Объединение независимых экспертов в области минеральных ресурсов,
металлургии и химической промышленности

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Medicinal Isotopes in Russia: Production, Market and Forecast

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Annotation

The present review is the 3rd edition of research of the Russian market **of medical isotopes**.

Research objective is the analysis of the Russian market of isotopes of medical purpose.

Monitoring of this market is conducted since 2007.

Object of research is the industrial isotopes used in medicine: Actinium-225, Americium-241, Boron-10, Tungsten-188, Gadolinium-153, Helium-3, Germanium-68, Iron-55, Iridium-192, Yttrium-90, Ytterbium-169, Iodine-124, Iodine-125, Iodine-131, Californium-252, Oxygen-18, Cobalt-57, Cobalt-60, Krypton-85, Xenon-129, Lutetium-177, Manganese-54, Molybdenum-99, Sodium-22, Nickel-63, Tin-117m, Palladium-103, Radium-223, Ruthenium-106, Samarium-153, Strontium-82, Strontium-89, Strontium-90, Carbon-13, Carbon-14, Phosphorus-32, Phosphorus-33, Caesium-131, and Caesium-137.

Chronological framework of research: 2007-2015, the forecast – 2016-2025.

Geography of research: the Russian Federation – the complex detailed analysis.

This work is **desk research**. As **sources of information** data of Rosstat, Federal Customs Service of the Russian Federation, scientific and technical literature, the industry, regional and international press, and also the websites of the enterprises – producers and consumers of medical isotope products were used.

The report consists of an Introduction and **5** Chapters, contains **247** pages, including **95** Tables, **38** Figures and **2** Appendices.

Chapter 1 is devoted to research of the main fields of medical application of radioactive and stable isotopes. This chapter describes the stable isotopes and radionuclides, which are most widely used for the diagnostic and therapeutic purposes, the main methods of nuclear medicine, and also gives the most perspective isotopes for further development of nuclear medical and biological technologies.

Chapter 2 of the report discusses the main methods of receiving radionuclides and stable isotopes. This chapter describes methods of the isotope separation, which are most widely used in the industry, the most important biomedical reactor and cyclotron radionuclides, gives the main nuclear reactions of their receiving, and also describes generators of short-lived radionuclides that are now used for medical purposes in Russia and abroad.

Chapter 3 is devoted to producers of medical isotopes and radiopharmaceuticals, and it describes the main nomenclature of the medical isotope products released by them. Estimates of production are given for the Russian

Federation, both of raw medical isotopes, and isotope products (in natural and value terms), and shares of the main producers are specified.

Chapter 4 considers the Russian foreign trade operations with radio pharmaceutical products and isotope raw materials of medical purposes. Besides, this chapter analyzes dynamics of the Russian export-import supply of medical isotopes for the last 9 years in monetary terms, describes in detail the nomenclature of export and import products, and provides data on the main exporters and importers of medical isotope products in Russia.

Chapter 5 is devoted to the research of the modern market of medical isotopes. The forecast of development for 2016-2025 is given.

Appendices provide the text of the order of the Government of the Russian Federation about the concept of development of nuclear medicine till 2020, contact information of the largest Russian producers and traders of medical isotope products and the list of the main references used in the report.

Target audience of research:

- participants of the market of medical isotopes - producers, consumers, traders;
- potential investors.

The offered research can serve as a **handbook** for the services of marketing and for specialists making administrative decisions on the market of medical isotopes.

Introduction

A growing interest of physicians in isotopes is due to, on the one hand, high performance of isotopes' application owing to unique physical and chemical properties, and on the other hand, "stagnation" of traditional pharmacology, which, apparently, has tried almost all known chemical compounds and mixes. Important reserves of isotopes are so-called isotope effects in biochemistry, which open new vital reactions in organism, and also the medical nanotechnologies potentially capable to deliver isotopes directly to target cells by means of nano-containers.

About 100 isotopes have significant medical value. About 30 isotopes have their market, including due to a considerable industrial (not medical) application. Part of isotopes are actively investigated within the research and development and are prepared for entry into the market.

Now nuclear medicine exists as an independent science and as independent medical specialty, same as cardiology, nephrology or ophthalmology. Having begun development relatively recently, after the discovery of the induced radioactivity at the beginning of the 20th century, nuclear medicine has made a huge contribution to diagnosis of diseases, using at the same time all preferential properties of the ionizing radiation and radioisotopes. It is believed that the main business in medicine is diagnostics. Isotopes in diagnostics have no alternatives.

In addition to diagnostics, nuclear and radio medical isotope techniques are used for sterilization of dressing, clothes, surgical materials (threads for suture), catheters, and also human tissues for operations and implantations.

Currently many countries of the world release radiopharmaceuticals; both for internal needs and export (the USA, Great Britain, Germany), others (France, Italy, Belgium) generally export radiopharmaceuticals to developing countries.

In the world more than 130 organizations representing more than 20 countries practice nuclear medicine, including the leading producers of the modern equipment for nuclear medicine (General Electric Health, Phillips, Siemens, Eckert & Ziegler, IBA, Mediso and so forth), and also isotopes (Mallinckrodt, Polatom, Urenco and so forth).

The largest consumer of radio pharmaceutics among the developed countries is the USA. Annually in the USA more than 13 million nuclear medical procedures with the use of >4000 nuclear medical installations are performed. Besides, more than 100 million laboratory studies (analyses) with the use of isotopes for treatment of such diseases as oncological, epilepsy, diseases of coronary system, are annually conducted. The use of isotopes when developing new pharmaceuticals, including "not isotope ones" is essential.

The countries of the European Union annually provided 15 million nuclear and medical procedures, from them 14 million are diagnostic ones. From 1 million therapeutic procedures the share of Germany is 40%, and of France – 15%.

The number of the most widespread devices – gamma cameras for scanning – can serve as one of indicators of the use of nuclear methods in medicine. According to

IAEA, the developed countries have on average 20 gamma cameras per 1 million people, and developing countries – 0.8.

Diagnostic and therapeutic uses of medical isotopes in oncology, rheumatology, and surgical cardiology were considerably extended recently thanks to development and research of new types of radiopharmaceuticals of specific actions. The lymphoscintigraphy is promising as a diagnostics method, which allows with the use of a radiotracer to find the lymph nodes affected by a tumor in patients with cancer of mammary gland and skin. We note the development of the radioisotope immunoscintigraphy on the basis of the monoclonal antibodies and peptides specific to different pathological processes, for example, the method of the anticarcinogenic therapy with the use of the α-generator on the basis of the ^{213}Bi isotope attached to a monoclonal antibody for destruction of cancer cells at leukemia.

The value of nuclear medicine consists in detection of diseases, which are not diagnosed by other methods at an early stage, when treatment and improvement of the state and extension of life of seriously ill patients is possible. In a large number of cases the application of radiotheraphy helps to keep the life of patients with such diseases as brain tumors, lymphoma, leukemia, when other means are inefficient.

Further development of the radioisotope diagnostics and therapy is connected with an increase in production and extension of the nomenclature of medical isotopes, with development of techniques of application of RFP, with the growth of the staff of qualified specialists.

The issues of radioactive drugs are in Russia under patronage of the state. In recent years the leadership of our country make the forced efforts on development of nuclear medicine. The FTP "Development of the pharmaceutical and medical industry of the Russian Federation till 2020" (the order of the government 2057-r of 3.11.2012) has two sections concerning supplies of equipment for nuclear medicine. Thanks to the state support NIIEFA named after D.V. Efremov releases cyclotrons and tomographs, and JSC SSC RIAR (Research institute of Atomic Reactors) has started production of ^{99}Mo.

Since 2015, radionuclide diagnostics and therapy are included in the system of obligatory medical insurance.

Now the Russian market has a number of suppliers of the equipment for nuclear medicine, who are either engaged in the assembly on the territory of Russia, or import the foreign equipment including the used one.

The unexpected imbalance has come to light: the equipment and medical isotopes are available, however, there are insufficient numer of the qualified personnel and money for the service of the import equipment. The use of the rated capacity in nuclear medicine of the Russian Federation can be estimated at 15% (for comparison, the similar indicator in the Rosenergoatom system is about 95%).

Now the concept of development of nuclear medicine is under preparation. It has to be reported to the Government of the Russian Federation in the 3rd quarter 2016. The Russian Ministry of Health has issued the special order 1013 of 28.12.2015 "About creation of the interdepartmental working group on development of technologies of nuclear medicine" under the leadership of the deputy minister of health care of the Russian Federation Sergey Krayevy. This working group included representatives of the Department of innovative development and scientific design of the Ministry of Health, Management of the organization of state control and registration of medical products of Federal service for supervision in the field of health care, Directorate on development of Rosatom, Federal Medical Biological Agency, Institute of biology of development of N. K. Koltsov of RAS, Kurchatov institute, Russian scientific center of radiology and surgical technologies, Development department of the pharmaceutical and medical industry of Minpromtorg, Federal Compulsory Health Insurance Fund, ROSNANO, the Central medical and sanitary part of the Ministry of Internal Affairs, Department of social development and innovations of the Ministry of Economic Development, FANO, OOO PET-Technology, AO National Immunobiological Company, Head department of research activity of the Ministry of Defence, OOO Center of Development of Nuclear Medicine.

1. The use of isotopes in medicine

It is necessary to distinguish semantically similar terms.

Radiation medicine represents the section of medicine, which studies the influence of an ionizing radiation on the human body, problems of diagnostics, treatment and prevention of diseases, which are caused by the action of an ionizing radiation. The radiation medicine studies the radio sensitivity and the radiation injury of the person. That is, **radiation medicine** studies the radiation sicknesses.

Nuclear medicine is a direction of modern medicine, which is characterized by the use of radioactive materials and properties of atomic nucleus for diagnostics and therapy of diseases in the different fields of the scientific and applied medicine – in oncology, cardiology, urology and nephrology, pulmonology, endocrinology, traumatology, neurology and neurosurgery, pediatrics, allergology, hematology, clinical immunology, etc. In other words, nuclear medicine determines a disease and treats it by means of effects of radioactivity.

The main direction of nuclear medicine is based on the use of radionuclides (radioisotopes) in the form of open sources of an ionizing radiation – radiopharmaceuticals. According to the state standard GOST R 52249-2009 (combined with the international GMP standard – Good manufacturing practice for medicinal products) radio pharmaceutical medicine (radiopharmaceutical) is any medicine containing in the finished form one or more radionuclides, used for medical purposes.

Radioactive drugs on professional slang are called radiopharmaceuticals or RFP for short.

In the world practice over 130 different radionuclide methods are applied now, carried out using about 200 various RFP.

In our country, the leading enterprises on RFP are Federal center for design and development of objects of nuclear medicine of FMBA (the Federal Biomedical Agency), the Obninsk branch of Research physical and chemical institute named after L.Ya. Karpov (NIFKhI of L.Ya. Karpov), V.G. Khlopin Radium Institute in St. Petersburg, Russian scientific center of radiology and surgical technologies of the Ministry of Health and Social Development of the Russian Federation in St. Petersburg. Besides, all operating in the country centers of the positron-emission tomography (PET), all several dozens of them, produce RFP for PET independently.

Short-lived nuclides for RFP are generated on nuclear reactors (including on research atomic reactors and on the industrial NPPs) and on accelerators of charged particles (for example, cyclotrons). Then "raw isotopes", for example in the form of simple chemical compounds, are used for synthesis of RFP, and often isotopes are transported for thousands of kilometers in special boxes. After that, ready for application RFP are delivered to clinics. The leading countries apply the principle of radio pharmaceutical drugstore when individual doses of RFP are brought to clinics in syringes. Ultrashort-lived nuclides are produced on a site using small-size accelerators of elementary particles (cyclotrons).

More than 75 nuclear reactors and more than 200 cyclotrons are operated in the world for production of radionuclides.

Standards of production of RFP are in detail described in the 51st point of the state standard specification P 52249-2009 Appendix 3.

In nuclear medicine the following groups of radionuclides are dominating:

- short-lived reactor and cyclotron radionuclides (^{99m}Tc, ^{123}I, ^{67}Ga, ^{111}In, ^{201}Tl); these radionuclides are used in more than 90% of all diagnostic tests;
- the ultrashort-lived positron emitters (generally ^{18}F, ^{11}C, ^{13}N, ^{15}O, ^{68}Ga, ^{82}Rb) used in positron-emission tomography;
- the short-lived radionuclides (for example, ^{131}I, ^{89}Sr, ^{90}Y, ^{186,188}Re, ^{103}Pd) applied in the radionuclide therapy;
- the α-emitting radionuclides (^{211}At, ^{212,213}Bi, ^{223,224}Ra, ^{225}Ac) of the therapeutic appointment have the high potential of application already in the short term.

It is necessary to distinguish: 1) production of radionuclides; 2) production of RFP on their basis; 3) rendering medical services on the basis of RFP. This is the typical scheme "raw materials" - "semi-finished products" - "commodity goods". Economic proportions approximately are such as 2% – 28% – 70%.

Russia has the experience in production of 145 radionuclides of 85 chemical elements for medical purposes; it corresponds to the highest world indicators.

According to the Russian classification, RFP are in a perimeter of competences of the industry "Production of the irradiating and electrotherapeutic equipment used for medical purposes". The OKVED code 26.60.1 — "Production of the devices used for medical purposes based on the use of x-ray, alpha, beta- and gamma- radiations".

1.1. Main fields of medical application of radionuclides

Radionuclides for nuclear medicine and the corresponding radiopharmaceuticals and the radiating devices are classified as diagnostic, therapeutic and auxiliary.

In diagnostics radionuclides and radiopharmaceuticals (RFP) are used for obtaining images and for biochemical analysis. The main methods of diagnostics with the use of radioisotopes for obtaining images are the one-photon emission computer tomography (OPECT), the positron-emission tomography (PET), and a biochemical analysis. Tomographic methods are based on registration of γ-radiation of the radionuclides entered into a human body as a radiopharmaceutical by the intravenous, peroral or inhalation way. The method of the radioimmune analysis, which does not require the radiation of the patient, is a variant of the biochemical laboratory analysis with the use of radiopharmaceuticals.

The radiotheraphy is applied both as an independent method, and in combination with other, non-nuclear methods of treatment. The use of the radioisotopes delivered directly to the affected organ allows to localize the radiation, reducing its impact on the tissues nearby. The same radionuclides can be used in diagnostics and radiotheraphy.

Auxiliary devices with isotopes serve for setup of the equipment.

1.1.1. Radionuclides for diagnostics

One-photon emission computer tomography (OPECT)

The method of one-photon emission computer tomography is based on a direct measurement of the γ-radiation, therefore for this method soft γ-emitters with a short half-life period are required. The nuclides, which are decaying with the formation of stable isotopes have a big advantage. For the use in computer tomography radioisotopes with the energy of the γ-quanta of 100-200 keV and a half-life period from several minutes to several days are optimum. The list of the γ-emitting radionuclides used and investigated for diagnostics is provided in Table 1.

Table 1: Main characteristics of radionuclides – γ-emitters used for the diagnostic purposes

Radionuclide	Half-life period	Energy of γ-radiation, keV	Radionuclide	Half-life period	Energy of γ-radiation, keV	Radionuclide	Half-life period	Energy of γ-radiation, keV
^{7}Be	53.2 days	478	^{81m}Kr	13 sec	190	^{128}Cs	3.6 min	441
^{28}Mg	21.1 h	401	^{85m}Kr	4.5 h	151	^{129}Cs	32.1 h	372
^{28}Al	2.2 min	1779	^{81}Rb	4.6 h	190	^{133m}Ba	38.9 h	276
^{38}Cl	37.2 min	1642	^{85}Sr	64.8 days	514	^{137m}Ba	2.6 min	662
^{43}K	22.6 h	373	^{87m}Sr	2.8 h	388	^{134}La	6.5 min	605
^{47}Sc	3.4 days	159	^{89m}Y	16.1 sec	909	^{139}Ce	138 days	166
^{51}Cr	27.7 days	320	^{90m}Nb	18.8 sec	122	^{140}Pr	3.4 min	307
^{54}Mn	312.2 days	835	^{95}Tc	20.0 h	766	^{144}Pr	17.3 min	697
^{52}Fe	8.3 h	169	^{97m}Tc	89 days	96,5	^{157}Dy	8.1 h	326
^{59}Fe	44.5 days	1099	$\boxed{^{99m}Tc}$	6.0 h	141	^{167}Tm	9.3 days	208
^{55}Co	17.5 h	477	^{97}Ru	2.9 days	216	^{169}Yb	32 days	63
^{57}Co	272 days	122	^{103m}Rh	56.1 min	40	^{172}Lu	6.7 days	1094
^{62}Cu	9.7 min	1173	^{109m}Ag	39.6 sec	88	^{178}Ta	9.3 min	93
^{64}Cu	12.7 h	1346	$\boxed{^{111}In}$	2.8 days	171	^{183m}W	5.2 sec	108
^{67}Cu	61.8 h	185	^{113m}In	99.5 min	392	^{191m}Ir	4.9 sec	129
^{62}Zn	9.3 h	597	^{115m}In	4.5 h	336	^{195m}Pt	4.0 days	130
^{69m}Zn	13.9 h	439	^{117m}Sn	13.6 days	159	^{195m}Au	30.5 sec	262
^{66}Ga	9.4 h	1039	^{117}Sb	2.8 h	159	^{197m}Au	7.8 sec	279
^{67}Ga	61.8 h	185	^{118}Sb	3.6 min	1230	^{198}Au	2.7 days	412
^{72}As	26 h	834	^{121}Te	16.8 days	573	^{197}Hg	64.1 h	77
^{74}As	17.8 days	596	^{123m}Te	119.7 days	159	^{197m}Hg	23.8 h	134
^{72}Se	8.4 days	46	$\boxed{^{123}I}$	13.3 h	159	^{203}Hg	46.7 days	279
^{73}Se	7.2 h	361	^{131}I	8.1 days	365	^{199}Tl	7.4 h	455
^{75}Se	120 days	136	^{132}I	2.3 h	668	$\boxed{^{201}Tl}$	72.9 h	167
^{77m}Se	17.4 sec	162	^{127}Xe	36.4 days	203	^{203}Pb	52.0 h	279
^{77}Br	56 h	239	^{127m}Xe	70 sec	125	^{204}Bi	11.2 h	6687
^{79m}Kr	50 sec	130	^{133}Xe	5.3 days	81	^{206}Bi	6.2 days	203

Source: analysis of scientific and technical literature

In practice ^{99m}Tc is most widely used (about 80% of all diagnostic procedures). The following by prevalence is the isotope ^{201}Tl; for example, in the USA it is used in

13% of diagnostic procedures. Besides, ^{123}I, ^{111}In are widely used, and in some cases – ^{51}Cr, ^{67}Ga, ^{81m}Kr and ^{131}I.

Positron-Emission Tomography (PET)

This method is based on registration of the annihilation gamma radiation (511 keV) arising at interaction of the positron, which is formed at the decay of radionuclides, with electrons of the surrounding materials. In medical diagnostics for PET, positron emitters with a half-life period from several seconds to several hours can be used (Table 2). The PET method is of great importance for medical purposes thanks to a possibility of the use of the isotopes, which are part of biologically important compounds – ^{11}C, ^{13}N and ^{15}O, and also ^{18}F, replacing the hydrogen connected with carbon and oxygen. The method allows to observe in real time a transfer of the studied substances in a human body, a course of biochemical processes and, in addition to the diagnostic purposes, it is useful to study the effects of medicinal preparations. The use of the generator isotopes ^{68}Ga and ^{82}Rb is being extended; the promising for PET are such radioisotopes as ^{38}K, ^{45Ti}, ^{62}Cu, ^{64}Cu, ^{75}Br, ^{76}Br, ^{94m}Tc and ^{124}I.

Table 2: The main characteristics of radionuclides – emitters of positrons

Radionuclide	Half-life period	Radionuclide	Half-life period	Radionuclide	Half-life period
^{11}C	20.4 min	^{51}Mn	46.2 min	^{77}Kr	74.7 min
^{13}N	9.96 min	^{52m}Mn	21.1 min	^{82}Rb	1.3 min
^{14}O	70.8 with	^{52}Fe	8.3 h	^{87}Zr	1.6 h
^{15}O	2.03 min	^{60}Cu	23.2 min	^{89}Zr	78.43 h
^{18}F	109.8 min	^{61}Cu	3.4 h	^{92}Tc	4.44 min
^{19}Ne	17.2 with	^{62}Cu	9.8 min	^{93}Tc	2.75 h
^{30}P	2.5 min	^{64}Cu	12.7 h	^{94m}Tc	52 min
^{34m}Cl	32.0 min	^{63}Zn	38.1 min	^{110}In	69 min
^{38}K	7.6 min	^{68}Ga	68.0 min	^{120}I	81 min
^{45}Ti	3.08 h	^{75}Br	98 min	^{122}I	3.6 min
^{49}Cr	42.0 min	^{76}Br	16.2 h	^{124}I	4.15 days

Source: analysis of scientific and technical literature

Markers for biochemical analysis

Different radionuclides – markers of organic compounds – are applied to biochemical analysis as, for example, ^{99m}Tc, widely used in diagnostics. For laboratory studies, special sets are issued for the radioimmunological analysis (RIA sets).

The method of the radioimmunological analysis (RIA) is used for determination of content of the specific antibodies, showing the infectious diseases (tuberculosis, malaria), and also of hormones, vitamins and medicines for identification of hormonal and other abnormalities, research of digestion of nutrients and actions of the medical technique. Another important application of the method of the radioimmunological analysis is the detection of malignant tumors, especially at early stages, and the control of course of disease and of the process of treatment. Biochemical analysis according to the standard terminology in the world does not belong to methods of nuclear medicine. But in Russia such methods traditionally are considered as the medical isotope methods.

Magnetic Resonance Tomography (MRT)

From the moment of the emergence in medicine the magnetic resonance tomography (MRT) became one of the main diagnostic methods allowing to look without any harm "into" different organs.

About 70% of the mass of the human body are the share of hydrogen, which nucleus, the proton, possesses a certain spin and the related magnetic moment. If a proton is placed in an external constant magnetic field, then the spin and magnetic moment are aligned either along the field, or towards, and the energy of the proton in the first case will be less than in the second. The proton can be transferred from the first state to the second, having giving it a strictly certain energy equal to the difference between these energy levels — for example, irradiating it with the quanta of the electromagnetic field of a certain frequency.

The MR-tomograph "sees" accumulations of protons, therefore it is perfectly suitable for studying and diagnostics of the soft tissues and organs containing large amounts of hydrogen (generally in the form of water), and also gives the chance to distinguish magnetic properties of molecules. In such a way it is possible to distinguish, say, the arterial blood containing hemoglobin (the main oxygen carrier in blood) from the venous blood, containing paramagnetic deoxyhemoglobin. FMRT (functional MRT), allowing to trace the activity of neurons of brain, is based exactly on it.

However, such a remarkable technique as MRT, is not suitable for studying of the lungs filled with air (even if to fill them with hydrogen, the signal from gaseous medium with a low density will be too weak against the background noise). And soft tissues of lungs are not too well visible by means of MRT as they are "porous" and do not contain enough hydrogen.

This restriction can be bypassed if to use the "magnetized" gas — in this case the average polarization will be defined not by the external field because all (or almost all) magnetic moments will be oriented in one direction.

The group of researchers from Princeton and the New York university in Stony-Brook became pioneers of the use of the polarized gases in medicine. In 1994 scientists have published in the journal Nature an article, in which the image of lungs of a mouse received by means of MRT has been shown for the first time. The technique has been based on a response of not the nuclei of hydrogen (protons), but of xenon-129. Besides gas was not usual, but hyper polarized, that is "magnetized" in advance. So, the new method of diagnostics was born, which soon began to be applied also in human medicine.

In addition to xenon-129, helium-3 is also applied. It is harmless and allows to receive more accurate images than xenon-129, has three times bigger magnetic moment that causes a stronger signal in nuclear magnetic resonance. Besides, the enrichment of xenon-129 because of proximity of its weight with other isotopes of xenon is an expensive process and an achievable polarization of the gas is significantly lower than that of helium-3. In addition, xenon-129 has sedative effect.

Advantages of MRT with the use of the hyper polarized gases are not limited to the above mentioned effects. As the gas is hyper polarized, then the level of a useful signal is much higher (approximately by 10 thousand times). It means that need for superstrong magnetic fields disappears, which leads to a design of the weak-field MR-tomographs — they are cheaper, more mobile and much more spacious. Such installations use the electromagnets creating the field of about 0.005 T that is one hundred times weaker than in standard MR-tomographs.

1.1.2. Radionuclides of therapeutic purposes

Radionuclide therapy (RNT)

The main advantage of radionuclide therapy (RNT) is the possibility of the targeted impact of radiopharmaceuticals (RFP) on the pathological centers due to organospecificity or the biochemical tropism. The second important advantage is that a single application (peroral or intravenous) of RFP affects in one step all pathological centers. At local introductions of RFP, for example, intra-joint, intra-cavitary introductions of radio colloids or radioactive microspheres, by the distribution of the applied solution it is possible to reach very targeted short-distance (in the millimetric range) irradiation of surfaces of complicated shapes with achievement of high absorbed doses (to several hundred of Gy (gray)).

Many types of RNT are in essence the target radiation therapy as they are based on the organotropic or tumor specificity. One can speak about a "molecular radiation therapy", because it works at the level of the molecular transport. The radioactive iodine (^{131}I), applied at the cancer of the thyroid gland and at thyrotoxicosis, belongs to organotropic medicines. The accuracy of delivery of the radioactive iodine into cells of the thyroid gland is caused by the unique natural mechanism – the Na-I- symport (it is connected with functioning of Na+/K+-ATPase). Let's remind: symport is a pair transport of two different organic molecules or ions through a cell membrane thanks to the active transport, which is carried out by the specific proteins located inside the membrane.

Monoclonal antibodies, marked by beta- or alpha- emitters, with tropism to tumor cells, are also the example of the targeted radiation impact on cells-targets. Such a high precision and specificity allows to create in the centers very high absorbed doses (up to several hundred Gy) at the minimum damage of surrounding tissues. Less specific is the accumulation of medical osteotropic RFP, applied for palliative therapy of patients with metastases in bone and a pain syndrome. Fixing of these medicines in a bone tissue is carried out due to tropism to pathologically strengthened mineral metabolism, characteristic of the metastatic centers, where osteoblastic processes prevail.

The advantage of high tropism and specificity is most clearly expressed at the radioiodine therapy (RIT), where its effects are unique. So, RIT is an uncontested method of treatment of the differentiated cancer of the thyroid gland with the remote metastasis, and even with metastasis in lungs it is possible to reach full remission of disease. It is exactly the specificity of radioactive iodine only to cells of the thyroid gland is the cornerstone of RIT and defines its unique efficiency. The same technology is used also at thyrotoxicosis where RIT is the most effective and safe type of treatment.

Radionuclide therapy is applied with success to palliative treatment of the patients having multiple metastasis in bones. The method consists in intravenous administration to the patients of osteotropic medical RFP, which are accumulated in bone metastases and affect them with the beta radiation.

Radionuclides have found the application also at treatment of not oncological diseases. So, for example, at resistant synovitis at patients with severe forms of rheumatic diseases, and also at the hemophilic joints radiosynovectomy is used as a method of choice. The treatment consists in the introduction directly to the affected joint of a colloidal solution of RFP that allows to reach a resistant, and frequently lifelong suppression of joint synovitis, when the inflamed synovial tissue under the influence of the local radiation became inactive.

Recently have been developed and have begun to be applied successfully such RNT methods as radio immunotherapy, which is carried out with the use of the monoclonal antibodies connected with ^{131}I, ^{90}Y, ^{111}In. The therapy of the neuroendocrine tumors having receptors to somatostatin, which are hard to treat by other methods, is carried out with the use of the synthesized analogs of somatostatin connected with ^{90}Y and ^{111}In.

The technology of embolization of tumoral vessels by radionuclide substances is applied for treatment of malignant tumors of liver and at its metastatic damage.

Open sources of radiation

In recent years there is an intensive research in the field of radiotherapy with the use of open sources of radiation. Promising results are obtained at the use of radiopharmaceuticals for treatment and prevention of spread of malignant tumors and rheumatoid arthritis, and also for reduction of hyperfunction of the thyroid gland and for anesthesia at metastases in bones. A recent trend is a prevention of restenosis after angioplasty. For internal local radiation (brachytherapy) are suitable radioisotopes, which decay with the formation of particles with a small free path:

- emitters of the β^--particles with the energy of 200–2000 keV;
- emitters of the α-particles having a high linear energy transfer ~100 keV/micron and a short free path (50–100 microns);
- the radionuclides decaying on the reaction of the electron capture (EC) or an internal electronic conversion.

As open sources of radiation for the therapeutic purposes more than 30 radionuclides (Table 3) were investigated. From them the greatest use have gained ^{32}P, ^{131}I and ^{90}Y, and also ^{89}Sr, ^{153}Sm, ^{186,188}Re, ^{192}Ir.

Table 3: Main characteristics of radionuclides for therapy with open sources

Radionuclide	Period of half-decay	Type of decay	Mean energy of β-radiation and energy of the most intensive α-and γ-emitters, keV
^{32}P	14.3 days	β^-	β 695,2
^{47}Sc	3.4 days	β^-	β 162,5, γ 159,4
^{67}Cu	61.8 h	β^-	β 147,5; γ 184,6
^{77}Br	56 h	EC;	γ 239, 521
^{86}Y	14.7 h	EC; β^+	γ 1077, 628
^{88}Y	106.6 days	EC; β^+	γ 1836, 898
^{90}Y	64.3 h	β^-	β 928
^{91}Y	58.5 days	β^-	β 606,6
^{89}Sr	50.6 days	β^-	β 583

^{97}Ru	2.9 days	EC	γ 216, 325
^{103}Pd	17.0 days	EC	γ 357,5
^{111}Ag	7.5 days	β^-	β 358
^{111}In	2.8 days	EC	γ 171,3; 245,4
^{115}Cd	53.5 h	β^-	β 324,5; γ 336,3
^{117m}Sn	13.6 days		γ 158,6
^{124}I	4.2 days	EC; β^+	γ 602,7; 1691
^{125}I	60.0 days	EC	γ 35,5
^{131}I	8.1 days	β^-	β 191,4; γ 364,5
^{149}Tb	4.2 h	EC; β^+; α	α 3967; γ 165, 362,3
^{153}Sm	46.7 h	β^-	β-223,2; γ 103,2
^{159}Gd	18.6 h	β^-	β 254; γ 363,3
^{166}Ho	26.8 h	β^-	β 668; γ 80,6
^{169}Er	9.4 days	β^-	β 99,1
^{170}Tm	128.6 days	β^-	β 315,5; γ 84,3
^{175}Yb	4.2 days	β^-	β 142; γ 396,3
^{177}Lu	6.7 days	β^-	β 136,8; γ 288,4
^{186}Re	90.6 days	β^-; EC	β 342,0; γ 137,2
^{188}Re	16.9 h	β^-	β 763,9; γ 155,0
^{192}Ir	74.1 days	β^-; EC	β 186,5; γ 316,5
^{194}Ir	19.2 h	β^-	β 812,6; γ 328,4
^{198}Au	2.7 days	β	β 314,8; γ 411,8
^{199}Au	3.1 days	β	β 87,0; γ 158,4
^{212}Bi	60.6 min	β^-; α	β 655; α 6054; γ 727,3
^{213}Bi	45.7 min	β^-; α	β 431,5; α 5870; γ 439,7
^{211}At	7.2 h	α	α 5870; γ 68,7;
^{225}Ac	10.0 days	α	α 5830
^{253}Es	20.5 days	α	α 6633
^{255}Fm	20.1 h	α	α 7024; γ 80,9

Source: analysis of scientific and technical literature

Implanted radioisotope sources of current

The separate direction in nuclear medicine is the use of radioisotopes for creation of the sources of current, which are applied in the implanted equipment for stimulation of the weakened or broken functions of human organs. The main type of the implanted medical equipment are currently pacemakers. This equipment demands reliable, small-size and long-lasting sources of the current with a power from 0.1 microwatt to 10 W. The choice of the radioisotopes suitable for medical sources of current is limited, mainly, for reasons of radiation safety, by isotopes ^{238}Pu, ^{147}Pm, ^{3}H, ^{67}Ni. Now ^{238}Pu and, seldom, ^{147}Pm are used. Thermal sources contain 0.15-0.5 g of $^{238}PuO_2$ (in the form of the pressed powder) or about 70 curie ^{147}Pm (in the form of oxide); the service life of these sources of the current is 10-20 years (^{238}Pu) and 7-10 years (^{147}Pm).

Radioiodine therapy at cancer of the thyroid gland

RIT (radioiodine therapy) is the most known and widespread RNT method in the world, which makes more than 2/3 of all medical procedures with the use of open sources of radiation. It is applied to treatment of patients with the differentiated cancer of the thyroid gland (DCTG) and has no alternative in the presence of the remote (especially pulmonary) metastases. It is important to remember, that it is used only in combination with surgical treatment. At first, the total thyroidectomy is performed, and, if necessary, lymphadenectomy of affected cervical lymph nodes and then the therapy by the radioactive iodine is carried out.

RIT has two important functions in treatment of patients with DCTG. First, it is used after a surgical stage for ablation (destruction, suppression) of the remains of the thyroid tissues. Secondly, and it its major role, it is necessary for treatment of the DCTG metastases. It is necessary to remind that it is the only effective method of treatment in the presence of the remote metastases of DCTG. The postoperative ablation of the remains of the thyroid gland at patients with the differentiated carcinoma of the thyroid gland considerably reduces mortality, and also authentically reduces the frequency of recurrence or development of the remote metastases in comparison with the patients receiving only treatment by thyroid hormones. The effect of RIT is based on the unique property of isotopes of iodine to be accumulated selectively in thyroid cells. This accumulation is carried out by an active transport of ^{131}I from blood by means of the Na-I-symporter into the follicular epithelium of the thyroid gland. The medical effect, that is the destruction of cells, which have absorbed ^{131}I, is implemented at the expense of β-particles with a small free path in tissues. 90% of the energy of the decay of β-particles in tissues are absorbed within 1-2 mm. Thus, the destroying effect of the radioactive iodine is limited to tissues in which it is actively accumulated. The isotope ^{131}I causes the ionization of molecules of cells and production of a large number of the free radicals and short-lived toxins capable to damage the vital biological structures, such as DNA and fermental systems. It also leads to the death of cells of the thyroid gland including cancerous ones. The isotope ^{131}I has also the gamma radiation that allows to receive the detailed image of the centers of accumulation at studies on the gamma camera. Complications at RIT are practically absent, side reactions are reversible. It is important that the medical effect can be implemented at all metastases at the same time, including those, which are not revealed by other methods of diagnostics.

In addition to medical effects, RIT allows:

·- to remove the substrate synthesizing thyreoglobulin,

that at further observation the level of this hormone in serum of blood could be used correctly as a tumoral marker;

·- to find the zones of progressing, recurrence and metastases, which are not revealed in other ways.

Radioiodine therapy at thyrotoxicosis

The therapy by the radioactive iodine is applied not only at cancer of thyroid, but also at treatment of other pathology of the thyroid gland. The thyrotoxicosis traditionally is the most widespread subject to the medical use of the radioactive iodine in foreign clinical practice, recognized in the majority of the developed countries as a method of choice. It allows quickly and with the minimum expenses to reach permanent suppression of pathological hyperfunction of thyroid. At the same time Russia and the CIS countries most often use a long-term drug treatment, which is effective only for 15-20% of patients. The application of thyreostatics lasts for years, and it is accompanied by risk of complications, first of all myelotoxic complications, and, what is very important, keeps the person in the atmosphere of the disease, without giving the chance to fully recover. At inefficiency of the drug treatment, the surgery is offered, which, in turn, is fraught with serious complications in the form of injury of returnable nerves, hypoparathyroidism as a result of travmatization and removal of the parathyroid glands, and also the different problems connected with anesthesia, bleeding, and intolerance of drugs.

Now, considering high performance and a fast disappearance of symptoms of thyrotoxicosis, treatment by the radioactive iodine it is recommended for patients with the revealed for the first time diffusion toxic goiter (with side effects at thyreostatic therapy), and not just at only heavy and complicated (cardiovascular insufficiency) forms and recurrence of disease. As ^{131}I has no the proved teratogenic effect, its appointment is permitted for patients of a reproductive age (excluding at pregnancy). The effect of RIT is delayed, therefore an observation by the endocrinologist within several months after the treatment is necessary. The radioiodine therapy does not increase risks of carcinogenesis or dangerous genetic effects. The absorbed ionizing radiation dose on gonads does not exceed 2 centrigray, that is below than when performing roentgenography of the lumbar department of backbone, intravenous urography or irrigoscopy with barium.

Efficiency of RIT exceeds 90%. It is important to understand that if in the treatment the patient acquires hypothyroidism instead of thyrotoxicosis, then it is not complication, and it is considered a natural result of the therapy. The hypothyroidism is easily compensated by a replaceable hormonal therapy. The administration of thyroxine and its analogs is safe for health, unlike a long administration of thyreostatics.

Radionuclide therapy in treatment of patients with metastases in bone

Development of bone metastases represents one of the most frequent manifestations of progressing of the oncological disease. The largest frequency of metastasis in bone is described at the cancer of the breast and prostate gland. In these groups metastases in bone can occur at 85% of patients, especially at late stages of the disease. The pain in bones caused by metastases steadily progresses and poorly responds to treatment, and often this pain is the dominating factor worsening quality of life of the patient. It is necessary to recognize that from the moment of identification in the patient of multiple bone metastases, the achievement of absolute recovery becomes almost unreal, and all treatment becomes palliative by definition. Nevertheless, these patients need continuous treatment to suppress the tumoral growth and to maintain functional conditions of organism. Different methods are applied to treatment of patients with metastases in bone: the remote radiation therapy, bisphosphonates, chemotherapy, hormonal therapy, symptomatic treatment (anesthetizing, etc. medicines, reflexotherapy, etc.), surgical treatment, different types of the supporting treatment. The radionuclide therapy with osteotropics is a modern method, which is widely applied in the developed countries. It became a necessary component of complex palliative treatment and allows to suppress the pain syndrome, to reduce the need for analgetics, to improve mobility, to increase quality of life, and in some cases to slow down process of progressing of metastases.

Radiopharmaceuticals on the basis of isotopes ^{153}Sm, ^{89}Sr, ^{32}P, ^{33}P, ^{186}Re, ^{188}Re, ^{117m}Sn, ^{177}Lu, ^{90}Y, ^{131}I are actively used in the world practice for the palliative therapy of bone metastases now. Also, the alpha-emitter ^{223}Ra is applied. Recently for a more effective help to patients of this group combinations of RNT with other types of the radiation therapy and with other methods of treatment are often used.

In Russia two drugs are now used: samarium-oxabifor, ^{153}Sm and ^{89}Sr-chloride. Efficiency of therapy makes 60-80%. The most successful results are received in patients with the breast and prostate cancer.

Radionuclide therapy in rheumatology. Radiosynovectomy

Radiosynovectomy (radiosynoviorthesis, radiosynovolysis) is the method of the radiation therapy consisting in the intra-joint introduction of the radiopharmaceutical (RFP) containing radionuclides with a high energy of the β-radiation. The principle of the therapeutic effect of a radionuclide is based on the influence of β-particles on synovial cover of a joint. The injected drug is taken due to phagocytosis by cells of the superficial epithelium of the synovial cover, having thereby the damaging effect. A local radiation by β-particles of tissues of the inflamed synovial cover of a joint results in a process of ablation, that is the death of functionally active cells responsible for maintenance of inflammation. After that there is usually a superficial fibrosis of synovia. In cases of a positive result there is a decrease in pain and in active inflammation. Radiosynovectomy by the efficiency is comparable to the surgical treatment, however it is less traumatic, it is much simpler in performance and does not demand difficult and long postoperative rehabilitation actions. Now quite a wide range of RFP is applied on the basis of isotopes ^{90}Y, ^{32}P, ^{169}Er, ^{165}Dy, ^{153}Sm, ^{89}Sr, ^{186}Re, ^{188}Re, and ^{177}Lu. The international experience shows that application of the radionuclide therapy for this group of patients allows to reach permanent remission of synovitis in 65-85% of patients.

Unfortunately, during the reorganization (perestroika) in the early nineties in Russia the release of radio colloids has stopped, and the whole direction in the domestic rheumatology and nuclear medicine has ceased to exist, despite high efficiency of the method, great needs and the social importance.

1.2. Main fields of medical application of stable isotopes

Application of stable isotopes in medicine includes the following main directions:

- as tracers when studying biochemical and physiological processes in live organisms, for diagnosis of diseases, and also in pharmacological researches;
- for treatment of malignant tumors;
- as starting materials for receiving medical radioisotopes.

1.2.1. Diagnostic application of stable isotopes

The isotope analysis in biomedical studies applies methods of mass-spectrometry, infrared absorption to, etc. A specific place in the analysis of labeled compounds is held by Nuclear Magnetic Resonance spectroscopy (NMR spectroscopy). Modern nuclear magnetic resonance studies use many stable isotopes; now ^{1}H and ^{13}C are most often used.

The nuclear magnetic resonance spectroscopy allows not only to determine the content of an isotope, but also to obtain structural and chemical information, including the location of a label, the mass and atomic structures of fragmentary ions.

The modern NMR spectroscopy is being quickly developed and improved both in the tool equipment, and in methodology of receiving and interpretation of spectra.

Now the isotopes of oxygen and hydrogen are used for research of processes of metabolism. ^{17}O and ^{18}O are used at measurement of the total water in organism, and also in researches of organ tissues, in particular for water research in normal and cancer cells. The method of twice labeled water ($D_2{}^{18}O$) is used for studying the energy costs of an organism in connection with a problem of adaptation of energy needs of the person to accommodation conditions.

Research of metabolism of drugs also applies compounds, labeled by both ^{15}N and ^{13}C.

One of methods of diagnosis of metabolic disorders and dysfunction of organs, and also of metabolism of drugs, is the test of the exhaled air (the isotope test of breath). These tests are based on the fact that a patient suffering from exchange violations has an oxidation rate of a special medicine labeled with a stable isotope ^{13}C or radioactive ^{14}C, that differs from a normal rate. After the introduction of a suitable labeled compound the isotope ratio is measured in the exhaled CO_2 and the violation is diagnosed. Recently this method began to be used successfully for diagnostics of a syndrome of an excessive development of microflora and a syndrome of dysfunction of intestines, and also for studying nutrition of newborn children, pregnant women and nursing mothers.

The medical preparation, taken by a patient undergoes in a body changes due to biochemical reactions in different organs (metabolism processes). After a while a preparation decays partially or completely and is removed from organism. The carbon, which is contained in a preparation, in the course of exchange reactions is oxidized and removed from an organism through lungs in the form of the carbon dioxide gas, which is present at exhaled air. If the isotope composition of the used carbon is different from the natural isotope composition, then the corresponding isotopic deviation of carbon in the exhaled air can be registered. Thus, having information on ways and speeds of metabolic transformations of the medical preparation and labeling it with an isotope carbon label, it is possible to draw conclusion on condition of the studied organ by analyzing the isotope content in the exhaled air.

1.2.2. Therapeutic application of stable isotopes

During the last decade, great success is achieved in treatment of malignant tumors with the use of the method of neutron-capture therapy (NCT). Boron-containing organic compounds were the most successful in this direction, and the attention of scientists of many countries has been drawn to a search of new ways of their synthesis.

The stable isotope ^{10}B has the unique physical and chemical properties, which have defined its importance for development of chemical and beam methods of treatment of tumors with use of the NCT method. If compounds of ^{10}B are introduced into tumor cells and then are irradiated with a neutron flux, then as a result of a nuclear reaction the α- particle with a high energy is formed, capable to selectively strike tumor cells of a tissue. The total free path of α- particles is equal to about 10-14 microns that is comparable to cell sizes and therefore injuries of healthy cells are improbable. Chemical properties of boron allow to synthesize its derivatives that expands borders of search of the compounds suitable for NCT.

A key problem in development of the NCT method is to provide a selective transport of boron into a tumor or, what is more important, into tumor cells. This aspect represents a special case of a medical problem – the delivery of medicinal agents to organs and tissues targets.

Today, NCT of tumors of brain use a drug of the "second" generation – mercaptoundecahydrododecaborate. This drug is quickly removed from blood, does not get into normal tissue of brain, is retained in the tumoral tissue and can transport more than 10 mkg of boron on 1 g of tissue of a tumor.

A decisive progress in the NCT area is expected in the case of the use of medicines of the "third" generation on the basis of biologically active compounds – the steroids, amino acids, nucleosides, porphyrines, antibodies and other compounds, which are characterized by an increased content or accumulation in tumors. It is expected that these drugs will provide concentration of boron in tumor of about 35 mkg/g, the ratio of ^{10}B above 10, with the period of a half-release of boron from a tumor up to several days. It is shown that boron derivatives of amino acids are capable to get selectively into cells of melanoma (melanocytes) and to create in them high concentrations of boron. Since 1987, Japan in clinical conditions uses boron-containing phenylalanine in the NCT treatment of melanoma of skin and its metastases, in particular into the skull bone.

In addition to boron-10, gadolinium-157 is being investigated in recent years. The nucleus of the isotope gadolinium-157 has the highest section of capture of thermal neutrons – 25,400 barn. Researchers study the binary medicine containing boron and gadolinium, which would possess certain tumor tropism to provide a concentration of the isotope ^{10}B, equal to 35-40 mkg on 1 g of a tumor, and for the isotope ^{157}Gd – more than 800 mkg on 1 g of a tumor. So, at the gadolinium neutron-capture therapy (GNCT) of melanoma of mucous membrane of mouth, research was conducted with the use of the gadolinium-containing drug Dipentast, in which gadolinium-157 was in its natural concentration of about 15%. Dipentast was introduced into a tumor by a pharmacopuncture just before of irradiation in a dose ~ 1 ml/g of tumor.

It should be noted that in medicine stable isotopes are applied considerably less than radioactive isotopes, and, it is improbable that stable isotopes will fully replace radiotracers. However, interest in stable isotopes does not weaken. They are used in the following cases:

- when the element has no suitable radioisotopes (nitrogen, titanium, etc.)
- in researches where the risk from the use of radioisotopes is considered inadmissible (small children, pregnant women, etc.);
- at measurement of very low concentrations (from nanogram to picogram) of biologically important molecules by isotope dilution methods. Though generally the radioimmune analysis is quicker and simpler, the technology of the isotope dilution has specific features, which are not reached in other ways.

It is expected that the application of stable isotopes gains the greatest scope in connection with specific diagnostic analyses, which yield fast results and exert a direct impact on treatment of patients. Besides, specific analyses, which can be used for overseeing the course of treatment of a specific patient, can attract interest.