43 in the tube section 40 of recirculation line 21. The rubber stopper 43 operates in a manner similar to that of rubber stopper 26 in FIGS. 2 and 3. The peristaltic pump 31 of FIG. 1 is replaced with a syringe 41 having a hypodermic needle 29 inserted through the withdrawal port 42. The hypodermic needle 29 of syringe 41 may be inserted, in the withdrawal port 42 to form a liquid tight seal with rubber stopper 43, as in the position depicted in FIG. 4. When in this position, the syringe 41 is operable both to recirculate eluate through the generator chamber 15 and to withdraw quantities of eluate through the withdrawal port 42. This is accomplished by working the piston 48 back and forth within the barrel 49 of the syringe 41 to alternately draw eluate into the barrel 49 through the check valve 30, and force eluate out of the barrel 49 through the check valve 36. The valve 14' differs from check valve 14 in FIG. 1 in that valve 14' operates at one setting as a choking mechanism to prevent additional eluant from entering the system when the syringe 41 is being used to recirculate eluate through recirculation line 21. The number

of strokes of the piston 48 required to bring the eluate up to the desired level of radioactivity varies depending upon the volume of the generator chamber 15, the cross section and length of the recirculation line 21, the volume of the barrel 49, and the composition and radioactivity of the parent radionuclide in the generator chamber 15. In its alternative setting, valve 14' serves as a check valve to allow eluant to enter the generator chamber 15 to replace eluate being withdrawn from the system through withdrawal port 42. It should be noted that a reservoir may be inserted in the recirculation line 21 of FIG. 4 to provide an appropriate volume of eluate which may be monitored for radioactivity, as in FIG. 1.

The embodiments depicted and the examples cited are for purposes of illustration only, and the invention is not intended to be limited thereto. For example, the different parent and desired daughter radionuclides to which this invention may be applied may be expanded far beyond even those listed in Table 1, and the applications of the eluate generated extend well beyond the field of nuclear medicine.

I claim:

1. A method of generating an eluate containing a desired daughter radionuclide in a closed generating system comprising passing an eluant from a source of said eluant through a generator chamber containing a parent radionuclide which spontaneously decays into a daughter radionuclide, selectively removing the daughter radionuclide in preference to said parent radionuclide to form an eluate, and recirculating the eluate produced thereby through said generator chamber in order to maintain a supply of eluate at a desired level of radioactivity in said generating system.

2. The method of claim 1 wherein the radioactive half-life of said parent radionuclide is at least two times as great as the radioactive half-life of said desired daughter radionuclide.

3. The method of claim 2 wherein said parent radionuclide is molybdenum-99 and said desired daughter radionuclide is technetium-99m.

4. The method of claim 3 wherein said molybdenum-99 is adsorbed on an alumina substrate in said generator chamber.

5. The method of claim 1 wherein said eluate is recirculated by pumping said eluate through said closed generating system.

6. The method of claim 1 wherein said eluate is passed through a microporous filter in said closed generating system prior to recirculation through said generator chamber.

7. The method of claim 1 wherein said eluate is passed from said generator chamber to a fluid reservoir in said closed generating system, and said eluate is passed through said reservoir for recirculation through said generator chamber.

8. The method of claim 7 further comprising continuously monitoring the radiation level in said fluid reservoir.

9. A closed radionuclide generating system for generating a relatively short-lived daughter radionuclide produced from a longer-lived parent radionuclide by spontaneous decay, comprising a source of eluant for eluting the aforesaid daughter radionuclide, a generator chamber having an inlet and an outlet with the inlet connected to said source and containing a quantity of the aforesaid parent radionuclide adsorbed on a supporting substrate, a recirculation line connected be-

tween the outlet and an inlet of said generator chamber, pumping means acting upon eluate in said recirculation line, and an eluate withdrawal port located in said recirculation line.

10. The generator system of claim 9 wherein said eluant is a saline solution and molybdenum-99 is adsorbed of the aforesaid supporting substrate, whereby technetium-99m is produced as the aforesaid daughter radionuclide.

11. The generator system of claim 9 wherein said recirculation line is formed of flexible tubing and said pumping means comprises a peristaltic pump exteriorly positioned with respect to said recirculation line and acting upon a section thereof.

12. The generator system of claim 9 further comprising a pair of valves located in said recirculation line closely adjacent to and on either side of said eluate withdrawal port to limit flow in said recirculation line to a single direction, and said pumping means comprises a syringe inserted in said withdrawal port, whereby said syringe is operable both to recirculate eluate through said generator chamber and to withdraw quantities of eluate through said withdrawal port.

13. The generating system of claim 9 further comprising a fluid reservoir located in said recirculation line.

14. The generating system of claim 13 wherein a radioactivity detecting means is positioned proximate to said fluid reservoir in order to measure the level of radioactivity in the eluate in said fluid reservoir.

15. A radionuclide generating system comprising a generator chamber having an inlet and an outlet containing a parent radionuclide that undergoes spontaneous radioactive decay to produce a daughter radionuclide, a source of eluant which selectively removes the daughter radionuclide in preference to the parent radionuclide, connected to the inlet of said generator chamber, a recirculation line conducting the solution containing the dissolved daughter radionuclide from the outlet of said generator chamber for recycling to the inlet of said generator chamber, pumping means for forcing the aforesaid solution through the recirculation line, and a withdrawal port for withdrawing solution from the radionuclide generating system.

16. The radionuclide generating system of claim 15 further comprising a microporous filter for removing particulate matter from the aforesaid solution.

17. The radionuclide generating system of claim 15 further comprising at least one valve in said recirculation line for checking flow in one direction and thereby limiting flow to the opposite direction in the recirculation line.

18. A radionuclide generating system comprising a generator chamber having opposing ends each having a fluid access connection, a charge of a granular material containing a parent radionuclide that undergoes radioactive disintegration to form a daughter radionuclide packed into the aforesaid generator chamber, a source of eluant that selectively removed the aforesaid daughter radionuclide in preference to the parent radionuclide in the generator chamber connected to one of the access connections, a recirculation line in communication with both of said access connections to recirculate to said generator chamber an eluate formed of the aforesaid daughter radionuclide in said eluant, pumping means to force said eluate through said recirculation line, and a resealable withdrawal port in communication with said recirculation line for withdrawing portions of said eluate.

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