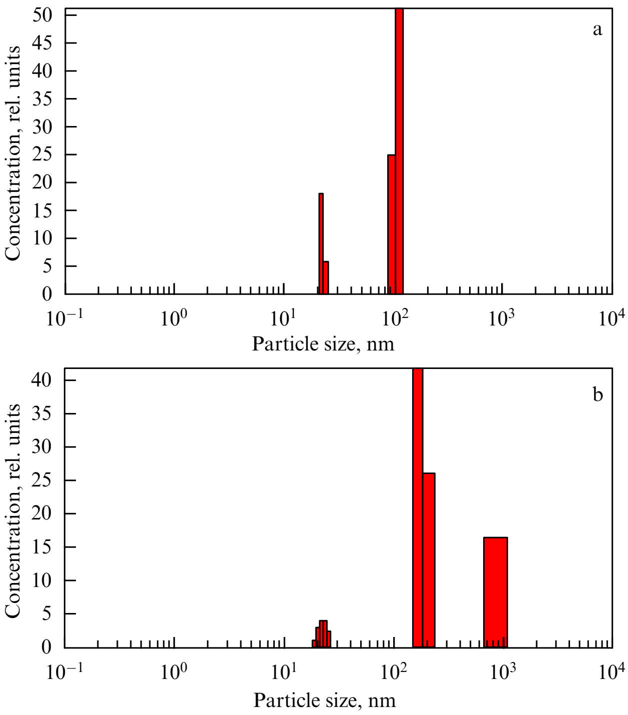

Figure 6. Spectrum of the sizes of the molecular makeup of blood serum: (a) a healthy patient, (b) a patient with cardiovascular abnormalities.

patients with cardiovascular abnormalities revealed the presence of protein–lipidic clusters of a large size (Fig. 6). It was also determined that the presence of large-size particles was characteristic of oncologic patients. Furthermore, in the case of a positive result from treatment, the peak accounting for large-size particles vanished, and reappeared in the case of a relapse. Therefore, the technique being developed is helpful for the diagnostics of oncological and cardiovascular diseases.

A new method of detecting organic compounds at extremely low densities was earlier developed at the GPI. The main components of the instrument were a laser, a time-of-flight mass spectrometer, and a nanostructured plate to adsorb the gas under investigation. This facility is currently being modified for blood examination, and this also provides a way for the early diagnostics of many diseases.

The solution to many medical problems is possible only by pursuing fundamental research in laser physics, radiation–substance interactions, energy transfer, and medicobiologic investigations, and developing medical treatment technologies.

In summary, we emphasize that the application of the methods of laser physics to medicine was pioneered by Aleksandr Mikhailovich Prokhorov, the founder of the General Physics Institute. Many of the studies referred to in the foregoing were undertaken on his initiative.

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Development of nuclear physics medicine at the Institute for Nuclear Research, RAS

L V Kravchuk

1. Introduction

Developments in the field of nuclear medicine at the Institute for Nuclear Research (INR), Russian Academy of Sciences (RAS), initially involved the making and operation of experimental facilities, like proton or electron accelerators and particle or radiation detectors. At later stages, some developments and projects acquired an independent and advanced status depending on the demand for them in the market for medical services, the availability of financing, and so on. This report is a brief outline of some of the most successful present-day INR projects in the area of nuclear medicine; a more detailed account of these projects, as well as of some other developments, is given in collection [1]. In this report, the emphasis is placed on the capabilities and state of the radionuclide production facility and the proton therapy complex based on the INR high-current linear proton accelerator in Troitsk, Moscow region. This accelerator, which was designed for energies up to 600 MeV and average currents up to 0.5 mA (Fig. 1) and is the only high-current linear proton accelerator in Russia and so far in Europe, is presently used for conducting fundamental and applied research in the areas of condensed-matter physics, nuclear physics, nuclear power engineering, and so on [2]. A considerable portion of the beamline time is allocated to medical uses and investigations either in parallel with physical investigations or at dedicated sessions.

2. Production of radionuclides for medical purposes

The demand for radioisotopes intended for the diagnostics of various (primarily, cardiovascular and oncological) diseases, according to recent data, shows a virtually linear annual increase, and an almost exponential increase for therapy. Several of these isotopes with due purity and in large quantities may be obtained with a relatively high efficiency using medium-energy (several hundred MeV) proton accelerators. There are only five facilities of this type in the world: at the INR (Troitsk), Los Alamos National Laboratory (LANL) and Brookhaven National Laboratory (BNL) in the USA; at the National Laboratory for Particle and Nuclear Physics (TRIUMF) (Vancouver, Canada), and at iThemba Laboratory (Cape Town, RSA).

An intermediate extraction of the proton beam with the energy 160 MeV was realized at the INR linear accelerator, which is used in a target irradiation facility to produce radioisotopes primarily for medical purposes. This facility, which has been validly operating for more than ten years, is the only one in Europe and Asia and is one of the biggest in the world (Fig. 2). This facility is highly automated and

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Figure 1. High-current linear proton accelerator of the INR, RAS: (a) initial (up to 100 MeV) accelerator section, (b) principal (100–600 MeV) accelerator section.

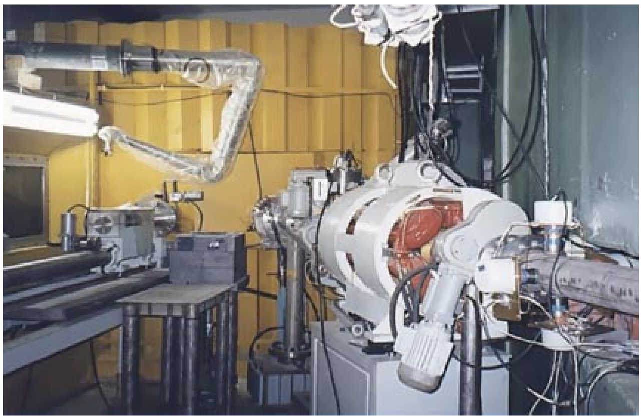

Figure 2. Central part of the facility for producing radionuclides at the INR linear proton accelerator.

perfectly safe in operation [2, 3]. The INR has elaborated and implemented technologies for producing radioactive isotopes, which are used to advantage in Russia and the USA. Targets irradiated at the accelerator in Troitsk have been regularly supplied to LANL, where pure radionuclides are radiochemically extracted and radiopharmaceuticals are produced, which are used in the diagnostics of several diseases. For example, with the use of strontium-82 produced at the INR, more than 110 thousand patients, primarily in the USA and Canada, have been diagnosed with positron-emission tomography (PET) facilities. Many other isotopes are produced in smaller amounts at the INR, but some of them may acquire major significance in the near future for the therapy of oncological and cardiovascular diseases, specifically, tin-117m from antimony-bearing targets, palladium-103 from silver targets, selenium-72 from gallium arsenide targets, germanium-68 from gallium targets, sodium-22 from aluminum or magnesium targets, cadmium-109 from indium targets, actinium-225 and radium-223 from thorium targets, and so on.

We consider the special features and problems of the production of some of the most promising radioisotopes. First and foremost, this means the production of strontium-82 [5] (with a half-life of 25 days) and strontium/rubidium-82 generators for PET. In 2010, there will be about 4000 PET facilities in the world, with about 3000 of them in the USA. The main facilities for providing positron-emission tomography in a clinic are typically a cyclotron for the synthesis of ultra-short-lived radionuclides, an automatic radiochemical laboratory, and the positron-emission scanner itself. The use of the generator of a short-lived nuclide, in this case rubidium-82 with the half-life 1.3 min (Fig. 3), which is charged once a month at a PET facility, obviates the need for the presence of a cyclotron and a radiochemical laboratory in a clinic. This makes the procedure of cardiac disease diagnostics, including the early recognition of myocardial infarction, substantially cheaper. It is in this way that PET diagnostics are primarily implemented in the USA, where the cardiovascular death rate (which occupies the first place in Russia in large measure due to the extremely low level of early recognition in the population) has moved to the second place, after the oncological death rate. The INR together with Canadian partners has elaborated a more efficient strontium/rubidium-82 generator [6] (see Fig. 3), which has successfully passed preclinical tests and is now at the stage of clinical tests in the Russian Research Center for Radiology and Surgical Technology (RRCRST) (St. Petersburg). The development of this on the basis of registered 'know-how' was awarded a Gold Medal from the All-Russia Exhibition Center (AREC) and honored with other prestigious awards. Until recently, the use of generators for PET was restrained in most countries of the world, except North America, by the limited availability of the initial material, strontium-82. The INR together with its partners, the State Scientific Center Physico-Energy Institute (SSC PEI) (Obninsk) and RRCRST, has organized the production of strontium-82, its chemical extraction, and the fabrication of the generators. Organizing their mass production and introduction into widespread medical practice in Russia and abroad requires investments.

Tin-117m is a unique and highly efficient medical therapeutic radionuclide, which emits soft Auger electrons with a short range in biological tissues. It is used primarily due to the unrivaled high bone-surface-to-marrow absorbed dose ratio for the therapy of bone oncological diseases. Furthermore, recent investigations suggest that the use of this isotope shows great promise for the therapy of vascular diseases. The INR, with the participation of BNL, has developed a technology for producing tin-117m in the 'carrier-free' state

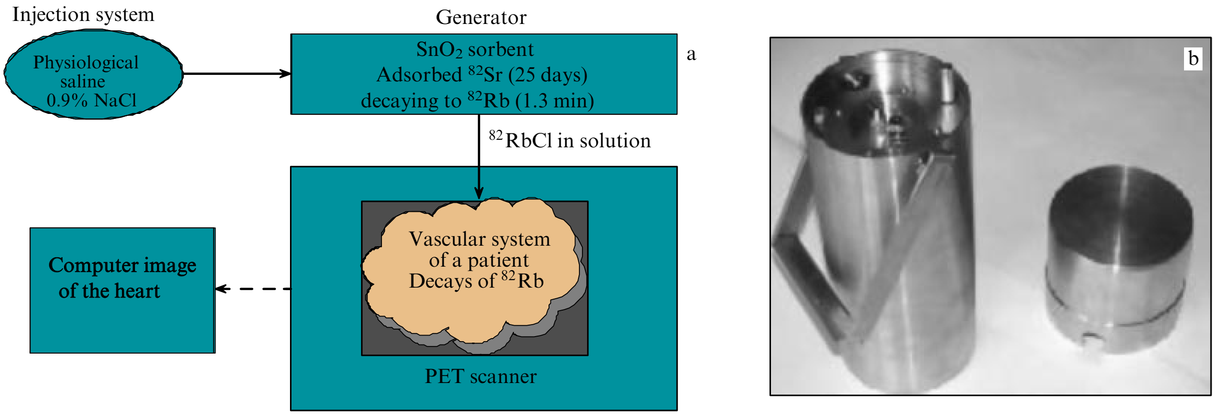

Figure 3. Generator of strontium/rubidium-82 for positron-emission tomography: (a) principle of operation of the generator, (b) external view of the generator.

from antimony-bearing irradiated targets [7]. The product made at the INR linear accelerator is extracted in the 'hot chambers' of SSC PEI. Test samples produced by the technology covered by Russian and foreign patents are undergoing tests in the USA. Under appropriate financing, it would take about three years to organize the production of this radionuclide on a regular basis, develop a Russian drug on its basis, and perform biological and preclinical tests in Russia with the participation of the Medical Radiological Research Center (MRRC), Russian Academy of Medical Sciences (Obninsk).

The Institute for Nuclear Research, with participation of the Karpov Physicochemical Research Institute (PRI) (Obninsk) and the Production Association Mayak, has developed a technology for the production of the nuclide palladium-103 from silver targets irradiated in the linear accelerator [8]. Using this as the base, the MRRC has made radiopharmaceuticals — albuminous microspheres intended for the treatment of prostate adenoma, liver cancer, breast cancer, ascitic tumors, and rheumatoid arthritis — that have demonstrated their efficiency in biological experiments and have shown a practical solution to the problem of egesting the preparation from the body during therapy.

Actinium-225 and radium-223 are novel alpha-active radionuclides that show great promise; they have a short range in biological tissues and exhibit a high energy release. The mass application of these radionuclides, either directly or as generators of the daughter short-lived radionuclides bismuth-213 and lead-211, may radically improve the state of affairs concerning the therapy of a large number of oncological diseases. Especially efficient is the use of alpha-active radionuclides in combination with nanostructures involving monoclonal antibodies for their delivery to malignant cells. The highly limited production of these radionuclides prevents their widespread use in the world. The Institute for Nuclear Research in collaboration with the Chemistry Department of Moscow State University and the Institute of Physical Chemistry and Electrochemistry, RAS, has developed a method for producing actinium-225 and radium-223 from thorium targets irradiated by an accelerated proton beam, which will enable increasing the production of these radionuclides by two orders of magnitude [9].

Currently, the INR only produces radionuclides at the linear proton accelerator, while the processing that involves the extraction of the final product and the fabrication of radiopharmaceuticals takes place in other laboratories, primarily abroad. The INR has completed the design of a radiochemical laboratory with 'hot chambers' intended for processing targets irradiated in the accelerator and obtaining pure radioactive isotopes. The project foresees for the construction of premises for the corresponding laboratory in the form of a structural addition to the existing building with fully functional utility lines. Furthermore, to substantially increase the production capabilities, it is planned to acquire, in addition to the operating linear proton accelerator, a new high-current cyclotron with an energy up to 120 MeV and its accommodation in the building of the Experimental Complex.

3. Facility for the radiation therapy of oncological diseases

The basic nuclear physics facility of the Experimental Facility in Troitsk is the INR linear proton accelerator, which satisfies the main radiation therapy requirements with the following beam parameters: the energy range 70–250 MeV, the current pulse duration up to 200 μs, and the pulse repetition rate up to 100 Hz. As is well known, the main advantage of proton therapy is the capability of causing damage to deeply located tumors of arbitrary shape and localization without appreciable damage to the ambient sound tissues, which is due to the proton dose distribution with depth. Proton therapy is given to about 20% of patients with malignant tumors, while the centers available in Russia can receive only slightly more than 1% of such patients. The INR has completed the first construction stage of a Radiation Therapy Complex [10], which comprises three main teleirradiation facilities (Fig. 4): a proton beam facility with a fixed horizontal beam, a photon radiotherapy facility based on the SL-75-5MT electron accelerator (with the electron energy 6 MeV), and an X-ray treatment facility, as well as a Toshiba X-ray tomograph. Modern three-dimensional computer systems for irradiation planning, systems for making individual shaping devices, and medical information systems for accompanying patients have been developed for proton and photon irradiation facilities. The combined irradiation by protons and photons improves the efficiency and reliability of proton accelerator employment and increases the accessibility of tumor radiotherapy, which requires a large number of irradiation fractions. In the course of development of the facility, INR staff members designed and constructed several devices and systems that

Figure 4. Radiologic facilities of the INR Radiation Therapy Facility: (a) proton therapy chamber, (b) SL-75-5 MT electron accelerator, (c) RTA-02 X-ray therapy facility.

outperform the existing analogs in parameters. For instance, INR staff members made multichannel air ionization chambers with record high transmittance and sensitivity, a precision automated system for fixing and transferring a patient, and a digital X-ray system for centering a patient [11]. The staff members of the INR Medical Physics Laboratory pursue research aimed at developing the technology of conformal irradiation by protons, neutrons, and photons, as well as the development of modern radiological instruments and of diagnostic and radiotherapy techniques with the employment of radiopharmaceuticals. The uniqueness of the proton accelerator and the INR experimental facility may be fully realized upon building and commissioning the second construction stage, for which design objectives have been formulated. It is planned that the new building, whose construction is being completed, will accommodate the laboratory of early diagnostics with the use of scanners of positron-emission computer tomography (PET/CT) and single-photon emission computer tomography (SPE/CT); a second proton facility with several beam directions; a laboratory of radionuclide therapy, including brachytherapy; and a laboratory of neutron, including neutron-capture, therapy.

4. Laser perforator with a built-in glucometer

The development of an optically pumped polarized proton source for the INR linear proton accelerator in the late 1980s led to the idea of using a solid-state laser for the contactless puncture of finger tissue with a laser perforator for blood sampling. In 1991, a small-scale enterprise, Engineering Center for New Technologies (ECNT), was established at the INR, which implemented these new ideas and set up the mass production of Ermed-304 laser perforators (Fig. 5a) [12], which are certified in Russia, the USA, and Europe. Currently, new laser perforators for blood sampling in medical institutions and small-size laser perforators with a built-in glucometer for the rapid analysis of the level of sugar in blood are being put into production and placed on the market. Both instruments use laser radiation of the three-micrometer spectral range. The active element of the laser perforator radiator is an erbium ion-doped yttrium aluminum garnet crystal (Er:YAG). This crystal is used because only Er:YAG lases at the wavelength at which the light absorption coefficient in water is extremely high (resulting in tissue evaporation). Other laser radiation wavelengths favor the carbonization of tissue. The fabrication of Er:YAG crystals deserves special attention, because virtually all other component parts, with the exception of the active element, are available on the market. The ECNT at the INR has developed a technology for the mass production of Er:YAG monocrystals and their high-quality optomechanical processing.

The new-generation *laser perforator*, which is small in size ($120 \times 80 \times 30$ mm) and weighs only about 200 g, permits minimizing painful sensations in blood sampling. The perforator has the unique property of sterilizing the tissue within a three-micrometer range of laser irradiation, which minimizes the probability of infection under arbitrary conditions of its use. The wound heals after its application an order of magnitude faster than with the use of metal scarifiers and lancets. The battery charge is rated for performing one hundred perforations.

Small-size laser perforator with a built-in glucometer — an instrument for painless and rapid self-diagnostics of the level of sugar in blood (contactless perforation of finger tissue and performing express analysis of blood), maintaining perfect sterility — is intended for pancreatic diabetes patients. The instrument dimensions are comparable to those of a mobile phone (Fig. 5b), and disposable parts are made in the form of replaceable cartridges with a three-day supply. The instrument offers several advantages over other contact analogs: little sensation of pain, rapid healing of the wound, perfect sterility, a lower cost due to cheaper disposable parts, a long operation life (over five years), and ease of handling. Today, pilot samples of this instrument are successfully passing tests in medical institutions in Russia, Europe, and South Korea. Its industrial design requires improvement with the use of a new radiator with a higher efficiency and smaller size, which

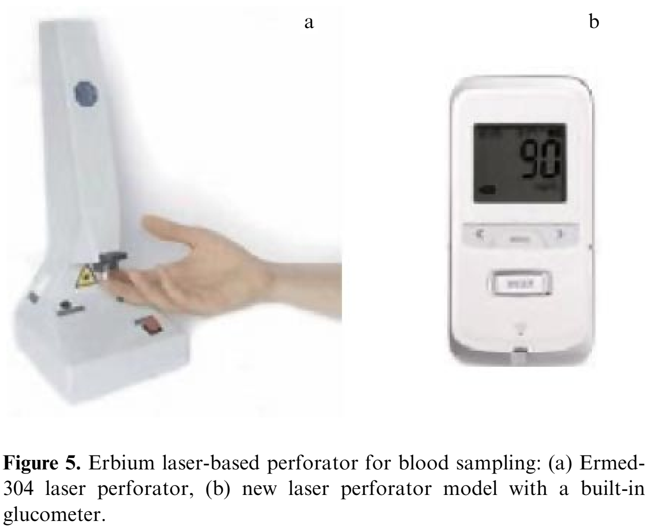

Figure 5. Erbium laser-based perforator for blood sampling: (a) Ermed-304 laser perforator, (b) new laser perforator model with a built-in glucometer.

will further lower the costs of manufacture and make the instrument more attractive to consumers.

5. Technology of anaesthesia and therapy by rare-gas–oxygen mixtures

It was shown in N E Burov's work that normal-pressure gas mixtures (50–80% of xenon with oxygen) provide narcosis that does not entail negative consequences and exerts a clearly defined therapeutic effect: improving the state of the immune system of a patient and recovering their capillary circulatory system. The INR staff members engaged in building a facility for the measurement of neutrino mass developed an adsorption cartridge with a low resistance to gas flow, which furnished efficient xenon absorption and made the administering of anaesthesia substantially cheaper. The work on the introduction of xenon narcosis in medical practice was awarded a Gold Medal from the 5th Moscow International Innovations and Investment Show (AREC, 2005). More recently, the INR, jointly with the RAS Hospital in Troitsk, designed and made a multifunctional respiratory facility for administering xenon anaesthesia and therapeutic treatment [13]. Subsequently, with accumulation of the experience of clinical practice, it was shown that subnarcosis xenon–oxygen mixtures (with less than 10% of xenon in the mixture) provide the same therapeutic effect as narcosis mixtures [14]. Their use in the RAS Hospital showed their high efficiency in the treatment of patients with abnormalities of the central nervous system (age-specific cerebral cortex atrophy, encephalopathy of post-hypoxic genesis, acute abnormality of cerebral circulation), in the treatment of patients with chronic stress syndrome, and in the rehabilitation of oncological patients after an operative intervention and combined treatment. A disadvantage of the xenon therapy is the high cost of xenon. Switching to krypton therapy may be the way out of this situation (krypton costs almost 20 times less than xenon). Preliminary tests performed in the Institute of Medicobiological Problems, RAS, have shown that krypton–oxygen mixtures also produce the desired therapeutic effect.

The goals and tasks of widespread medical practice treatment of technologies reliant on rare-gas–oxygen mixtures, which the INR aspires to realize, are as follows: further development of the techniques for treating various diseases by xenon–oxygen and krypton–oxygen mixtures, development of instruments for the measurement of krypton and oxygen densities in the breathing mixture of a closed circuit, introducing the multifunctional respiratory facility into medical institutions and performing clinical trials of krypton–oxygen mixtures.

6. Digital X-ray densitometer

The INR has developed a digital X-ray densitometer DENIS (abbreviated from DENsitometer for Investigations), intended for the diagnostics of osteoporosis and the quality control of the operations of femoral neck prosthetics [13]. The main components that constitute the subject of the development are a CCD-matrix-based digital device for obtaining images (the CCD is a charge-coupled device), a calibration wedge, and software. The direct functional purpose of the instrument is to measure the mass of the bone tissue (the density) of a bone in the immediate vicinity of the osteoporosis region without surgical intervention and any auxiliary operations, and to simultaneously obtain bone and prosthesis images for performing the corresponding investigation. In the course of clinical trials conducted at the Priorov Central Research Institute of Traumatology and Orthopaedics, 128 patients who had undergone a hip replacement operation in connection with degenerative dystrophic diseases or a femoral neck fracture against the background of osteoporosis were subjected to examinations. During the observation period, each of the patients was examined from 2 to 5 times, with 559 examinations conducted in all. To estimate the precision of the measurements of the mass of bone tissue from its density in the same Gruen zones, 116 patients were examined with a Lunar-Prodigy densitometer. In comparison with foreign analogs, the DENIS instrument affords more stable results, allows a higher precision of measurements, and costs several times less. The instrument has been awarded several medals and certificates from different innovation shows. To organize its mass production requires completing the development activity as regards its modern design and salable condition and calls for purchase orders from medical institutions.

7. Summary

Owing to the limitations on the volume of this report, it outlines only a part of the developments of the Institute for Nuclear Research, RAS, for medicine involving the techniques and means of nuclear physics. The majority of developments and projects are in their final stages and call for the investment of capital for setting up their manufacture and introducing them into widespread medical practice.

A considerable portion of the projects was performed in the framework of the Program of the Presidium of the RAS "Basic Sciences to Medicine"; the author, in the name of the authors of the projects, expresses his genuine appreciation to the program management. The author is deeply grateful to V A Matveev for supporting the work in this area, as well as to B L Zhuikov, S V Akulinichev, V G Polushkin, B M Ovchinnikov, and V G Nedorezov for placing materials at the author disposal.

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