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A little something from physics for medicine
(Scientific session of the Physical Sciences Division of the Russian Academy of Sciences, 23 April 2014)

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A scientific session of the Physical Sciences Division of the Russian Academy of Sciences (RAS), entitled "A little something from physics for medicine", was held on 23 April 2014 at the conference hall of the Lebedev Physical Institute, RAS.

The agenda posted on the website of the Physical Sciences Division, RAS, www.gpad.ac.ru, included the following reports:

(1) **Rumyantsev S A** (D Rogachev Federal Research and Clinical Center of Pediatric Hematology, Oncology, and Immunology, Moscow) "Translational medicine as a basis of progress in hematology/oncology";

(2) **Akulinichev S V** (Institute for Nuclear Research, RAS, Moscow) "Promising nuclear medicine research at the INR, RAS";

(3) **Nikitin P P** (Prokhorov General Physics Institute, RAS, Moscow) "Biosensorics: new possibilities provided by marker-free optical methods and magnetic nanoparticles for medical diagnostics";

(4) **Alimpiev S S, Nikiforov S M, Grechnikov A A** (Prokhorov General Physics Institute, RAS, Moscow) "New approaches in laser mass-spectrometry of organic objects".

The publication of the article based on the oral report No. 2 is presented below.

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Promising nuclear medicine research at the Institute for Nuclear Research, Russian Academy of Sciences

S V Akulinichev

1. Introduction

Nuclear technologies, along with other physical methods, are acquiring increasingly greater importance in modern medicine. Today, over half of cancer patients are successfully managed with remote or contact radiation treatment in the form of either mono- or combined therapy. The number of such patients continues to grow: in developed countries, almost every patient suffering from oncological or another severe pathology undergoes radiodiagnostics (X-ray computed tomography, positron emission tomography (PET), single-photon emission computed tomography, etc.). Investigations designed to develop new technologies for nuclear medicine and radiotherapy are priority topics in the research programs of many centers and universities of developed countries, from CERN in Geneva to most local universities. In these countries, investments in nuclear medicine and radiation therapy research are regarded as an indispensable prerequisite for the improvement of the quality of life of individuals and populations.

Figure 1. Linear proton accelerator at the Institute for Nuclear Research, RAS.

The unique characteristics of the Institute for Nuclear Research (INR) linac in Troitsk (Fig. 1) provide an opportunity to carry out basic and applied nuclear and neutron physics research, as well as to produce most isotopes for modern medicine and proton therapy of neoplasms of any localization [1]. At present, the accelerator generates proton beams with an energy ranging 100–220 MeV and average current of 100 μA (to be increased in the long run to 600 MeV and 0.5 mA, respectively). Today, the INR linac is the sole high-current medium-energy proton accelerator in this country. Its energy range is optimal for proton beam therapy; it is also used to produce radioisotopes that cannot be obtained in reactors or ordinary low-energy proton accelerators, e.g., ^{82}Sr and ^{103}Pd. All the main characteristics of proton beams generated at the Troitsk accelerator, such as

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energy range, pulse frequency and length, and emittance, are optimal for proton therapy. Moreover, the research complex in Troitsk makes possible combined radiation therapy based on proton and electron accelerators in two adjoining treatment rooms.

The research program for medicine being implemented at INR was formulated based on the experience of other nuclear centers, taking into consideration current trends in modern medicine, and the specific characteristics of the accelerator. The main goals of the program are proton beam therapy, production of radioisotopes for diagnostic and therapeutic purposes, the manufacture and clinical application of radionuclide brachytherapy sources, and radiodiagnostics.

2. Proton beam therapy

Accelerated protons are known to exhibit a specific behavior when passing through any medium; namely, the ionizing energy they release does not decrease as protons are slowed down (in contrast to that of electrons or photons) but increases to a maximum when they stop. Liberation of ionizing energy in biological tissues causes cell disintegration at a specific target site. Choosing proton energy on an individual basis makes it possible to locally destroy a tumor localized at any depth. The practical implementation of proton therapy is thus far a difficult scientific and technical problem. Not a single new proton therapy center has been built in Russia during the last four decades, whereas several such centers have been annually set up in other countries. Today, there are almost 50 of them all over the world. As a result, proton beam therapy is available only to 1% of those Russian patients for whom it is indicated for treatment. Meanwhile, according to various estimates, from 40 to 50 thousand patients per year need to be treated with this technology.

Trials of the first proton radiotherapeutic unit with a fixed horizontal beam (Fig. 2) are currently underway. Results of the latest irradiation session indicate that the characteristics of the proton beam fit the main therapeutic requirements, which makes it possible to treat tumors up to 9 cm wide of any localization. Figure 3 illustrates the depth-dose distribution of a proton beam. It shows that the beam is sufficiently homogeneous at the presumed tumor site (plateau on the plot) where fluctuations of its intensity do not exceed 5%. In the course of creation of the proton therapy complex (PTC),

Figure 2. Proton beam therapy unit.

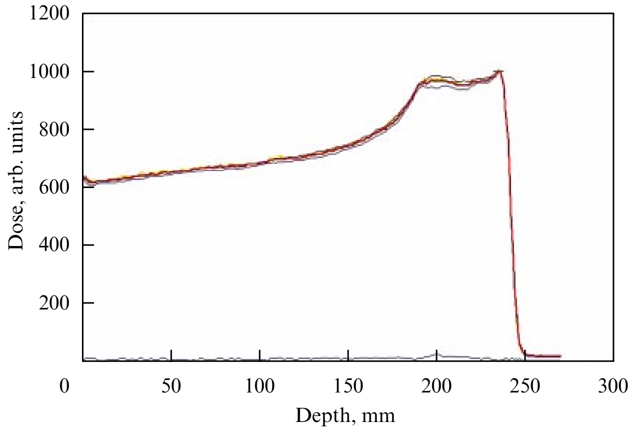

Figure 3. Depth-dose distributions of protons with an energy of 209 MeV measured in a water phantom (results of measurements with the use of different brush filters).

researchers at INR designed and manufactured a few tens of unique devices, such as an automated high-precision patient positioner allowing irradiation in both sitting and lying positions (see Fig. 2), multichannel air-ionization chambers for monitoring the proton therapy beams, and an original beam formation system.

Even now, the conventional radiotherapeutic and diagnostic facilities at INR are extensively used for the practical high-tech treatment of oncological patients. They comprise a photon ray unit based on the SL-75 medical electron accelerator, close-focus X-ray therapeutic apparatus, and Aquilion LB16 CT simulator. Over 300 cancer patients admitted to the RAS Troitsk hospital have been examined and treated during the last 3 years. Statistical data on the outcome of beam therapy give evidence of its high effectiveness.

Despite the unique beam characteristics of the high-current proton accelerator, it would be optimal to use a new specialized medium-energy accelerator for proton therapy and other medical applications. The fact is that the INR linac was initially developed in then Soviet Union for the solution of nonmedical problems and is actually very expensive to maintain and operate. At the same time, a new modern medium-energy proton accelerator can be installed in the INR Experimental Hall (bldg 25) without laying additional structures or groundwork. Only biological protection will be needed for the new accelerator. One of the most promising variants of the new proton accelerator is the combination of a cyclotron and an additional booster linac. Such a combination is known as 'cyclinac' (blend of cyclotron and linac). The cyclotron generates high-intensity proton beams with an energy ranging 30–100 MeV, and the linac further accelerates to 250 MeV a small fraction of protons from the cyclotron needed for therapy. In such a case, the cyclinac makes it possible to simultaneously produce practically any medical isotopes and perform proton therapy in a few treatment rooms. Moreover, the use of high-intensity neutron fluxes generated in the high-current cyclotron allows simultaneously activating radionuclide sources for medicine and carrying out other applied and basic neutron studies. Construction of the first radiological center intended for using this combination of accelerators is currently underway in Rome with the participation of CERN specialists [2]. A layout of this center is depicted in Fig. 4. Cooperation

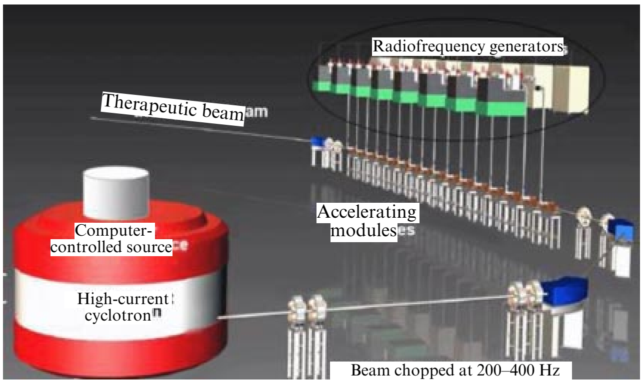

Figure 4. Schematic of the future proton therapy center in Rome, Italy combining a high-intensity cyclotron and a low-intensity linear accelerator.

between Russian and European researchers in the development and creation of new accelerators of this type for medical applications would significantly reduce the cost and construction time of new-generation proton therapy centers.

3. Production of medical isotopes

Requirements for diagnostic and therapeutic radioisotopes grow steadily year after year. The cost-effective production of some of them is only possible based on high-current medium-energy proton accelerators. Thus far, there are fewer than ten such facilities in the world, with one being operated by INR. A proton beam with an energy of 160 MeV was extracted in the middle of this accelerator, to be employed for target irradiation with a view of producing medical isotopes (Fig. 5). This facility has been successfully operated for more than 10 years. It is the world's largest machine of such a type and the sole one in Europe and Asia. It is a highly automated and operationally safe facility. INR has developed and implemented into practice a number of technologies for the production of radioisotopes that are successfully employed in Russia and USA. In the past 10 years, targets irradiated in the Troitsk accelerator have been delivered on a regular basis to the Los Alamos National Laboratory (LANL), USA, where they are exploited for radiochemical extraction of radionuclides and the manufacture of radiopharmaceutical products (RPPs). By way of example, cardiovascular PET imaging with strontium-82 produced at INR was performed to examine over 100,000 patients, mostly in the USA and Canada [1]. Some other important isotopes produced at INR have good prospects of finding use in the future for diagnostics and the treatment of oncological and cardiovascular diseases.

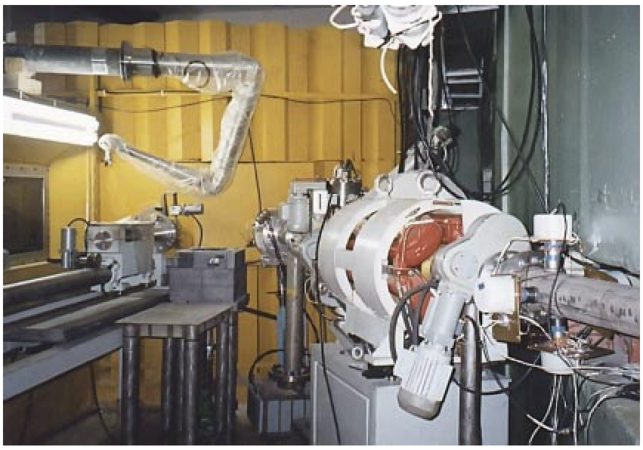

Figure 5. INR isotope production facility.

Let us discuss now certain problems related to the employment of strontium-82 with a half-life of 25 days and strontium/rubidium-82 generators for PET diagnostics. The use of a short-lived radionuclide generator (in this case, rubidium-82 with a half-life of 1.3 min) permits us to avoid construction of a cyclotron and organization of a radiochemical laboratory directly in the clinic. This enhances the availability of early diagnostics of myocardial infarction and some other diseases. Such an approach to PET diagnostics has been adopted in the USA, where cardiovascular pathology is the second main cause of death after oncological diseases, in contrast to Russia, where cardiovascular mortality prevails, in the first place as a consequence of the very low incidence and quality of early diagnostics. INR, jointly with its partners, has developed a new strontium/rubidium generator that successfully passed preclinical trials and is now undergoing clinical studies in the Russian Research Centre of Radiology and Surgical Technologies (RRCRST), Saint Petersburg. The designers of the new generator were awarded with Gold medal of All-Russian Exhibition Center. The utilization of this generator for PET in other countries has until recently been limited by the poor availability of strontium-82. In partnership with other institutions, INR organized production of strontium-82, its chemical extraction, and the manufacturing of generators. Additional investments are needed to scale up the production and implement the generators in healthcare practices in this country and abroad.

INR has developed manufacturing technologies for some other medical isotopes, such as tin-117m — a promising radionuclide for therapeutic applications. It finds use first and foremost in the treatment of bone cancer. Recent studies have shown that this tin isotope is suited equally well for the management of vascular disorders. INR and Brookhaven National Laboratory (BNL), USA have jointly developed the technology for the production of 'carrier-free' tin-117m from irradiated targets. In cooperation with the L Ya Karpov Research Physicochemical Institute (RPCI) in Obninsk, and the Mayak Production Association, INR developed technology for the separation of palladium-103 from silver targets irradiated in the INR accelerator. This technology was employed in the Research Medical Radiology Centre (RMRC) in Obninsk to obtain new RPPs, including albumin microspheres that proved highly efficacious in biological experiments and can find use in the treatment of prostate adenoma, liver and breast cancer, and other oncological diseases. Actinium-225 and radium-223 also serve as promising medical radionuclides capable of emitting alpha-particles with a short range in biological tissues. Wide application of these radionuclides may considerably improve the therapy of various oncological diseases. They may be of special value for targeted delivery of oncological drugs to affected cells in combination with nanoparticles bound to monoclonal antibodies. Their extensive worldwide application is curtailed by limited production. Jointly with the Lomonosov Moscow State University Faculty of Chemistry and the A N Frumkin Institute of Physical Chemistry and Electrochemistry, INR developed a new method for the production of actinium-225 and radium-223 isotopes from proton-irradiated thorium targets.

Today, INR only turns out radionuclides at its proton linear accelerator, whereas the irradiated targets are transferred to other (mostly foreign) laboratories for processing and extracting end products and RPPs. However, INR has just completed a project on designing a radiochemical laboratory with 'hot chambers' for the processing of accelerator-irradiated targets and production of pure radioactive isotopes.

INR plans to expand its experimental facility by commissioning a new high-current proton cyclotron with an energy of 70 MeV in the Experimental Hall (bldg 25), in addition to the existing proton linac (see Section 2). It is expected to essentially extend the potential for the production of medical radioisotopes. The cyclotron will serve several purposes, viz. the generation of an intense beam to produce a variety of isotopes for medicine, the use of a part of the beam for further acceleration and performance of proton therapy, and utilization of secondary neutrons for various applications (e.g., activation of medical radionuclide sources) and neutron physics research. INR has the proper manufacturing premises, engineering support facilities, and sanitary protective zone needed for the implementation of this project. The novel technologies and unique facilities for proton therapy and isotope production developed at INR are prerequisites for the rapid initiation of the second phase of the project of a nuclear medicine center based on the new specialized proton accelerator.

4. Production of new radionuclide sources for contact radiotherapy

INR research projects pertaining to other aspects of nuclear medicine and ray therapy include, in particular, the development of brachytherapeutic technologies for the effective and organ-sparing radical treatment of a number of malignant neoplasms, such as prostate, breast, and gynecological cancers. Brachytherapy is based on the administration of sealed radionuclide sources directly into the affected region. In most cases, it is possible to avoid post-radiation complications, and the duration of the treatment does not exceed a few days. In terms of the type and activity of radiation sources, brachytherapy is categorized into low-dose rate and high-dose rate brachytherapies (LDR and HDR, respectively). In the former mode, the sources are usually left in the tissue forever, while in the latter one they are removed after short-term irradiation of the affected site.

HDR is currently performed using two types of sealed radionuclide sources: one based on cobalt-60, and the other on iridium-192. The high radiation energy of cobalt-60 leads to the strong irradiation of vitally important organs of patients. Moreover, the application of this isotope requires building expensive HDR cabinets with concrete walls for a heavy shielding. For this reason, cobalt-based sources are increasingly rarely used in clinical practice abroad. Iridium-192 emits much softer radiation, with the radiation energy center around $E = 0.36$ MeV. True, the application of iridium-based sources also implies the necessity of a heavy shielding for HDR facilities.

At present, ytterbium-169 is considered by certain experts to be a promising radionuclide for HDR. The advantages of ytterbium-based sources include, first, a softer gamma-ray energy spectrum (radiation energy center around 93 keV) and, second, its high specific activity. Finally, the use of this radionuclide for HDR does nor require a heavy shielding. Experts believe that only 20% of the clinics in the USA can practise HDR with iridium-192, whereas ytterbium-based HDR is possible to perform in any hospital.

LDR is currently performed with the employment of radionuclide sources containing I-125, Pd-103, or Cs-131 isotopes and having an activity on the order of 1 mCi. I-125 sources are the most widely used. LDR with these sources ensures great success in the treatment of prostate cancer (PC), with the mean 5-year survival rate for stage I PC exceeding 90%. Brachytherapy (both HDR and LDR) is currently a leading therapeutic mode for the management of PC. One disadvantage of iodine-based LDR is the slow accumulation of the total focal dose (TFD) of this radionuclide due to its long half-life (see Table 1). Due to this, LDR with I-125 is not prescribed to most patients with a large focal area. The advantages of LDR based on ytterbium-169 sources are due to its shorter half-life than that of iodine-125 and the optimal mean radiation energy.

Table 1. Main isotopes used for brachytherapy.

Isotope	Half-life, days	Mean energy, keV
I-125	60	28.4
Cs-131	9.7	30.4
Pd-103	17	21
Ir-192	74	356.8
Co-60	5 years	> 1 MeV
Yb-169	32	92.8

To recall, new Yb-169 sources may prove highly suitable for both HDR and LDR that can be performed at any hospital. The requirements for these variants of brachytherapy in Russia are estimated to be at least 50,000 procedures per year. Only this country has the potential for the mass cost-effective production of Yb-169 sources by the unique technologies of separation of ytterbium isotopes, implemented for the first time in Russia [3]. These technologies allow reducing energy consumption for laser separation of the starting Yb-168 isotope by a factor of 8 over the traditional electromagnetic technique. These highly promising methods for the production of radionuclide sources and materials for them are in great demand both in this country and abroad.

The main lines of recent research on developing new radionuclide sources include (a) investigations into the radiation properties of nucleotide sources obtained by irradiation with thermal neutron fluxes in the INR Neutron Complex facilities and in reactors, and (b) the development of technologies for manufacturing Yb-168-based internal ceramic cores with a view to improving the operational characteristics of the end products. In particular, new specimens of ceramic ytterbium cores were prepared jointly with L F Vereshchagin Institute of High Pressure Physics, RAS. Formation of ytterbium oxide nanogranules observed in the course of this work made it possible to increase the density of the source basic material to 10 g cm^{-3}.

The use of high pressures and temperatures for sintering the ytterbium-based material allowed obtaining modified ytterbium oxide with a cubic (density 9.247 g cm^{-3}) and monoclinic (10.08 g cm^{-3}) structures. Investigations into ytterbium oxide sintering regimes demonstrated the possibility of production of ultrahigh-density ceramic cores with an

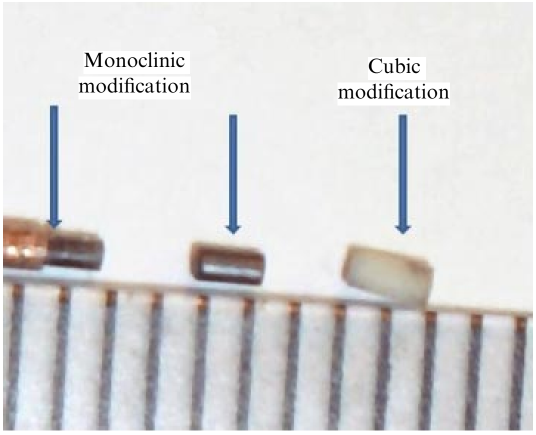

Figure 6. Specimens of ceramic ytterbium-based cores with different modifications of the crystal lattice for high-dose brachytherapy.

acceptable strength and hardness. At the same time, the optimal sintering parameters (pressure, temperature, hold-up time) remain to be elucidated.

Figure 6 shows on a millimeter scale certain specimens of ceramic ytterbium-based cores with different modifications of the crystal lattice for high-dose brachytherapy. The density of the source material permits its therapeutic properties to be improved and adapted to the requirements of modern radiotherapy. The activity of finished ytterbium sources for HDR irradiated by thermal neutrons may exceed 10 Ci.

The results of research along these lines provide tools for the implementation of a novel promising technology, brachytherapy with the exploitation of ytterbium sources, in advanced clinical practice in Russia and abroad. The wide application of these technologies in medicine is promoted by their weighty advantages over conventional ones, such as the lower costs of radionuclide sources, treatment rooms, and logistic operations. Moreover, the therapeutic properties of ytterbium-based sources are no worse than those of currently used analogs with other isotopes.

5. Radiodiagnostics

INR contributed to the development of radiodiagnostic techniques by the development of the digital X-ray densitometer DENIS (Russian acronym for 'research densitometer') designed for the detection of osteoporosis and quality control of endoprosthetic hip replacement. The main components of this instrument are a digital imaging charge-coupled device (CCD), a calibration wedge, and a software package [4]. The densitometer is intended for measuring bone tissue mass (density) in the immediate proximity of an osteoporotic lesion (without surgical or other invasive intervention) and simultaneous visualization of the bone and endoprosthesis for their examination.

A clinical trial based at the N N Priorov Central Research Institute of Traumatology and Orthopedics in Moscow included 128 patients who had undergone total hip arthroplasty for degenerative-dystrophic diseases or femoral fractures resulting from osteoporosis. Each patient was examined 2–5 times during the period of observation (a total of 559 studies). The accuracy of bone mass measurements was estimated by a comparison with the tissue density data obtained under the same conditions with a Lunar-Prodigy densitometer (USA). It turned out that DENIS yielded more accurate and stable results than its several-fold more expensive foreign analogs. The device was awarded medals and licenses from various innovation exhibitions. Its large-scale fabrication will be possible after completion of a research and experimental development program, the creation of a prototype design and marketable form of the product, and securing orders from healthcare providers.

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