Application of Ion-Exchange Resin Column for Basic Development of Strontium-90/Yttrium-90 Generator for Preparation of Radiopharmaceutical Therapy

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ABSTRACT

Y-90 is used to label specific antibody which subsequently used for the treatment of particular tumors. Y-90 can be produced in a generator through a reaction of decaying strontium-90 to yttrium-90. The aim of this study is to examine the possible use of ion-exchange resin on Dowex AG 50x8 in separating Y-90 from Sr-90 which then could be applied in the basic of manufacture of producing Sr-90/Y-90 generator for the production of radiopharmaceutical cancer therapy. The distributive coefficient of Sr-90 and Y-90 from each type of resin used were determined in cation-exchange resin on Dowex 50x8 due to distributive coefficient is an important factor in the process of selecting cation-exchange. The findings showed that a distributive coefficient of Sr-90 and Y-90 with HCl 6 M solvent showed that distributive coefficient of Sr-90 in cation-exchange resin on Dowex 50x8 was greater than Y-90. Y-90 in HCl 6 M solvent was more easily eluted, while Sr-90 was bound to the resin. In conclusion, resin on Dowex AG 50x8 with HCl 6 M elution solvent might be able to separate Y-90 from Sr-90 as the basis for the Sr-90/Y-90 generator.

Keywords: *generator; strontium-90; yttrium-90; ion-exchange resin*

ABSTRAK

Y-90 digunakan untuk menandai antibodi spesifik yang biasanya dipakai untuk terapi tumor. Y-90 dapat diproduksi dalam generator melalui reaksi peluruhan strontium-90 menjadi yttrium-90. Tujuan dari kajian ini adalah untuk menguji kemungkinan penggunaan resin penukar ion dalam Dowex AG 50x8 untuk memisahkan Y-90 from Sr-90 yang kemudian akan di dapat diaplikasikan sebagai dasar dalam pabrikasi produksi generator Sr-90/Y-90 untuk menghasilkan sediaan terapi kanker radiofarmaka. Koefisien distribusi dari Sr-90 dan Y-90 dari masing-masing jenis resin resin yang digunakan diukur dengan menggunakan resin penukar kationpada Dowex 50x8 karena koefisied distribusi merupakan faktor penting dalam proses menseleksi pertukaran kation. Penemuan menunjukkan bahwa dengan pelarut HCl 6 M koefisien distribusi Sr-90 dalam resin penukar kation Dowex AG 50x8 lebih besar daripada koefisien distribusi Y-90. Y-90 dalam pelarut HCl 6 M lebih mudah dielusikan sementara Sr-90 terikat lebih kuat pada resin daripada Y-90. Kesimpulan dari penelitian ini adalah bahwa resin Dowex AG 50x8 dengan elusi larutan HCl 6 N mampu memisahkan Y-90 dari Sr-90 sebagai dasar pembuatan generator $^{90}Sr/^{90}Y$.

Kata Kunci: *generator; strontium-90; yttrium-90; resin penukar ion*

INTRODUCTION

According to a previous study, 27-70% of cancer patients are bone cancer patients (bony metastases) and more than 40% bone cancer is originated from prostate cancer, breast cancer and lung cancer[1-2]. The therapy with yttrium-90 radiocolloid, specifically, for lung is invented by Pochim and coworker [3-4]. Ytrrium-90 (Y-90) itself is a pure β-ray emitter with a maximum energy of 2.26 MeV with a half-life of 64 h [4]. It is established applications in targeted therapy [5].

Nowadays, Y-90 is utilized to label specific antibody which subsequently used for the treatment of particular tumors. It is in line with the speed of antibody accumulation in tumor cells [6-7]. In a tumor cell, the energy of 2.26 MeV will produce an attacking effect by delivering radiation to a tumor cell; a cell adjacent to tumor cell—a tumor cell that hides its self as antigens as well as bulky tumor [8].

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There are some radiopharmaceuticals incorporating Y-90 in application for radionuclide therapy, for example; Y-90-ibritumomab-tiuxetan for n-Hodgkin's lymphoma [9], Y-90-eilicate/citrate colloid (rheumatoid arthritis/hemophilia therapy) [10], Y-90-microspheres (for liver cancers therapy) [11], Y-90-lanreotide (lung cancer therapy) [12], Y-90-anti-CEA MAb (for breast cancer therapy) [13], and Y-90-DTPA-coupled for antitumor antibodies [14].

Ytrrium-90 is produced in a generator through a reaction of decaying strontium-90 to yttrium-90 [3,8]. In this case, generator Sr-90/Y-90 should be designed at its best in order to make it applicable to medical officers in hospitals. Due to strontium-90 characteristic which has very high β- energy, it is carcinogenic and also possible to destroy the bone marrow [15-16], hence the product of yttirium-90 produced should be completely free from any contamination of strontium-90 [17].

The production of Sr-90/Y-90 generators was reported with the various methods in some countries [18]. India reported the creating of Sr-90/Y-90 generators based on an electrochemical separation technique. The SLM-based Y-90 generator was developed by using a polytetrafluoroethylene (PTFE) membrane impregnated with a suitable extractant. However, ion chromatography separation technique system was applied for Sr-90/Y-90 generators in Cuba. While application resin chromatography for separation of Sr-90 and Y-90 is applied by Mikolajczak et al. [19].

The significance of this research is due to the fact that the distributive coefficient values (K_d) of both ions for each type of different cation-exchange resin have not known yet. On the other hand, the similarity between Sr and Y in the form of positive ion will produce an imperfect result of separation [20].

The statement of the problem in the research is that Sr-90/Y-90 generator made must be able to produce Y-90 with a high degree of purity [3]. A high purity separation using cation-exchange resin will occur if the difference of distributive coefficient between Sr-90 and Y-90 is appreciable.

The invention of this research is apparent from the way of determining the distributive coefficient of Sr-90 and Y-90 from each type of resin used, since distributive coefficient is an important factor in the process of selecting cation-exchange, and the most efficient ion-exchange resin will be utilized as a silent phase medium in chromatography Sr-90/Y-90 generator column.

This objective of this research is to examine the possible use of resin on Dowex AG 50x8 in separating Y-90 from Sr-90 which is subsequently applied in the manufacture of designing Sr-90/Y-90 generator to produce a radiopharmaceutical therapy for cancer.

EXPERIMENTAL SECTION

Materials

The materials used in this research were strontium-90 and yttrium-90. In this case, strontium-90 was the result of isolating RFW (Resources Fluid Waste) sewage (PT Batan Technology), Y_2O_3, $SrCl_2.6H_2O$ (Strem Chemical), 37% hydrochloric acid pro analysis (MERCK), nitric acid 65% pro-analysis (MERCK), cation-exchange resin on Dowex AG 50x8 (Bio-Rad Laboratories, Inc.), scintillator POPOP [1,4-bis-2-(5-phenyloxazolyl)-Benzene], Insta-Gel (Packard Instrument Co. Inc.).

Instrumentation

The instruments used in this research were a liquid scintillation analyzer (Packard Instrument Co. Inc), a beta-gamma counter (The Nucleus), gamma ionization chamber, Atomlab 100 Plus (Biodex Medical System), spectrometry gamma; multi-channel analyzer (Tennelec), vial plastic, centrifuge (Hettich EBA 8S), parafilm (Pechiney).

Procedure

Preparation of RFW

RFW (0.5 mL) was taken by syringe and put in a small test tube. It was then added with distilled water until it reached 1 mL and shaken. After that, it was taken as much as 100 μL and a small test tube were inserted, then added $SrCl_2.6H_2O$ was added until 2 mL and also 10 μL of concentrated HNO_3.

Preparation of Sr-Spec column

Sr-Spec column was mounted on a clamp. While beaker glass was placed beneath the column, the cover of the top of the column was opened and let the content flow into the beaker. Subsequently, 5 mL of 8 M HNO_3 was taken, put into the column and let it flow into the beaker. In this way, the addition of 5 mL of 8 M HNO_3 should be done up to three times.

Separation of Sr-90 from Sr-Spec column

RFW solution which had been prepared was put into the column, then let it flow, and added with 5 mL of 8 M HNO_3 up to three times in a row.

Identification of Sr-90 in the eluates

Take 100 μL eluate was taken by micropipette and put in a small test tube. Five mL of distilled water was added, and then it was shaken. The solution was

taken as much as 100 μL and filled into the polyethylene vial (plastic). One mL of distilled water was added and then it was shaken. After that, a scintillator (POPOP) was added as much as 5 mL and it was shaken until it became homogeneous. It was measured by applying LSC (Liquid Scintillation Counter). The existence of strontium-90 was determined from maximum energy 546 keV.

Irradiation of Y_2O_3 target

Y_2O_3 of 5 mg was weighed and wrapped in aluminum foil. It was put into vials (plastic) and wrapped again in aluminum foil, and then irradiated in a reactor by applying the pneumatic method for ± 1 h. The result of irradiated Y_2O_3 was further dissolved with HCl in accordance with molar variation wanted (for example, 4, 6 and 8 M) for 10 mL. Measure the activity of Y-90 with GIC (*Gamma Ionization Chamber*).

Separation of Sr-90 from Sr-Spec column

Prepared RFW solution was inserted into a column and let it flow. Five mL of 8 M HNO_3 was added up to three times in a row.

Ascertaining Sr-90 charge with electrophoresis paper

Whatman paper with 33 cm length and 1.5 cm width was prepared and a region: -16, -15,….0….,15, 16 was made. A half mL of Sr-90 sample was taken from the result of isolating RFW with Sr-Spec column, then dilute it with distilled water until 1 mL, and take 50 μL of it. Put it in a small test tube and add $SrCl_6.6H_2O$ solution as a carrier. Take 20 μL of it, then spot it on 0 (zero) region on electrophoresis paper. After that, dry it up with hair dryer, and plug electrophoresis paper with negative region position on the side of the anode, while the negative region is a plug on the side of the cathode. Wet the entire surface of the paper with borate buffer pH 8.0 or phosphate buffer pH 7.0. Electrophoresis is done in 1 h at a voltage of 400 volt. After 1 h, remove the paper and dry it. Dried paper is coated with a transparent insulation and cut to the region. The count of each piece of the region is measured by beta-gamma counter. The highest value of the count is considered as Sr-90 count. Furthermore, the existence of Sr-90 is identified by dissolving 2 mL of HNO_3 0.05 M to the related region, and the shake it. After that, take as much as 200 μL of it, put it into polyethylene vial, and add 4 mL of the scintillator (POPOP), and identify its maximum energy spectrum with LSC eventually.

Determination of distributive coefficient

The use of both resins, whether cation-exchange or anion-exchange could be utilized in two ways: batch method and column method. Determining distributive coefficient in this research employs the batch method. It is done by directly adding a sample into the resin and shaking it, or using stirrer as an alternative. In addition, the distributive coefficient can be calculated by this formula [21]:

$$K_d = \frac{A_o - A_t}{A_o}$$

A_0 is the count of the sample that is not mixed with resin, while A_t is the count of the sample that is added to the resin during shaking (t).

RESULT AND DISCUSSION

Separating Sr-90 from RFW

The source of Strontium-90 was obtained from the sewage of the process in producing 99Mo generator through thermal neutron bombardment against targets 235U by using a medium of nitric acid and sulfuric acid solution. This acidic waste was called AW (Acid Waste). Strontium-90 from RFW (Resources Fluid Waste) sewage was used since the strontium-90 degree was quite great. To enlarge the strontium degree, added $SrCl_2$ $6H_2O$ as a carrier. Adding this carrier would not affect strontium-90 count because $ScrCl_2.6H_2O$ was not radioactive compound. Separating strontium-90 from other radionuclide using Sr-Spec (100-150 μm) column (Eichrom Industries, Inc) 3 g with the principle of chromatography extraction was the separation of substances based on the solubility differences in particular solvents. Strontium-90 was eluted in HNO_3 0.05 M solvent, while the other radionuclide was eluded in HNO_3 8 M solvent. Identifying strontium-90 with LSC (*Liquid Scintillation Counter*) using vial glass and vial polyethylene (plastic) showed different results. The use of vial glass in LSC would produce *bremsstrahlung*, which means that the count measured exceeds the actual count because vial glass has a larger background (60 CPM) than vial plastic which comes from ^{40}K contents.

The result of identifying Sr-90 eluate from RFW was separated by using Sr-Spec column with vial plastic (20 CPM background).

Preparation of Y-90

Yttrium-90 (Y-90) was obtained by irradiating the target compounds of Y_2O_3 for one hour in the Siwabessy multipurpose reactor through pneumatic system. The result of irradiating Y-90 target is dissolved with hydrochloric acid, and then its activity was determined by GIC instruments (Gamma Ionization Chamber). Determining the distributive coefficient of Y-90 was measured from the Y-90 count as measured by beta-gamma counter, since GIC

instrument is, in fact, less selective in detecting the activity of a radioactive substance in μCi scale (microCurie). The limitation of optimal detection of GIC instrument was in mCi scale. A beta-gamma counter tool was utilized, for it was able to detect counts, both beta-ray and gamma-ray. The result of irradiating Y-90 was a pure beta emitter thus the detected count on beta-gamma counter instrument is beta-ray from Y-90.

Determination of Sr-90 Charge

Theoretically, strontium is charged 2+ as compared to yttrium which is charged 3+ [20]. Separating yttrium from strontium would be easily implemented if yttrium was in the form of the complex anion. On the other hand, strontium was still charged 2+. Adding acid (HCl with high concentration, 6 M, 8 M) was expected to produce yttrium in the form of the complex anion. Therefore, by using electrophoresis paper, complex anion yttrium will move towards the cathode, while in a state whereby HCl was in the same normality, strontium cation would move towards the anode.

At this point, this research only focused on determining strontium charge by employing electrophoresis paper. This electrophoresis paper used phosphate buffer pH 7.0 and borate buffer pH 8.0 as an electrolyte solution. Buffer solution (electrolyte) served as a one-way electric current carrier, while Whatman paper was as a medium for the passage of electric current carried by the buffer solution. The buffer would be able to carry electric current if the constituent component was really different from the analyte. Whatman paper used was in a small size—1.5 cm x 32 cm. This small-sized paper was intended to minimize the center effect, thus it could be obtained a high resolution (separation power). The movement of electric current caused the heat, which will increase the mobility as much as 2% per °C [22].

Electrophoresis paper using phosphate buffer pH 7.0 proves that strontium ion did not move at all either to cathode or anode (Fig. 1), although Sr-90 sample had been filtered with the millipore membrane (Millex). The new strontium ion moved towards the anode (the region on electrophoresis paper: -5) if the electrolyte solution of borate buffer pH 8.0 was used. This result proves that strontium ion in HNO_3 0.05 M solutions would be mobilized by the electric current if current carrier solution (its electrolyte) was the base. If strontium ion was acid (HNO_3 0.05 M) and borate buffer pH 8.0 was base, there will be a huge difference between analyte and borate buffer solution. In consequence, borate buffer was able to conduct one-way electrical current which further affects the movement of Sr^{2+} ion towards the anode.

The existence of Sr-90^{2+} in the highest region count (region-5) was known after it was identified by spectrometry gamma, which asserted that there was no gamma emitter. By applying LSC, it was obtained the spectrum of maximum energy of Sr-90 characteristic as shown in Fig. 2.

In another study, the high affinity of the reagent 2-ethylhexyl 2-ethylhexyl phosphonic acid was employed for a novel extraction paper chromatography technique for Y-90. This method is used for detecting levels of Sr-90 [23]. Here we determined the distributive coefficient to know the effectiveness of separating Sr-90 and Y-90.

Table 1. Preparation of Yittrium-90

Y_2O_3 (mg)	Solvent of HCl (M)	Activity Y-90 (μCi)
15.0	3	1770
5.4	6	574
5.1	8	629
5.2	10	540

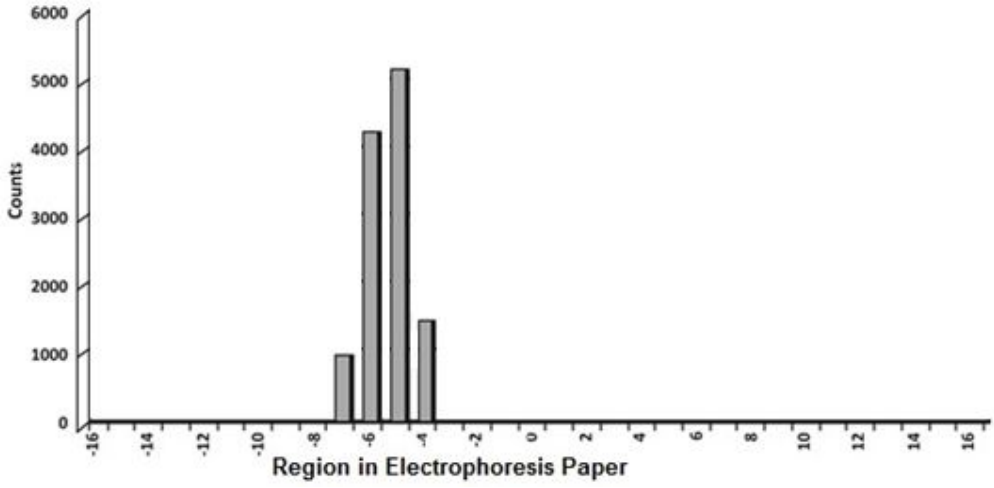

Fig 1. Graph of Electrophoresis Results of Sr-90 with buffer electrolyte borate in pH 8.0

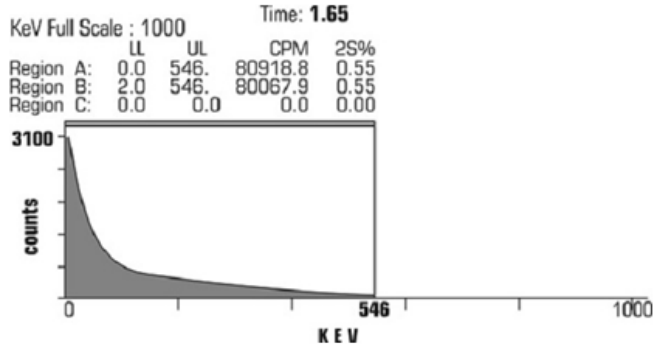

Fig 2. Spectrum of Maximum Energy of Sr-90 in Region-5

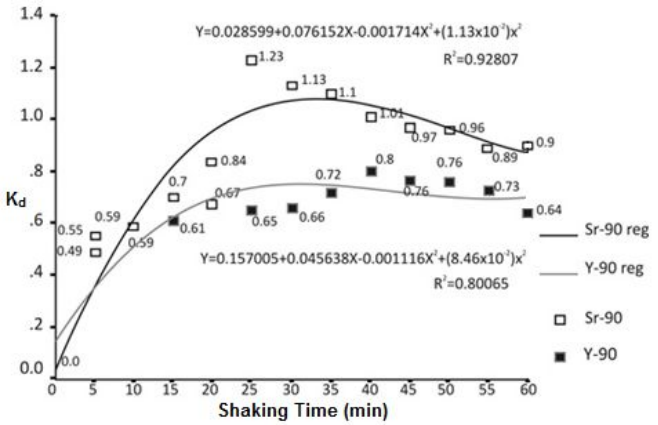

Fig 3. A coefficient distribution Curve (K_d) of Sr-90 and Y-90 with HCl 6 M as solvent versus Shaker Time

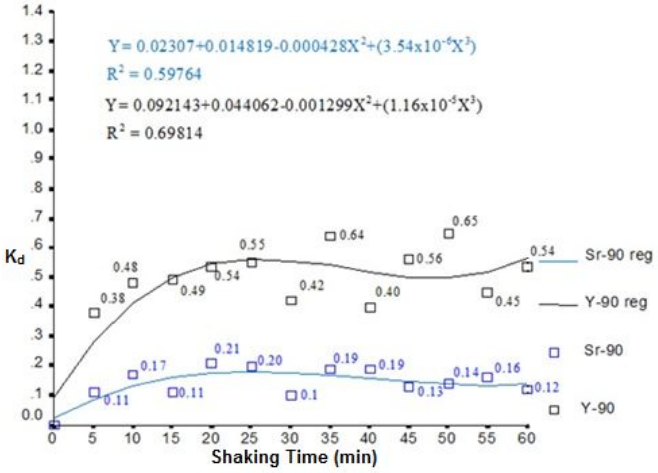

Fig 4. Coefficient distribution curve (K_d) of Sr-90 and Y-90 with 8 M HCl as a solvent versus shaking time

Determination of Distributive Coefficient of Sr-90 and Y-90

A distributive coefficient of Sr-90 and Y-90 was determined by a batch method, in a way, mixing strontium-90 and yttrium-90 directly into the cation-exchange resin which had been added to its solvent (HCl 6 M or 8 M). However, the actual separation employed column method. In this context, the batch method was chosen due to its simplicity and efficient timing. Here is the result of distributive coefficient of strontium-90 and yttrium-90 test.

The regression curve of K_d Sr-90 and Y-90 with HCl 6 M solvent showed that K_d Sr-90 in the cation-exchange resin on Dowex AG 50x8 was greater than K_d Y-90. At this point, by using HCl 6 M solvent, Sr-90 bonded more tightly to resin than Y-90.

Sr-90 and Y-90 in HCl 6 M solvents hydrated. The occurrence of hydration process could be described by equating hypothesis reaction as follows:

$$Sr\text{-}90^{2+} + 4H_2O \rightarrow \left[Sr\text{-}90(H_2O)_4\right]^{2+} \quad (1)$$

$$Y\text{-}90^{3+} + 6H_2O \rightarrow \left[Y\text{-}90(H_2O)_6\right]^{3+} \quad (2)$$

The amount of H_2O molecule bound to Y-90 in the hydration process caused ionic radii $[Y\text{-}90(H_2O)_6]^{3+}$ to be greater than $[Sr\text{-}90(H_2O)_4]^{2+}$ [24-25]. The influence of hydrated complex ionic radii was greater than hydrated complex ions charge in the process of forming a bond with anions (sulfonate functional groups on the resin), therefore, although complex ionic radii was hydrated in Y-90 with a charge of 3+, the strength of bond with sulfonate functional groups on the resin was weaker than hydrated Sr-90 with a charge of 2+ [20]. Consequently, hydrated Sr-90 ion was more tightly to the resin than the hydrated Y-90 ion.

In Fig. 3, the highest regression value obtained for Sr-90 and Y-90 is at t = 30 min. Thus, for 30 min of shaking, the optimal separation between Y-90 and Sr-90 with HCl 6 M solvent was obtained. Furthermore, that way could be used as a procedure in separating Y-90 from Sr-90 by employing column method containing resin on Dowex AG 50x8 based on the previous study [26]. Mikolajczak et al. were applied DGA resin column with the detection limit of 10^{-5}%. The DGA resin is soaked by HNO_3 6 M. While, DOWEX resin was soaked by HCl 6 M thus separate Y-90 from Sr-90 [19].

Regression curve of K_d for Sr-90 and Y-90 with HCl 8 M solvent showed that K_d Y-90 in the cation-exchange resin on Dowex AG 50x8 is greater than K_d Sr-90. Sr-90 and Y-90 were charged 2+ and 3+, while $Y\text{-}90^{3+}$ had a greater charge than $Sr\text{-}90^{2+}$. Hence, Y-90 bound more tightly to the resin than Sr-90. In Fig. 4, the highest regression value for Sr-90 and Y-90 was obtained in t = 25 min. At this point, in 25 min of shaking, optimal separation is obtained between Y-90 and Sr-90 with HCl 8 M solvent using resin on Dowex AG 50x8. Based on these results, Strontium-90 and yttrium-90 in 6 M HCl solvent have been hydrated. However, in HCl 8 M solvent, the contents of HCl (concentrated) was greater than the contents of water,

therefore hydration did not occur. In Fig. 4, the highest regression values obtained for Sr-90 and Y-90 at t = 25 min. So for 25 min agitation, obtained the optimal separation between the Y-90 and Sr-90 with 8 M HCl solvent using Dowex resin AG 50x8.

CONCLUSION

Based on the findings, a distributive coefficient of Sr-90 and Y-90 with HCl 6 M solvent showed that distributive coefficient of Sr-90 in cation-exchange resin on Dowex 50x8 was greater than Y-90. Y-90 in HCl 6 M solvent was more easily eluted, while Sr-90 was bound to the resin. The optimal timing of shaking to separate Y-90 from Sr-90 was 30 min. If HCl 8 M solution was used as a solvent, the distributive coefficient of Sr-90 was lower than Y-90. Therefore, Sr-90 was eluted while Y-90 was bound to the resin. It could be concluded that resin on Dowex AG 50x8 with eluted HCl 6 M solvents might be able to separate Y-90 from Sr-90, as the basis for the Sr-90/Y-90 generator.

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