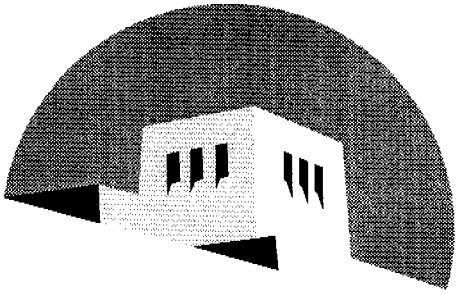

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Radionuclide Generator Systems for Nuclear Medicine

by:

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RADIONUCLIDE GENERATOR SYSTEMS FOR NUCLEAR MEDICINE

STATEMENT OF OBJECTIVES

The primary purpose of this lesson is to provide a fundamental understanding of radionuclide generator systems as they relate to the needs and practice of diagnostic and therapeutic nuclear medicine. To accomplish this purpose a general overview of generator technology is provided; then some of the most pertinent generator systems are discussed. Also provided is a review of potential generator systems, citing references that can lead the reader to a broader knowledge of the research and development being conducted on generator systems with potential utility in the practice of medicine.

Upon successful completion of this material, the reader should be able to:

1. describe a radionuclide generator.

2. explain how the decay characteristics of the parent and daughter radionuclides relate to the development and applicability of a generator.

3. discuss the importance of radionuclide production to the development and availability of clinical generators.

4. describe how basic chromatographic equilibrium principles pertain to the development of a successful column generator system.

5. define the concepts of yield and breakthrough for column generator systems and explain how these relate to the development of clinical generators.

6. list some of the other separation technologies used in generator systems.

7. discuss in some detail five radionuclide generators of significance to diagnostic nuclear medicine (Mo-99/Tc-99m, Pb-201/Tl-201, Rb-81/Kr-81m, Sr-82/Rb-82, and Ge-68/Ga-68).

8. discuss in some detail three radionuclide generators of significance to therapeutic nuclear medicine (Sr-90/Y-90, W-188/Re-188, and Ra-224/Bi-212).

9. develop awareness of and access to the literature pertaining to biomedical generator development.

COURSE OUTLINE

I. INTRODUCTION

II. DEFINITIONS AND CONCEPTS

- A. What is a radionuclide generator?
- B. Decay equations for generators
- C. Production of generator parent radionuclides
- D. Separation considerations for radionuclide generators
  1. Column-based generator separation principles
  2. Concepts of ion-exchange equilibrium
  3. Yield in column-based generator systems
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III. SPECIFIC GENERATOR SYSTEMS

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     - a. Mo-99/Tc-99m column generator systems
     - b. Mo-99/Tc-99m sublimation generator
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- B. Generators for therapy
  1. Sr-90/Y-90
  2. W-188/Re-188
  3. Ra-224/Bi-212

IV. SUMMARY AND CONCLUSIONS

RADIONUCLIDE GENERATOR SYSTEMS FOR NUCLEAR MEDICINE

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INTRODUCTION

Over 70% of all diagnostic nuclear medicine procedures performed in the United States each year use radiopharmaceuticals labeled with Tc-99m.[1] This important medical radionuclide is derived in the radiopharmacy or clinic from its parent, Mo-99, using a clinical radionuclide generator system. Indeed, in large measure nuclear medicine owes its emergence to the simultaneous development of this generator system and the Anger gamma camera in the late 1950s and early 1960s. Other generator systems have found applicability in nuclear medicine and numerous other parent-daughter radionuclide pairs are being investigated for diagnostic and therapeutic applications based upon generator technology.

A generator of utility in a diagnostic application must provide a daughter radionuclide that will support one of the common nuclear imaging modalities. For gamma imaging (planar, SPECT) the daughter radionuclide will ideally emit gamma photons in the energy range of 100-200 keV and have no accompanying particulate emissions (beta particles or positrons) which contribute to the radiation dose to the patient. For positron emission tomography (PET), the daughter will be a high yield positron emitter with a low yield of gamma photons apart from the annihilation photons. With the advent of new high energy collimators, the number of potential generator systems available for imaging is increasing. If the generator is going to be used for therapy, a daughter radionuclide that decays with high yield by par-

ticulate emission (beta particles, auger electrons, or alpha particles) is needed.

Why are generators of interest to the practicing nuclear medicine clinician? Radionuclide generators make short-lived radionuclides available at sites remote from production facilities. The parent radionuclide can be produced at a reactor or accelerator facility, packaged in a relatively easy-to-use generator form, and shipped to the radiopharmacy or clinic for use. The clinician does not need radionuclide production expertise, nor does he or she bear the burden of building and maintaining a radionuclide production facility. The generator can supply a medical radionuclide in very high specific activity, often a very important concern in modern radiopharmaceutical formulation. It can also be designed to supply the radioelement in a chemical form that is practically useful in the pharmacy or clinic.

Despite these advantages, there are only three commercially-available generators approved by the FDA for routine clinical use. These are the Mo-99/Tc-99m, Rb-81/Kr-81m and Sr-82/Rb-82 systems, all of which will be described in some detail in this module. Table 1 summarizes the diagnostic indications for which these generators are approved. Many factors determine whether a generator system emerges from the realm of scientific curiosity to clinical utility. After completion of this course, the reader will have a basic understanding of these factors, and will have a knowledge of several of the important biomedical generators currently being used or investigated. This lesson begins with an overview of the basic physical and chemical considerations involved in developing a successful medical generator, and then some specific generator systems are examined.

DEFINITIONS AND CONCEPTS

What is a radionuclide generator?

In its broadest definition, a radionuclide generator is a system that quantitatively separates a radioactive daughter nuclide from its radioactive parent. (See Figure 1) The system can be continually or intermittently operated to provide a supply of the daughter. The mode of operation is determined by the desired application and the physical decay characteristics of the daughter radionuclide. In order to understand why this is so, it is necessary to review the basic concepts of the radioactive decay of a parent-daughter pair.

Decay equations for generators

A detailed derivation of the pertinent decay equations for parent-daughter pairs is beyond the scope of this continuing education lesson. For the reader interested in the derivation of the equations discussed below, please refer to the textbook by Friedlander, et al.[2] These equations apply for the case where the parent half-life is significantly longer than the daughter half-life, a condition generally desirable for a viable clinical generator system.

In a parent-daughter pair, the daughter will be formed at a rate determined by the half-life of the parent, but will also be decaying at a rate determined by its own half-life. The number of daughter nuclei, N_2, present at a given elapsed time, t, is given by the equation:

eq. (1)

$$N_2 = \frac{\lambda_2}{\lambda_2 - \lambda_1} N_1^0 (e^{-\lambda_1 t} - e^{-\lambda_2 t}) + N_2^0 e^{-\lambda_2 t},$$

where N_1^0 is the number of parent nuclei at t = 0, λ_1 is the decay constant for the parent radionuclide, λ_2 is the decay constant for the daughter radionuclide, N_2^0 is the number of daughter nuclei at t = 0. After a sufficient time t has elapsed, $e^{-\lambda_2 t}$ becomes negligible relative to $e^{-\lambda_1 t}$ and $N_2^0 e^{-\lambda_2 t}$ (number of daughter nucleii initially present and a small number just after a column has been eluted) also becomes negligible, so that:

eq. (2)

$$N_2 = \frac{\lambda_2}{\lambda_2 - \lambda_1} N_1^0 e^{-\lambda_1 t}.$$

Note that the number of parent nuclei at this elapsed time t is given by $N_1 = N_1^0 e^{-\lambda_1 t}$ so

Table 1.

FDA Approved Indications for Generator Derived Radionuclides

Mo-99/Tc-99m	**Indications for Adults* Brain Imaging (including cerebral radionuclide angiography) Thyroid Imaging Salivary Gland Imaging Placenta Localization Blood Pool Imaging (including radionuclide angiography) Urinary Bladder Imaging (direct isotopic cystography) for the detection of vesico-ureteral reflux Nasolacrimal Drainage System Imaging **Indications for Children* Brain Imaging (including cerebral radionuclide angiography) Thyroid Imaging Blood Pool Imaging Urinary Bladder Imaging (direct isotopic cystography) for the detection of vesico-ureteral reflux
Sr-82/Rb-82	*Indications in Adults* Heart Perfusion Imaging by PET
Rb-81/Kr-81m	*Indications* For use in the study of pulmonary ventilation

**Note that these indications are for Tc-99m only in the chemical form of pertechnetate

eq. (3) $$N_2 = \frac{\lambda_2}{\lambda_2 - \lambda_1} N_1 .$$

Remember that the decay constant for a radionuclide is inversely related to its half-life by the equation

eq. (4) $$\lambda = \frac{0.693}{t_{1/2}} .$$

Applying these equations it can be shown that the time at which the daughter activity reaches its maximum value will be after t exceeds about five times the half-life of the daughter radionuclide.[3] It can also be shown that the rate of production of daughter activity is given by the equation:

eq. (5) $$dA_2/dt = A_1^0 \lambda_2 ,$$

where A_1^0 is the parent activity.

Two important observations should be made regarding these equations. There must be an adequate amount of parent activity, A_1^0, available in the generator to make it practically useful and, assuming this condition is met, the amount of available daughter activity will be determined by the daughter half-life; i.e., the shorter the daughter half-life, the more daughter activity available from the generator.

Production of generator parents

One may peruse a chart of the nuclides and identify a relatively large number of parent-daughter pairs that might have application in nuclear medicine. Once a potential generator has been identified, the next consideration is whether there is a good way to reliably produce the parent radionuclide. If there is not a good way to produce and distribute the parent radionuclide, a generator that has theoretical potential will never be developed. The great success of the Mo-99/Tc-99m generator has depended upon the reliable supply of the relatively short-lived Mo-99. Having multiple site production capability provides stability to the supply of generator parents, and gives confidence to the practitioner in the clinic that the imaging or therapeutic modality that a generator supports will be available for the patient.

In the two most common methods of producing radionuclides, the fundamental physical process that occurs involves the transformation of a stable nucleus to a radioactive nucleus. In one approach, high energy particles, e.g. protons, deuterons, or alpha particles, are accelerated into a target with sufficient energy to eject subnuclear particles, neutrons and protons, to yield unstable (radioactive) nucleii. This is done using cyclotrons or linear accelerators, both of which require substantial material and technical resources to install and operate. The induced nuclear reaction processes caused by accelerated charged particles generally result in neutron deficient radionuclides. Thus the radioactive parent nuclides produced by this method will generally decay by electron capture or positron emission. There will be x-rays and gamma photon emissions that will accompany these processes, factors that must be considered when using these parents as they will determine the nature of the shielding required if a generator is developed. The interested reader is referred to the review article by S. M. Qaim for a discussion of the cyclotron production of a variety of generator radionuclides.[4]

Nuclear reactors are also used to produce radionuclides which are usually neutron rich. Mo-99 used in most commercial generators today is produced in nuclear reactors by inducing nuclear fission of enriched U-235. When fission is induced by thermal neutron absorption in a U-235 nucleus, there is a 6.1% probability that the fission process will yield a Mo-99 nucleus. Thus a significant quantity of Mo-99 can be produced and chemically recovered from U-235 targets placed into thermal neutron fluxes generated in nuclear reactors. Certainly, there are other nuclides produced in the fission process that could conceivably be recovered and used in clinical generators. This is particularly true for some generators that might have PET and therapeutic applicability.

Nuclear reactors can also be used to induce simple neutron capture reactions on a variety of target materials. Most commonly these are n,γ reactions, however, multiple neutron capture reactions can also be used. These processes generally produce neutron rich isotopes that decay by beta particle emission. Some

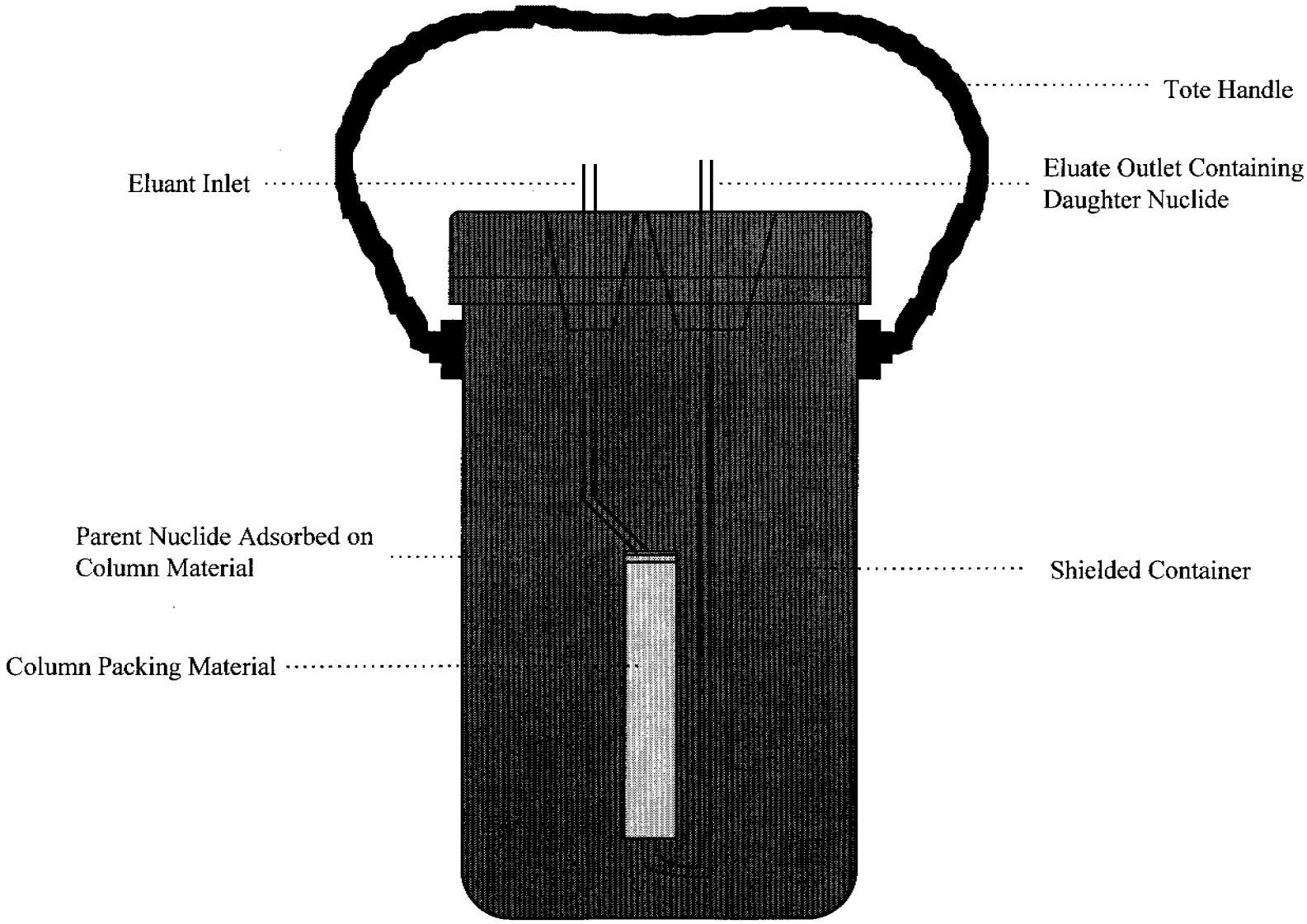

Figure 1. *A representation of a column-based generator system.*

Mo-99 for generator use has been produced using the Mo-98(n,γ) reaction. Another example of a potentially clinically significant generator produced by neutron capture processes is W-188/Re-188.[5] The W-188 can be produced by the double neutron capture reaction on enriched W-186.[6,7] More will be said about this generator in a later section of this lesson; the point here is that a production modality exists for the parent that supports the viability of this potential therapeutic generator.

It is important to remember that the availability of a radionuclide depends not only upon the ability to induce the necessary nuclear transformations, but upon the availability of a chemical or physical process to recover the radionuclide in pure form from the irradiated target material. This requires the separation of the radionuclide from its bulk target material, and subsequent purification from contaminant radionuclides that are also produced in the target. The complexity of separating radionuclides is one of the arguments for making generators available to the clinic. The clinician can obtain a pure radionuclide for the desired application simply by operating a well conceived generator system, without being an expert in radiochemical separations. Of course, a well conceived generator will also require that the technology exist for a clean, quantitative separation of the daughter radionuclide from the parent.

Separation considerations for generator systems

In this section, some of the most promising approaches for separating the daughter from its parent in a generator system will be reviewed. Typically, these are based upon chemical separation processes, developed to meet a variety of requirements. These include:

- high, reproducible yield of the daughter radionuclide;
- low contamination of the separated daughter by the parent radionuclide and other radiocontaminants;
- daughter in chemical and physical form suitable for the desired application;
- daughter in highest possible specific activity;
- daughter in highest possible concentration in solution from the generator;
- daughter available in isotonic, non-toxic, sterile, and apyrogenic form if it is to be used directly from the generator;
- ability to store the generator system without compromising its functionality and applicability;
- capability to automate or remotely operate and adequately shield the generator to minimize radiation exposure to operators and patients.

All separation approaches require establishing a situation where there is a significant chemical or physical difference between the parent and the daughter that provides the means for the separation. Since column-based generators are the most common ones used, principles relevant to these generators will be considered in detail. In addition, some other concepts that have been used for generator separations will be listed.

Column-based generator separation principles. In the ideal column-based generator, the parent will be quantitatively sorbed onto a material by passing a solution containing the parent through the column containing this stationary solid phase. The sorption mechanism depends upon the nature of the stationary phase and its chemical or physical interaction with the parent radioelement. In most generators, this interaction involves a positively or negatively charged ionic form of the parent being strongly attracted to an oppositely charged site on the stationary phase. When the parent radionuclide decays into the daughter, its chemical characteristics change so that the daughter is no longer retained by the stationary phase. Then, when an appropriate solution, called the eluant, is passed through the column, the daughter is quantitatively removed in the eluted solution. This solution is called the eluate, and ideally should contain none of the parent radioelement. This approach generally works when the ionic character of the daughter is significantly different from that of the parent. In the most ideal situation, one of the parent/daughter pair would be positively charged

(cationic) in solution while the other is negatively charged (anionic). For example, if the parent radionuclide were in a chemical form that is anionic, it could be sorbed onto a material highly attracted to negative ions (anion-exchange material). If it then decayed to a daughter with positive (cationic) or neutral character in the solution used as the eluant, the daughter would have no affinity for the anion exchange material and would be completely washed off the column by a sufficient volume of the eluant.

The ideal situation is rarely realized in a practical generator system. If the parent and daughter chemical forms have the same charge sign, then the relative affinity for the solid exchange material would have to be significantly different between the daughter and parent. This can be the case if there is a significant difference in the density of the charge between the parent and daughter chemical species. In general, an anion with a -3 charge would have a significantly greater affinity for an anion exchange material than one with a charge of -1. If the charge is the same between two ionic species, then the smaller solvated chemical form will have a higher charge density and consequently a greater affinity for the stationary phase. If the difference between these affinities is great enough, a functional generator can be designed. However, even in the best situations, complete quantitative sorption of the parent and complete quantitative elution of the daughter will not be realized, because all sorption processes will involve equilibrium distributions between the stationary phase and the elution solution phase.

Concepts of ion-exchange equilibrium. If a solution containing an exchangeable ionic species is contacted with a stationary phase with an affinity for the ion, an equilibrium will be established between the ion sorbed on the stationary phase and the ion in solution. For example, consider the exchange of a sodium ion from a sodium chloride solution for a hydrogen ion on the stationary phase:

eq. (6) $\quad Sta\text{-}H^+ + Na^+ \leftrightarrow Sta\text{-}Na^+ + H^+$

After the equilibrium is established, there will be a distribution of the ions between the stationary phase and the solution that is determined by the relative magnitudes of the constant called the mass distribution ratio, D_m, for the hydrogen ion and the sodium ion. The mass distribution ratio is defined as:

eq. (7) $$D_m = \frac{\text{amount of ion on stationary phase}}{\text{amount of ion in solution}}.$$

The larger the value of D_m, the greater the affinity the ion has for the stationary phase.

If the stationary phase is put into a column, and a solution containing the exchangeable ion (sodium in the above example) is poured through the column, the equilibrium will be established several times as the solution moves down the column. To visualize this, imagine the column divided into several sections from top to bottom, the size of each section being sufficient to allow complete equilibrium to be established. As the solution moves into the first section of the column, equilibrium will be established with the ratio between the stationary phase and the solution determined by the distribution ratios of the exchangeable ions. This removes a fraction of the sodium ions from the solution. As it passes into the second section of the column, the solution has a low concentration of sodium, but reestablishes equilibrium determined by the same distribution ratios, further lowering the sodium concentration. Thus, as the solution passes into successive segments, the sodium concentration becomes successively lower. After passing through several segments, if the distribution ratio for sodium is sufficiently large, its concentration will become so low that it in effect has been completely removed from the solution. If the distribution ratio is high enough, this condition will be established in a very small portion of the top of the column.

If the mass distribution ratio for a given ion on a given stationary phase is known, one can evaluate whether a near quantitative retention of the ion on a column is feasible. In the literature we generally find a slightly different, but easily measured value, related to the distribution of an ion on a stationary phase. This is called the distribution coefficient, D_g, defined as:

eq. (8)

$$D_g = \frac{\text{amount of ion on stationary phase/grams stationary phase}}{\text{amount of ion in solution/mL solution}}$$

For a practical generator, one would identify a stationary phase with a very large distribution coefficient for a chemical species containing the parent radionuclide in a given eluant, and a very low one for the chemical species containing the daughter radionuclide. Under these conditions, the generator would provide maximum yield of the daughter with minimum breakthrough from the generator.

Yield in column-based generators. Generally, a goal for any generator concept is to provide the daughter radionuclide in maximum possible concentration in the eluate from the generator. This is accomplished by obtaining maximum daughter yield in minimum eluate volume (defined as the elution profile). When discussing yield, we need to know which of two possible elution methods is being considered. In the continuous method, the generator is constantly operated while continuously providing a significant fraction of the available daughter radioactivity. Recalling that the production rate of daughter activity on a generator is inversely related to the half-life of the daughter, the continuous method will only be applicable to generators with very short daughter half-lives (seconds to minutes). Considering, for example, the Sr-82/Rb-82 generator, which is used clinically in the continuous elution method, we can apply equations (4) and (5) to calculate the maximum possible elution rate of the Rb-82 for a generator loaded with 100 mCi of Sr-82. The half-life of Rb-82 is 78 seconds. Thus,

$\lambda_{Rb\text{-}82}$ = 0.693/78 s = 0.00888 s^{-1} and

d(Rb-82) /dt = (100 mCi) 0.00888s^{-1}

= 0.888 mCi/s.

This is the maximum amount of Rb-82 that could theoretically be eluted per second from the 100 mCi generator, but it is probably not the amount that would be eluted in a clinical situation. The amount actually eluted per second divided by this maximum amount gives the yield in the continuous elution mode. So, if the 100 mCi Sr-82/Rb-82 generator were eluting 0.75 mCi Rb-82/s, the elution yield would be:

0.75/0.888 = 0.84.

[Note: In the clinical setting, yield (as defined in this lesson) is often referred to as "efficiency."]

The other mode of operating a generator is the "bolus" or batch method which elutes in some volume all of the available daughter activity in equilibrium with the parent (again defined as the elution profile). This method can be applied to any generator, but is generally essential to generators with longer-lived daughters (hours to days). In this elution method, the yield, Y, is defined as the ratio of the total eluted activity (TEA) to the maximum available activity (Q). Assuming transient equilibrium (i.e., at the time of elution the daughter is decaying at the same rate that is being formed by the parent), Q is equivalent to the total parent activity on the column (taking into account the fraction of parent decays that lead to the daughter nuclide, i.e., the branching ratio).

Eq . (9) $$Y = \frac{TEA}{Q}.$$

A variety of methods exist for measurement of generator yields.[3] Yields will generally be less than the theoretical maximum for several reasons including:

- finite affinity of the daughter for the stationary phase. In most practical generator systems the daughter will have a measurable, though presumably small, distribution coefficient on the stationary support phase. Thus, some of the daughter nuclide will be retained by the column in a practical elution volume.
- mechanical entrapment of the daughter in void spaces in the column. Due to non-uniformity of shape and size of support-phase particles it is impossible to pack a column that is completely free of small pockets where eluant can be trapped during the elution process. Thus the daughter nuclide will not be eluted in this volume.
- adsorption of the daughter on the walls of the column. Electrostatic and chemical interactions between the daughter nuclide and the material of the column will lead to retention of some of the

daughter on the interior walls of the column.

- formation of multiple chemical species containing the daughter radionuclide, one or more of which has a significant affinity for the column. A good example of this phenomenon is observed in the Mo-99/Tc-99m generator system. The Tc-99m daughter is not retained by the alumina support if it is in the pertechnetate form (Tc[VII]), but if by some process the pertechnetate ion is reduced to a lower state (e.g. Tc[IV]), it is strongly retained by the alumina.
- elution rates not optimum. The distribution coefficient of a species on a support phase is a thermodynamic (equilibrium) quantity. It is presumed that the flow of eluant through a column is not too fast relative to the kinetics of the exchange reaction that the distribution coefficient defines. If the flow-rate is too rapid, there could be incomplete exchange of the daughter nuclide between the eluant and the stationary phase (i.e., equilibrium is not established) leading to reduced yield.

Breakthrough in column-based generators. Since sorption of a species on a column stationary phase is an equilibrium process, even substances with very large distribution coefficients will have a small but finite elution from a column. Parent elution also occurs due to chemical and radiological decomposition or mechanical disruption of the stationary phase. Thus a generator will demonstrate elution of a small amount of the parent radionuclide. This undesired elution of the parent radionuclide is called "breakthrough." It is defined quantitatively as follows:[3]

Eq. (10)

$$B = \frac{\text{Parent activity eluted / elution volume}}{\text{Total parent activity on the column}}.$$

A good clinical generator will have breakthrough values of 10^{-6} per milliliter or less. Breakthrough is a significant concern for generators that would involve direct infusion of the eluate into a patient. This is because the parent radionuclide is generally relatively long-lived, so if the biological half-life and biodistribution (i.e., the pharmacokinetic behavior) of the parent radionuclide is such that there could be long-term retention in a vulnerable organ system, the radiation dose delivered by even a small amount of the parent radionuclide could be problematic. In addition, no diagnostic value is obtained from the parent emissions.

Generators based upon column separations are generally preferred because of their relative ease of construction, packaging, shipping, use, and storage. Throughout its useful life time, the clinical generator needs to maintain high yield, low breakthrough, acceptable pyrogen levels, and sterility. For this reason, most long shelf-life column generators use inorganic ion exchange materials such as alumina, hydrous zirconium oxide, zirconium phosphate, silica gel, hydrous tin oxide, or polyantimonic acid. These materials are much less prone to radiolytic decomposition than the more common organic polymer-based ion exchange resins. Radiolysis of the organic materials can lead to parent breakthrough, reduced yield, and the formation of elutable pyrogenic materials. The organic ion-exchangers are also more likely to support growth of potentially-infectious organisms.

Generators based upon other separation methods. Though column-based generators are preferred, there have been a number of generator systems developed or proposed based upon other separation modalities. These include solvent extraction,[8,9,10] precipitation and filtration,[11,12] distillation,[13] sublimation,[14] and electrochemistry.[15,16]

SPECIFIC GENERATOR SYSTEMS

Having discussed generators in general, some specific generator systems used, or proposed for use, in diagnostic and therapeutic nuclear medicine will now be considered. Table 2 lists many of the generators that have been studied or proposed for diagnostic applications based upon planar gamma imaging and SPECT. Table 3 lists some of those generators that have been proposed as potential systems for PET. Table 4 shows generators that yield

Table 2.
Generators of Gamma Emitting Radionuclides for SPECT and Planar Imaging

Parent ($t_{1/2}$) (refs)	Decay Mode (Branch)	Daughter ($t_{1/2}$)	Decay Mode (Branch)	Imageable Gamma, keV (Branch)
Mo-99 (2.75 d) (17-28)	β^-	Tc-99m (6.01 h)	IT (99.996) β^- (0.004)	140.47 (87.2)
Pb-201 (9.4 h) (31-32)	EC	Tl-201 (73 h)	EC	68-82 (95 % Hg x-rays)
Rb-81 (4.58 h) (33-40)	EC	Kr-81m (13.1 s)	IT	190 (67)
Xe-123 (2.0 hr) (75)	EC	I-123 (13.1 h)	EC	159 (82.9)
Sn-113 (115 d) (76 ,77 ,78)	EC	In-113m (1.66 h)	IT	391.7 (64.2)
Hg-195m (40.0 h) (79)	EC	Au-195m (30.5 s)	IT	261.8 (67.9)
Cd-109 (1.267 y) (80)	EC	Ag-109m (39.6 s)	IT	88.0 (3.6)
Br-77 (57.0) (81)	EC	Se-77m (17.4 s)	IT	162 (52.5)
W-178 (21.5 d) (82 ,83)	EC	Ta-178	EC (98.9) β+ (1.1)	93 (6.6) 57 (95% Hf x-rays)
Os -191 (84 ,85 ,86)	β^-	Ir-191m	IT	129.4 (25)

Table 3.
Generators of Positron Emitting Radionuclides for PET

Parent ($t_{1/2}$) (references)	Decay Mode (Branch)	Gamma, keV (Branch)	Daughter ($t_{1/2}$)	Decay Mode (Branch)	Gamma, keV (Branch)
Sr-82 (25.0 d) (41-48)	EC (100)	none	Rb-82 (1.25 m)	β^+ (96) EC (4)	511 (192) 776 (13.6)
Ge-68 (288 d) (49)	EC (100)	67.85 (88) 78.38 (95)	Ga-68 (68.1 m)	β^+ (90) EC (10)	511 (180)
Sn-110 (4.11 h) (87)	EC (100)	280.5 (97)	In-110 (1.15 h)	β^+ (62) EC (38)	511 (126) 658 (98)
Ti-44 (47 y) (88 ,89)	EC (100)	67.85 (88) 78.38 (95)	Sc-44 (3.93 h)	β^+ (95) EC (5)	511 (190) 1157 (100)
Se-72 (8.4 d) (11,12,16,90)	EC (100)	46 (57)	As-72 (26.0 h)	β^+ (77) EC (23)	511 (154) 834 (80) 630 (7.9)
Te-118 (6.0 d) (91)	EC (100)	none	Sb-118 (3.5 m)	β^+ (76) EC (24)	511 (152)
Zn-62 (9.2 h) (92 ,93 ,94)	β^+ (6.9) EC (93.1)	409 (25) 508 (14) 511 (13.8) 548 (15) 597 (24)	Cu-62 (9.73 m)	β^+ (97.8) EC (2.2)	511 (195.6)
Fe-52 (8.3 h) (95)	β^+ (56.5) EC (43.5)	169 (99) 511 (113)	Mn-52m (21 m)	β^+ (97)	511 (194) 1434 (98)
Xe-122 (20.1 h) (96 ,97 ,98)	EC (100)	none	I-122 (3.6 m)	β^+ (77) EC (23)	511 (154) 564 (18)

Table 4.
Generators of Therapeutic Radionuclides

Parent ($t_{1/2}$) (refs)	Decay Mode	Daughter ($t_{1/2}$)	Decay Mode	E_{max}, MeV
Sr-90 (28.5 y) (55-59)	β^-	Y-90 (2.67 d)	β^-	2.218
W-188 (69.4 d) (60-67)	β^-	Re-188 (17.0 h)	β^-	2.118
Ra-224 (3.66 d) (68-73)	α	Bi-212 (61 m)	α β^-	α (6.0) β^- (2.25)
Ba-140 (12.75 d) (99)	β^-	La-140 (1.68 d)	β^-	1.67
Os-194 (6.0 y) (100)	β^-	Ir-194 (19.2 h)	β^-	2.24
Cd-115 (2.23 d) (101)	β^-	In-115m (4.49 h)	β^-	0.83
Ni-66 (54.6 h) (74)	β^-	Cu-66 (5.1 m)	β^-	2.6
Pd-112 (21.0 h) (74)	β^-	Ag-112 (3.1 h)	β^-	3.94
Ac-227 (22 y) (102)	α	Ra-223 (11 d)	α	5.72
Ac-225 (10.0 d) (102)	α	Bi-214 (45.6 m)	α β^-	α (5.9) β^- (1.4)

daughters with potential therapeutic applicability. A discussion of all of these generators is beyond the scope of this lesson, so the focus will be upon some of the most important, most promising, and most interesting systems.

Generators For diagnostics use

Mo-99/Tc-99m Generator Systems. It is generally acknowledged that the foundational radionuclide of diagnostic nuclear medicine is Tc-99m because of the many radiopharmaceuticals that have been developed using this radiotracer. This position of preeminence in the radionuclide armamentarium is in large part due to the early and consistent availability of the Mo-99/Tc-99m generator. The idea of this generator was conceived in the late 1950s at Brookhaven National Laboratory (BNL).[17] Until 1966, BNL produced and distributed the generators, based upon column chromatographic separation, to a variety of users, at which time commercial distributors took over the task of generator production and distribution.[18] Commercial generator systems have evolved over the years, initially depending upon Mo-99 produced by the Mo-98(n,γ) reaction. Presently fission-produced Mo-99 is used because of its high specfic activity making it applicable to small column generator systems. Boyd has written excellent review articles providing an overview of the development and evolution of Mo-99/Tc99m generators.[19,20] There are three basic technologies that have been applied to large scale Mo-99/Tc-99m generators; these are column chromatography, sublimation, and solvent extraction. Only the column generator is currently approved for clinical applications in the United States, but the other two systems have both historical significance and significant applicability in countries where the supply of fission-produced Mo-99 is limited. Thus all three systems will be considered in some detail.

Mo-99/Tc-99m Column Generator System. The column generator takes advantage of the fact that the molybdate ion (MoO_4^{2-}) has a very high affinity for aluminum oxide (alumina) whereas the pertechnetate ion (TcO_4^-) has a very low affinity.[21] The Mo-99-molybdate is loaded onto a column prepared with alumina and, after equilibration, the Tc-99m pertechnetate can be eluted by passage of physiological saline over the alumina.

The primary factor adversely affecting elution efficiency is the formation of reduced Tc-99m species which, when formed have a significant affinity for the alumina, thus reducing yield. Chemical oxidants have been used successfully to maintain the oxidized TcO_4^- species, so that very high elution yields are obtained from today's commercially-available column generators.

These generators, when prepared and eluted properly, have extremely low Mo-99 breakthrough. The primary causes of breakthrough are: 1) exceeding the ion-exchange capacity of the alumina column; 2) eluting the column with saline at pH greater than 7; 3) elution of very fine alumina particles containing sorbed Mo-99; 4) channeling in the column due to improper fabrication or mechanical disruption; 5) and excessive elutions whereby the Mo-99-molybdate eventually begins to elute. Because today's column generators are prepared under strict quality control using very high specific activity fission-produced molybdenum, breakthrough is not a serious problem.

The alumina-based generator yields a Tc-99m pertechnetate eluate that is chemically and radionuclidically pure. This is important when the material is to be used in the synthesis of modern radiopharmaceutical formulations. The primary stable elemental contaminant of concern for eluates from this generator is aluminum. Aluminum contamination can occur if ultra-fine particles of alumina are eluted, or if the alumina is solubilized by the eluant. If the acid-form of alumina (crystalline γ alumina) is heat treated to at least 400 °C, then properly washed and sieved before column fabrication, aluminum contamination is not a problem. Standard colorimetric kit procedures, using indicators, are supplied through generator manufacturers that allow convenient monitoring of eluates for the aluminum ion.

The U. S. Pharmacopoeia (USP) has strict requirements on the radionuclidic purity of Tc-99m. The USP and the U. S. Nuclear Regulatory Commission (or equivalent Agreemen

State regulations) specify a limit of no more than 0.15 μCi Mo-99 per mCi Tc-99m at the time of administration to the patient. Total gamma-emitting impurities cannot exceed 0.5 microcurie per millicurie of Tc-99m administered. The most common potential eluate impurities (apart from Mo-99) from fission produced Mo-99 include I-131, I-132, Ru-103, and Sr-89. In addition, there can be no more than 0.1 microcurie of all other beta-emitting nuclides per millicurie of Tc-99m. If the current FDA-approved procedure for production and purification of the Mo-99 parent, and procedures for generator fabrication, are followed, radionuclidic purity of Tc-99m eluates is well within these limits. Many procedures for radiopharmaceutical formulation are selective for the Tc-99m, and further enhance the Tc-99m radiochemical purity. It is important to remember that Tc-99m decays by isomeric transition to the long-lived Tc-99. If a generator has not been eluted for a long period of time, larger amounts of the Tc-99 may be present than is desirable. Specific methods of assaying eluates for Mo-99 and Tc-99m are recommended by generator manufacturers in package inserts. Measurement and calculation of the relative amounts of Mo-99, Tc-99m, and Tc-99 found in a generator presents an interesting and challenging radionalytical challenge, but since it is not a required part of the routine quality control protocol for commercial generator systems in the clinic, the interested reader is referred to the literature.[22]

In summary, with the availability of high specific activity fission produced Mo-99, column generators are available that are easy to fabricate, ship, shield, use, and store. They give high yields, with excellent elution profiles, providing pharmaceutically-pure Tc-99m in high concentration in physiologically-compatible saline solution. Such generators will be preferred in radiopharmacies and clinics as long as there is a consistent, reliable, and economical supply of fission product Mo-99.

Mo-99/Tc-99m Sublimation Generator. Shortly after the discovery of technetium in 1937, the volatility of its oxide, Tc_2O_7, was noted.[23] This volatility can be used to separate Tc-99m from molten targets containing Mo-99-MoO_3. The Mo-99 is produced by the Mo-98(n,γ) reaction on natural molybdenum trioxide targets, in which the Mo-98 makes up 24.13 % of the stable molybdenum isotopes. In the early 1970s, Robson and Boyd developed a practical generator based upon a sublimation separation process well suited to recovery of Tc-99m from these targets.[24,25]

In this system, neutron irradiated natural molybdenum trioxide is placed inside a high temperature tube furnace through which is passed a stream of oxygen. The furnace heats the material to a temperature of 850 °C, melting the molybdenum trioxide and subliming the Tc-99m-technetium heptoxide. Since some of the molybdenum trioxide is volatilized at this temperature a porous plug filter is placed after the tube furnace. The filter is maintained at a temperature between that of the furnace and the boiling point of technetium heptoxide. Thus the Tc-99m compound will pass through the filter while trapping the molybdenum trioxide. The Tc-99m is condensed on a rod after the porous plug. After the process, the rod is removed from the apparatus and placed in a saline solution to yield a Tc-99m-pertechnetate product solution.

A big advantage of this generator over the column generator is that large masses (up to 200 g) of low specific activity (1 Ci Mo-99 per gram of molybdenum) neutron irradiated molybdenum oxide can be processed to yield up to 75 Ci of Tc-99m in less than 20 mL of sterile saline solution.

Radiocontaminants in the product include Mo-99 (around 10^{-4} % of the total radioactivity), Re-186, Re-188, Ru-103, and radioiodines. The rhenium radionuclides are produced by neutron capture reactions on stable rhenium and tungsten impurities in the molybdenum oxide target. The Ru-103 and radioiodines are produced by fission of uranium impurities in the natural target material. These chemical impurities are generally quite low, especially if the molybdenum oxide is heated to remove volatiles before irradiation.

The Tc-99m yield from this approach is relatively low, rarely exceeding 50%. Moreover, the apparatus requires the shielding provided by

a hot-cell, and thus is not conveniently set up in a clinical laboratory. However, a small sublimation generator has been designed for use in the clinical laboratory. This device uses fission product Mo-99, and operates at efficiencies between 70 % and 80 %.[26]

Proponents of the sublimation generator cite its advantages of inexpensive target material (natural molybdenum trioxide), high radionuclidic, radiochemical and chemical purity, the improbability of microbiological contamination, and the ability to produce highly concentrated solutions (>1 Ci Tc-99m/mL). It is suggested that the sublimation generator would be a preferred system to supply Tc-99m to a region from a central radiopharmacy equipped with the necessary reactor and hot-cell facilities.[24]

Mo-99/Tc-99m Extraction Generator. The ability to extract Tc-99m from Mo-99 using an organic solvent was first reported in 1956.[27] A full-scale plant that utilized extraction techniques was built to supply a large fraction of the Tc-99m requirements of the entire nation of Australia.[28] The extraction process involves the following steps:

- dissolve $MoO_3(n,\gamma)$ target (up to 250 g in excess of 1 Ci Mo-99 per gram of MoO_3) into an alkaline solution (approximately 1 molar KOH) as potassium molybdate;
- allow methyl ethyl ketone (MEK) to contact the aqueous solution by bubbling a dispersion up through the solution;
- allow the phases to separate, observing the less dense MEK, containing extracted Tc-99m, in the upper layer;
- drain the aqueous layer containing the Mo-99-molybdate into a holding tank where residual MEK is distilled out under an air sparge;
- remove trace residual Mo-99 from the MEK using a dilute aqueous alkaline scrubber solution;
- evaporate the MEK solution to dryness under a stream of warm air;
- dissolve the Tc-99m residue in sterile physiological saline, and transfer it through a small alumina column to the product bottle.

This is obviously a relatively complicated process, but it was successfully automated to reliably operate with up to three extractions per day for many years. Extraction efficiency data were not provided in the literature in which this generator system was described, but high efficiency was implied because of the following attributes that optimize efficiency.

Radiolytic effects can adversely impact efficiency of the extraction in two ways. Radiolytic reduction of molybdate causes a black molybdenum-containing precipitate in alkaline solutions which absorbs some of the Tc-99m, making it unextractable. Further, Tc-99m is extractable into ketones only in its heptavalent form. Radiolytic reduction of some of the Tc-99m from Tc(VII) to Tc(IV) makes it unextractable into MEK. Both of these problems are overcome by continuously bubbling heated air (O_2 serving to oxidize both the molybdenum and technetium to the necessary valence) through the molybdate solution in its holding tank prior to extraction. Some losses also occur with incomplete phase separations and volatility losses during the evaporation step. These losses are minimized by optimal design and process controls.

For the same reasons as discussed above for the sublimation generator, the common radionuclidic impurities in the product of the extraction generator are Mo-99 (from "breakthrough"), Re-186 and Re-188. These impurities are generally present at levels of about 10^{-5} % of the total eluted activity.

A significant draw-back for the use of MEK derived Tc-99m is that organic aldol condensation products in the Tc-99m can interfere with certain labeling processes in radiopharmaceutical formulation. This problem has been somewhat mitigated by adding a final purification step involving electrolytic deposition of the Tc-99m from the saline product solution onto a platinum cathode, followed by redissolution in fresh saline.

Clearly, the column-based generator presents several advantages over the sublimation and extraction generators, particularly for use in pharmacies and clinics remote from the Mo-99 production site. As long as there continues to be an adequate reliable supply of the fission product Mo-99, the column generator will be the preferred embodiment for the clinical Mo-99/Tc-99m generator.

Other Generators for Gamma Camera Imaging. Table 2 lists several other generators being advanced as candidates for diagnostic applications. Generally the daughters of these generators emit photons that are compatible with existing imaging equipment, and provide unique advantages in regards to the chemical properties for radiopharmaceutical development. It is worth noting that with high energy collimators, annihilation photons from positron emitters could be imaged on conventional camera systems.[29] The Pb-201/Tl-201 generator will be briefly discussed because of its great significance to diagnostic cardiology, and the Rb-81/Kr-81m generator because of its somewhat unique character. The reader may review the references listed in Table 2 for detailed information regarding these and other generators.

Pb-201/Tl-201 Generator. After Tc-99m, Tl-201 is the next most extensively used radionuclide in clinical diagnostics.[30] It is used in both planar and SPECT perfusion imaging for the non-invasive diagnosis of heart disease. The radionuclide has been produced by direct irradiation of mercury-containing targets with deuterons or protons to yield a product with relatively poor radionuclidic purity, unless highly enriched Hg-201 is used. [31,32] The alternative approach to production of high specific activity Tl-201 of high radionuclidic purity is to produce Pb-201 ($t_{1/2}$ = 9.4 h) and allow its decay to Tl-201 ($t_{1/2}$ = 73.5 h), followed by separation of the lead and thallium.[31,32] It is interesting to note that this is not a classical generator in which a longer-lived parent decays to a short-lived daughter. Indeed the parent half-life is shorter than the daughter. Thus there is not a generator system that can be developed and shipped to the end-user. Instead the Pb-201 is produced regularly by commercial suppliers and the Tl-201 is separated from this parent and distributed to the clinical users.

Natural thallium targets can be irradiated with protons to induce the reactions Tl-203(p,3n)Pb-201 and Tl-205(p,5n)Pb-201.[31] Excitation functions indicate the optimum proton energy for the first reaction to be about 28 MeV and the second to be about 48 MeV. Going to 48 MeV provides higher yields of Pb-201, but also introduces greater impurity. Production at 28 MeV on unenriched thallium targets, to minimize impurities from the higher energy reaction, still yields Pb-203 via the Tl-205(p,3n) reaction, and Pb-204m via Tl-205(p,2n) reaction, in sufficient quantity to complicate processing because of the added activities from these radionuclides. By using enriched (90-95%) Tl-203 as the target material and irradiating at 28 MeV incident proton beam, contributions from these lead contaminants are greatly reduced, and the actual production yield of Pb-201 per microamp-hour of beam time is increased by a factor of 3 over natural (non-enriched) targets.

After an irradiation is completed, the Tl-203 target material is immediately processed to recover a radiochemically-pure lead fraction containing no-carrier-added Pb-201 (and traces of Pb-204m and Pb-203). The lead fraction is allowed to "age" for about 30-35 hours to allow the Tl-201 to grow in to maximum possible activity. The Tl-201 is then separated from the lead to yield carrier-free Tl-201 and reduced to Tl^{1+} for diagnostic purposes. An approach to this chemical separation scheme based upon a combination of precipitation and chromatographic methods is suggested in the article by Qaim et al.[32]

Rb-81/Kr-81m. As a radionuclide of an inert gas, Kr-81m has been used clinically in lung ventilation studies and pulmonary function scans. Because of its very short half-life (13 s), and thus favorable dosimetry, this radionuclide is particularly effective for pediatric pulmonary function tests. It has also been used in an injectable form for right heart evaluation. Since it is used in these two different forms, a generator ideally allows "elution" of both the gas phase and injectable solution. [Note: The package insert for the commercially-available product provides information only for operation as an inhalation unit.]

Both inorganic and organication exchangers have been successfully used as supports for column Rb-81/Kr-81m generators.[33,34,35,36,37,38,39] The poor availability and limited loading capacity of the inorganic exchanger make it less advantageous than the organic exchanger. Since the half-life of the

parent Rb-81 is quite short (4.58 hours), these generators can be fabricated as "disposable" devices; thus, the problems of radiolysis and biological contamination do not prevent the use of the organic exchanger in viable clinical generators.

The parent Rb-81 can be made nearly carrier free in good yield using (p,xn) reactions on enriched krypton targets using 40 MeV protons. A unique "generator-assisted" production method has been perfected to produce multicurie quantities of Rb-81 in Rb-85-RbCl targets using 70 MeV protons. At this energy the Rb-85(p,p4n)Rb-81 reaction goes at high yield, and the production rate is assisted by the Rb-85(p,5n)Sr-81→ Rb-81 reaction.[38] Rubidium-81 from either of these production modes can be used effectively on the organic ion-exchange support, though the RbCl targets are limited to about 200 mg by the capacity of the exchange material. Loadings of 3 to 25 mCi are used for medical generators.

It is important to realize, that because of the 4.6 hour parent half-life, this generator must be fabricated and used at a location close to the production site. To illustrate this point, consider that in the United States, Amersham currently manufactures Rb-81/Kr-81m at only one location, South Plainfield, New Jersey, for commercial distribution. Because of this, the majority of sales are to customers located in the northeastern part of the country.

The generator can be eluted either by flowing moist air or oxygen gas through the column at about 1 L/min to a face mask for inhalation in ventilation studies. It can also be continuously eluted for injection using 5% glucose solution. In either mode, elution yields are high, exceeding 90%. Breakthrough for the gaseous elution is undetectable, and is less than 10^{-8}/mL for the solution elution. Both forms of the generator are automated for ease of use in the clinic.

A novel Rb-81/Kr-81m generator prepared by ion implantation of the Rb-81 into plastic foils, with elution by both air and liquid, has been tested that demonstrates interesting potential.[40]

Commercially-available Sr-82/Rb-82 generator

Another commercially successful diagnostic true generator system is the Sr-82/Rb-82 generator. It is the only generator with an FDA approved application in PET.[41] With its 75 second half-life and its monovalent charge, Rb-82 is an excellent, if not ideal, tracer for first pass myocardial perfusion PET studies, and it is for this application that the generator received FDA approval in 1990. It can also be used to study blood-brain barrier leakage, since the normal brain parenchymae is impermeable to this cation.[42] It should be noted, however, that the generator is not approved for this latter application by the FDA.

The generators being successfully used in the clinic are based upon column chromatographic separation techniques. A variety of column supports and eluants have been proposed and tested, but those finding use in clinical settings are tin dioxide (SnO_2) or alumina (Al_2O_3) eluted with 1 and 2 % saline, respectively.[43,44,45] Considerable work has been done evaluating these two generator approaches. Because of its more favorable yield and breakthrough characteristics, and the ability to elute with large volumes of physiologically-compatible eluant, hydrous stannic oxide (SnO_2) has become the favored generator support.

The respective distribution coefficients for Sr and Rb on hydrous tin oxide with pH 7 normal saline are 20,000 mL/g and 1 mL/g. Below pH 6 the distribution coefficient for Sr drops sharply to about 200. Above pH 7 the distribution coefficient for Rb rises to about 50 at pH 9. Thus, fortuitously, the optimum pH for elution of rubidium from strontium is ideal from a physiological perspective.

Automated systems for continuous elution directly into patients have been developed and approved for routine clinical application.[46] These systems involve placing the commercially-available Sr-82/Rb-82 column in a shielded cavity, pumping the saline eluant through the column, quantitatively measuring the eluted activity from the column, and delivering the necessary diagnostic dose intravenously to the patient. All of the operations are accomplished by a combination of pumps, valves, detector system, and analyzer built into

the infusion system. The procedure is done while consistently maintaining sterile and pyrogen-free conditions.

A typical generator has an initial load of 100-150 mCi of Sr-82. The common suppliers of the Sr-82 in North America are Los Alamos National Laboratory,[47] Brookhaven National Laboratory,[48] and Nordion, International of Canada. The material supplied by Los Alamos is produced by spallation reactions using 600-800 MeV protons on molybdenum targets. The non-selective spallation process ejects various nuclear fragments from the target nucleus, with a peak product distribution about 10-20 mass numbers below the mass of the target nucleii. Thus the molybdenum targets give a high yield of the Sr-82 radionuclide. Brookhaven irradiates RbCl targets with 68 MeV protons inducing Rb(p,xn)Sr-82 reactions. Nordion uses metallic Rb targets to induce the same reactions as Brookhaven. The material supplied by all of these institutions also contains Sr-85 at the time of generator loading, which decays to stable Rb-85. At the time of generator calibration, the ratio of Sr-85 ($t_{1/2}$ = 65 days) to Sr-82 ($t_{1/2}$ = 25 days) cannot exceed 5:1.

A patient dose might be 40-50 mCi of Rb-82 for a single myocardial perfusion scan. Depending upon the infusion flow rate of the pH 7 saline solution, the yield of the generator is between 40-90%. In general, the higher the infusion rate, the higher the elution yield. However, strontium breakthrough also increases with flow rate. Breakthrough decreases as the total accumulated elution volume for the column increases, equilibrating after about 200 mL at about 10^{-6} per milliliter at elution flow rates of 5-50 mL/min. A generator loaded with 100 mCi Sr-82 and 150 mCi Sr-85, continuously eluted with pH 7 normal saline for 3 minutes at a flow rate of 5 mL/min might yield 40 mCi of Rb-82, 8 nCi of Sr-82 and 11 nCi of Sr-85.

Common radiocontaminants in the generator load solution potentially include Cr-51, Mn-54, Co-56,57,58, Y-88 and Zr-88. Sometimes these contaminants are detected in the generator eluate, but always well below acceptable whole body burdens and at levels less than 0.25 nCi/L.[41,42] Estimates of dosimetry show that the heart wall (13 mrad/mCi Rb-82), kidneys (19 mrad/mCi Rb-82) and lungs (6.9 mrad/mCi Rb-82) receive the bulk of the dose. Sr-82 and Sr-85 breakthrough contributes an insignificant amount to the absorbed dose of these organs, however the red marrow and bone each receive about 0.15 mrad/mCi Rb-82 from these two strontium radionuclides following a typical diagnostic injection of Rb-82 with a breakthrough of about 10^{-8} per mL.

Other Promising PET Generators

It should be noted that over twenty years of work went into the development of the Sr-82/Rb-82 generator from its conception to FDA approval for routine clinical use. Other generators are in various stages of development that can fill important niches in PET diagnostics. Whether any will emerge for routine clinical use depends upon many complex issues, that ultimately relate to whether there are applications that economically bring new benefits to diagnostic medicine. Following is a brief discussion of some of these prospective generators.

Ge-68/Ga-68 Generator. Several systems for the Ge-68/Ga-68 generator have been evaluated. There are several potential applications of gallium radiopharmaceuticals in PET. This generator is especially attractive because the parent Ge-68 has a long 270 day half-life while the daughter Ga-68 has a 68 minute half-life which is well suited to a variety of potential diagnostic procedures. McElvany et al. have reviewed some of the most promising generators and applications.[49] Probably the best candidate for clinical application uses stannic oxide as the support phase and 1 M HCl as the eluant. This system provides high yield (70-75%) with breakthrough in the range of 10^{-8} to 10^{-7} in 3 mL bolus elutions. It can be stored dry for extended periods, quickly recovering its physical characteristics. Therefore the generator is compact, efficient, easy to use, and storable with a long shelf-life. The generator is commercially available, though it is not approved for any routine clinical application. Its future in the clinic depends upon the development of some compelling applications in PET.

Other Interesting PET Generators. Several literature resources exist that provide reviews of work on a number of potential generators of

positron emitting radionuclides that are being developed.[3,50,51,52] These generators are generally being touted as capable of providing radionuclides that can fill useful niches in PET, either in research or the clinic. The interested reader is encouraged to refer to the literature references cited in Table 3 for information on several other potential PET generators.

Generators for Therapy

Table 4 lists a variety of generators that yield daughter radionuclides having potential therapeutic application. Indeed, it is probable that significant new commercial generators for nuclear medicine are more likely to be for therapeutic nuclides than diagnostic.[53] At the 1983 American Chemical Society meeting in Seattle, Washington in the symposium entitled "Radionuclide Generators: New Systems for Nuclear Medicine," 20 papers were presented, of which 12 were related to development of generators for diagnostic applications and 8 were related to therapeutic generator systems.[51] In a symposium of the same title held at the 1992 American Chemical Society meeting in Washington, DC, which had 21 presentations, 15 described generators for therapeutic applications and only six papers discussed issues associated with generators for diagnostics.[53]

Because of this apparent move toward therapy generators, discussion will focus on one generator that has already established a niche in therapeutic applications, Sr-90/Y-90, and two others that have significant potential in this area, W-188/Re-188 and Ra-224/Bi-212. Information concerning other potential therapy generators can be found in the references given in Table 4. Therapy generators yield daughters which are either beta-emitters (e.g., Y-90, Re-188) or alpha-emitters (e.g., Bi-212). An excellent discussion of the effectiveness of beta- and alpha- emitting nuclides for cancer therapy is presented by Laven and Hinkle.[54]

Sr-90/Y-90 Generator. Beta-emitting radionuclides of appropriate half-life and chemistry have long been recognized as potential agents for in vivo therapy of certain diseases. This is because the beta particles have high linear energy transfer over a relatively short range in tissue. Thus, if the beta-emitting nuclide can be delivered to and localized in a site where diseased tissue (e.g., cancer cells) exists, then healing can be induced by cell-kill in the diseased tissue. This technique has been applied effectively and has become known as radionuclide therapy (RNT) or, if the radiopharmaceutical is an antibody directed toward the antigen in the diseased tissue, radioimmunotherapy (RAIT). The majority of studies in RNT and RAIT have been done with I-131.[55] It has been reported that Y-90 would have greater cell-killing capacity than I-131.[56] Because of its excellent physical properties (64 hour half-life, 2.3 MeV maximum energy beta particle and absence of accompanying gamma photons) as well as its good chelation properties with agents such as DTPA, EDTA, and others, Y-90 has become a popular radionuclide for therapeutic investigations. The fact that it is available from both in-house generators and commercial sources enhances its position as a radionuclide of choice for RNT and RAIT.

An example of a study on the use of a generator system for preparation of carrier-free Y-90 is reported by Hsieh et al.[57] In this approach a teflon-supported solvent extraction agent, di-(2-ethylhexyl)phosphoric acid (D2EHPA), is used in a reverse-generator system in which the daughter radionuclide is retained on a column and the parent radionuclide is eluted. The column is loaded with Sr-90/Y-90 and washed with 0.3 N HCl to remove the Sr-90 parent. The retained Y-90 is then washed from the column using 8 N HCl. Chemical yields of Y-90 were as high as 90% with Sr-90 contamination less than 10^{-6} % of the total activity in the product. The column is then reloaded and the elution process repeated to yield a fresh batch of Y-90. An advantage of this approach is that the system can be used for numerous separation cycles with no significant radiation damage to the supported organic extraction agent since the Sr-90 parent is not retained by the column. It is interesting to note that since Y-90 emits no gamma photons, the generator efficiency was determined using Sr-85 and Y-88 as surrogates so that tracer methods could be employed. A Zr-88/Y-88 generator system has been reported and rec-

ommended as a source of high specific activity Y-88 as a stand-in for Y-90 methods development.[58] The references in the Hsieh report provide information on other approaches to the Sr-90/Y-90 generator including ion-exchange chromatography, conventional solvent extraction, and precipitation.

Bray et al. report the processing of tank-wastes at the Hanford reservation for large scale recovery of Y-90 using precipitation and extraction techniques.[59] This material is distributed directly to researchers exploring applications of Y-90.

W-188/Re-188 Generator. Perhaps the most promising generator system for therapeutic applications is the W-188/Re-188 generator. Not only does the Re-188 emit a beta particle useful in RAIT and other therapeutic applications, it also emits an imageable 155 keV gamma photon with a 16% abundance. Since the chemistry of rhenium is very similar to that of technetium, it is believed that many of the radiopharmaceuticals developed over the years for technetium may have rhenium analogs. Moreover, work related to the labeling of biologically active molecules with rhenium is being vigorously pursued.[60] The large-scale reactor production of W-188 by the W-186(2n, γ) reaction is well established.[61,62] Several well-developed generators already exist, at least one of which is being routinely distributed for research applications.[63,64,65,66,67] Probably the most mature of the generators is the alumina-based system. A sterilized column containing 13 g of alumina loaded with 140 mCi (40 mg) of irradiated W-188-sodium tungstate and eluted with 20 mL volumes of normal saline was tested.[63] This generator consistently yielded greater than 72% of the available Re-188 with breakthrough of W-188 of 10^{-6} per mL. Passing the eluate through a commercially-available alumina SepPak® column substantially reduces breakthrough in the perrhenate product solution.[67]

Ra-224/Bi-212 Generator. Alpha-emitting nuclides have been advocated as potential therapeutic agents because of the exceptionally high linear energy transfer for alpha particles. Bi-212 derived from the Ra-224/Bi-212 generator has been applied to the treatment of cancerous conditions.[68,69,70] The parent in this generator (Ra-224) does not decay directly to the daughter of interest (i.e. alpha-emitting Bi-212). In fact there are four preceding decay steps:

Ra-224(3.66 d)$\rightarrow$Rn-220(55.6 s) + $\alpha\rightarrow$Po-216(0.15 s) + $\alpha\rightarrow$

Pb-212(10.64 h) + $\alpha\rightarrow$Bi-212(60.6 min) + β^- ($\rightarrow$Pb-208(stable) + α)

A generator system has been developed based upon this decay scheme.[71] The Ra-224 for this generator system is extracted from commercially-available Th-228 as follows. The thorium is dissolved in 8 M nitric acid. The resulting solution is percolated through a bed of anion exchange resin pretreated to the nitrate form. The anionic thorium-nitrato complex formed in the nitric acid binds to the resin (distribution coefficient = 300). Some of the thorium passes into the eluate from this step, so this is evaporated to dryness, dissolved again in 8 M HNO_3 and passed through a second anion exchange column to remove residual Th-228. The eluate from this column contains the daughter Ra-224 from the initial load of Th-228. It is evaporated to dryness and brought up in 0.1 M HCl; then passed through a cation exchange column to form the generator system from which Bi-212 can be eluted. It is eluted with a small volume of either 0.5-2M HCl or 0.2-2.0 M HI. Obviously with an eluate of this nature, subsequent labeling chemistries will require conversion to a final radiopharmaceutical product that is physiologically capatible.

The separation of radium from thorium is 99.9% efficient with very little (less than 1 ppm) of the thorium appearing in the radium product. Maximum yield of Bi-212 from the generator with HI eluant is 50% using 0.2 M HI, with very little breakthrough of the lead or the radium parent.[68] The Pb-212 (in equilibrium with Bi-212) elutes with 90% yield in 2 M HCl with very little Ra-224 in the eluate. The estimated "worst-case" breakthrough for the generator is in the range of 10^{-5} to 10^{-6} per mL.

Though the alpha-emission from Bi-212 is well suited to cell-kill using RAIT, its half-life is generally too short to allow adequate localization in tumor tissue. The Pb-212 half-life is

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QUESTIONS

1. Which of the following is the best definition for a clinical radionuclide generator system?

   a. A system that produces clinically useful radionuclides from stable isotope starting material.

   b. A system that is used to separate a clinically useful daughter radionuclide from a parent radionuclide.

   c. A universal system that can generate multiple, unrelated, clinically useful radionuclides simultaneously.

   d. A set of radionuclides that generate diagnostic information when injected into a patient.

2. Given the radionuclides and decay constants below, which radionuclide has the longest half-life?

   a. Sn-121, $\lambda = 0.614\ d^{-1}$

   b. In-114, $\lambda = 0.578$ m-1

   c. Te-118, $\lambda = 0.241$ d-1

   d. Xe-125, $\lambda = 0.0405$ h-1

3. Which of the following generators would be applicable to PET diagnostic applications?

   a. Sr-90/Y-90

   b. Ra-224/Bi-212

   c. Mo-99/Tc-99m

   d. Ge-68/Ga-68

4. Which of the following is <u>not</u> a desirable characteristic for a clinical generator system?

   a. High parent radionuclide breakthrough.

   b. High yield.

   c. Ease of operation.

   d. Long parent half-life.

5. What is the maximum possible elution rate of Ag-109m for operation of a 50 mCi Cd-109($t_{1/2}$ = 462 days)/Ag-109m($t_{1/2}$ = 39.8 seconds) generator in the continuous elution mode?

a. 39.8 mCi/s

b. 50 mCi/s

c. 0.871 mCi/s

d. 0.0174 mCi/s

6. Which of the following is not important for the successful development of a clinical generator system.

a. Adequate reliable production and supply of the parent radionuclide.

b. An efficient reliable method for separation of the daughter and parent radionuclides.

c. Adequate reliable production and supply of the daughter radionuclide.

d. An important clinical application for the daughter radionuclide.

7. Which of the following circumstances would be most desirable for development of a viable column generator system?

a. Parent radionuclide with a small distribution coefficient and daughter radionuclide with a large distribution coefficient.

b. Parent radionuclide with a large distribution coefficient and daughter radionuclide with a small distribution coefficient.

c. Parent radionuclide with a large distribution coefficient and daughter radionuclide with a large distribution coefficient.

d. Parent radionuclide with a small distribution coefficient and daughter radionuclide with a small distribution coefficient.

8. Which one of the following might be a cause of a low yield from a column generator eluted after equilibrium has been established between the parent and daughter radionuclides?

a. Parent distribution coefficient is too large.

b. Daughter distribution coefficient too large.

c. Parent half-life too short.

d. Daughter half-life too short.

9. Which of the following is the most important reason to minimize breakthrough in generator systems.

a. Parent radioactivity can add adversely to patient radiation dose.

b. If breakthrough occurs it causes low daughter yield.

c. Breakthrough is a primary cause of radiolytic decomposition of the generator.

d. Breakthrough shortens the half-life of the parent radionuclide.

10. Which of the following is not a commonly used chemical separation technique used in generator development?

a. distillation

b. solvent extraction

c. combustion

d. sublimation

11. Which of the following generators is most extensively used for clinical nuclear medicine?

a. Sr-82/Rb-82

b. Sr-90/Y-90

c. Rb-81/Kr-81m

d. Mo-99/Tc-99m

12. Which of the following stationary phases is used in commercial column Mo-99/Tc-99m generator systems?

a. alumina

b. organic cation exchange resin

c. organic anion exchange resin

d. zirconium phosphate

13. Under which of the following circumstance is Tc-99 likely to be found in increased quantities in the eluate of a Mo-99/Tc-99m generator.

a. When the generator is prepared using Mo-99 produced by neutron induced fission on U-235 targets.

b. When the generator is prepared using Mo-99 produced by thermal neutron

capture on enriched Mo-98 targets.

c. When the generator has not been eluted for a long period of time.

d. When the generator is eluted before equilibrium has been established between the Mo-99 parent and the Tc-99m daughter.

14. What advantage do the sublimation and extraction technologies have over the column for the Mo-99/Tc-99m generator?

a. They are cheaper and easier to operate in the clinical environment.

b. They can be used with large masses of un-enriched neutron irradiated molybdenum oxide target material.

c. They produce Tc-99m of higher quality than the column generator.

d. They are smaller and more portable than the column generator.

15. What is unusual about the Pb-201/Tl-201 parent/daughter pair as it pertains to clinical generators?

a. It is useful for both diagnostic and therapeutic applications.

b. It is the only FDA approved generator for PET applications.

c. The parent half-life is shorter than the daughter half-life.

d. It can be easily placed in any clinical setting.

16. Why is enriched Tl-203 preferred over natural Tl as a target material for the production of Pb-201 for the Pb-201/Tl-201 generator?

a. It is less expensive.

b. It is easier to work with.

c. It introduces lower levels of lead contamination in the Pb-201.

d. It can be irradiated in either accelerators or reactors to produce Pb-201.

17. What is unusual about the Rb-81/Kr-81m generator system?

a. It is useful for both diagnostic and therapeutic applications.

b. It is the only FDA approved generator for PET applications.

c. The parent radionuclide is naturally occurring.

d. It can be eluted in both the gas phase and injectable solution.

18. The Rb-81/Kr-81m generator is useful in pediatric imaging because

a. of the favorable dosimetry resulting from the short half-life and soft emissions of the Kr-81m.

b. it can use an organic ion-exchanger for the column support phase.

c. the Rb-81 can be produced in carrier free form, thus eliminating the need for shielding for the generator.

d. the generator is disposable.

19. What is unusual about the Sr-82/Rb-82 generator system?

a. It is useful for both diagnostic and therapeutic applications.

b. It is the only FDA approved generator for PET applications.

c. The parent radionuclide is naturally occurring.

d. It can be eluted in both the gas phase and injectable solution.

20. For what clinical application is the Sr-82/Rb-82 generator approved?

a. Imaging of bone lesions.

b. Treatment of bone cancer.

c. Cardiac perfusion imaging.

d. Diagnosis of heart tissue viability.

21. What is unusual about the W-188/Re-188 generator?

a. It is useful for both diagnostic and therapeutic applications.

b. It is the only FDA approved generator for PET applications.

c. The parent radionuclide is naturally occurring.

d. It can be eluted in both the gas phase and injectable solution.

22. Why is Y-90 viewed as a promising therapeutic radionuclide.

a. It has excellent physical and chemical properties.

b. Yttrium metal is particularly toxic to cancer cells.

c. Its chemistry is very similar to that of I-131.

d. Its gamma photon emissions make it easy to trace.

23. What is <u>not</u> true about Ra-224/Bi-212 generator system.

a. The Bi-212 is an alpha emitter potentially useful in therapy.

b. There are multiple decay steps between the parent and daughter radionuclides.

c. It is the only FDA approved generator for therapy applications.

d. Pb-212 can be derived from the generator and used as an in vivo therapy generator.

24. Why are alpha emitters viewed as potentially superior for in vivo therapy.

a. Alpha particles possess exceptionally high linear energy transfer.

b. Alpha emitters are easier to handle in the clinical setting than beta emitters.

c. There are more approved alpha emitting radionuclides for therapy than there beta emitting nuclides.

d. Generator systems for alpha emitters are easier to develop than those for beta emitters.

25. Which professional group is essential to the successful development of a true clinical generator.

a. Nuclear chemists involved in targetry for radionuclide production.

b. Radiochemists and radiopharmacists involved in developing radionuclide recovery and separation technologies and labeling chemistries.

c. Nuclear physicians and technologists involved in clinical research and practice who use the generator.

d. All of the above.