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PACS numbers: 42.62.Be, 87.50.W-, **87.63.–d**
DOI: 10.3367/UFNe.0180.201006i.0661

Laser physics in medicine

I A Shcherbakov

The Prokhorov General Physics Institute (GPI), Russian Academy of Sciences (RAS), cooperates with various organizations in the area of laser medicine, these being several Academy institutions: Institute for Laser and Information Technologies (ILIT), RAS; Institute for Spectroscopy, RAS; Institute for Analytical Instrumentation, RAS; Lomonosov Moscow State University; leading Russian medical centers: Fedorov Federal State Institution Intersectoral Research and Technology Complex Eye Microsurgery, Rosmedtechnology; Gertsen Moscow Oncology Research Institute, Roszdrav; Russian Medical Academy of Postgraduate Education; Bakulev Center for Cardiovascular Surgery, Russian Academy of Medical Sciences; Central Clinical Hospital No. 1, Russian Railways; and a number of commercial enterprises: OptoSystems, Visionica, New Energy Technologies, Laser Technologies in Medicine, Cluster, and the Scientific and Technological Center of Fiber-Optical Information-Measuring Systems.

The unique properties of a laser, which has the capacity to ultimately concentrate energy in space, time, and the spectral range, make this device an indispensable instrument in many areas of human activity, in medicine in particular.

Figure 1 shows the wavelengths of lasers that have found use in medical practice to some extent. We can see that the spectral domain ranges from the ultraviolet to the middle infrared. The energy density range spans three orders of magnitude (from 1 J cm^{-2} to 10^3 J cm^{-2}), the power density range spans 18 orders of magnitude (from 10^{-3} W cm^{-2} to 10^{15} W cm^{-2}), and the temporal range spans 16 orders of

I A Shcherbakov Prokhorov General Physics Institute, Russian Academy of Sciences, Moscow, Russian Federation
E-mail: director@gpi.ru

Uspekhi Fizicheskikh Nauk **180** (6) 661 – 665 (2010)
DOI: 10.3367/UFNr.0180.201006i.0661
Translated by E N Ragozin; edited by A M Semikhatov

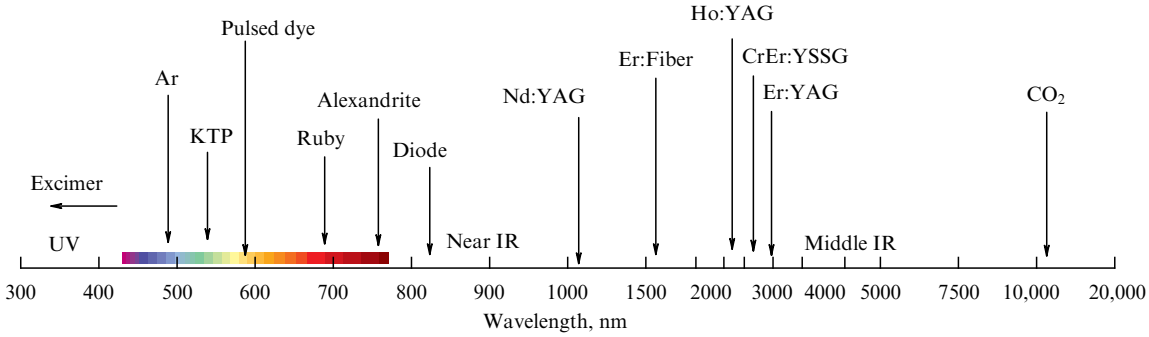

Figure 1. Laser types and radiation wavelengths used in medical practice.

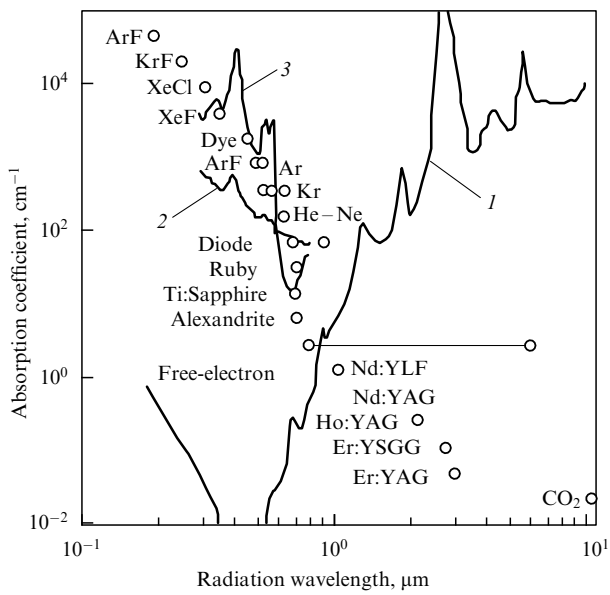

Figure 2. Dependence of absorption on the wavelength of propagating radiation for water (*1*), the aorta (*2*), and blood (*3*). Schematically shown are the wavelengths of different lasers and their radiation absorption coefficients in water.

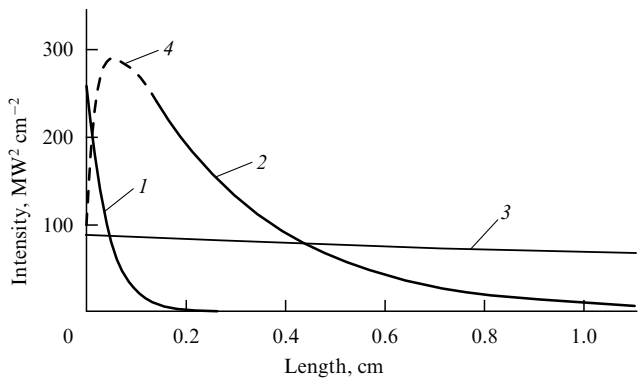

Figure 3. Intensity distribution of the radiation propagating through the tissue of a canine prostate gland calculated in the diffusion approximation: *1* — Ho:YAG laser with the wavelength $\lambda \approx 2.09$ μm, *2* — Nd:YAG laser with the wavelength $\lambda \approx 1.064$ μm, *3* — Nd:YAG laser radiation intensity in the absence of scattering, *4* — expected shape of the radiation intensity distribution in the surface layer.

magnitude, from continuous radiation (~ 10 s) to femtosecond pulses (10^{-15} s). The wide ranges of radiation parameter variation permit engaging a wide diversity of mechanisms for exerting an effect on biotissue.

Early in the development of laser medicine, the model of biotissue was perceived as water with 'impurities,' because human beings are known to consist of 75–80% water. Therefore, the absorption by water underlies the mechanism of laser radiation action on biotissues. In the application of continuous lasers, this was a relatively viable concept. When it is required to produce an effect on the surface of a biotissue, it is expedient to select a radiation wavelength strongly absorbed by water. To exert a volume action on biotissues, by contrast, there is good reason to select radiation wavelengths with weak absorption in water. But it subsequently turned out that other components of biotissue also have the capacity to absorb radiation. In particular, blood exhibits a strong absorption in the visible spectral region (Fig. 2). It was then realized that biotissue is not merely water with impurities, but a substantially more complex entity.

Simultaneously, the use of pulsed lasers began. In this case, the influence exerted on biotissues is defined by the combination of the wavelength, energy density, and duration of the radiation pulse. In particular, the laser pulse duration is a significant factor that permits distinguishing between thermal and nonthermal action.

Pulsed lasers with pulse durations spanning a wide range — milliseconds, microseconds, nanoseconds, picoseconds, and femtoseconds (10^{-15} s) — were introduced into practice. Various nonlinear processes turn out to be effective: optical breakdown on the target surface, multiphoton absorption, plasma production and development, and the generation and propagation of shock waves. It became evident that there is no way of devising a single algorithm for the search of a desired laser, and that a separate algorithm is required in each specific case. On the one hand, this was a major complication of the problem, but on the other hand, this opened endless possibilities to vary the ways of acting on biological tissues.

Scattering is also a factor of major importance in radiation–biotissue interactions. Figure 3 gives two specific examples of radiation intensity distribution in the tissue of the prostate gland of a dog under the exposure of its surface to laser radiation with different wavelengths: $\lambda = 2.09$ μm (Ho:YAG laser) and $\lambda = 1.064$ μm (Nd:YAG laser). In the former case, absorption prevails over scattering, and in the latter case, the situation is the reverse (Table 1).

In the case of strong absorption, the radiation penetration obeys the Bouguer–Lambert–Beer law, i.e., an exponential attenuation occurs.

Table 1. Laser radiation parameters and optical characteristics of canine prostate gland tissue.

	Nd : YAG	Ho : YAG
λ, μm	1.064	2.09
E, J	1.0	3.0
τ, μs	1.0	1.0
μ_a, cm^{-1}	0.27	26.93
μ_s', cm^{-1}	17.6	—
δ_{eff}, cm	0.26	0.04

When scattering prevails over absorption characteristic of the majority of biological media in the visible and near-infrared wavelength ranges, trustworthy estimates may be obtained if the analysis of laser radiation propagation through a biotissue relies on the diffusion approximation model, which has quite clear limits of applicability that are not always taken into account.

The aforesaid suggests a conclusion that several nonlinear processes and the relation between scattering and absorption are to be taken into account in the application of one laser or another for specific operations.

On the basis of this approach, the Lazurit laser surgical facility was created at the GPI, which may fulfill the function of a scalpel coagulator as well as of a lithotripter, i.e., an apparatus for crumbling stones in human organs. Furthermore, this lithotripter depends for its operation on a new original principle, which underlies its unique properties. For this, two-wavelength irradiation is used: the fundamental Nd:$YAlO_3$ crystal laser radiation ($\lambda = 1.0796$ μm) and its second harmonic (in the green spectral region). The apparatus is equipped with an image processing unit and allows viewing the operation in real time.

The microsecond-long two-wavelength laser irradiation underlies the photoacoustic mechanism of stone fragmentation, which relies on an optico-acoustic effect — the generation of shock waves in the laser radiation–liquid interaction — discovered by Prokhorov et al. [1]. The action is nonlinear and multistage [2, 3] (Fig. 4), and comprises

(i) an optical breakdown on the stone surface;

(ii) plasma spark formation;

(iii) development of a cavitation bubble;

(iv) shock wave propagation in the collapse of the cavitation bubble.

Therefore, the stone crumbling occurs approximately 700 μs after laser irradiation of the stone surface due to the action of the shock wave generated in the collapse of the cavitation bubble. The obvious advantages of this lithotripsy technique are as follows:

(i) the safety of action on the soft tissues surrounding the stone is afforded, because the shock wave is not absorbed in them and does not therefore cause any damage to them, which is inherent in other laser lithotripsy techniques;

(ii) a high fragmentation efficiency for stones of arbitrary localization and chemical composition (Table 2);

(iii) a high fragmentation rate (see Table 2), with the fragmentation of stones ranging between 10 and 70 s in duration, depending on their chemical composition;

(iv) the absence of damage to the fiber in the transport of radiation owing to the optimal selection of the pulse duration;

(v) a radical reduction in postoperative complications and a shortening of postoperative treatment.

The Lazurit facility also includes a scalpel coagulator, which allows carrying out successful unique operations on

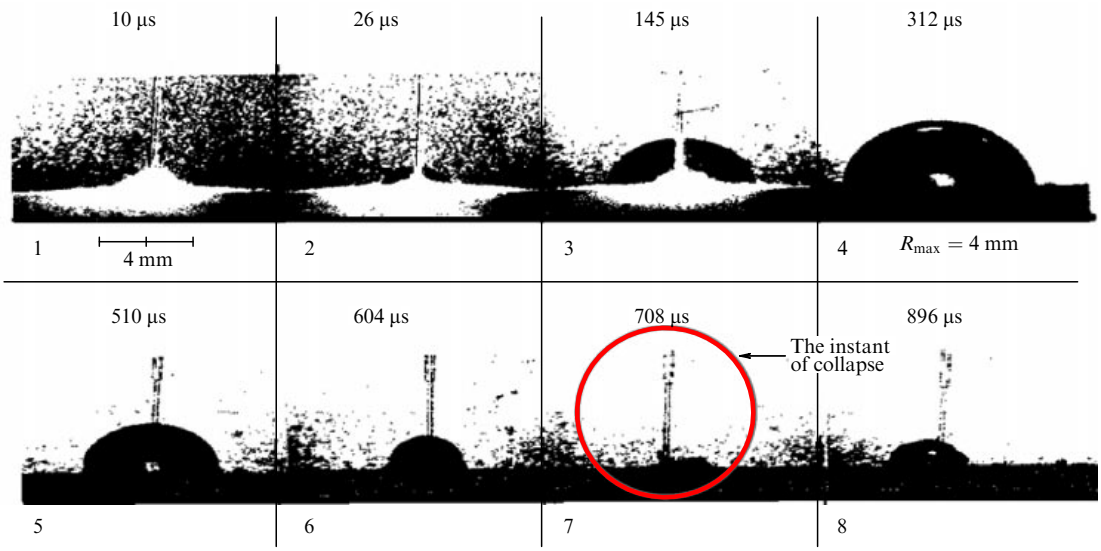

Figure 4. Development of a cavitation bubble: *1* — plasma 10 μs after laser irradiation of the stone surface; *2–4* — growth of the cavitation bubble to the maximum radius $R = 4$ mm in 312 μs; *7* — the instant of cavitation bubble collapse 708 μs later [3].

Table 2. Chemical composition of the stones and parameters of laser radiation in the fragmentation in *in vitro* experiments.

No.	Type of stone	Frequency, Hz	Energy, mJ	Duration, s	Number of pulses
3	Sodium urate monohydrate	10	90	16.2	162
11	Whewellite (calcium oxalate monohydrate)	9	100	46.8	421
17	Cystine	9	123	76.4	687

blood-filled organs (e.g., kidneys), performing malignant tumor resection with minimal hemorrhage, without cross-clamping kidney vessels and without producing an artificial ischemia of the organ, which corresponds to the presently adopted ways of operative intervention. The resection is performed using a laparoscopic approach. For an effective penetration depth ≈ 1 mm for pulsed one-micrometer-wavelength radiation, the tumor resection, coagulation, and hemostasia are effected simultaneously and wound ablastics is achieved. The new medical technology of kidney resection is currently at the stage of development and obtaining authorization to perform operations on a mass scale.

Modern ophthalmology without the use of lasers is hard to perceive. At the GPI, the Mikroskan ophthalmologic laser system was made for refractive surgery based on an ArF excimer laser with the wavelength 193 nm. It is used for correcting myopia, hyperopia, and astigmatism. The so-called flying spot technique has been realized: it consists in the cornea being illuminated by a radiation spot approximately 0.7 mm in diameter, which is scanned over the cornea surface according to a computer-defined algorithm and changes its shape. For the pulse repetition rate 300 Hz, vision correction by one diopter is effected in 5 s. The action is superficial, because the $\lambda = 193$ nm radiation is strongly absorbed by the cornea. An eye-tracking system ensures a high quality of operation irrespective of the mobility of patient's eye. Forty-five Russian clinics have been equipped with the Mikroskan facility. The ophthalmologic excimer systems for refractive surgery developed at the GPI account for 55% of the domestic market. The Mikroskan facility has been certified in Russia, CIS countries, Europe, and China.

Under the auspices of the Federal Agency for Science and Innovations, the GPI, ILIT, and MSU jointly developed an ophthalmologic facility that comprises an updated Mikroskan facility, Mikroskan Vizum, which is a diagnostic equipment consisting of an aberration meter and a scanning ophthalmoscope, as well as a unique femtosecond laser ophthalmologic system Femto Vizum. The construction of this facility is an example of the fruitful cooperation of Academy institutions with the Lomonosov MSU in the framework of a common program. In this case, the GPI developed the surgical instrument, and MSU and the ILIT developed the diagnostic equipment that allows performing a variety of unique ophthalmologic operations.

It is worth discussing the principle of operation of the femtosecond ophthalmologic facility in more detail. A neodymium laser with the wavelength 1.06 μm forms the basis of the system. While there was strong absorption in the cornea when an excimer laser has used, the linear absorption for a wavelength about 1 μm is quite weak. However, owing to a short pulse duration (400 fs), high power density is realized in the radiation focusing and therefore multiphoton processes become effective. When appropriate focusing is ensured, it is possible to realize the kind of irradiation whereby the cornea surface remains perfectly intact and multiphoton absorption occurs in the cornea volume. Therefore, the mechanism of action involves the radiation-induced destruction of the cornea tissue under multiphoton absorption (Fig. 5), such that there is no thermal damage to the neighboring tissue layers and the realization of high-precision intervention becomes possible.

The excimer laser photon energy (6.4 eV) is comparable to the dissociation energy, but for one-micrometer radiation (1.2 eV), it is at least two times, if not seven times, lower than

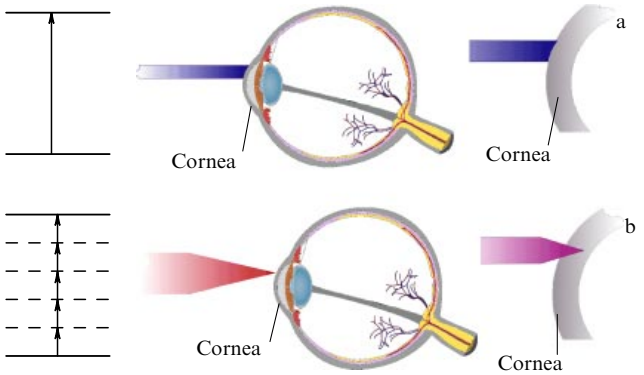

Figure 5. Single- and multiphoton radiation absorption in cornea tissue: (a) Mikroskan laser with the wavelength $\lambda = 0.193$ μm and the photon energy 6.4 eV; (b) Femto Vizum laser with the wavelength $\lambda = 1.06$ μm, pulse duration $\tau = 250-400$ fs, and photon energy 1.2 eV.

the dissociation energy, which furnishes the effect outlined above and offers new possibilities in laser ophthalmology.

Rapid strides are presently being made by photodynamic diagnostics and cancer therapy. These methods are underlain by the use of a laser whose monochromatic radiation excites the fluorescence of a photosensitizer dye and initiates photochemical reactions that cause biological transformations in tissues. The rate of application is 0.2–2 mg per 1 kg. The photosensitizer accumulates primarily in tumors. The photosensitizer fluorescence permits determining the tumor localization. Due to the effect of energy transfer and the increase in laser power, singlet oxygen, which is a strong oxidizer, is produced, resulting in tumor destruction. Therefore, the above technique affords not only the diagnostics but also the treatment of oncological diseases. It is pertinent to note that the introduction of a photosensitizer into a human organism is not an absolutely harmless procedure, and therefore in several cases it is possible to use the so-called laser-induced autofluorescence. It turns out that in some cases, especially when short-wavelength radiation is used, malignant cells exhibit the effect of fluorescence, while sound cells do not. This is the technique of choice for treatment; however, it is used primarily for diagnostic purposes, although recent effort has been mounted to realize the therapeutic effect as well. Series of devices intended both for fluorescence diagnostics and for photodynamic therapy were developed at the GPI. This equipment has been certified and is being commercially produced. Fifteen Moscow clinics are equipped with these devices.

A laser facility component required for endoscopic and laparoscopic operations is the means of radiation transport and its field formation in the interaction region. At the GPI, these devices were elaborated on the basis of multimode optical fibers, which permit operating in the spectral range from 0.2 μm to 16 μm.

Developed under the auspices of the Federal Agency for Science and Innovations is a technique for determining the particle size distribution in liquids, in human blood in particular. This technique relies on the spectroscopy of quasielastic light scattering. It turns out that the presence of nanoparticles in a liquid results in the broadening of the central Rayleigh scattering peak. Measuring this broadening permits determining the nanoparticle sizes. An investigation of the size spectra of nanoparticles in the blood serum of

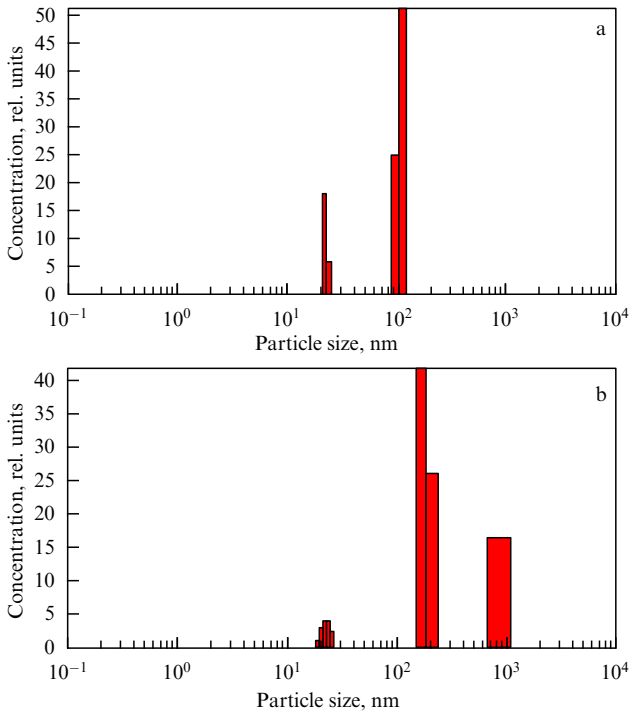

Figure 6. Spectrum of the sizes of the molecular makeup of blood serum: (a) a healthy patient, (b) a patient with cardiovascular abnormalities.

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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PACS numbers: **29.20.–c**, **42.62.–b**, **87.56.–v**
DOI: 10.3367/UFNe.0180.201006j.0670

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

L V Kravchuk Institute for Nuclear Research, Russian Academy of Sciences, Moscow, Russian Federation
E-mail: kravchuk@inr.ru

Uspekhi Fizicheskikh Nauk **180** (6) 665–670 (2010)
DOI: 10.3367/UFNr.0180.201006j.0670
Translated by E N Ragozin; edited by A M Semikhatov