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Radioisotope Generators for Clinical Use*

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In recent years, short-lived gamma-emitting radio-nuclides have attracted considerable interest in medical applications particularly for the visualization of internal organs by scintillation scanners and cameras. Because of their short half-lives, large amounts of radioactivity may be administered to patients without excessive radiation dosage, thereby increasing the photon yield resulting in greatly improved images. The development and introduction of the radioisotope generator have made the use of short-lived nuclides feasible in hospital facilities far removed from the sites of production. A generator is a device with which a short-lived daughter radionuclide may be conveniently and repeatedly separated from its longer-lived parent nuclide.

The general relationships of parent-daughter radio-nuclide systems are based on the decay constants of the

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two nuclides. Figure 1 shows a growth-decay curve for a typical system. After separation of the daughter from the parent, the daughter activity grows in from the continual decay of the parent until a state of equilibrium is reached and the ratio of the two activities remain constant, both appearing to decay with the half-life of the longer-lived parent. This fact allows more time for shipment, permits a longer shelf life, and results in a continuing source of the short-lived daughter at the place of use. The separation may be made as frequently and for as long as there is sufficient activity available to carry out the desired procedures. The separated daughter activity, of course, decays with its own characteristic half-life.

A generator system to be of value for every day use must be simple, convenient and rapid to operate. It must also yield a product of very high purity with respect to radioactive and stable contaminants during the life of the generator and after repeated separations. The product activity should be in a chemical form suitable for use with a minimum of further treatment or processing. Finally the device should be rugged and compact enough for economical

shipment and shielding.

Separation of nuclides on generators is usually based on differences in chemical behavior. Of the various procedures available for chemical separations the inherent simplicity of column chromatography makes it the method of choice for generator systems. In principle this method is based on the adsorption of the parent nuclide on a bed of suitable ion-exchange material. Elution of the column with the proper reagent solution removes the daughter activity without disturbing the parent. This procedure is repeated after regrowth of the daughter nuclide. Figure 2 shows the generator of this type that was developed at Brookhaven National Laboratory some years ago, and which has been the basis for all generator systems in routine use today.

The development of the $\text{Tc}^{99\text{m}}$ generator at Brookhaven and the introduction of this nuclide as a scanning agent has created considerable interest in short-lived isotopes and in the routine clinical use of generators. Recent refinements in the design of the generator have simplified the milking procedure, reduced radiation exposures and improved the quality of the product solution. Figure 3

represents a typical generator of this type. The top and bottom of the column have been closed with multi-injection type stoppers and the unit enclosed in a lead shield. To milk the column a length of plastic tubing with needles at either end is used, one is inserted in the bottom of the generator and the other in a shielded bottle. The desired volume of eluting solution is injected into the top, forced through the column and collected in the receiving bottle.

The problems involved in the routine use of nuclides eluted from a generator, although greater than those previously encountered, should not be insurmountable. It is felt that the resulting improvement in scans and the reduced radiation dosage to the patient warrant the additional effort. The major problem in the use of generators, and which applies to the use of short-lived nuclides generally, is the inability to test the material for sterility and pyrogenicity prior to administration. The product solutions can be sterilized by autoclaving or microfiltration and tested repeatedly, but it is only possible to check the adequacy of the system rather than the individual solutions to be injected. The situation

has been improved by commercial distribution of the completely enclosed generator system described previously which may be sterilized during preparation and tested prior to and during shipment. The supplier is also able to test for stable and radiocontaminants before shipping. Further checks of subsequent milkings may be made using simple chemical spot checks and by gamma-ray spectrometry.

The best and simplest method of assaying the radioactivity content of milked solution is with a well-type ionization chamber that has been calibrated against a standard source of known activity. Figure 4 shows an instrument of this type. The sample is placed in the well and the current output is proportional to the total activity of the sample. The volume of sample is determined by the elution of the generator with a known volume or by weighing the collection vessel.

Five radioisotope generators have been developed to the point where they are routinely available commercially. Tables 1-5 indicate the decay chains involved in the milking systems, half-lives and photon energies. Clinical applications are listed for the ionic forms of the nuclides

as eluted from the generators as well as for some labeled compounds. Certain advantages and disadvantages of the various systems have been included.

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FIG. 1

$\text{Tc}^{99\text{m}}$ GENERATOR

FIG. 2

ENCLOSED GENERATOR SYSTEM

FIG. 3

Table 1
Iodine-132 Generator

^{132}I gamma energy – 670, 780 KeV (other)

Applications

1. Thyroid studies – ^{132}I –
2. Double tagging

Advantages

1. Lower dosage
2. Repeat studies

Disadvantages

1. High energy gammas
 2. Beta activity
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Table 2
^{99m}Tc Generator

^{99m}Tc gamma energy – 140 KeV

Applications

1. Brain scanning – ^{99m}TcO₄⁻, ^{99m}Tc-DTPA
2. Thyroid studies – ^{99m}TcO₄⁻
3. Blood pool – ^{99m}Tc-albumin
4. Lung scanning – ^{99m}Tc-albumin aggregates
5. Liver, spleen, marrow – ^{99m}Tc-sulfur, aggregates
6. Kidney studies – ^{99m}Tc-DTPA

Advantages

1. Excellent gamma energy
2. No betas
3. Low internal conversion
4. Low dosage

Disadvantages

1. Short T_{1/2} of parent

Table 3
Strontium-87m Generator

$^{87\text{m}}\text{Sr}$ gamma energy – 390 KeV

Applications

1. Bone studies

Advantages

1. Low dosage
2. Repeat studies
3. No betas

Disadvantages

1. High internal conversion
 2. Expensive
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Table 4
Gallium-68 Generator

^{68}Ga gamma energy – 510 KeV

Applications

1. Brain scanning – ^{68}Ga -EDTA
2. Bone studies – ^{68}Ga -citrate
3. Marrow – ^{68}Ga -Fe colloid

Advantages

1. Long $T_{1/2}$ of parent
2. Positron scanning

Disadvantages

1. Short $T_{1/2}$ of ^{68}Ga

Table 5
Indium-113m Generator

$^{113\text{m}}\text{In}$ gamma energy – 390 KeV

Applications

1. Brain scanning – $^{113\text{m}}\text{In}$ -DTPA
2. Lung scanning – $^{113\text{m}}\text{In}$ -Fe particles
3. Liver scanning – $^{113\text{m}}\text{In}$ -Fe colloid
4. Blood pool – $^{113\text{m}}\text{In}^{+++}$

Advantages

Disadvantages

1. Long $T_{1/2}$ of parent 2. Multiple uses 3. Same equipment as ^{131}I 4. No betas.	1. Product requires pre-treatment

BROOKHAVEN NATIONAL LABORATORY MEDICAL RADIONUCLIDE DEVELOPMENT

HIGHLIGHTS

1954 Iodine-132 generator

1955 Magnesium-28 production technology

1956 Fluorine-18 reactor production technology

1957 Technetium-99m generator

1960 Copper-67 technology

1960 Iodine-124 technology

1961 Gallium-68 generator

1961 Technetium-99m - introduction to nuclear medicine

1961 Potassium-43 technology

1963 Strontium-87m generator

1963 Technetium-99m sulfur colloid development

1964 Iron-52 technology

1965 Iodine-123 technology

1967 Technetium-99m HSA - high specific activity

1968 Technetium-99m DTPA development

1970 Dysprosium-157 technology

1970 Iron-52 - millicurie production

1970 Iodine-123 - high-purity production technology

1971 Bismuth-204 technology

1971 Technetium-99m instant compounds

1971 Technetium-99m labeled red blood cells

1971-2 Brookhaven Linac Isotope Producer (BLIP)