Radionuclides for biomedical studies. Nuclear data and production methods in charged-particle accelerators

S. N. Dmitriev and N. G. Zaĭtseva
Joint Institute for Nuclear Research, Dubna

Fiz. Élem. Chastits At. Yadra **27**, 977–1042 (July–August 1996)

An analytical review is given of the role and status of nuclear data and of experimental methods and results concerned with the production of the most important and widely used or promising cyclotron radionuclides in nuclear medicine and biochemical research. Brief information is given about the contemporary status and projected development of research in this field.
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1. INTRODUCTION

The father of the nuclear-physics method for investigating living organisms is G. Ch. de Hevesy (1885–1966). He was the first to use, in 1923, a natural radioactive isotope ^{212}Pb (ThB, $T_{1/2}$= 10.6 h) to study the distribution of this isotope in the roots, stems, leaves, and fruits of a plant (Vicia fabe) with the aid of an electroscope, and in the following year, using ^{210}Bi (RaE, $T_{1/2}$= 5 days), he performed the first experiments on mice.

The study of the possibilities of employing artificial radioactive isotopes in biochemical research and nuclear medicine started soon after the discovery of the artificial transmutation of elements, first discovered for ^{30}P by Joliot Curie in 1934. In the past 20 years the use of radioactive isotopes and labeled compounds, specially synthesized for medical–biological studies, has greatly expanded as a result of both an increase in the number and constant improvement of cyclotrons and the development of in-vivo techniques for detecting the distribution of radionuclides (RNs) in humans and animals. In different nuclear centers possessing accelerator complexes or reactors, radionuclide production programs based on the results of investigations in application to the possibilities of a specific laboratory have been developed.[1–4]

More than 2300 radionuclides are now known. Of these, more than 200 are used in different fields of science, technology, and medicine. These RNs are predominantly artificially produced in reactions of charged particles or neutrons with a target in accelerators or nuclear reactors.

Reactor and fuel-element RNs, respectively obtained by special irradiation of targets or produced in fuel elements as a result of fissioning of nuclear fuel and having, as a rule, excess neutrons (the decay of these nuclides is accompanied by β^- emission), comprise the main product of radioisotope production. These nuclides include ^{60}Co, ^{131}I, ^{99}Mo, ^{137}Cs, and many others. Neutron-deficient radionuclides, decaying via electron capture or with the emission of positrons, are predominantly formed in charged-particle accelerators as a result of the interaction of protons, deuterons, and other accelerated ions with target nuclei. The type of decay found in these so-called cyclotron RNs (these include RNs obtained in photonuclear reactions with the aid of bremsstrahlung from electron accelerators) is preferred over nuclides with excess neutrons for applications in a number of fields, including nuclear medicine. In modern nuclear medicine more than 50 cyclotron radionuclides with half-lives ranging from several minutes to several years (Table I) are used for scientific research, diagnostics, and therapeutic purposes. In the present review we examine the data on the most widely used or promising cyclotron RNs. These include ultrashort-lived (USL) isotopes (^{11}C, ^{13}N, ^{15}O, ^{18}F), some γ emitters (^{123}I, ^{201}Tl, ^{67}Ga, ^{111}In), and generator radionuclides (^{81}Rb/^{81m}Kr, ^{82}Sr/^{82}Rb, and others). The generator ^{99}Mo/^{99m}Tc, for which the isotope ^{99}Mo can be obtained in both reactors and cyclotrons, is a special case.

Promising or special-purpose RNs comprise quite a large group, which now includes ^{26}Al, ^{52}Fe, ^{67}Cu, ^{75,77}Br, ^{97}Ru, ^{211}At, ^{237}Pu, and a number of other isotopes.

The objective of the present review is to present, on the basis of an analysis of data obtained in the last few years (mainly over the last 5–10 yrs), the current status of the production of radionuclides for studies in biochemistry and nuclear medicine.

2. CLASSIFICATION OF RADIONUCLIDES. BRIEF INFORMATION ABOUT APPLICATIONS IN NUCLEAR MEDICINE

Cyclotron RNs can be conventionally classified in separate groups according to their distinguishing indicators. The basic characteristics include the chemical properties of the elements, the nuclear-physical properties of the nuclides, and their areas of application in nuclear medicine (Tables II and III).

Radionuclide studies of the state of internal organs, based on the study of the vital functions of an organism, such as the regional blood flow, intercell exchange, and metabolism, make it possible to assess the degree to which a pathological process has spread and the effectiveness of the corresponding medical treatment. Individual RNs are used for therapeutic purposes (radiotherapy).

A limited number of RNs, which include ^{123}I, ^{201}Tl, ^{82}Rb, and ^{128}Cs, as well as inert gases, are used in the pure ionic form. All other RNs are used for labeling different compounds—radiopharmaceuticals (RPs), which are organotropic, i.e. they possess a specific selectivity for separate organs.

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TABLE I. Cyclotron radionuclides for nuclear medicine.

Isotope	$T_{1/2}$	Isotope	$T_{1/2}$	Isotope	$T_{1/2}$
^{11}C	20.4 min	^{62}Zn	9.13 h	^{122}Xe	20.1 h
		↓		↓	
^{13}N	9.96 min	^{62}Cu	9.74 min	^{122}I	3.6 min
^{15}O	2.03 min	^{66}Ga	9.4 h	^{123}Xe	2.08 h
				↓	
^{18}F	109.7 min	^{67}Ga	78.3 h	^{123}I	13.2 h
^{28}Mg	20.9 h	^{68}Ge	271 d	^{125}Xe	16.8 h
		↓		↓	
^{26}Al	$7.2 \cdot 10^5$ yr	^{68}Ga	68.1 min	^{125}I	60 d
^{30}P	2.5 min	^{72}As	26.0 h	^{127}Xe	36.4 d
^{34m}Cl	32.06 min	^{74}As	17.8 d	^{128}Ba	2.43 d
				↓	
^{38}K	7.64 min	^{73}Se	7.1 h	^{128}Cs	3.9 min
^{43}K	22.2 h			^{157}Dy	8.1 h
^{44m}Sc	2.44 d	^{75}Br	97 min	^{167}Tm	9.25 d
↓					
^{44}Sc	3.92 h	^{76}Br	16.0 h	^{172}Hf	1.87 yr
^{44}Ti				↓	
↓		^{77}Kr	74.4 min	^{172}Lu	6.7 d
^{44}Sc		↓			
		^{77}Br	57.0 h	^{178}W	21.7 d
^{40}Cr				↓	
^{51}Cr	47.3 yr	^{79}Kr	34.9 h	^{178}Ta	9.3 min
^{52}Fe	3.9 h	^{81}Rb	4.58 h	^{194}Hg	367 yr
↓		↓		↓	
^{52m}Mn	21.6 h	^{81m}Kr	13.3 s	^{194}Au	39.5 h
^{55}Co	27.7 d			^{195m}Hg	40 h
^{56}Co				↓	
^{57}Co	8.2 h	^{82}Sr	25.5 d	^{195m}Au	30.5 s
^{56}Ni		↓			
^{57}Ni	21.1 min	^{82}Rb	1.27 min	^{199}Tl	7.42 h
^{61}Cu	17.54 h	^{85}Sr	64.9 d	^{201}Tl	73.1 h
^{62}Cu	78.76 d	^{87}Y	80.3 h	^{203}Pb	51.9 h
^{64}Cu	271.3 d			^{205}Bi	15.3 h
^{67}Cu	6.1 d	^{88}Y	106.6 d	^{206}Bi	6.24 d
	36.0 d	^{97}Ru	2.9 d	^{211}At	7.2 h
	3.4 h	^{101m}Rh	4.4 d	^{237}Pu	45.6 d
	9.74 min	^{111}In	2.83 d		
	12.7 h	^{117m}Sn	13.6 d		
	61.9 h	^{117}Sb	2.80 h		

3. FACTORS DETERMINING THE STATUS OF RADIONUCLIDES IN BIOMEDICAL STUDIES

Figure 1 displays a diagram illustrating the problems which must be solved in order to obtain radionuclide preparations for nuclear medicine. These problems can be conventionally divided into four groups, logically following one after another ($A \rightarrow B \rightarrow C \rightarrow D$). We give below a brief analysis of the known solutions, based on knowledge of nuclear data for radionuclides, to problems grouped in this manner.

3.1. Choice of radionuclides. Significance of data on nuclear properties

The choice of radionuclide for biomedical studies is determined by a number of requirements which must correspond to the properties of the radionuclide. These include the following:

- selectivity of the nuclide or compounds labeled with it for different organs (heart, kidneys, brain, liver, lungs, marrow, and so on);
- type of radiation (γ, β, α), depending on the character of the studies being performed (diagnostics, therapy);
- high specific activity;
- minimum radiation dose.

The last three properties of RNs are determined by a group of nuclear data which include the half-lives and the structural properties of the decay, information about which can be found in many handbooks, for example, Refs. 5–7. The structure and decay characteristics of nuclei are considered when choosing RNs for in-vivo studies from the standpoint of two factors—the possibility of effective detection of the distribution of the radionuclides in organs, using appropriate equipment, and the admissible radiation dose.

The type of equipment employed in radionuclide studies is determined by the properties of the radiation from the radionuclide and the capability of this radiation to give high resolution of an image showing the distribution of the RN. Different types of standard scintillation γ chambers and one-beam tomography machines exist for detecting γ rays. These devices require the use of radionuclides whose γ-ray energies fall predominantly in the range 60–300 keV and which make possible good-quality scanning. Examples are iodine isotopes, employed in nuclear medicine, of which ^{123}I is considered to be ideal from this standpoint (Table IV). If higher-energy γ rays are present, the scan quality decreases. In such cases it is necessary to use thick tungsten collimators, which make it possible to avoid or reduce substantially the distorting effect of high-energy γ rays. For example, such collimators are employed in studies with the ^{201}Tl (x rays Hg, $E_\gamma = 135$ keV) preparations containing an admixture of ^{202}Tl ($T_{1/2} = 12$ days, $E_\gamma = 439$ keV). Of course, this requirement on the energy of the γ rays limits the number of RNs which are suitable with respect to other indicators.

TABLE II. Cyclotron radionuclide groups according to chemical and nuclear-physical properties.

Property	Group	Radionuclides
Chemical properties	"Organic" nuclides	^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{30}P
	"Inorganic" nuclides	^{28}Mg, ^{47}Sc, ^{48}Cr, ^{73}Se, ^{201}Tl and others
	Alkali metals	^{43}K, ^{82}Rb, ^{128}Cs
	Halogens	^{18}F, ^{34m}Cl, $^{75,77}Br$, ^{123}I, ^{211}At
	Inert gases	^{79}Kr, ^{81m}Kr, ^{127}Xe
Nuclear-physical properties	γ emitters	^{67}Ga, ^{97}Ru, ^{111}In, ^{123}I, ^{127}Xe, ^{201}Tl and others
	Positron emmitters	^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{30}P, ^{38}K, ^{52m}Mn, ^{68}Ga, ^{75}Br, ^{82}Rb, ^{128}Cs and others
	α emitters	^{211}At

TABLE III. Cyclotron radionuclide applications in nuclear medicine.

Purpose	Nuclide	Area of application
Diagnostics	^{11}C, ^{13}N, ^{15}O, ^{18}F	Positron-emission tomography (PET)
	^{52}Fe	Hematology
	$^{67,68}Ga$	Oncology
	$^{73,75}Se$	Metabolism, oncology
	^{82}Rb, ^{128}Cs, ^{201}Tl	Cardiology
	^{97}Ru	Oncology, lymphoangiography
	^{111}In	Oncology, nephrology, and others
	^{123}I	Cardiology, oncology, endocrinology, and others
	^{81m}Kr, ^{127}Xe	Pulmonology
	^{178}Ta	Cardiology, neurology
	^{195m}Au	Angiography
	^{26}Al, ^{237}Pu	Metabolism
Therapy	^{67}Cu, ^{97}Ru, ^{85}Sr ^{167}Tm, ^{211}At and others	Oncology
Labeled monoclonal antibodies	^{67}Cu	Therapy, diagnostics
	^{97}Ru	Therapy, radioimmunology
	^{100}Pd, ^{101m}Rh, ^{211}At	Therapy
	^{111}In, ^{123}I	Diagnostics

Low-energy detectors based on multiwire proportional γ chambers, created by the Nobel Laureate Sharpak,[17] have been under development for the last few years for γ emitters with $E_\gamma < 100$ keV. In nuclear medicine, such detectors have made it possible to employ low-energy γ emitters, for example, ^{178}Ta ($E_\gamma = 54-93$ keV).

Positron-emission tomography (PET), an especially effective method of medical diagnostics, which is undergoing increasing development, is based on the detection of annihilation γ rays emitted together with positron radiation from RNs. The γ rays are detected by many pairs of detectors connected in coincidence and forming a circular system. For PET studies it is important to choose RNs with a low maximum β^+-particle energy, which makes it possible to obtain high image resolution. The best nuclide for this application is considered to be ^{18}F, which has the maximum β^+-particle energy, 635 keV. Other positron emitters [with the exception of ^{11}C ($E_{\beta^+} = 960$ keV)] emit β^+ particles with energy exceeding 1 MeV.

Another important factor that is taken into account when choosing RNs for in-vivo studies is a low radiation dose. On the basis of estimates of radiation loads for man, other conditions being equal, short-lived RNs are preferred. An example of such a choice is once again ^{123}I, whose radiation dose, calculated for the thyroid gland and for the whole

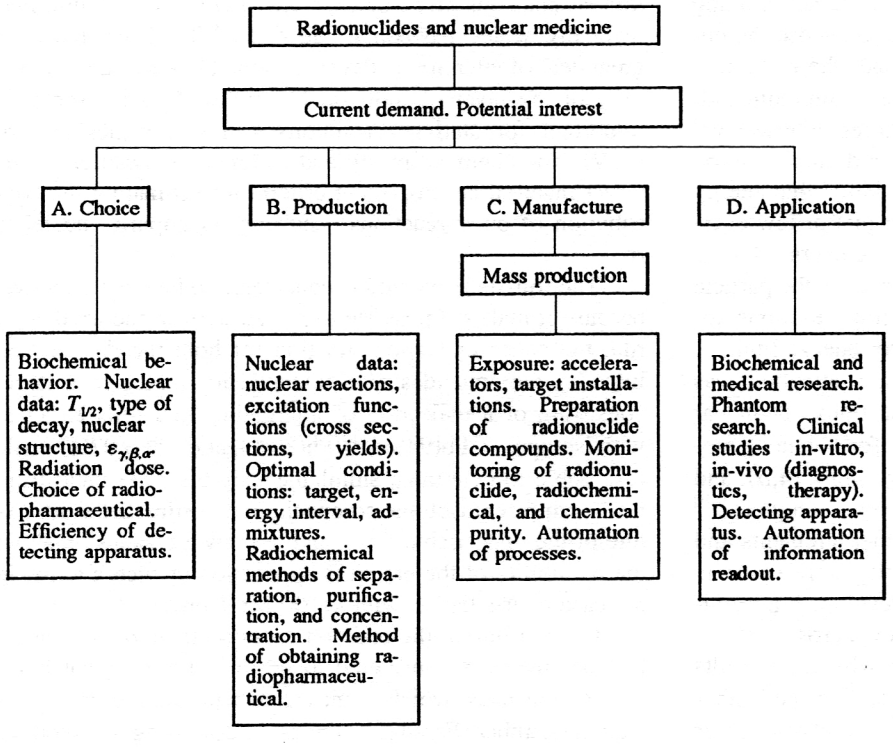

FIG. 1. Status of radionuclides in nuclear medicine.

TABLE IV. Properties of iodine radionuclides used in nuclear medicine.[8]

Nuclide	$T_{1/2}$	Type of decay (%)	E_γ, keV (%)	Radiation dose, mrad/mCi	
				Thyroid gland	Whole body
^{123}I	13.2 h	EC (100)	159(83)	20	0.07
^{124}I	4.1 d	EC (77), β^+ (23)	602(61) 1691 (10.5)	1200	14.2
^{125}I	60.1 d	EC (100)	kx-rays	1200	2.0
^{131}I	8.0 d	β^- (98.9)	364(81)	1200	0.2

body, is almost two orders of magnitude lower than for other iodine isotopes (Table IV).

It is customarily assumed that in the ideal case the average lifetime of a radionuclide should be of the same order of magnitude as the time required to perform the studies after the preparation is introduced. In practice, however, many studies are performed with RNs whose half-lives are hours or even days, but the properties of their radiation make it possible to record, using appropriate equipment, their distribution in organs.

Thus, progress in biomedical research is closely linked with the development and extensive use in clinical practice of electronic equipment which reconstructs quickly and accurately the pattern of localization of RNs in organs with the aid of computer technology. The quality and quantity of such technologies determine ultimately the assortment of radionuclides available for nuclear medicine.

3.2. Production of radionuclides

The methods for producing RNs are based on data on nuclear reactions in which RNs are produced and which are described by excitation functions (EFs)—the energy dependence of the reaction cross section σ of the interaction of a target nucleus with charged particles. The magnitude of the cross sections of nuclear reactions is one of the determining characteristics which are required in order to choose the energy range of the reactions, which determines the maximum possible yield of the target nuclide and the minimum (admissable) quantity of radionuclide admixtures, whose level influences the radiation dose to the patient and the resolution of the distribution pattern of the RN. The admissible energy interval is estimated starting from the fact that at low energies the number of reactions is limited by the energy threshold of one or another of the possible reactions; as the particle energy increases, the number of competing reactions increases and this factor determines the upper energy limit.

Up to the beginning of the 1970s, less attention was devoted to information about the cross sections of nuclear reactions with charged particles, necessary for obtaining isotopes, than for neutron-type reactions (n,γ), (n,p), (n,α), and (n,f), whose data base is even now much more complete.[9,10] The first steps with respect to systematic measurements and collection of such data for charged particles were made in Karlsruhe (Germany) by Keller, who developed a semiempirical method for calculating the unknown cross sections of nuclear reactions.[11] Reference works, in which the results for reactions with protons, deuterons, ^{3}He, ^{4}He, and other heavier charged particles[9,12,13] as well as for photonuclear reactions[9,14] are systematized, have appeared. These investigations were later elaborated in many scientific centers where radioisotope programs for biochemistry and nuclear medicine were initiated (Refs. 15 and 16, and the literature cited therein).

The last few years have been marked by the development of numerous computer banks of experimental data and computer programs for estimating reaction cross sections. This is especially important in the case when there are no experimental data (Ref. 2, p.17).

Investigation of the excitation functions of nuclear reactions

Two methods are employed to determine excitation functions: irradiation of isolated thin samples in particle beams with fixed energy and the foil-stack method, consisting of irradiation of a collection of samples with a particle beam with a prescribed initial energy, varying from sample to sample and calculated according to the data on the absorptance of the material.[18] Samples for determining the reaction cross sections σ consist of metal foils,[15,19–22] tablets pressed from powders of salts,[15,23,24] thin-layered samples prepared by depositing uniform layers of matter on a substrate by vacuum sputtering,[25] electrodeposition,[26] or "smearing on" thin suspensions of particles,[27] and a collection of thin hermetically sealed gas-containing cells.[28] To determine σ, a great deal of attention is devoted to the thickness and uniformity of the layer of individual samples. This is especially important for studying reactions at low energies ($E<20$ MeV). The chemical purity and isotopic composition of the target material are important criteria for estimating the contribution of other reactions occurring on impurity nuclei to σ.

The foil-stack method is considered to be most effective, because it makes it possible to measure, over one irradiation run, the entire excitation function for both the desired and impurity radionuclides. For example, irradiation of a target consisting of a collection of alternating lead foils enriched with isotopes ^{206}Pb(94%), ^{207}Pb(89%), and ^{208}Pb(97%) made it possible to determine simultaneously the ^{201}Tl yield from lead of different isotopic composition, to estimate the admixture of the undesirable ^{202}Tl, and to draw a conclusion about the possibility of the practical application of such a target in the case of irradiation with ≤ 100 MeV protons.[29]

In determining the reaction cross sections σ, an important parameter is considered to be the current of the bombarding particles, which is measured with the aid of an ionization chamber (Faraday cylinder) or according to a monitor

TABLE V. Monitor reactions.[30]

Nuclear reaction	Reaction threshold, MeV	Nuclear reaction	Reaction threshold, MeV
$^{12}C(p,pn)^{11}C$	20.3	$^{nat}Ti(^3He,X)^{48}V$	
$^{27}Al(p,3pn)^{24}Na$	24.6	$^{63}Cu(^3He,p3n)^{62}Zn$	>13.1
$^{27}Al(p,3p3n)^{22}Na$	20.0	$^{65}Cu(^3He,2n)^{66}Ga$*	5.0
$^{59}Co(p,pn)^{58}Co$	10.7	$^{65}Cu(^3He,p2n)^{65}Zn$	10.3
$^{63}Cu(p,n)^{63}Zn$*	4.2	$^{27}Al(^4He,4p3n)^{24}Na$	68.5
$^{63}Cu(p,2n)^{62}Zn$*	13.5	$^{63}Cu(^4He,n)^{66}Ga$*	8.0
$^{65}Cu(p,n)^{65}Zn$*	2.2	$^{63}Cu(^4He,pn)^{65}Zn$	13.4
$^{nat}Cu(p,X)^{61}Cu$		$^{63}Cu(^4He,2n)^{67}Ga$*	15.0
$^{27}Al(d,3p2n)^{24}Na$	36.2		
$^{51}V(d,2n)^{51}Cr$*	3.9		
$^{nat}Fe(d,X)^{57}Co$			

*Independent reactions, for the rest there is a contribution from other reactions.

reaction whose excitation function is well known.[30] For more accurate measurements, however, it is recommended that both methods be used simultaneously.

The choice of the monitor reaction is determined by the type of particle, the energy range of the reaction, the half-life of the RN, and, correspondingly, the irradiation time. A list of some nuclear reactions which are recommended as monitor reactions for determining the particle flux on the basis of the systematic measurements of their cross section σ, the decay properties of the RNs, and the suitability of materials for targets is given in Table V. In practice, however, a very limited number of monitor reactions, mainly on Al and Cu, are used.

The accuracy of the experimentally measured excitation functions of nuclear reactions is determined by errors which arise in the determination of the particle flux, sample thickness, and correspondingly the absorbed energy, and activity measurements. At the present level of the measurement methods, the error for each of the listed quantities is 3–5%.

Theoretical excitation functions of reactions are obtained by computer methods (Ref. 2, p. 17), of which the most popular are different variants of the ALICE program (Ref. 2, p. 115), which are based on a hybrid model of the evaporation of particles with excitation energies $\leqslant$200 MeV (Weisskopf–Ewing statistical model). In the case of protons, the calculated values of σ are close to the experimental values; in calculations of σ for reactions with heavier particles, the results are less satisfactory.[32]

The yield of a radionuclide, specifically, the yield for a "thick" target (within a chosen energy range ΔE) in the units mCi/μA·h or Bq/μA·h according to the experimental or theoretical excitation functions, is also determined for practical assessment of the RN production process. The theoretical excitation functions give the maximum yield of a RN that can be expected for a given target under prescribed experimental conditions. As a rule, the experimental values of the yields are lower; this could be connected with the nonuniform distribution of the beam on the target and radiation defects, which result in a loss of the desired product during the irradiation process. Since these losses are determined by the conditions of a specific experiment, the yields can only be a secondary parameter for predicting the conditions for obtaining a RN; the cross sections of the nuclear reactions are considered to be the main quantities.

As an example of making a choice, on the basis of investigations of the excitation functions of nuclear reactions, of the production conditions for RNs we mention the studies devoted to the measurement of σ for reactions which are considered for ^{123}I production by the generator method: $^{127}I(p,5n)^{123}Xe \xrightarrow{2.08\ h} {}^{123}I$ and $^{127}I(p,3n)\ ^{125}Xe \xrightarrow{16\ h} {}^{125}I$ (60 days).[33,34] The monoisotopic composition of the target (100% ^{127}I) provides clear limits for the energy range of the reaction $(p,5n)$, which is the only channel for the formation of ^{123}I. To obtain ^{123}I with the required radionuclide purity and high yield, as a rule, an energy window is chosen within the limits 60→46 MeV. In this case, the contribution of ^{125}Xe is decreased by the low-energy limit, keeping in mind the fact that for the reaction $(p,3n)$ the energy effect is $Q=-18.76$ MeV and $\sigma_{max}=730$ mb at $E_p=30$–32 MeV, while for the reaction $(p,5n)$ it is $Q=-36.76$ MeV and $\sigma_{max}=350$ mb at $E_p=57$ MeV. In this case the impurity ^{125}I present in the ^{123}I preparation as a result of irradiation (2 h) and subsequent decay of radioxenon (6 h) (standard conditions) is estimated experimentally as ~0.2%. The upper limit of the proton energy is determined by the level of the impurity ^{121}Te formed in the reaction $^{127}I(p,7n)^{121}Xe \xrightarrow{38.8\ m} {}^{121}I \xrightarrow{2.12\ h} {}^{121}Te$ (16.8 days), for which $Q=-56.40$ MeV and $\sigma_{max}=70$ mb at $E_p=80$ MeV. Since traces of tellurium are easily and effectively removed from radioiodine,[33] there is no need for an upper limit on the proton energy. Moreover, as the proton energy increases from 66 to 100 MeV, the ^{123}I yield increases from 20 to 27 mCi/μA·h with the impurity level remaining at the level $^{125}I \leqslant 0.2\%$.

Experimental methods

The main operations in the RN production process are target preparation, irradiation, and obtaining the final radioactive preparation.

Targets and target systems. The construction of the targets and target complexes is determined by the physical-chemical properties of the target material. The aggregate state (solid, liquid, gas), chemical composition (element, compound), degree of enrichment with respect to the isotope–nucleus of the target, all determine the ways to optimize the process not only from the standpoint of the conditions for conducting a nuclear reaction but also for engineering the process. Since in the ideal case a target should accept the maximum possible charged-particle currents, important parameters are the thermal and chemical stability of the target and constructional materials and their thermal conductivity. In practice, all three types of aggregate targets are used.[64–69]

When possible, metals can be used as solid targets. In these cases the number of working target nuclei is almost 100% (very few impurities are present); moreover, the target is easier to construct because it is more compact and therefore its dimensions are small. When possible, preference is given to refractory metals; for example, Mo ($T_{melt}=2620$ °C),[43] Tc (2000 °C),[20] and Rh (1963 °C)[21] are

used to obtain ^{97}Ru, and Ta (3000 °C) is used to obtain ^{178}W.[44] For metals with low melting points, in a number of cases alloys with a higher melting temperature are prepared, for example, Cu_3As (31% As, T_{melt}=830 °C) for obtaining ^{75,76,77}Br in the reactions ^{75}As (^{3}He, xn) and (^{4}He, xn) with a particle current of 30 μA.[45,46] The alloy Ga_4Ni (80% Ga, T_{melt}=900 °C) was prepared for obtaining ^{68}Ga in the reactions Ga(p, xn) under irradiation with a 45-μA proton beam.[47] In a number of cases, comparatively easy-melting metals are used, for example, Tl for obtaining ^{201}Tl (Ref. 40) and Ag and Cd for obtaining ^{111}In,[19,41,42] which create the conditions for obtaining RNs with the required purity.

Different salts and oxides are widely used. In the last few years, targets specially prepared from ice—$H_2O(^{18}O)$ and $CO_2(^{18}O)$— have appeared for obtaining ^{18}F (Refs. 48 and 39 (5), p. 69) and xenon (^{124}Xe) for obtaining ^{123}I.[49]

Examples of liquid targets are H_2O for obtaining ^{18}F;[50] the solutions CH_2I-I_2 or $LiI-I_2$,[51] melts of NiI (Refs. 33, 52, and 53) and CsCl (Ref. 54) for obtaining ^{123}I.

In recent years, gaseous targets, such as O_2, Ne, and the mixture CF_4-H_2 for obtaining ^{18}F (Refs. 55–57), natural and enriched Xe (^{124}Xe) for obtaining ^{123}I (Refs. 58–61), and natural and enriched Kr (^{82}Kr, ^{83}Kr) for obtaining ^{81}Rb and ^{82}Sr (Refs. 62 and 63) have been extensively developed.

In summary, the target material is chosen and target complexes of different degrees of complexity are produced in accordance with specific RN production programs and the accelerator parameters. They include a target, which can be stationary or rotating and must possess a strong container case for isolating the material and conducting irradiations in vacuum or in a gaseous atmosphere (air, helium, and so on); forced heating or cooling systems (when necessary); systems for collecting radioactive products formed during the irradiation process; and, sensors for recording the irradiation conditions. The construction of the production targets, which are highly active after irradiation,[53] is based, first of all, on radiation-safety principles both during irradiation and during the mechanical disassembly of the target unit and subsequent radiochemical processing of the targets.

Questions associated with the solution of all these problems are regularly discussed at international conferences on "Target Systems and Target Chemistry."[39]

The results of investigations of the phenomena appearing when charged particles interact with the target material (gas, liquid, solid) and the constructional materials serve as the basis for the solutions of problems concerning target systems. Examples of target systems are conical cryogenic targets $H_2O(^{18}O)$, CO_2 (Ref. 39 (5), p. 69) for obtaining ^{18}F in low-energy cyclotrons (~17 MeV protons and a current of 18 μA), and a metal Na target (Ref. 39 (5), p. 77), developed for obtaining ^{18}F in a proton beam (E_p=72 MeV, current 100 μA).

The behavior of constructional materials under different conditions is investigated for the purpose of estimating how their properties influence the final yield of RNs. For example, it was discovered that the microstructure of different brands of the alloy Al 6061 (T0, T4, T6), employed in the fabrication of the casing of the gas target for obtaining ^{123}I, influences the retention of ^{123}I by the chamber walls (Ref. 39 (5), p. 105):

6061 Al	T0	T4	T6
Grain size (ASTM)	6	3	2–3
Retention ^{123}I(%)	49	65	63

Many other examples connected with investigations of target systems can be found in Ref. 39.

Irradiation, accelerators, and process automation. In practice, charged-particle beams (p, d, ^{3}He, and ^{4}He) are used to obtain RNs in nuclear reactions. Protons are most widely used. Reactions with γ rays of bremsstrahlung from electrons as well as reactions with multiply charged heavy ions are much less attractive because of the low cross section σ of the nuclear reactions and, correspondingly, the low yields of RNs.

Accelerators employed for obtaining RNs, classified by type of particle and their energies, are conventionally divided into three groups:

- low-energy machines ($E \leqslant 15$–20 MeV), employed mainly for obtaining ultrashort-lived nuclides;
- medium-energy machines ($E \leqslant 100$–200 MeV) for obtaining a wide spectrum of RNs;
- high-energy machines ($E > 200$ MeV), which accelerate predominantly protons and serve for producing spallogenic RNs.

Of course, the use of accelerators is not limited to producing RNs alone. They can also be used for other studies in the fields of fundamental and applied nuclear physics, materials science, and biology.

The regular use of cyclotrons for producing RNs for medical applications started in the 1950s, and since then the number of cyclotrons for this purpose has been increasing and their technical possibilities are being optimized. Small cyclotrons for strictly medical purposes, the so-called baby cyclotrons ($E \leqslant 20$ MeV), are convenient for use directly in medical centers, where they serve for the production of ultrashort-lived isotopes and for PET studies with them. High-current compact cyclotrons ($E \leqslant 42$ MeV) form the foundation of the commercial production of a large class of RNs.

Information about accelerators installed in different centers, the technical parameters of the accelerators, and the time required to complete one or another program, including isotope production, can be found in the proceedings of regular international conferences on cyclotrons and their applications.[35,36] Analysis of data over the last few years shows that the technical possibilities of cyclotrons for solving applied problems are constantly increasing. To this end, the previously built machines (for example, the cyclotron at the Russian Science Center "Kurchatov Institute," Moscow) are being updated and new, modern accelerators are coming on line. For example, a compact cyclotron with E_p=65 MeV and a current of 20 μA was put into operation in 1990 in Nice, France; a high-current linear electrostatic accelerator with proton and deuteron energies of 3.7 MeV and a current of 750 μA was developed in the USA for producing

ultrashort-lived nuclides in curie quantities (Ref. 39 (4), p. 4; Refs. 37 and 38).

The production of RNs and radiopharmaceuticals based on them has entailed, especially in the last few years, intense development of equipment for automating the installation and removal of machines, irradiation, processing of irradiated targets, including different chemical operations or, under the required conditions, extraction of radioactive products in the process of irradiation, preparation of the final product and quality control. Such equipment, produced on the basis of electronics and computer technology with the corresponding software, organizes both remote control of the entire process and monitoring of separate operations, which is important for maintaining stable operation with highly active materials. Automation in the production of ultrashort-lived nuclides and other short-lived isotopes plays an especially important role. Examples of such automation for ultrashort-lived nuclides can be found in Refs. 77–80, and for ^{123}I and ^{81}Rb in Ref. 59.

Preparation of radionuclide compounds. Different variants of the standard methods (combination of methods) are used to separate the desired radionuclide from the target material and to purify and concentrate it: deposition, extraction, ion-exchange chromatography, distillation, and electrodeposition.[70,71,131,271] The choice of methods is determined by the physicochemical properties of the target material and of the generated radioactive elements contained in it, on the one hand, and by the requirements for quality of the preparation (high degree of purity, carrier-free state of the RN, high specific activity), on the other. The time factor plays an important role for separation of short-lived nuclides.

Most RNs obtained as a result of radiochemical processing of targets are used for labeling different, most often organic, compounds. These RPs, employed in nuclear medicine and in biochemical studies, must meet definite quality criteria with respect to the radionuclide, radiochemical and chemical purity, sterility and apyrogenicity, as well as with respect to the specific activity. All these estimates are specially important for applications of RNs in clinical in-vivo studies.[73] The sources of undesirable impurities in a radionuclide preparation could be impurities in the target material; the lack of enrichment of the preparation with respect to the required isotope; products of radiolytic processes; and, impurities in the reagents. The radiometric and physicochemical monitoring methods make it possible to determine the required characteristics of the RPs, which include the following:

- content of radionuclide impurities, which should not exceed prescribed limits for an established time; for example, ^{125}I content in ^{123}I preparations should be $\leqslant 0.2\%$ over the calibration time of the preparation, which is taken to be 36 ± 5 h after the preparation process is completed;[52]
- chemical formula of the radionuclide in the preparation (for example, iodide for ^{123}I, univalent thallium for ^{201}Tl), position in biomolecules (cis–trans isomerism); with all this, the time factor is taken into account from the standpoint of the stability of the prescribed chemical state of the RN in the preparation;
- chemical impurities;
- sterility, which is most often accomplished by filtering the solutions through microporous filters; apyrogenicity of sterile solutions;
- specific activity (the RN in a preparation can be with or without a carrier).

The most sensitive methods, such as activation analysis, γ spectrometry, mass spectrometry, laser spectrometry, and others, are used for quality control of radiopharmaceuticals. The choice of the methods of analysis depends on the aggregate state of the preparation and on the duration of the analysis, which is especially important for short-lived isotopes. All factors listed above, and taken into account in monitoring the purity of the RN in a preparation, have been examined in Refs. 74–76 quite illustratively for a number of examples.

4. CURRENT STATUS OF THE PRODUCTION OF SOME CYCLOTRON RADIONUCLIDES FOR NUCLEAR MEDICINE

Individual groups of RNs can be distinguished among the large number of cyclotron RNs employed in nuclear medicine. These are the currently most widely used ultrashort-lived radionuclides ^{11}C, ^{13}N, ^{15}O, and ^{18}F; γ emitters ^{123}I, ^{201}Tl, ^{67}Ga, and ^{111}In; and, generator nuclides ^{81}Rb/^{81m}Kr and ^{82}Sr/^{82}Rb. Radionuclides which on the basis of many investigations are considered to be potentially promising comprise a large group. At the present time these radionuclides include ^{26}Al, ^{52}Fe, ^{67}Cu, ^{75,77}Br, and ^{96}Ru and the generators ^{52}Fe/^{52m}Fe and ^{178}W/^{178}Ta. Brief information about the properties and methods of production of these RNs (nuclear reactions, targets, quantities generated, and so on) are presented below. Here it should be kept in mind that for each nuclide listed the existing and constantly added results of studies serve as a basis for individual reviews.[273–276]

4.1. Ultrashort-lived radionuclides (USL)

^{11}C, $T_{1/2}=20.4$ min; $\beta^+(99.8)$; EC(0.2); no γ; max $E_{\beta^+}=960$ keV;

^{13}N, $T_{1/2}=9.96$ min; $\beta^+(99.8)$; EC(0.2); no γ; max $E_{\beta^+}=1190$ keV;

^{15}O, $T_{1/2}=2.03$ min; $\beta^+(99.9)$; EC(0.1); no γ; max $E_{\beta^+}=1723$ keV;

^{18}F, $T_{1/2}=109.7$ min; $\beta^+(96.9)$; EC(3.1); no γ; max $E_{\beta^+}=635$ keV.

The development of methods for producing USL positron emitters for nuclear medicine was stimulated by the development, in the 1970s, of positron-emission tomography (PET),[81] which had a revolutionary effect on the study of the functions of internal organs in humans. The so-called "organic" RNs, which are capable of being incorporated in molecules which are important for the organism but without changing their chemical and functional properties, find the greatest applications in this field. Pharmaceutical preparations labeled with ^{11}C, ^{13}N, ^{15}O, and ^{18}F are used to investigate metabolic processes and for diagnostics of diseases of the heart, brain, liver, and kidneys.

The status of the nuclear data for USLs is good: σ for different nuclear reactions have been determined with a high degree of accuracy, the operation of targets has been investigated, and methods for on-line separation of RNs and

preparation of RPs on their basis have been automated, and the conditions required for their routine production have been optimized. Since the half-life is short, the application of USLs in nuclear medicine requires territorial sharing of the production processes for RNs, preparation of their RPs, and applications for in-vivo studies, i.e. the tandem arrangement "cyclotron-PET-setup" should be part of the diagnostics complex. As a rule, the production of the required quantities of the USLs is accomplished in small cyclotrons,[81] and in countries where they are routinely produced the total volumes reach several curies per week.[1]

Among USLs, ^{18}F is a relatively long-lived isotope ($T_{1/2}$= 109.7 min), whose RPs play the main role in PET studies, which require scanning from 1 to 4 h from the moment the preparation is introduced. Fluorine-18 can be used in large quantities and with a high specific activity compared with ^{11}C, ^{13}N, and ^{15}O. The nuclear reactions in which ^{18}F is formed by a direct or indirect method have been well studied, and are used in practice to produce this nuclide (Table VI). Of these reactions, ^{20}Ne(d, ^{4}He)^{18}F and ^{18}O(p, n)^{18}F are of the greatest practical interest. They require particle energies $\leqslant$15 MeV and relatively moderate currents, which provide an acceptable yield for further work with the isotope.[83] In developing targets for producing ^{18}F (Refs. 39 (4 and 5) and 83) the high chemical activity of the element is taken into consideration, since its interaction with the constructional materials of the target and other apparatus for producing RPs could decrease the actual yield of the product and change its chemical form. For example, after preliminary studies were performed, the latter circumstance made it necessary to silver-plate the inner walls of the irradiated vessel. This made it possible to obtain carrier-free ^{18}F with a reproducible yield in the required anionic form (Ref. 39 (4), p. 123).

The choice of target material depends on the method used to introduce ^{18}F into the RP molecule: In the case of nucleophilic reactions, ^{18}O-enriched water serves as the target; for electrophilic substitution, ^{20}Ne- and ^{18}O-enriched gaseous targets, which have been widely used in the last few years, are employed.[82,83] An $H_2{}^{18}O$ target[84] has definite advantages over other materials: It is cheap, the target apparatus is simple, the ^{18}F yield is high, and the isotope is obtained in the required ionic form. But there are also problems, which arise especially in the case of irradiation with intense particle beams. These difficulties are associated with the heating of the target and radiolysis of the water, which result in the release of a large amount of gas and a high pressure inside the target and therefore can damage the target.

Further studies of different processes for producing ^{18}F are being stimulated by the expansion of PET studies with ^{18}F-marked RPs and the fact that in the last few years such work has been initiated in different centers, for example, in Belgium (Ref. 39 (4), p. 41), Japan (Ref. 39 (5), p. 39), Australia (Ref. 39 (4), p. 245), Russia,[272] the USA (Ref. 39 (5), pp. 279, 339, 353), and elsewhere (Ref. 39 (6)).

4.2. Iodine-123, thallium-201

^{123}I, $T_{1/2}$= 13.2 h; EC(100%); main γ-rays with E_γ= 159.0 keV (83.3%);

^{201}Tl, $T_{1/2}$= 73.1 h; EC(100%); main γ-rays with E_γ= 135.3 keV (2.8%).

The application of these two RNs in nuclear medicine is difficult to overestimate. Iodine-123, first proposed for clinical diagnostics in 1962,[85,86] is considered to be an ideal RN because of its nuclear-physical and chemical properties, which can make possible wide applications of its numerous RPs for in-vivo multifunctional studies. Thallium-201 was proposed in 1970 for obtaining an image of the myocardium with the aid of a scintillation camera, likewise on account of its nuclear-physical and biological characteristics.[87,88] There have been many studies devoted to methods for producing these nuclides. We give a number of references to the generalizing materials: Refs. 89–93 for ^{123}I, and Refs. 94 and 95 for ^{201}Tl.

Iodine-123. There are approximately 20 nuclear reactions (Table VI(4)) for producing ^{123}I. These reactions form the foundation of the two fundamental production methods: direct, in which ^{123}I is formed directly in the nuclear reactions (α,xn) on antimony or (p,xn) on tellurium, and indirect (generator), in which ^{123}I is formed as a result of the decay of ^{123}Xe.

The nuclear data for ^{123}I have been well studied. The excitation functions of the nuclear reactions have been investigated by different groups, as a result of which extensive experimental and computational material has been obtained. As an example, the values of the cross section σ of the reactions (p,3n) and (p,5n) on ^{127}I, which were obtained in different studies,[112–118] are presented in Ref. 33.

On the basis of studies of different nuclear reactions, both methods, direct and indirect, are now used to produce ^{123}I together with a well-developed technology for producing highly active preparations (Ref. 91, pp. 17 and 31; Refs. 53, 59, and 61). Predominantly enriched ^{124}Te targets and less often ^{122}Te or ^{123}Te are used for direct production of ^{123}I. Sb is almost never used. The radionuclide purity of ^{123}I obtained from tellurium targets on low-energy high-current proton accelerators does not exceed ~96%; the main contaminant is ^{124}I ($T_{1/2}$= 4.1 days, E_γ= 603 keV. This circumstance as well as the high cost of highly enriched target material and the need to regenerate the target make the generator method, in which the separation of radioxenon does not require special chemical operations, preferable. This method also has the advantage that ^{123}I is characterized by a quite high radionuclide purity ($\geqslant$99.5%; ^{125}I $\leqslant$0.2%). On account of this, preparations of generator ^{123}I are suitable for wide applications in diagnostics of diseases of different organs, while ^{123}I, obtained by the direct method, is suitable mainly for diagnostics of diseases of the thyroid gland.[96]

The production of ^{123}I by the generator method imposes time limits on the "irradiation-accumulation" processes, which are determined by the half-lives of the xenon and iodine isotopes. As a rule, the total time $\Sigma_t = \Delta t_{irr} + \Delta t_{acc}$ does not exceed 12 h; variations of, for example, Δt_{irr}= 2 h and Δt_{acc}= 7 h are possible in this interval. This regime results in a decrease of the impurity ^{125}I, formed from ^{125}Xe, which is also decreased by choosing a lower energy limit ($E_p \geqslant$ 46–48 MeV).

Until recently, NaI, KI, Cs, and CsCl, CH_2I_2–I_2 have

TABLE VI. Preparation of radionuclides that are widely used in nuclear medicine.

Nuclear reactions	Fraction of nuclei in target %	−Q, MeV	E_0, MeV	σ_{max}, mb	$E(\sigma_{max})$, MeV	Thick target yield, mCi/μA·h	References
			(1) Ultrashort-lived isotopes				
^{11}C							
$^{14}N(p,\alpha)$	99.63	2.92	15	243	7.6	280	[208, 209]
$^{11}B(p,n)$	80	2.76	22	360	9	756	[209, 210]
$^{10}B(d,n)$	20	−6.47	7.5	200	5	3	[210–212]
$^{11}B(d,2n)$	80	5.70	11.5	40	10	10	[210–212]
^{13}N							
$^{16}O(p,\alpha)$	99.76	5.22	18	19	17.5	24	[210, 212, 213]
$^{13}C(d,n)$	98.9	0.28	7.5	150	5	100	[209, 210]
$^{14}N(p,pn)$	96.63	11.00	22	44	17.7	460	[209, 210]
^{15}O							
$^{14}N(d,n)$	99.63	−5.06	15	28	4	65	[210, 212]
$^{12}C(^4He,n)$	98.9	8.5	25	26	14.5		[11]
$^{16}O(p,pn)$	99.76	15.7	33	76	32.8	25	[210, 212]
^{18}F							
Direct reactions							
$^{18}O(p,n)$	0.2	−2.43	15	630	5.2	56	[55, 210]
$^{20}Ne(d,^4He)$	90.51	2.79	76	12	<25	15	[214, 215]
$^{16}O(^4He,pn)$	99.76	18.54	40	260	36	11	[210]
$^{16}O(^3He,p)$	99.76	−2.03	20	400	8	9	[210, 212]
Indirect reactions: $^{18}Ne \xrightarrow[\beta^+]{1.67\ s} {}^{18}F$							
$^{20}Ne(^3He,^4Hen)$	90.51	15.52	31	2.7	30.9	~7	[83, 214]
$^{16}O(^4He,2n)$	99.76	15.5	40			14	[210, 212]
$^{16}O(^3He,n)$	99.76	3.20	36			10	[210]
$^{20}Ne(d,p3n)$	90.51	30.73	76	23	57.5	≤11	[83, 214]
$^{27}Al(p,X)$	100		70	7	65	23	[216]
$^{23}Na(p,X)$	100		70	50	45	88	[216]
			(2) ^{67}Ga				
$^{68}Zn(p,\ 2n)$	18.8	11.98	42	883	21	3.8	[130]
$^{67}Zn(p,\ n)$	4.1	1.78	22	673	10	4.3	[223]
$^{n}Zn(p,X)$			100	125	19	~3.0	[270]
$^{66}Zn(d,\ n)$	27.9	−3.04	11	221	8.4		[246]
$^{n}Zn(^4He,\ X)$			36	277	19		[224]
$^{75}As(p,\ X)$	100		800	28			[2, p. 14]
Rb, Br$(p,\ X)$			800	41			[2, p. 141]
			(3) ^{111}In				
$^{111}Cd(p0,\ n)$	12.75	1.62	16	530	13	0.5	[212]
	95.9		30	809	11.8	2.0	[137]
$^{112}Cd(p,\ 2n)$	24.07	11.02	22	1000	22	1.5	[209]
	98.1		30	−1000		7.6	[137]
$^{113}Cd(p,\ 3n)$	12.26	17.56	22	900	31	4.0	[212]
	95.8		65	682	32	16.5	[19]
$^{114}Cd(p,\ 4n)$	98.9	26.60	65	500	42	15.6	[19]
$^{109}Ag(^3He,\ n)$	48.65	−6.55	30	500	14	0.2	[209, 225]
$^{109}Ag(^4He,\ 2n)$	48.65	14.03	44	1200	26	0.3	[209, 226]
			(4) ^{123}I				
Direct reactions							
$^{124}Te(p,\ 2n)$	4.82	11.41	30	1010	22.2	10.5	[27]
$^{123}Te(p,\ n)$	0.908	1.98	15	210	11	4	[218]
$^{122}Te(d,\ n)$	2.6	−2.71	14	351	11.5	0.7	[212, 219]
$^{121}Sb(^4He,\ 2n)$	57.3	15.35	28	~816	27.0	0.1	[93]
Indirect reactions: $^{123}Cs \xrightarrow[\beta^+]{6\ min} {}^{123}Xe \xrightarrow[EC,\beta^+]{2.08\ min} {}^{123}I$							
$^{124}Xe\{(p,\ 2n)+(p,\ pn)\}$	99.8	15.11	35	500–600	25	10	[217, 220]
$^{127}I(p,\ 5n)$	100	36.76	67.5	380	56	20	[34]
			100	350	57	27	[33]
$^{127}I(d,\ 6n)$	100	38.99	90	290	70		[221]
$^{124}Te(^3He,\ 4n)$	4.82	22.58	52	165	45		[222]
$^{124}Te(^3He,\ 3n)$	0.908	13.16	30	178	26	0.7	[222]
$^{124}Xe(\gamma,\ n)$	0.1	10.5	40	500	15	$3\cdot10^{-3}$/1yr	[105, 107]
Cs, Ba, La$(p,\ X)$			590;660	30–40		0.5	[141, 142]

TABLE VI. (*Continued.*)

Nuclear reactions	Fraction of nuclei in target %	−Q, MeV	E_0, MeV	σ_{max}, mb	$E(\sigma_{max})$, MeV	Thick target yield, mCi/μA·h	References
			(5) ^{127}Xe				
^{127}I(p, n)	100	1.44	67.5	178	11.7	0.1	[34]
^{127}I(d, $2n$)	100	3.67	90	470	15.8		[221]
^{133}Cs(p, X)	100		100	262	91	~0.5	[24]
			590	88			[142]
^{139}La(p, X)	99.91		590	72			[142]
			(6) ^{201}Tl				
Direct reactions							
^{202}Hg(p, $2n$)	29.8	8.95	24	1100	20	0.38	[39(4), p. 73; 2, p. 131]
Indirect reactions: ^{201}Bi→$^{1.8\ h\ and\ 59\ min}$ ^{201}Pb→$^{9.3\ h}$ ^{201}Tl							
^{203}Tl(p, $3n$)	29.52	17.23	45	1250	27.4	2.2	[127, 129]
^{205}Tl(p, $5n$)	70.48	31.43	60	880	45.7	2.0	[128]
^{206,207,208}Pb(p, xn)	enr. ≥90%		100			8.0	[29]
Pb, Bi(p, X)	nat.		660, 800	50–60		0.54	[72, 132]

been used as targets for the production of ^{123}I by the generator method. NaI and CsCl are used for routine production.[52,53,97,98] However, from the standpoint of radionuclide purity, the method of irradiation of highly enriched ^{124}Xe with up to 30-MeV protons is considered to be the best method (Table VI(2)); since 1984, this method has been implemented on cyclotrons in Karlsruhe (Germany),[59,99] Vancouver (Canada),[100] and Eindhoven (Holland).[101] In Russia (Russian Science Center "Kurchatov Institute," Moscow) the development of a technology for irradiating ^{124}Xe has been completed.[61] This technology has now been automated and put into production.[102] Irradiation of a target with intense proton beams in small and medium-size cyclotrons, the absence of corrosion problems in the target systems, the simple chemistry, the high radionuclide purity of the product (^{125}I content $>10^{-3}$%), and the quite high yield all make this method the most promising method for routine production of ^{123}I. The complex apparatus for obtaining ^{123}I from ^{123}Xe consists of three main units—a high-pressure gas target with a system for beam diagnostics, a chemical container holding the cell for concentrating ^{123}I and for monitoring its quality, and a microprocessor for automated control and monitoring of the process.[59]

Highly pure ^{123}I can be obtained from ^{124}Xe by another method: via the photonuclear reaction ^{124}Xe(γ,n)^{123}Xe $\rightarrow$ ^{123}I.[103–105] Despite the relatively low efficiency of this method, the linear electron accelerators (LEAs) and microtrons can compete with the (more expensive to operate) proton cyclotrons and meet the requirements for separate clinics and regions. This possibility has now been studied at a number of centers,[105–111] but there is still no regular production of ^{123}I in electron accelerators.

Thallium-201. This nuclide can be obtained in the reactions (p, xn) and (d, xn) on Hg or by the generator method via the decay ^{201}Pb$\xrightarrow{9.4\ h}$ ^{201}Tl by irradiating Tl, Pb, or Bi targets with protons. The second method has been found to be preferable, since it permits production of ^{201}Tl with radioisotopic purity (the minimum impurities are ^{200,202}Tl), meeting the requirements of nuclear medicine.

Of the reactions producing ^{201}Tl which are presented in Table VI(6), only ^{203}Tl(p, $3n$)^{201}Pb, in which highly enriched ^{203}Tl is irradiated in high-current cyclotrons (E_p~30 MeV), is used at the present time for commercial purposes. Other targets have limited applications. For example, a mercury target enriched with ^{201}Hg up to 98.6% in the (p, n) reaction makes it possible to obtain approximately 2 mCi/μA·h ^{201}Tl with up to 3–4% radioisotopic contaminants;[21] a ^{205}Tl (>99% ^{205}Tl) target requires for the (p, $5n$) reaction a proton beam with energy <45 MeV, with which the ^{202}Tl impurity decreases.

In the last few years targets consisting of natural and enriched lead (^{204}Pb, ^{206}Pb, ^{207}Pb, ^{208}Pb) have been investigated (Ref. 15; Ref. 95, pp. 6, 22, 77; Refs. 29 and 122–125). The advantage of a lead target lies in the fact that the ^{201}Tl losses associated with the decay of ^{201}Pb in the irradiation process and subsequent transport of the target to the reprocessing location are virtually eliminated; the separation of the target material and extraction of thallium occur simultaneously, while the ^{203}Tl target requires two-step processing—first ^{201}Pb is separated and then, after ^{201}Pb has decayed, the accumulated ^{201}Tl is separated; contamination of the ^{201}Tl preparation with stable thallium is completely eliminated; the total activity of the Pb target decreases substantially over the time of 30–40 h required for accumulating ^{201}Tl, and this eases the conditions of radiochemical reprocessing.

Analysis of the published data for nuclear reactions producing ^{201}Tl on different targets shows that the status of the data is good. The experimental and computed results make it possible to estimate σ and, correspondingly, the yield of both the main nuclide ^{201}Tl and the impurity nuclides ^{200,202}Tl in reactions on mercury (Ref. 95, p. 16), thallium,[119,120,126–130] and lead[29,122–125] nuclei. For bismuth and natural lead, the cumulative reaction cross sections under

TABLE VII. Production of generator radionuclides.

Nuclear reactions	Fraction of nuclei in target, %	$-Q$, MeV	E_0, MeV	σ_{max}, mb	$E(\sigma_{max})$, MeV	Yield of "thick target," mCi/μA·h	References
			(1) ^{44}Ti/^{44}Sc				
^{45}Sc(p, $2n$)	100	12.37	85	65	32		[238]
^{45}Sc(d, $3n$)	100	14.59		25	35		[2, p. 131]
^{nat}Ti(^{4}He, x)			170	3.3	>170		[239]
^{44}Ca(^{3}He, $2n$)	2.08	13.2		24	34		[2, p. 131]
^{51}V(p, X)	99.75	70.4	100	0.66	81	$0.015\cdot10^{-3}$	[183]
			200			0.06	[184]
			(2) ^{52}Fe				
^{55}Mn(p, $4n$)	100	34.88	73	1.4	54	0.67	[165]
			100	1.3	55	0.8	[15]
			200	1.29	54	1.94	[167]
^{59}Co(p, $2p$, $6n$)	100	71.40	100	0.36	>80	0.1	[15, 234]
^{52}Cr(^{3}He, $3n$)	83.79	16.37	45	5	35	0.05	[235]
^{50}Cr(^{4}He, $2n$)	4.34	15.64	44	20	30		[236]
^{58}Ni(p, X)	68.27		200	2.79	66	11	[167]
			800	1.54		3.3	[168]
^{nat}Cu(p, X)			590	0.25			[237]
			(3) ^{68}Ge/^{68}Ga				
^{69}Ga(p, $2n$)	60.1	11.48	55	500	19	0.054	[11, 209]
^{71}Ga(p, $4n$)	39.9	28.4	55	140	43	0.015	[11, 209]
^{69}Ga(d, $3n$)	60.1	13.7	32	550	28		[11]
^{66}Zn(^{3}He, n)	27.9			8	11		[2, p. 131]
^{67}Zn(^{3}He, $2n$)	4.1			130	17		[2, p. 131]
^{68}Zn(^{3}He, $3n$)	18.8	12.6		493	29		[2, p. 131]
^{nat}Zn(^{4}He, xn)			35	150	32	0.001	[224, 209]
Rb, Br(p, X)			800	19			[240]
Y, Rb, Br, As(p, X)			593	6.7–11.1			[237]
			(4) ^{81}Rb/^{81m}Kr				
^{82}Kr(p, $2n$)	11.6	14.0	30	50	20	48	[229]
			116	194	49.4		[269]
^{85}Rb(p, p $4n$)	72.17	43.61	70	200	69	31	[230]
^{81}Br(^{3}He, $3n$)	49.31	11.9	40	320	29	2.7	[231]
^{79}Br(^{4}He, $2n$)	50.69	14.37	40	380	30	2.0	[231]
^{81}Br(^{4}He, $4n$)	49.31	32.4	50	70		2.9	[232]
			(5) ^{82}Sr/^{82}Rb				
^{85}Rb(p, $4n$)	72.17	31.56	70	200	51	0.5	[230]
^{nat}Rb(p, xn)			100	180	51	0.43	[15]
^{85}Rb(d, $5n$)	72.17		65			0.19	[160]
^{nat}Kr(^{3}He, xn)			33	42		0.001	[28]
^{80}Kr(^{4}He, $2n$)	2.25	16.3	120	60	90	0.05	[62]
^{nat}Mo(p, X)			800			0.1	[233]
			(6) ^{128}Cs/^{128}Ba				
^{133}Cs(p, $6n$)	100	43.98	100	322	63	8.4	[15]
			67	298	65	3.1	[23]
^{133}Cs(d, $7n$)	100	46.19		490	75		[2, p. 131]
^{128}Xe(^{3}He, $3n$)	1.91	14.3		730	28		[2, p. 131]
			(7) ^{178}W/^{178}Ta				
^{181}Ta(p, $4n$)	99.99	22.99	48	780	36		[175]
			100	495	40	1.3	[44;39(5), p. 208]
^{176}Hf(^{4}He, $2n$)	5.2	17.9		870	29		[2, p. 131]
^{177}Hf(^{3}He, $2n$)	18.6	3.7		5.3	21		[2, p. 131]
^{177}Hf(^{4}He, $3n$)	18.6	24.6				0.002	[209]
^{178}Hf(^{3}He, $3n$)	27.1	11.3		110	28		[2, p. 131]

TABLE VIII. List of possible nuclear reactions leading to ^{44}Ti producton in interactions of ^{51}V with E_p=100 MeV.[183]

Reaction	−Q, MeV	Reaction threshold, MeV	Reaction	−Q, MeV	Reaction threshold, MeV
p,^{6}He2n	41.10	41.9	p,$pt4n$	61.88	63.1
p,^{5}He3n	42.96	43.8	p,$t5n$	62.64	63.9
p,^{4}He4n	42.10	42.9	p,$2d4n$	65.92	67.2
p,$2t2n$	53.40	54.4	p,$pd5n$	68.14	69.5
p,$dt3n$	59.66	60.8	p,$2p6n$	70.40	71.8

irradiation with 660- and 800-MeV protons were also determined.[72,132]

In the irradiation of lead (^{204}Pb, ^{206}Pb, ^{207}Pb, ^{208}Pb) for ^{201}Tl and ^{200}Tl, the (p, xn) reactions make the determining contribution. The cross sections of these reactions at energies ranging from 50 to 100 MeV are several hundred millibarns, while the cross sections of the reactions (p, pxn) and (p, αxn) are estimated to be several tens or several millibarns.[133,134] The relatively low yield of ^{202}Tl is due to the reactions producing this nuclide, and the variation of the curves of the excitation functions shows that the purity of ^{201}Tl obtained from enriched lead targets is determined by the proton energy. The most favorable conditions for producing ^{201}Tl are obtained by irradiating ^{206}Pb with protons with energies $E_p \leqslant 65$ MeV, and the results presented in Ref. 29 show the conditions under which the ^{201}Tl yield increases up to ~8 mCi/μA·h in the case of irradiation of a three-layer target consisting of ^{206}Pb, ^{207}Pb, and ^{208}Pb with protons with energies in the range 76→49 MeV.

4.3. Gallium-67, indium-111

^{67}Ga, $T_{1/2}$=78.3 h; EC(100%); main γ rays with E_γ=93.3 keV (37.0%), 184.6 keV (20.4%), and 300.2 keV (16.6%);

^{111}In, $T_{1/2}$=2.83 d; EC(100%); main γ rays with E_γ=171.3 keV (90.3%), 245.2 keV (94.0%).

These nuclides belong to a group of five cyclotron RNs that play an exceptional role in nuclear medicine (^{67}Ga, ^{111}In, ^{81m}Kr, ^{123}I, ^{201}Tl). For this reason, for them, despite the fact that the nuclear data have been well studied, the data are revised from time to time[135,136] or σ and the yields are determined for the specific conditions of a particular laboratory.[19,130]

The most widely used methods for obtaining ^{67}Ga and ^{111}In are presented in Table VI(2). The results of the latest studies for ^{111}In were connected with an estimation of its production in the (p, xn) reactions on the separated isotopes of Cd (^{111}Cd, ^{112}Cd, ^{113}Cd, ^{114}Cd).[19,136,137] The optimal conditions for obtaining ^{111}In were found by analyzing the experimental and calculated excitation functions of the reactions (p,3n) and (p, 4n) on the nuclei ^{113}Cd and ^{114}Cd. The results in Table VI(3) show that ^{111}In can be obtained with the highest yield from enriched ^{113}Cd, and this quantity can be increased by irradiating with 65-MeV protons a double-layer (^{113}Cd+^{114}Cd)[19] or multilayer (^{111}Cd, ^{112}Cd, ^{113}Cd, and ^{114}Cd) target enriched with Cd.

4.4. Xenon-127

^{127}Xe, $T_{1/2}$=36.4 d; EC(100%); main γ rays with E_γ=172.1 keV (25.5%), 202.9 keV (68.3%), and 375.0 keV (17.2%).

Radionuclides of the inert gases have been found to be the most suitable of all radioactive gases that can be used in lung-ventilation studies.[139] The fact that the inert gases are less soluble in water than in fatty materials (the solubility coefficients at 37 °C in water and fat (fatty tissues) are, respectively, 0.06 and 0.43 for Kr and 0.085 and 1.70 for Xe) has turned out to be an important factor for applications of their radionuclides as physiological tracers of transport phenomena in the body (Ref. 139, p. 3). The pioneering work in this direction was the application of ^{133}Xe in 1955,[138] and in 1973 the first clinical studies with ^{127}Xe were performed.[140] On the basis of its nuclear properties, ^{127}Xe is considered to be a better isotope than ^{133}Xe in nuclear medicine. The advantage of ^{127}Xe is that there is no β^- radiation. Therefore the radiation dose is lower, and photons with energy suitable for detection during the circulation time of the gas are present. It is sufficient to supply ^{127}Xe to research institutions once per month, while ^{133}Xe ($T_{1/2}$=5.3 d) must be supplied daily.

Xenon-127 can be obtained by means of direct and indirect reactions (Table VI(5)). The reaction ^{127}I (p,n)^{127}Xe is realized in low-energy cyclotrons ($E_p \leqslant 20$ MeV), and reactions with emission of several particles occur at higher energies and serve as a basis for the indirect method for producing ^{127}Xe. A CsCl target, which has been well investigated for obtaining ^{123}Xe→^{123}I with high-energy protons (up to 660 MeV),[141,142] is used for producing curie quantities of ^{127}Xe by irradiating a target at the blocker of the proton beam. The excitation function of the total reaction forming ^{127}Xe with the irradiation of ^{133}Cs nuclei was measured up to E_p=100 MeV; calculations of the excitation functions for separate reactions contributing to the formation of ^{127}Xe have also been performed.[24] In reactions of Cs with 100-MeV protons, other xenon radionuclides (^{122}Xe, ^{123}Xe, ^{125}Xe) whose half-lives (20.1 h, 2.08 h, and 16.8 h, respectively) are much shorter than the half-life of ^{127}Xe are formed. Therefore to obtain pure ^{127}Xe the target must be allowed to stand for several days after irradiation. This eliminates contamination of ^{127}Xe with other isotopes which increase the radiation dose.

TABLE IX. Production of radionuclides that are promising for individual studies.

Nuclear reactions	Fraction of nuclei in target, %	$-Q$, MeV	E_0, MeV	σ_{max}, mb	$E(\sigma_{max})$, MeV	Yielf of "thick" target, mCi/μA·h	References
			(1) ^{26}Al				
^{26}Mg(p, n)	11.01	4.98	22			$1.3\cdot10^{-9}$	[244]
			100	15	7		[198]
^{nat}Mg(d, xn)			22	100	6	$2.3\cdot10^{-9}$	[244]
^{nat}Mg(^{4}He, pxn)			44			$2.2\cdot10^{-9}$	[244]
			45	160	25		[202]
^{23}Na(^{4}He, n)	100	3.48	10.2	334	10		[203]
^{24}Mg(^{20}Ne, X)	99.87		105	26.4			[245]
			(2) ^{67}Cu				
^{68}Zn(p, $2p$)	18.8	9.99	85	6		0.142	[238]
			200	14.3			[268]
^{69}Ga(p, $3p$)	60.1	16.59	55	2		0.0081	[224, 209]
^{64}Ni(^{4}He, p)	0.91	4.67	40	15.9	15.5	0.063	[206, 207]
^{75}As(p, X)	100		590	0.9			[237]
			(3) ^{77}Br				
Direct reactions							
^{77}Se(p, n)	7.6	2.147	25	232	10	0.3	[241]
^{78}Se(p, $2n$)	23.6	12.64	25	800	22	1.0	[241]
^{nat}Se(p, xn)			50	238	20	0.92	[191]
^{nat}Se(d, xn)			22			0.48	[241]
^{75}As(^{4}He, $2n$)	100	13.51	40	950	25		[191]
Indirect reactions: ^{77}Kr $\xrightarrow[\beta^+EC]{1.24\ h}$ ^{77}Br							
^{79}Br(p, $3n$)	50.69	22.8	65	178	35	0.8	[192]
^{81}Br(p, $5n$)	49.31	40.8	85	41	60		[193]
^{nat}Br(p, xn)			100	107	35	0.8	[15]
^{nat}Br(d, xn)			90	58	43	0.64	[242]
^{76}Se(^{3}He, $2n$)	9.0	6.22	35	370	22	0.65	[26]
^{77}Se(^{3}He, $3n$)	7.6	13.65	35	356	31		[26]
Mo(p,X)			800			0.01	[190]
			(4) ^{97}Ru				
^{103}Rh(p, $2p$ $5n$)	100	49.6	67.5	56	52	1.36	[21]
^{99}Tc(p, $3n$)	100	18.13	100	438	32	10.5	[20]
^{nat}Mo(^{3}He, xn)			36			0.12	[227]
^{nat}Mo(^{4}He, xn)			40			0.12	[43]
			70			0.47	[228]
^{94}Mo(^{4}He, n)	9.25	8.01	36	702	18		[22]
^{95}Mo(^{4}He, $2n$)	15.92	15.39	36	1293	28		[22]
			(5) ^{211}AT				
^{209}Bi(^{4}He, $2n$)	100	20.34	30	750	30	0.5	[243]
Th, U(p, X)			660			2	[197]
			(6) ^{237}Pu				
^{234}U(^{4}He, n)	99.6	11	44	3.09	35.6		[248]
^{235}U(^{4}He, $2n$)	99.8	17.9	46	20.8	25.5		[248]
^{235}U(^{3}He, n)	50.3		27	1.6	27		[251]
	99.99		43	0.13	41.6		[39(4), p. 82]
^{238}(^{3}He, $4n$)	99.7		27	2.8	27		[251]

Generator radionuclides

Generator radionuclides play a large role, which has increased in the last two decades, among cyclotron radionuclides employed in nuclear medicine.[149] Widespread use of short-lived isotopes would be impossible without the development of different generator systems based on the principle "long-lived parent radionuclide→short-lived daugher radionuclide." The generator method of obtaining SLI makes it possible to introduce repeatedly a nuclide in medical studies and to work with such generators for a long time.

The preparation of a "long-lived/short-lived" generator, as a rule, is based on the principles of ion-exchange chromatography with fast extraction of the daughter radionuclide with an appropriate eluting solution from a column with a sorbent, in which the parent radionuclide is strongle fixed. For this reason, a great deal of attention is devoted to the choice of the sorbent material (Al_2O_3, SnO_2 ion-exchange resins, SnO_2, Zr and Ti phosphates, and others).[161,162]

Among generator pairs, a series of which is presented in Table I, some have wide applications (^{81}Rb/^{81m}Kr, ^{82}Sr/

TABLE X. ^{237}Pu production cross sections in nuclear reactons of ^{235}U and ^{238}U with ^{3}He and ^{4}He ions and ^{237}Np with protons.

Nuclear reaction	E, MeV	σ, mb [248]	σ, mb [254]
^{235}U(^{4}He,2n)	19.2	0.337	
	20.4	0.32	
	21.6	1.79	
	21.9	3.04	4.43
	22.8	7.77	
	23.6		13.3
	24.0	16.5	
	24.2	13.99	
	24.3	10.79	
	25.5	17.7;20.8	
	27.3		15.8
	28.3	14.1	
	30.0		8.3
	30.8	11.1	
	32.7	13.5	
	33.4	9.77	
	33.7	5.76	
	34.0	8.63;7.48	
	34.7		6.8
	35.3	6.09	
	35.6	6.26	
	36.0	5.76	
	36.5	3.17	
	37.0	4.23	
	38.2	5.13	
	39.5		5.65
	40.0	3.79	
	41.9	3.3	
	42.8		4.8
	44.1	3.44	
	45.4		3.5
	46.0	2.44	
^{235}U(^{3}He,n)	17.2	0.0042	
	25.5	0.036	
	27		1.6
	31.4	0.09	
	36.8	0.12	
	41.6	0.13	
^{238}U(^{3}He,4n)	21.9		0.48
	24.5		0.69
	27.0		1.0;2.8
	[226]		
^{237}Np(p,n)	10.4	1.27	
	11.8	2.81	
	12.9	3.72	
	14.0	4.54	
	15.0	3.93	
	16.0	5.38	
	17.0	5.24	

^{82}Rb), while others are less applicable. Generators are developed on the basis of studies of numerous problems: nuclear reactions for obtaining the parent nuclide, finding the best method for separating pairs, including from the standpoint of increasing the operating time of the generator up to breakthrough of the parent nuclide, and a highly efficient technology for preparing them, including process automation.

^{99}Mo/^{99m}Tc

^{99}Mo, $T_{1/2}$=66 h; β^-(100%); main γ rays with E_γ=140.5 keV (90.7%), 181.1 keV (6.08%), and 739.4 keV (6.08%); max E_{β^-}=1200 keV;

^{99m}Tc, $T_{1/2}$=6.02 h; IC(100%); main γ rays with E_γ=140.5 keV (87.7%).

As is well known, among radio-isotopic generators the "noncyclotron" (as a rule) generator ^{99m}Tc based on ^{99}Mo has the greatest applications in nuclear medicine.[149] According to estimates by experts at IAEA, approximately 30 million doses of ^{99m}Tc are dispensed every year in clinics throughout the world (a diagnostic dose of ^{99m}Tc is on the average 10 mCi). In the commercial list of radionuclide producers, this generator is always in the first place, both with respect to the increase in the sales volume of ^{99}Mo and in the constant improvement of the characteristics of the generator.

The production of ^{99}Mo in nuclear reactors—in fission reactions of ^{235}U or in (n,γ) reactions on ^{98}Mo—is the economically best justified method. ^{99}Mo is obtained with a specific yield of 10 or 100 Ci/g, respectively, on enriched ^{98}Mo and ^{235}U targets with high neutron flux densities ($10^{13}-10^{14}$ neutrons/cm$^2\cdot$s). The technology for reprocessing these targets in order to obtain generators is quite complicated. This is a "wet" radiochemistry with a large quantity of highly active wastes requiring burial. The radioecological considerations are now the reason why in recent years alternative methods for obtaining ^{99}Mo have been proposed. Methods for obtaining ^{99}Mo by irradiating natural and enriched molybdenum with 30-MeV protons[150,151] and 70-MeV protons[152] have been investigated. In these cases ^{99}Mo is formed in the direct reaction ^{100}Mo(p, pn)^{99}Mo and indirectly in the reaction

$$^{100}\mathrm{Mo}(p,\ 2p)^{99}\mathrm{Nb} \xrightarrow[\beta^-]{15\text{ s and }2.6\text{ m}} {}^{99}\mathrm{Mo}$$

with a total yield of 0.47 mCi/μA·h for ^{nat}Mo. Moreover, ^{99m}Tc can be obtained in a direct reaction ^{100}Mo(p, 2n) ^{99m}Tc with a yield of 19.7 mCi/μA·h for ^{nat}Mo in the energy interval 67.5→7.6 MeV.[152] Therefore ~20 Ci/h of ^{99m}Tc and ~470 mCi/h of ^{99}Mo can be obtained in high-current cyclotrons (~100 μA) over 1 h of accelerator operation by irradiating ^{100}Mo (97%).

The possibility of obtaining ^{99}Mo in photonuclear reactions was recently studied,[153] and it was shown that 200–300 mCi of ^{99}Mo can be obtained by irradiating 100 g of ^{100}Mo (95–98% enrichment) with an electron current of 20–25 μA and electron energy E_{e^-}=20.5 MeV for 100 h. Despite its low efficiency, this method can be adopted for regional use if electron accelerators are available.

^{81}Rb/^{81m}Kr

^{81}Rb, $T_{1/2}$=4.58 h; β^+(27%); EC(73%); main γ rays with E_γ=446.3 keV (23.3%); max E_{β^+}=1050 keV;

^{81m}Kr, $T_{1/2}$=13.3 h; IC(100%); main γ rays with E_γ=190.3 keV (67.0%).

In recent years, besides the well-proven method of irradiating NaBr or $CuBr_2$ targets with ^{3}He or ^{4}He ions or RbCl with protons (Table VII(4)), the possibility of using a gas-

TABLE XI. ^{237}Pu production (yield and purity of preparations).

Nuclear reaction	Target (thickness, enrichment)	Particle energy, MeV	^{237}Pu yield, kBq/100 A·h	Pu isotope ratio, Bq/Bq			References
				^{236}Pu/^{237}Pu	^{238}Pu/^{237}Pu	$^{239+240}$Pu/^{237}Pu	
^{235}U(^{4}He,2n)	thick	23.0		$2\cdot10^{-4}$*)			[257]
		25.5	60	$1.5\cdot10^{-3}$			
		27.5	150	$4\cdot10^{-3}$			
		29.0	180	$9\cdot10^{-3}$			
	1 g/cm^2, 93%	~30	200	$1.2\cdot10^{-3}$	$8\cdot10^{-5}$	$4.1\cdot10^{-4}$	[249]
	300 mg/cm^2, 90%	24		$2.4\cdot10^{-4}$	$2.3\cdot10^{-4}$	$3.8\cdot10^{-3}$	[250]
	10 mg/cm^2; 99.99%	24	35	$1.7\cdot10^{-5}$	$1.1\cdot10^{-4}$	$2.3\cdot10^{-6}$	
	5 mg/cm^2; 99.99%	25		$1.6\cdot10^{-4}$	$1.3\cdot10^{-4}$		[255]
					$2.0\cdot10^{-7}$**		
				$<2\cdot10^{-7}$	$<10^{-7}$***		[280, p. 75]
^{235}U(^{3}He,n)	1.5 mg/cm^2; 50.3%	27	8000	$2.8\cdot10^{-2}$			[250]
	10 mg/cm^2; 99.99%	42		3.3		$2.5\cdot10^{-3}$	[258]
^{238}U(^{3}He,4n)	3.7 mg/cm^2; 99.7%	27	1830	$7.3\cdot10^{-3}$	$5.5\cdot10^{-2}$		[251]
	1.9 mg/cm^2; 99.7%	27	1330	$2.3\cdot10^{-3}$	$1.2\cdot10^{-2}$		
	3.6 mg/cm^2; 99.7%	24.5	1160	$7.5\cdot10^{-4}$	$3.6\cdot10^{-2}$		
	3.7 mg/cm^2; 99.7%	21.9	1000	$8.0\cdot10^{-4}$	$4.9\cdot10^{-2}$		
	0.175 mm; 99.275%	28	4	$1\cdot10^{-2}$	$1\cdot10^{-3}$		[252]
	thick; 99.275%	38	63	$1.2\cdot10^{-2}$	$1.3\cdot10^{-2}$		[253]
^{237}Np(d,2n)	0.7 mg/cm^2	15	1400	$7\cdot10^{-2}$*)			[259]
		25	4800	$1.6\cdot10^{-1}$*)			
^{237}Np(p,n)	2 mg/cm^2	12	300	$5\cdot10^{-2}$			[259, 267]
		14	1000	$1\cdot10^{-1}$			
		16	1500	$1.5\cdot10^{-1}$			

*Sum ratio $^{236+238}$Pu/^{237}Pu.
**After enrichment of ^{237}Pu in a mass separator.
***Latest results (1994).

TABLE XII. List of some centers with isotope programs.

Center [reference]	Accelerator	Isotope production time, %
Canberra, Melbourne (Australia) [39(4), p. 243, 245]	VEC (30MeV p), **CYCLONE**-10/5 (10 MeV H$^-$, 5 MeV D$^-$)	100
São Paulo (Brazil) [39(4), p. 246]	**CS-30** (24 MeV p)	100
Vancouver, TRIUMF (Canada) [36, p. 206,209]	**TR-13**(13 MeV p), **TR-30**(30 MeV H$^-$), **CP-42**(42 MeV H$^-$)	>90
Jyväskylä(Finland) [264]	**K-130**(90 MeV p, H1)	>25
Nice (France) [36]	**MEDICYC**(65 MeV p)	80
Karlsruhe, KfK(Germany) [59]	**CP-42**(42 MeV H$^-$)	100
Chiba, NIRC(Japan) [36]	**MC-40**(30 MeV p), **AVF**(70 MeV p)	100
Obninsk TSIKLOTRON (Russia) [39(4), p. 54, 251]	**U-150**(20 MeV p, 20 MeV d, 41 MeVα)	100
Moscow, RSC Kurchatov Institute (Russia) [39(4), p. 252]	**U-150**(30 MeV p)	
Troitsk, Institute of Nuclear Research (Russia) [265]	**MMF-LINAC**(160 MeV p)	
Dubna, JINR (Russia) [36, p. 213]	**U-200**(36 MeV α, MZI) Phasotron (680 MeV p)	
Faure, NAC(South Africa) [39(4), p. 60, 247]	**SSC**(200 MeV p)	100
Villigen, PSI(Switzerland) [39(4), p. 68, 242]	**IP II**(72 MeV p)	>20
Riyadh, RC(Saudi Arabia) [2, p. 54]	CS-30(26 MeV p, 30 MeV α)	⩾30
Aberdeen, Amersham, Birmingham, Harwell(UK) [2, p. 37]	CS-30(26 MeV p, 15 MeV d, 38 MeV α), **CP-42, MC-40**(40 MeV p), **VEC**(60 MeV p, 42 MeV d, 85 MeV ^{3}He, 86 MeV α)	90–100
Davis, CnL; Upton, BNL; Los-Alamos, LANL; Miami (USA) [96,98,262,263]	**IC**(68 MeV p) **BLIP** (200 MeV p) **LAMPF**(800 MeV p), **CS-30**(30 MeV p)	20–100

eous target consisting of natural or enriched Kr has been studied for the purpose of obtaining ^{81}Rb.[59,63,154] The excitation functions of the nuclear reactions have been measured, and the target and generator structure have been developed. The investigations showed that when a ^{nat}Kr target with thickness 10 MeV (40→30 MeV) is irradiated with a gas pressure of 6 atm, ^{81}Rb can be obtained within 15–90 min in a sufficient quantity for preparing approximately 10 generators with activity from 10 to 80 mCi at the end of irradiation.[154]

An elegant method of ion implantation of ^{81}Rb (^{81}Rb$^+$, $3\cdot10^{10}$ ions/s) in different foils (mylar, polyethylene, aluminum) in a mass separator operating on-line with an $E_p=600$ MeV proton beam (ISOLDE-2 setup) was recently developed to obtain the isotopically pure generator ^{81}Rb/^{81m}Kr.[155] This method, which makes it possible to obtain an ^{81}Rb source, fixed in a foil matrix, on-line by irradiation of Nb_{met} with 600-MeV protons, eliminates the standard operations of separating, concentrating, and introducing the parent isotope into an appropriate carrier. At the end of irradiation the foil with the implanted ^{81}Rb was placed in a setup from which ^{81m}Kr was removed either by means of an airflow or with a physiological solution. ^{81}Rb with the activity required for one generator (~20 mCi) was obtained within several minutes. An important advantage of the proposed method is that there are no wastes. The first medical studies with such a generator were undertaken in the Canton Hospital of Geneva.

It should be noted that this method can be implemented only in centers where complex setups, providing an on-line system "accelerator–mass-separator" have been built. Such setups operate at CERN in Geneva (ISOLDE-2), the Joint Institute for Nuclear Research in Dubna (YASNAPP-2), and the Leningrad Institute for Nuclear Physics in St. Petersburg (IRIS).

TABLE XIII. List of cyclotron radionuclides obtained at the main production centers of the USA [data at October 1988 (Ref. 263) and 1993 (Ref. 39(5)].

USA centers		
Los Alamos		Brookhaven
1988	1993 (additional)	1988
^{7}Be	^{49}V	^{7}Be
^{22}Na	^{65}Zn	^{28}Mg
^{26}Al	^{67}Ga	^{52,59}Fe
^{32}Si	^{75}Se	^{56}Co
^{44}Ti	^{85}Sr	^{67}Cu
^{44,46}Sc	^{92}Nb	^{68}Ge
^{48}V	^{95m}Tc	^{81}Rbh/^{81m}Kr
^{52}Mn	^{101,102}Rh	^{82}Sr/^{82}Rb
^{52,59}Fe	^{108}Ag	^{97}Ru
^{56}Co	^{146}Pm	^{117m}Sn
^{67}Cu	^{194}Hg/^{194}Au	^{118}Te
^{68}Ge		^{123}I
^{72}Se		^{127}Xe
^{72,73}As		^{128}Ba/^{128}Cs
^{77}Br		^{203}Pb
^{82}Sr		
^{82,83,86}Rb		1993 (additional)
^{88}Zr		^{67}Ga
^{88}Y		^{96}Tc
^{109}Cd		^{55}Co
^{105,109m}Ag		^{73}As
^{123,125}I		^{77}Br
^{127}Xe		
^{139}Ce		
^{145}Sm		
^{145}Pm		
^{146,148}Gd		
^{163}Ho		
^{172,173}Lu		
^{207}Bi		

*LAMPF—Los Alamos Meson Production Facility, $E_p=800$ MeV.
**BLIP—Brookhaven Linac Isotope Production, $E_p=200$ MeV.

^{82}Sr/^{82}Rb

^{82}Sr, $T_{1/2}=25.5$ d; EC(100%); no γ rays;

^{82}Rb, $T_{1/2}=1.27$ min; β^+(95%); EC(5%); main γ rays with $E_\gamma=776.5$ keV (13.4%), max $E_{\beta^+}=3350$ keV.

An on-line method combining irradiation of an Nb target with high-energy protons, high-temperature evaporation of the radioactive strontium formed, and mass separation and implantation of ^{82}Sr ions in foil, has also been used for obtaining the isotopically pure generator ^{82}Sr/^{82}Rb.[156] To produce ^{82}Sr in large (curie) quantities, however, high-energy fission reactions of molybdenum in high-current proton beams[157] and the (p, xn) reactions accompanying the irradiation of rubidium targets (Rb_{met}, RbCl, natural or enriched with respect to ^{85}Rb) are used (Table VII(5)).[158,159] In connection with the increased demand for this generator for PET studies, methods for obtaining ^{82}Sr are still bening developed at a number of centers where high-current proton accelerators at energies above 40 MeV are available. The excitation functions of the reaction Rb(p, xn)Sr and the ^{82}Sr yield in thick targets are measured,[15] the target setups are constructed in application to the target material ($Rb_{met.}$; RbCl), and an estimate is given of the radioisotopic purity as a function of the conditions under which ^{82}Sr is obtained.[59,160] In recent years, it has been determined that for commercial production of ^{82}Sr it is best to use a rubidium metal target.[159]

^{128}Ba/^{128}Cs

^{128}Ba, $T_{1/2}=2.43$ d; EC(100%); main γ rays with $E_\gamma=273.4$ keV (14.5%);

^{128}Cs, $T_{1/2}=3.9$ min; β^+(61%), EC(39%); main γ rays with $E_\gamma=442.9$ keV (25.8%), max $E_{\beta^+}=2285$ keV.

For cardiological studies with the aid of "inorganic" radionuclides emitting positrons, the SLI of a heavy alkali element ^{128}Cs is considered to be promising. Its nuclear properties, specifically, the short half-life and, correspondingly, the low radiation load on the patient, make it possible to use this radionuclide in PET studies.

The parent ^{128}Ba is obtained in the reaction ^{133}Cs$(p, 6n)$ ^{128}Ba in proton accelerators with $E_p>60$ MeV.[15,23] The excitation functions of the reactions ^{133}Cs $(p, xn)^{134-x}$Ba have been calculated, and the experimental values of σ have been obtained for initial proton energies of 100 MeV (Ref. 15) and 65 MeV (Ref. 23). The ^{128}Ba yield in a thick CsCl target was

TABLE XIV. Possibilities for obtaining some radionuclides in accelerators at the Joint Institute for Nuclear Research [Refs. 3, 39(4), p. 79; 36, p. 215].

Nuclide	Accelerator	Production reaction	Energy interval, MeV	Yield, mCi/μAh·h	Exposure, h	Production volume, mCi**
^{26}Al	A	^{24,25}Mg(^{4}He,pxn)	35→15	$2.2\cdot10^{-9}$	100	$2.2\cdot10^{-5}$
^{67}Cu	A	^{64}Ni(^{4}He,p)	35→5	0.063	10	63
^{68}Ge/^{68}Ga	A	^{66,67}Zn(^{4}He,xn)	35→15	0.001	200	20
	E	^{69}Ga(p,2n)	35→15	0.044	100	440
^{81}Rb/^{81m}Kr	E	^{82}Kr(p,2n)	35→15	6.5	5	2750
^{97}Ru	A	^{np}Mo(^{4}He, xn)	36→14	0.1	20	180
	B	^{99}Tc(p,3n)	50→20	7.0	20	760
	E	^{99}Tc(p,3n)	35→20	3.7	20	6700
^{111}In	A	^{109}Ag(^{4}He,2n)	35→10	0.7	20	1280
	E	^{112}Cd(p,2n)	30→20	6.0	20	10900
	E	^{113}Cd(p,3n)	35→25	9.45	20	17000
^{123}I	C	^{124}Xe(γ,n)	25	0.1/1 g ^{124}Xe	10(+2)***)	~200/~15 g
	D	^{124}Xe(γ,n)	36		13	~2200
	E	^{24}Xe[(p,2n)+(p,pn)]	30→25	10	4(+7)***)	4000
^{127}Xe	E	^{127}I(p,n)	35→10	0.015	100	145
^{178}W/^{178}Ta	A	^{176,177}Hf(^{4}He,xn)	35→18	0.07	100	625
	B	^{181}Ta(p,4n)	60→30	1.3	50	370
	E	^{181}Ta(p,4n)	35→30	0.3	20	580
^{201}Tl	E	^{203}Tl(p,3n)	30→22	0.7	10(+32)***)	700
^{211}At	A	^{209}Bi(^{4}He,2n)	30→10	0.5	10	335
^{237}Pu	A	^{235}U(^{4}He,2n)	32→21	0.0003	100	~3
			25→24	0.00005	100	~0.5

A—U-200 cyclotron; $^4He^+$, 36 MeV, 100 μA; G. N. Flerov Laboratory of Nuclear Research;
B—"F" phasotron; H^+, internal beam* 20–660, 8 μA; extracted beam 660 MeV, 2 μA, Laboratory of Nuclear problems;
C—MT-25 microtron; e^-, 25 MeV, 20 μA; G. N. Flerov Laboratory of Nuclear Research;
D—LUÉ-40 lineaer electron accelerator, e^-, 40 MeV, 60 μA; I. M. Frank Laboratory of Nuclear Physics;
E—cyclotron, H^-, 30 MeV, 100 μA (design discussion stage).
*70% of the proton beam intensity is actually used.
**Taking account of the decay over the irradiation time.
***Accumulation time.

8.4 and 3.1 mCi/μA·h, respectively. For the generator ^{128}Ba/^{128}Cs the main radionuclide contaminations could be due to the pairs ^{129}Ba/^{129}Cs and ^{131}Ba/^{131}Cs from the (p, 5n) and (p, 3n) reactions, respectively. However, allowing the CsCl target to stand for 22–24 h after irradiation is completed virtually eliminates the impurity ^{129}Ba ($T_{1/2}$=2.1 h and 2.2 h) and correspondingly ^{129}Cs (32.1 h). The contamination with ^{129}Ba (14.6 min and 11.8 d) can be neglected, since the decay of this radionuclide and, correspondingly, the accumulation of ^{131}Cs (9.7 d) occur much more slowly.

The radiochemistry of the generator ^{128}Ba/^{128}Cs has been studied in a number of investigations, where the production ^{128}Cs with a high specific activity in a carrier-free state was investigated. Al_2O_3 (Ref. 162 and 163) or the resin Chelex-100 (Refs. 23 and 164), which exhibit good qualities required for generators, were used as the carrier sorbents for ^{128}Ba.

^{52}Fe/^{52m}Mn

^{52}Fe, $T_{1/2}$=8.2 h; β^+(56%), EC(44%); main γ rays with E_γ=168.7 keV (99.2%);

^{52m}Mn, $T_{1/2}$=21.1 min; β^+(98%), EC(2%); main γ rays with E_γ=1434.1 keV (98.3%), max E_{β^+}=2631 keV.

The radionuclide ^{52}Fe is the most suitable of the other iron isotopes (^{55}Fe, $T_{1/2}$=2.7 yr, no E_γ and ^{59}Fe, $T_{1/2}$=45.1 d, E_γ~1 MeV) for in-vivo investigations of marrow, which is the blood-forming organ (Fe ions are incorporated into erythrocytes). Another application of ^{52}Fe is as a generator for ^{52m}Mn, which is used in cardiology. Reactions yielding ^{52}Fe, among which ^{55}Mn(p, 4n)^{52}Fe gives the most ^{52}Fe, are presented in Table VII(2). The excitation function of this reaction was studied in the energy intervals 73→39 MeV,[165] 100→36 MeV,[15,166] and 200→42 MeV.[167] From these data it follows that for $E_p \geq 80$ MeV the quantity σ decreases slowly from 0.4 mb (Ref. 166) to 0.2 mb at 200 MeV.[167] The values of σ obtained for ^{52}Fe in the reaction ^{55}Mn(p, 4n) in Refs. 151 and 165–167 agree well, and it has been shown that the ^{55}Fe impurity amounts to 0.45–0.48%.

The results of investigations of ^{52}Fe production in reactions of intermediate-energy protons (100–200 MeV) with Co targets[15,166] and Ni targets[167] showed that in the first case the ^{55}Fe yield in a thick target (100→64 MeV) as a result of the reactions ^{59}Co(p, X)^{52}Fe in the possible channels (p, 2p6n) and (p, α4n) was equal to 106 μCi/μA·h, and in the second case in the fission reactions Ni(p, X) for a thick target of natural Ni (200→45 MeV) the ^{52}Fe yield was two orders of magnitude higher and equal to 11 mCi/μA·h. These data show that a Ni target irradiated with initially 200-MeV protons in a high-current accelerator can serve for obtaining commercial quantities of ^{52}Fe.[167,168]

^{178}W/^{178}Ta

^{178}W, $T_{1/2}$=21.7 d; EC(100%); no γ rays;

^{178}Ta, $T_{1/2}$=9.3 min; EC(98.9%); main γ rays with E_γ=93.2 keV (6.6%).

Tantalum-178 has been investigated in nuclear medicine in application to cardiodiagnostics.[169,170] The decay of this radionuclide is accompanied by x ray emission, which is effectively detected with multiwire proportional chambers.[17] This nuclide is especially promising for pediatric cardiology because of the low radiation load compared with the widely used ^{99m}Tc and also because of the possibility of continuous, repeated, and subsequent repetition of the functional examinations.

Tantalum-178 produced in the decay ^{178}W 21.7 d/EC ^{178}Ta 9.3 min/EC ^{178}Hf$_{stabl.}$, does not contain the high-spin isomer ^{178m}Ta (2.2 h).[171] The nuclear reactions forming ^{178}W are given in Table VII(7). Of these reactions, the reaction ^{181}Ta(p, $4n$)^{178}W,[172,173] whose excitation function was measured experimentally in Refs. 44, 174, and 175 and calculated[44] for $E_p \leq 100$ MeV, is used in practice. Data on the proton-energy dependence of σ showed that the ^{178}W production efficiency is approximately the same ($\sim$0.7 mCi/μA·h) in the energy range adjoining the range of maximum cross sections ($30 \leq E_p \leq 50$ MeV) and in the tail part of the curve ($50 \leq E_p \leq 80$ MeV) (Ref. 39 (5), p. 208). They show that an efficient thickness of a Ta target is 6.5–7.0 g/cm^2 for $E_p \sim 70$ MeV.

The radiochemistry of the generator system ^{178}W/^{178}Ta is based on ion-exchange chromatography and has been studied quite well.[172,176,177]

^{44}Ti/^{44}Sc.

^{44}Ti, $T_{1/2}$=47.3 yr; EC(100%); main γ rays with E_γ=67.8 keV (88.0%); 78.4 keV (94.5%);

^{44}Sc, $T_{1/2}$=3.9 h; EC(98.9%), β^+(95%); main γ rays with E_γ=1157.0 keV (99.9%), max E_{β^+}=1500 keV.

Among the radioactive scandium isotopes ^{44}Sc(3.9 h), ^{46}Sc(83.8 d), and ^{47}Sc(3.3 d), employed as bone scanning agents,[178] labels for monoclonal antibodies,[179] and investigations of metabolism,[180,181] the isotope ^{44}Sc is preferred, especially for PET studies.[182] The generator ^{44}Ti 47 yr/EC ^{44}Sc(3.9 h) can serve as a constant source of this relatively short-lived isotope, but it has not yet entered clinical practice because of difficulties in obtaining ^{44}Ti. This is due to the small ^{44}Ti production cross sections in the nuclear reactions (Table VII(1)). Analysis of existing data showed that only the fission reactions of vanadium V(p, X) are acceptable for producing long-lived ^{44}Ti. In this case the prolonged irradiation of a V target can be conducted on the blocker of a high-energy proton beam together with irradiations for other problems without paying attention to the interruptions in the sessions.

Experimental measurements of the ^{44}Ti production cross sections accompanying the irradiation of vanadium and theoretical calculations of the excitation function of the reaction (p, $2p6n$) were recently performed.[183] The values of σ (a function of the proton energy in the interval 100→54 MeV) are cumulative, since many reactions, leading to the formation of ^{44}Ti, of which the reaction (p, $2p6n$) refers to the high-energy part of the excitation function, can occur under these conditions (Table VIII). Comparing the experimental values of σ with the calculated values obtained for the (p, $2p6n$) reaction with E_p from the threshold value up to 100 MeV, one finds that there is a difference of approximately a factor of three. The cumulative yield of ^{44}Ti in the energy interval 100→54 MeV was equal to 0.015 μCi/μA·h, which is more than three orders of magnitude lower than the value 60 μCi/μA·h obtained by irradiating vanadium with 200-MeV protons.[184]

^{68}Ge/^{68}Ga

^{68}Ge, $T_{1/2}$=271 d; EC(100%); no γ rays;

^{68}Ga, $T_{1/2}$=68.1 min; β^+(90%), EC(10%); main γ rays with E_γ=1077.4 keV (2.93%), max E_{β^+}=1900 keV.

This generator system is becoming increasingly more important in connection with the expansion of the assortment of RPs labeled with ^{68}Ga—a positron emitter—for PET studies. The nuclear reactions leading to ^{68}Ge production are shown in Table VII(3). This nuclide can be obtained in proton beams of medical cyclotrons using a Ga target (alloy Ga_4Ni, which withstands relatively high currents[47]). Germanium-68 is also obtained in high-energy fission reactions by irradiating a RbBr target with 800-MeV protons on the blocker of the proton beam of the LAMPF accelerator. For example, 125 mCi of ^{68}Ge were produced within two weeks of irradiation of 48 g of RbBr with a 340-μA proton beam.[185,240] The method for obtaining a working generator is based on the general principle of loading the ^{68}Ge separated from the target into an ion-exchange column for subsequent elution of ^{68}Ga.[186,187] Monitoring of ^{68}Ge breakthrough, which did not exceed $10^{-6}-10^{-5}$% in the bolus (the eluent volume in a single extraction of the daughter nuclide) in routine operation, showed that such a generator can be used for one year.

4.6. Radionuclides for separate studies

An entire series of radionuclides has a narrow, but important application in nuclear medicine and biochemistry. Among these nuclides, ^{77}Br, ^{97}Ru, ^{211}At, ^{26}Al, ^{67}Cu, and ^{237}Pu are studied below. Of these, there is a demand for ^{77}Br, ^{97}Ru, ^{211}At, and ^{67}Cu for studies with monoclonal antibodies, which contain these nuclides; ^{26}Al and ^{237}Pu are used for metabolism studies.

Bromine-77

^{77}Br, $T_{1/2}$=57 h; EC(99.26%), β^+(0.74%); main γ rays with E_γ=239 keV (23.9%), 520.7 keV (23.2%).

The radionuclides ^{75}Br, ^{76}Br, and ^{77}Br, which belong to the halogen group, have not found as wide application as ^{18}F or ^{123}I, but they are employed as labels for some RPs because the bromine bond with carbon is stronger than that of iodine. In consequence, their RPs are more stable and find application in studies of biological parameters (Ref. 92, p. 703). The most favorable nuclide for these purposes is considered to be ^{77}Br, since its relatively long half-life makes it possible to conduct quite prolonged studies. The other isotopes have limited applications: ^{75}Br($T_{1/2}$=98 min, β^+(75%)), which decays into ^{75}Se(120 d), whose admixture

is undesirable in in-vivo studies; ^{76}Br(16.1 h; β^+(57%)) is undesirable because of the high positron energy (up to 3.9 MeV).

Nuclear reactions forming ^{77}Br (direct and indirect) which are employed in practice are presented in Table IX(3).[45,188–190] The indirect (generator) method of obtaining ^{77}Br from ^{77}Kr has been extensively investigated from the standpoint of finding the optimal conditions for obtaining pure preparations of ^{77}Br. The cross sections of the reactions Br(p, xn)^{77}Br have been measured in the interval 85→24 MeV,[191–193] and the results have shown that the maximum cross section σ_{max} of the reaction (p, $3n$) fluctuated from 150 to 250 mb. The excitation function of the reactions ^{79,81}Br(p, xn)^{77}Kr up to 100 MeV was measured in Ref. 15. The total experimental cross sections for the formation of ^{77}Kr in the reactions (p, $3n$) and (p, $5n$) on natural ^{79,81}Br agree satisfactorily with the calculated cross sections. Irradiation of a KBr target for 2 h and subsequent decay of ^{77}Kr for 7 h make it possible to obtain preparations of ^{77}Br with minimum contamination with ^{76}Br from the decay ^{76}Br 14.6 h/EC ^{76}Br(16.1 h).

Ruthenium-97

^{97}Ru, $T_{1/2}$=2.9 d; EC(100%); main γ rays with E_γ=215.7 keV (85.8%), 324.5 keV (10.2%).

The combination of nuclear-physical and chemical properties for ^{97}Ru (ruthenium possesses several stable degrees of oxidation) makes it a potentially important object for nuclear medicine. This assessment was first made in 1970,[143] and since then studies of the radiopharmaceutical chemistry of ^{96}Ru-containing compounds for diagnostic and therapeutic purposes have been continuing.[144,145] ^{97}Ru is also promising because in a number of cases ^{97}Ru-containing compounds are found to be more stable than ^{99m}Tc and ^{111}In radiopharmaceuticals, which makes ^{97}Ru pharmaceuticals preferable for medical studies.[145]

Ruthenium-97 can be obtained in several nuclear reactions (Table IX(4)). Until recently it was obtained by irradiating Rh metal with 70-MeV protons[21] and in reactions of ^{4}He ions with Mo;[43] the possibility of obtaining ^{97}Ru by irradiating Tc with protons was previously only mentioned, but not investigated.[146,147] The reaction ^{97}Tc(p, $3n$)^{97}Ru has recently been studied,[20] the excitation function in the energy range 100→26 MeV has been measured and theoretically calculated, and a ^{97}Ru yield equal to 10.5 mCi/μA·h for a thick target (12.2 g/cm^2) was obtained.

Since the maximum cross section for the formation of ^{97}Ru (440 mb) is reached at an energy of 32 MeV,[20] the optimal initial energy can be $E_p \simeq 50$ MeV. The yield for a thick target (3 g/cm^2) in this case is ~7 mCi/μA·h. If the proton energy is increased to 60 MeV, then the ^{97}Ru yield increases by 15%, but then the thickness of the Tc target increases to 4.6 g/cm^2, and its total activity increases by an order of magnitude mainly on account of the activity of the isotopes ^{95}Tc ($T_{1/2}$=61 d and 20 h) and ^{96}Tc ($T_{1/2}$=1.65 d), which form in the reactions ^{99}Tc (p, pxn)$^{99-x}$Tc and with the decay of ^{95}Ru ($T_{1/2}$=1.65 h).

Tc metal is an excellent material for cyclotron targets. It is a hard but elastic metal with specific weight 11.5 g/cm^3, it is corrosion-resistant up to 300 °C, its thermal conductivity is high, and it melts at approximately 2500 K. Irradiation of Tc in high-current accelerators ($\geq$100 μA) will make it possible to obtain ^{97}Ru in large quantities even with cyclotrons with E=30 MeV. In this case the low yield of ^{97}Ru (~1 mCi/μA·h) is compensated by the possibility of directing high proton currents on a Tc target. Experiments performed in a 50-MeV proton beam with a current of ~8 μA showed that the ^{97}Ru production is quite high, 40–50 mCi/h at the end of irradiation (Ref. 39 (5), p. 208; Ref. 148). It should be noted that such quantities of ^{97}Ru can be obtained in reactions of Mo with 35-MeV ^{4}He ions only with currents exceeding 500 μA.

To separate gram quantities of irradiated ^{99}Tc and ultratrace quantities of ^{97}Ru and to purify and concentrate ^{97}Ru, an efficient method giving a chemical yield of 95–98% ^{97}Ru and a purification coefficient $\geq 10^4$ has been developed, even though the chemistry of these two elements is close.[148]

Astatine 211

^{211}At, $T_{1/2}$=7.2 h; EC(58.3%), α(41.7%); main γ rays with E_γ=92.4 keV (2.3%), 687.0 keV (0.25%); E_α=5866 keV.

The isotope ^{211}At of the fifth and heaviest element in the halogen group is one of a few neutron-deficient isotopes employed in radiotherapy.[194] The nuclear data on its production are presented in Table IX(5). The reaction ^{209}Bi(^{4}He, $2n$)^{211}At with $E_\alpha \leq 29$ MeV, which makes it possible to obtain ^{211}At with the highest yield and lowest contaminations with ^{210}At(8.3 h), is most widely used.[195] The excitation function of the reaction ^{209}Bi(^{4}He, $2n$)^{211}At has been studied by several authors.[195,196] The radiochemical separation of At from irradiated Bi targets has been performed in recent years most often by the method of gas thermochromatography.[197] Preparations of At with the required radiochemical purity are obtained in a sublimation process in a flow of air from Bi melt (700°C), followed by selective deposition on the surface of an Ag spiral placed in the section of a column with T~250°C.

For α therapy, ^{211}At is employed in the form of a preparation of colloidal Te metal (particle size 3–5 μm) on which ^{211}At, monoclonal antibodies, and other labeled preparations are sorbed.[194,277,278]

Aluminum-26

^{26}Al, $T_{1/2}=7.2\cdot10^5$ yr; β^+(82.1%), EC(17.9%); main γ rays with E_γ=1808.6 keV (99.7%); E_{β^+}=1160 keV.

Until recently, this isotope was mainly an object of astrophysical studies as a cosmogenic nuclide, formed with the interaction of galactic protons with cosmic matter. The mechanism of ^{26}Al formation in meteorites is modeled on the basis of studies of the interaction of proton beams of different energy (up to several GeV) in Mg, Si, and Ni targets.[198,199]

The investigation of the metabolism of Al, which is a common element in industry, was first made possible by the development of a highly sensitive method of accelerator

mass spectrometry (AMS). Studies of the metabolism of trace amounts of Al, which are important because of the toxicity of Al, not only for workers in the aluminum industry, are impeded by the limited possibilities for obtaining ^{26}Al, which is the only radionuclide of Al that can be used for these purposes in combination with the AMS detection method.[200,201]

The nuclear reactions forming ^{26}Al are presented in Table IX(1). Of these, the reactions ^{24,25}Mg(^{4}He, pxn) and ^{23}Na(^{4}He, n) are most acceptable for obtaining the nuclide in a carrier-free state.[202,203,244] A method for obtaining highly pure ^{26}Al preparations in quantities required for in-vivo studies by irradiating highly pure magnesium (99.99%) with 36-MeV ^{4}He ions has recently been developed (Ref. 280, p. 71). The new construction of the target made it possible to use a current of up to 80 μA, which made the production of ^{26}Al quite efficient (Ref. 39 (5), p. 365).

Copper-67

^{67}Cu, $T_{1/2}$=61.97 h; β^-(100%); main γ rays with E_γ=93.3 keV (16.1%), 184.6 keV (48.7%); max E_{β^-}=577 keV.

The radionuclides ^{62}Cu, ^{64}Cu, and ^{67}Cu are used in investigations of metabolism of copper traces, for labeling monoclonal antibodies, and in radioimmunotherapy.[204,205] ^{67}Cu has advantages over the other two isotopes on account of its nuclear-physical characteristics. The reactions producing ^{67}Cu are given in Table IX(2). Analysis of the existing data shows that the ^{67}Cu production cross sections in these reactions are small; they do not exceed several millibarns. For the reaction ^{64}Ni(^{4}He, p)^{67}Cu (σ_{max}=15.9 mb for E_α=15.5 MeV (Ref. 206)), calculations of the excitation function[207] show that the theoretical values of σ are higher than the few available experimental values, which were obtained in only one study.[206] The computed ^{67}Cu yield in a thick target (35→4 MeV) enriched with ^{64}Ni (~92%) is ~63 μCi/μA·h, on the basis of which it can be predicted that ~63 μCi of ^{67}Cu will be produced over a period of 10 h of irradiation with a 100-μA current of α particles.[207]

Plutonium-237

^{237}Pu, $T_{1/2}$=45.6 d; EC(99%), α(0.033%); main γ rays with E_γ=97.1 keV (12.5%), 101.1 keV (20.1%), 113.9 keV (7.6%); E_α=5370 keV, 5660 keV.

^{237}Pu is of interest for studies of the metabolism of traces of plutonium in the human body.[247,257] Such studies are important and necessary because many people work in the plutonium industry and also because of environmental contaminations, especially near locations of nuclear explosions or accidents. ^{237}Pu is the only isotope of this transuranium element which meets the requirements of nuclear medicine for in-vivo studies. It decays by means of e^- capture, its x-rays have energies up to 100 keV, and it has a small admixture of α branching and therefore low radiation dose.

^{237}Pi can be obtained in the nuclear reactions (^{4}He, $2n$) and (^{3}He, n) on ^{235}U (Refs. 248–251) and (^{4}He, $5n$) and (^{3}He, $4n$) on ^{238}U (Refs. 252 and 253). The excitation functions of some of these reactions have been investigated in a limited number of studies,[248,254] whose results, as one can see from Table X, must be refined, and additional experiments must be performed.

The conditions under which ^{237}Pu is obtained in different laboratories are presented in Table XI. Analyzing them, it can be concluded that the best method for obtaining ^{237}Pu preparations with the minimum admixtures of other Pu isotopes is the method recently proposed in Ref. 255. Irradiation of highly enriched ^{235}U(99.99%) with ^{4}He particles in a high-current accelerator, subsequent radiochemical separation of Pu from the irradiated target by the method of ion-exchange chromatography, and then additional isotopic enrichment of ^{237}Pu in an electromagnetic isotope separator have made it possible to obtain an ultrapure ^{237}Pu preparation with isotope ratios ^{236}Pu:^{237}Pu$<10^{-7}$ and ^{238}Pu:^{237}Pu $<10^{-7}$. The ^{237}Pu preparation obtained in this manner at the present time has no equals with respect to purity; it has been used in in-vivo studies of the metabolism in several volunteers in Harwell (Great Britain).[256]

5. OVERALL PICTURE OF RADIONUCLIDE PRODUCTION. PROSPECTS FOR RADIONUCLIDE PRODUCTION AT THE JOINT INSTITUTE OF NUCLEAR RESEARCH

A local isotope-production program is determined, on the one hand, by the availability of a certain type of apparatus (reactor, accelerator) and, on the other, by the current or potential demand for one or another radionuclide. On this basis, national or regional programs are formulated.[280] According to the radionuclide production data for 1992, there are both specialized cyclotrons constructed for this purpose, with 80–100% utilization of cyclotron time, and accelerators in which, among other problems, radionuclide production takes up from 10 to 70% of the working time. A list of countries which have programs for producing cyclotron radionuclides for nuclear medicine is given in Table XII. In Table XIII we give a list of radionuclides obtained in two of the main production centers in the USA, reflecting the demand for particular isotopes, depending on various developments in biomedical research.

The possibilities for obtaining cyclotron radionuclides at the Joint Institute for Nuclear Research are determined by the potential of existing accelerators. The U-200 cyclotron, the phasotron with proton beams up to 660 MeV, the MT-25 cyclotron, the LUE-40 linear electron accelerator—all these setups provide, on account of their parameters (different types of accelerated particles, energy characteristics, and intensities of the beams), a good foundation for obtaining a wide spectrum of radionuclides. Moreover, at the present time a design for a specialized accelerator with H^- ion energies of 30 MeV is under discussion. Data concerning production methods and the expected production volumes of some radionuclides, whose production can be organized at the Joint Institute for Nuclear Research on the basis of preliminary studies which in a number of cases have already been performed, are presented in Table XIV.

In examining the radionuclide production programs at the Joint Institute for Nuclear Research, from the standpoint of requests for the radionuclides for different studies, it

should be kept in mind that at the present time the demand for some radionuclides (^{67}Ga, ^{111}In) is satisfied quite well both in Russia and abroad. For ^{82}Sr, besides existing sources of commercial production in the USA (LAMPF, BLIP) from Mo and RbCl targets, respectively,[157,158] at the present time this radionuclide is produced from Rb metal targets based on work done during the Russian–Canadian collaboration of the Institute of Nuclear Research (Troitsk), the Institute of Biological Physics (Moscow), and TRIUMPH (Vancouver).[159,260]

For a number of radionuclides listed in Table XIV, the demand is still not adequately met, and in such cases the development of their production becomes important. This refers to ^{123}I, a regional radionuclide because of its relatively short half-life; ^{201}Tl, which is still not produced in adequate quantities (especially in Russia), not only for diagnostics of mycardium infact but also in connection with the problem[261] of prophylactic survey of the public for cardiological diseases, which at the present time are the most important diseases worldwide. For example, the demand for ^{201}Tl in Moscow is ~40 Ci/yr, and only ~5 Ci/yr is produced.[95] Among other radionuclides, in recent years the demand for ^{67}Cu and ^{97}Ru and the generators ^{68}Ge/^{68}Ga and ^{178}W/^{178}Ta has been increasing.

Analysis of the data presented in Table XIV shows that among accelerators, the cyclotron designated as "D" plays the main role in the radionuclide production program at the Joint Institute for Nuclear Research. This confirms the need to build at the Joint Institute a specialized high-current proton accelerator which in many countries (Germany, Canada, and others) has become the main apparatus for commercial production of radionuclides for nuclear medicine.

6. CONCLUSIONS

The following trends can be discerned in the present status of the production of cyclotron radionuclides for biomedical in-vitro and in vivo-studies.

Studies directed toward the measurement of new data or refinement of existing nuclear data (nuclear decay properties, excitation functions of nuclear reactions, yields of radionuclides depending on the experimental conditions—target, particle currents, energy intervals of nuclear reactions), and collection and analysis of these data for subsequent practical use, are continuing.

New methods of radionuclide production are being developed and existing methods are being improved for the purpose of obtaining highly pure preparations of radionuclides (nuclear reactions, targets, radiochemical separation methods, purification and concentration of radionuclides).

The list of radionuclides being produced is determined by the development of directions in nuclear medicine (diagnostics and therapy with new marked radiopharmaceutical compounds, investigations of the metabolism of elements) and instrumental possibilities (detection apparatus, computerization of information acquisition, and so on). Depending on these factors, the production of individual radionuclides has periods of "ebb and flow" (an example is ^{67}Ga (Ref. 262)).

In recent years the demand for ultrashort-lived radionuclides (^{11}C, ^{13}N, ^{15}O, ^{18}F) has increased in connection with the development of PET studies and the creation of new PET centers for this purpose. There are now ~140 such centers worldwide, half of which are in North America.[279] Investigations of the metabolism of a number of elements have required, specifically, the preparation of ^{26}Al and ^{237}Pu; investigations with monoclonal antibodies and their application in radioimmunology have made it necessary to increase the production volumes of ^{67}Cu, ^{97}Ru, ^{111}In, ^{211}At, and a number of other nuclides.

The number of newly designed or updated specialized accelerators for the production of radionuclides for medical purposes is increasing, and the possibilities of existing accelerators are being expanded as a result of an increase in the number of channels for extracting particle beams for irradiating targets. The "workhorse" in industry for most medical radionuclides is now cyclotrons with intense particle beams, primarily 30-MeV protons and 42-MeV H^- ions, whose era started in the 1970s–1980s, and in the case of ultrashort-lived radionuclides the "baby" cyclotrons with particle energy $\leqslant$20 MeV.

The last few years have been marked by intense development of technical equipment for radionuclide production, including automation of the entire production cycle. This makes possible not only commercial implementation of radionuclide preparations but also the sale of the radionuclide technologies themselves.

In summary, it is obvious that the entire path, starting from investigations of nuclear data, which serve as the basis for the choice and preparation of radionuclides for nuclear medicine, and up to production and realization of radionuclides is a complex of different problems, which are solved in nuclear centers in application to local conditions.

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