

INFLUENCE OF ELECTROMAGNETIC AND NUCLEAR RADIATION IN MEDICINE FOR THERAPY AND DIAGNOSIS THROUGH PROCESSES, FACTS AND STATISTICAL ANALYSIS

by

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Contemporary medicine (biomedicine) cannot be imagined without diagnostics and therapeutic methods based on nuclear, laser, acoustical and other processes. The application of these methods is linked to common computer support, signal processing, measuring monitoring techniques, high degree of automatization, and image analyses. The paper analysed contemporary technical issues related to neonatology, ophthalmology, based on the influence of nuclear radiation and laser beams. Some statistical processing and presentations of results obtained in the IGA KCS Hospital, Belgrade, Serbia, in curing vision of prenatal type newborns with a different degree of pathological state of retinopathy of prematurity are presented. The general conclusion is that, in spite of the good results, a multidisciplinary approach is needed for a deeper understanding of the role of lasers and laser techniques in medicine as well as possible couplings. Potential new applications of lasers important for the fields of neonatology and ophthalmology were also considered.

Key words: retinopathy of prematurity, neonatology, laser, nuclear radiation, damage, dosimetry

INTRODUCTION

Among diagnostic and therapeutic applications of electromagnetic (EM) and nuclear radiations in medicine, the basics are the mechanisms of beam interactions with material. Techniques of magnetic resonance (MR), tomography (nuclear and optical), holography with non-linear systems are the areas where the answers should be found. Not involving the mechanisms of nuclear magnetic resonance (NMR), the obtained signals and signal processing deserve specific attention, as well as the signal/noise (S/N) ratio, image generation, reconstruction, and selective excitation. Pulse sequences, the influence of microcentres moving, correction of moving through the image series, imaging flow, MR spectroscopy and system design are also of interest, too [1]. An approach to the new energy resources combines lasers and nuclear physics and techniques, as well as biology. This applies to therapy, diagnostics, for power

sources through plants, bioconversion and biological sensors, as well as optical recording through bacteria. World catastrophes such as Chernobyl, accidents, Three Miles Island, Fukushima, provoke discussions about doses, caused biological effects of radiation and genetics (early and late effects). Unfortunately, new facts are provided through accidents in nuclear and laser technologies [2-14]. In tab. 1 the levels of radiobiological processes [9-13] are presented. Biological entities and hardness of organic/inorganic materials and systems are connected with doses with appropriate definition, measurements, uncertainties, as well as biological radiation effects [2-17]. Many theoretical models on various organization levels are developed. From the position of a systematic approach to the processes and modelling principles, concepts of biophysical models on molecular, genetic and cell levels are derived. Models should be compared and some investigations are in [13] regarding boundary conditions, applications and disadvantages. The probability estimation through many criteria should follow the analysis for their inves-

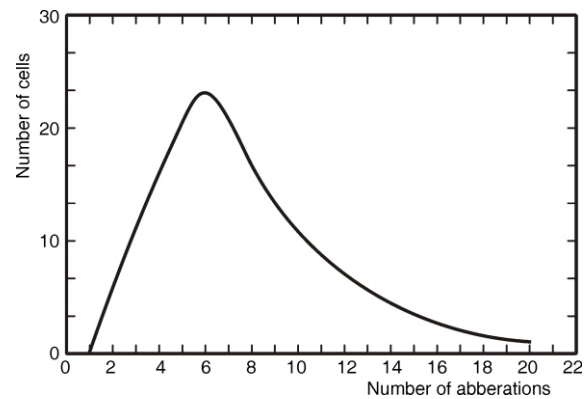
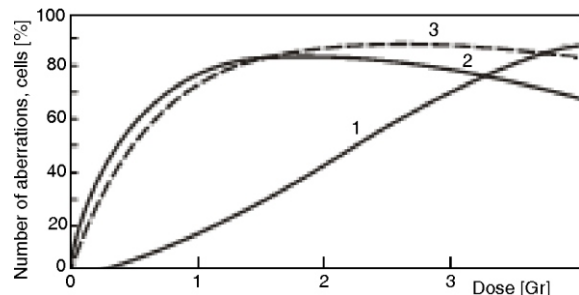
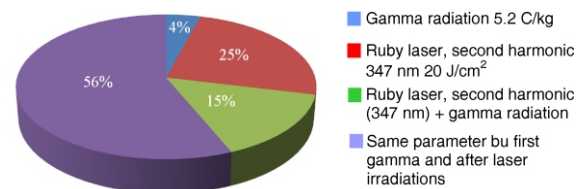
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Table 1. Levels of processes in biology caused by radiation

Level	Existence time on level [s]	Processes on the presented level; possible modifications
Physical	10^{-18} - 10^{-8}	Excitation, ionisation, elastic collisions-thermalization and formation of high reactivity radicals of macromolecules and short lived free radicals of water and organic molecules; no modification
Chemical	10^{-14} - 10^{-4}	Reactions of free radicals mutually, with organelles – forming primary damage (DNA damages, dimerizations); modification by protector, oxygen, temperature
Biochemical (subcell)	10^{-4} - 10^5	Reparation, interactions of damaged microcenters (mutation, aberration, modification by temperature and other agents)
Biological (cellular)	10^3 - 10^7	Division of cells and molecular chains, exchange of performances as a result of mutations

tigation and experimental assessment. Theoretical approaches and results based on appropriate formalisms are of importance in the field of radiation protection and dosimetry, which are constantly competing due to new sources in radiology. Molecular biology (for structure, DNA functioning and repair processes), uses only the simplest biological effects (inactivations of phages, viruses, and gene-mutations). The explanation through complex biological processes and behaviour could rather remain without results. The cell inactivation model based on physical considerations, and later models as radiobiological ones (on the genetic level without the existence of repair processes and chromosome structures) are developed. Self-repair, interactions of damages, dynamics of the processes, stochastic energy transfer to the cells are also important topics. Micro dosimetry, the structure of the cell traces, stochastics, classification and conceptual analyses appeared as typical. Characteristics of physical models, the theory of dual effect, and modifications are compared. They include the radiobiological effects to DNA and model of cell /systems inactivation. It is important to implement physical doses, target theories and modifications. The two-component dual effect model of probability on molecular and genetic levels (*E. coli* mutations and mammals) deals with various effects (lymphocytes irradiated by neutrons). Table 1, figs. 1-2 based on results [13] show some trends in modelling and experimental irradiations of different cells and aberrations. Figure 3 presents the qualitative behaviour of different beams and radiation on plants.

Sensitivity of mammal cells to the irradiation of heavy ions depending on the viability level (or survival) of the human and animal cells, (lymphocytes, diploid fibroblasts, and kidney cells) are studied [13]. The defined threshold for survival as well as energy loss per range of ions are parameters of interest.

**Figure 1. Chromosome aberration for lymphocytes irradiated: moderate neutrons (0.35 MeV; 3.3 Gr)****Figure 2. Aberrations of cells vs. the neutron dose (0.35 MeV (1), 0.85 MeV (2), and for γ radiations of ^{60}Co (3))****Figure 3. Frequency of changed barley seeds (type Nadya) in the case of combined radiation of gamma rays and frequency doubled ruby laser (347 nm)**

The same goes for sensitivity of the mammalian cells to the irradiation of ions, induced number of structural changes after X-ray irradiation of the tumour cell vs. dose. Models of: inactivation, Karpos and Foloty, repaired and unrepaired damages include/(do not include) saturation processes, viability of prokaryotes, sensibility of *E. coli* to neutrons, eukaryotes, and fatal damages. Thermal damage and critical temperatures, threshold for effects and concentration limits are important. Couplings between the nuclear power engineering, laser technique and medicine are multiple (some are connected by the laser excitations in the nuclear reactions and pumping neutrons, protons, α and β radiations). Modern problems include gamma and X-rasers (X-ray Amplification by Stimulated Emission of Radiation), or preionizations to decrease the lasing threshold, but also for disposal of various waste.

The biological damage threshold is studied for various cell types and systems. An epidemiological study and variation of estimated doses and the real damage are the subjects of a wide investigation in the theory of microdosimetric cellular radiobiological action, lymphocytes and stochastic/astochastic effects.

Considering vision, in the sense of colour prejudice in various problems, it should start from the primary eye functions and its mechanisms. Medically speaking, there are numerous links between ophthalmology, neonatology and lasers techniques. Diagnostic techniques and operatives, including biostimulative treatments with lasers penetrated into many branches of medicine and could be applied for many tissues and organs. There are two phenomena where we have to stay in one of the natural organs which is the eye: structure complexity and simple functioning, describe modern problems for techniques-medicine-protection couplings and tasks. Since the first application of lasers in medicine, the area of application has significantly expanded, in eye surgery and diagnostics. Medical terminology and diagnostics are expressed through quantitative indicators for biomaterial and generalized processes. Modern methods of coherent, linear and nonlinear optics, have to be involved in the world of medical diagnostics and monitoring. The dynamics of human and animal cells, protoplasmatic and blood circulation, tissue pathology, could be observed due to the development of photon beating and Laser Doppler Anemometry (LDA) techniques.

The paper intends to show the role of lasers in diagnostics, gynaecology and ophthalmology. Vision problems incurred in neonatal infants, require a complete diagnosis and medical history. Similar types of lasers are used both in diagnostic and operative treatments. The treatments differ in accessories, but essentially, models of interaction and diagnosis are associated with many of the general applications, where optical beams have the role of a knife (scalpel), therapy or diagnosis. Sources are beams of coherent radiation in the visible, infra red (IR), far infra red (FIR) or ultra violet (UV) portion of the EM spectra. The study of the ocular performances has come a long way from the first images of muscle tissue and Helmholtz's assumption up to the present, with computer diagnostics, polarizing microscope, Stokes parameters and Mueller matrices [12].

Besides many diagnostic techniques in ophthalmology, some of the relevant laser techniques of interest to several branches of medicine are analysed. One of them is used for the early diagnosis of glaucoma. The solutions appeared based on methods: (a) Laser Induced Fluorescence (LIF) and (b) monitoring of the Stokes parameters through ellipsometric measurement [7, 12]. Fluorescence methods were not new in medicine, however, Raman, IR and UV spectroscopies and new areas of nonlinear laser spectroscopies with tunable lasers, made precise application possible. Measurements of turbidity belong to the category of reliable, but less accurate mea-

surements. Harmonics of the Nd³⁺: YAG (yttrium aluminium garnet) laser are favourable for biosamples in the picosecond (ps)-region (in mastitis tissue diagnosis).

The eye system is well studied in the linear region. There is data available on absorption of the eye and its constituents, spectral sensitivity curves relative spectral brightness and eye adaptation to the light vision (photopic and scotopic). However, the variety of eye-damages existed even before the use of lasers. Damages occurred in the process of welding, by the focused radiation of the sun and sources in other portions of the EM spectrum. Nowadays most of the relevant data concerning laser (laser era) damage originate from accidents. With the first giant laser pulses, it was possible to organize the study of nonlinear effects. The first ophthalmic devices applied on to rabbits appear as new experimental material. The people working in space and next to the terrestrial accelerator devices are experiencing sparkles of light due to the environment of cosmic and gamma rays. Absorption of the photopigments in human eye receptors (cones and rods), versus different wavelengths was studied. Saturation effects were likewise found [18]. Data of the normalized absorbance of the photoreceptors, or photopigment molecules, are obtained through microphotometry methods, and further investigations explained the human feeling for colours. Main data comparison between the physics, metrics of colours, and psychological concepts can be a subject of discussion.

RETINOPATHY OF PREMATURITY INCIDENCE IN THE IGA KCS HOSPITAL

Important topics in the field of neonatology are retinopathy of prematurity (ROP) and risk factors. In the light of new methods for treating ROP, comprehensive theoretical and experimental support is needed and it requires a multidisciplinary approach. Optical methods in diagnosis and treatment, light influence on the eye systems, damage threshold, scattering and absorption processes are of interest. Lasers and fiberoptics are also unavoidable topics in ophthalmology. Laser surgery is rivalled by the cryo-surgery technique, but for the moment it seems that lasers have more advantages. The institutional procedure with questionnaires for parents before the intervention in cases of ROP can be found on the internet. Many questions exist concerning ROP progress, laser treatments, complications and measures of protection.

Laser methods and hazards

Laser surgery for cases of ROP is actually causing partial damage to the ischemic retina. We will not describe the processes on a microscopic level con-

nected to ribonucleic acid (RNA), process of peripheral retinal vascularization and other important factors. Destruction of ischemic retina can be performed with various laser types: Ar⁺ ion (488-515 nm; 200 mW, in the appropriate regime) or semiconductor laser (IR range, 810 nm). The binocular microscope – ophthalmoscope, is the second necessary component, and the systems for beam positioning and shaping with the low power He-Ne laser. Various reference data confirms the positive outcome with the different laser types and details about advantages and disadvantages of the ROP laser treatment [19-24]. Reduced vascularisation can be observed 7 days after the intervention (photocoagulation). A detailed database should be made for both lasers and cryogenics, which is necessary for decision making and analysing the laser ROP treatment compared to other techniques. Perhaps it is important to note that for now the χ^2 test gives no significant difference method.

Regulations, ecology and laser (eye and skin damage)

The application of lasers in everyday life, biology, ecology, medicine, pharmacy and military is related to many administrative regulations worldwide that vary in different countries. In particular, principal parameters and protections are defined. Nominal Ocular Hazard Distance (NOHD) was one of the first regulated definitions. The classification of lasers varies from one state to another, however most countries share the same regulation. The lasers are classified into four groups, assuming that both the III class as well the IV class would lead to laser induced damage. Therefore many investigations of laser influence on animal eyes and plants were performed including the investigation of the impact of various environmental conditions (fog, smoke, and fume), using different chemical products. The threshold for laser damage depends on the different parameters of investigated bio-objects, (biomaterials, biotargets) and pupil size; quantitative presentation of those investigations is connected to protection and regulation for selected lasers and working regimes. Therefore relevant data of transparent, absorptive, parts of the ocular performances are needed. Absorption of EM radiation in the eye deals with four principal bands: (a) Microwaves and γ rays. (b) Far UV and FIR, (c) Near (N) UV, (d) Visible and NIR regions.

There are four categories of laser (equipment) interactions with tissue: (a) optical radiation hazards to the eye and skin, (b) chemical, (c) electrical, and (d) casual hazards [4]. Most of the Nd³⁺: YAG laser beam energy is absorbed inside the optical structure of the eye (cornea, lens and vitreous). Note that this laser type is also used in everyday applications in ophthalmology and other branches of medicine. The retinal

effects are expected in the visible and close IR-A case (400-1400 nm). Minimal sizes of the image on the retina depend on wavelength and are limited by diffraction. Radiation in the UV or FIR portion of the spectra is absorbed in the inner part of the eye. High levels of exposure can permanently damage the cornea or lens. Medium levels of the UV beams cause serious damage, which is severe but temporary (analogue to industrial welder flash, *i. e.* photokeratitis). Description of the biological effects of radiation, according to the International Commission on Illumination (CIE), is performed in 7 spectral bands [4].

Skin damage is far less likely to occur, except in cases of high-power lasers. The skin is usually not injured by common lasers, *i. e.* low and medium power lasers. Levels of skin injuries visible and IR areas require at least a few Wcm⁻², and depend on the skin's surface characteristics [4]; exposure conditions are presented by dosimetry (a laser can be viewed as a thermal damage source). Radiation (200-300 nm) causes burns, the same as those caused by the sun (cancer, erythema). Electrical hazards will not be described in detail, however a source of high voltage present in lasers, can provoke electric shock resulting in electro-cauterisation. Therefore appropriate electrical and electronic standards have to be applied. Considering standards and regulations in chemistry, many highly volatile or even explosive or highly toxic materials are used in laser laboratories. During laser processing of a material (welding/cutting) much chemical evaporation is created. Standards for industrial manufacturing require adequate ventilation during the laser operation. Items connected to retina treatment risks (injuries) are: blue/UV light, retinal image, retinal burns, intensity and spectral characteristics of coherent sources.

ROP is the subject of research in many clinics worldwide, as well as in Serbia. For this type of study, trained teams, originating from various branches of expertise (beside experts in gynaecology and ophthalmology) are needed. As ROP presents a disorder of retinal blood vessel development in prematurely born infants, it can be interrupted by laser beam interactions with tissue. The process can affect the vitreous body and lead to detachment of the retina. In the most severe ROP forms, it leads to partial retinal detachment. This can cause blindness in childhood and is considered to be one of the main causes. We will consider some of the important approaches in ROP diagnostics and treatment. ROP was mentioned for the first time in 1942, and has been regularly mentioned to this day. Various methods of operation have been attempted during almost three quarters of a century. It was identified as a fibrous state process of the retina and vitreous body (retrolental fibroplasia). The correlation between these processes and prematurity of childbirth was established. The name ROP (1952.) was first mentioned in the middle of the last century. The study of

pathogenesis was enhanced through development of the animal models. The International Classification of Retinopathy Prematurity – ICROP has been formed over time. It represents an important and unifying criterion for the diagnosis and treatment of active forms of ROP. Screening, monitoring and treatment of ROP are implemented in several countries. In Serbia, since May 2003, many cases of ROP, as an active disease, have been diagnosed. In Belgrade, Serbia, the IGA KCS hospital initiated systematic ophthalmological examinations. The method of using an indirect ophthalmoscope, provided an early diagnosis of disease, and monitoring of severe forms of active retinopathy.

Parameters and stages of ROP

Various stages of the disease are described [20, 22, 25-29]. The zone of interest is divided into the central area of growth in the retina, which encompasses the macula, the highest ROP and the last area of growth. Different descriptions and classifications of the main parameters of ICROP exist. Most of them agree that the most important parameters are: severity (pathological mutation) with different stages, localization with 3 characteristic zones, prevalence – number of hours, tab. 2, and fig. 4.

RESULTS OF ANALYSIS

The results of the study of ROP should in principle be related to the frequency of prevalence and the appropriate time of observation in order to obtain the data that have sufficient statistical importance. In the analysis, several factors are included: prematurity time, birth weight (small weight at birth), hyperoxia and oxygen therapy duration, sepsis, respiratory diseases, coherent/incoherent EM irradiation. Figure 5 represents the percentage display of the data on the numbers of births and treatments applied. Percentage data are related to several hundreds of prematurely

Table 2. Stages of retinopathy

1 stage	Normal but incomplete growth
2 stage	Medium abnormal growth
3 stage	Very abnormal growth
4 stage	Partially detached retina
5 stage	Retina with entirely detached retina

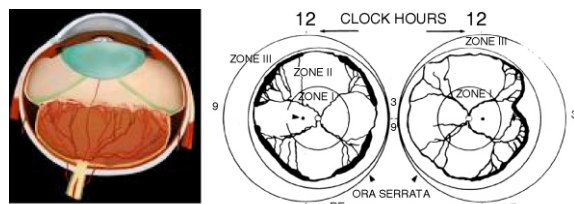


Figure 4. Typical stages of ROP and eye anatomy [30]

■ A – transferred to another institution
■ B – died
■ C – cured and released

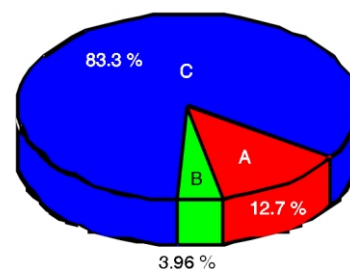


Figure 5. Percentage display of early childbirth with different final outcomes – transferred to another institution, fatal and treated in the maternity hospital and allowed to go home

Table 3. Incidence of ROP related to weight at birth in 2004

Incidence of ROP	Number [%]
<999 g	3 newborns [0.52 %]
1000-1499 g	13 newborns [2.2 %]
1500-1999 g	7 newborns [1.19 %]

born infants; therefrom, the cases of ROP are present in a few percents (~4 %). Table 3 covers the number of data with respect to the weight. In figs. 6-10 the results of the study are graphically presented.

Prematurely born infants or infants with low body weight are the most indicated groups for ROP, however only a small percentage of them end up with a severe form of the disorder.

Ophthalmologic results of the examined children despite the risk for retrolental fibroplasia, were within normal limits, with no statistically significant differences compared to the reference values, $-p > 0.05$ (DF = 67, $t = 0.2371$), [21].

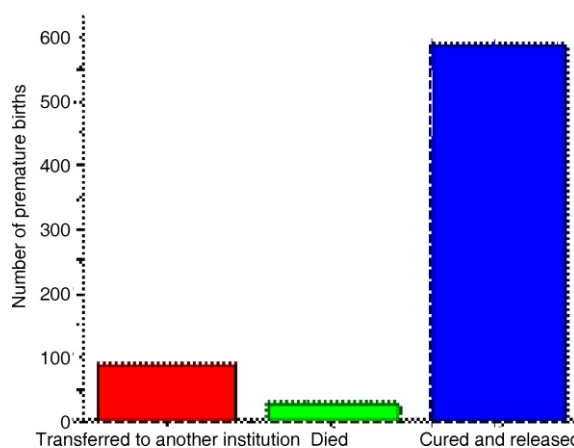


Figure 6. Number of premature births with different outcomes – transferred to another institution, fatal and treated at the maternity hospital and released home

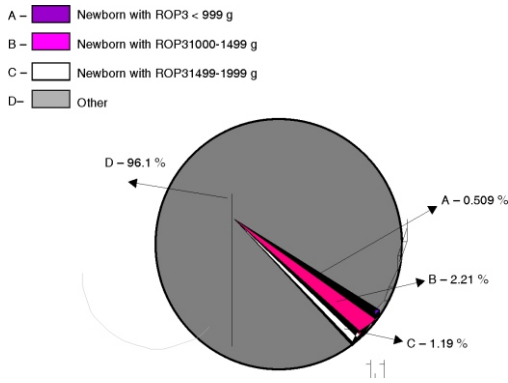


Figure 7. Premature births treated at the maternity hospital and discharged afterwards – percentage of patients' cases according to weight

A < 999 g
 B 1000-1499 g
 C 1500-1999 g

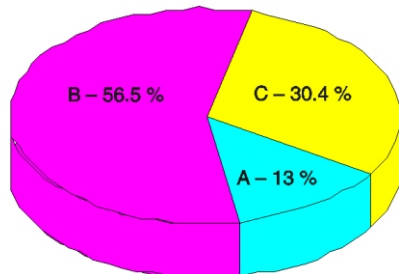


Figure 8. Incidence of ROP with respect to body weight (2004)

Table 3 and fig. 9 represent the cases of ROP developed in children who have not been exposed to an elevated concentration of O₂. They contain information on the ROP and sanitation.

Usually, the shortest O₂ therapy lasts 3 days and the maximum lasts 86 days. The average duration of therapy is 23 days.

According to the data analysis, a large number of newborns with ROP has been successfully treated. From the statistical data regarding ROP, the largest number of detected ROP cases occurred with newborns weighting between 1000 g and 1499 g. In tab. 4 it can be seen that most cases are diagnosed with asphyxia prenatal and RDS. The number of perinatal infections and pneumonia is somewhat smaller. It would be of great interest to collect data and create a database for diagnosis and laser treatment of ROP in Belgrade, Serbia.

CONCLUSIONS

Discussions about the correlation between the oxygen therapy and ROP occurrence are still present. ROP is considered to be a serious disease and here are the results of the study from the IGA KCS Hospital in

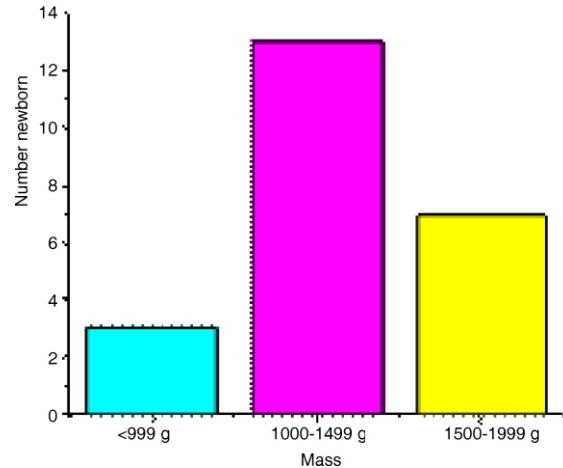


Figure 9. Number of ROP incidence depending on body weight (2004)

Table 4. Pathology and oxygen therapy for children with ROP

Pathology	Number of newborns
Asphyxia prenatal	48 children
RDS	47 children
Perinatal infections: sepsis	32 children
Candida	4 children
Pneumonia	21 children
Haemorrhagia pulm	3 children
BPD	8 children
IVH I and II	41 children
IVH III and IV	13 children
Hydrocephalus post-haem	4 children
Ventriculodilatatio	3 children

Belgrade, Serbia. One of the methods for ROP treatment are laser techniques (semiconductor lasers are also favourable).

Besides the ROP treatment, there are other laser applications in gynaecology, neonatology and ophthalmology. One of the very important applications is the analysis of milk quality for newborns. There are different methods to control the quality of milk through the measurement of turbidity (He Ne laser or with Nd³⁺:YAG and its harmonics in the ps-region). Measurements of turbidity belong to the category of reliable, but not highly accurate. Adjusted selection with the excitation wavelength and the fluorescence method with pulse lasers, present for a long time is a more precise method for mastitis diagnosis. From the references it could be seen that the distinction could be made in the quality of milk (whether it is pathogenic or healthy). Another application of laser treatment is the rehabilitation of the mastitis affected tissue.

AUTHORS' CONTRIBUTIONS

The idea and results for the presented research were initiated and performed by M. Živković at the IG

KCS Hospital. The data processing and graphic presentation *i. e.* manuscript preparation were carried out by M. Ž. Srećković, T. M. Stojić, and B. M. Bokić. The manuscript was written by M. Živković and M. Ž. Srećković and all the authors participated in the discussion of the results presented in the final version of the paper.

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**УТИЦАЈ ЕЛЕКТРОМАГНЕТНОГ И НУКЛЕАРНОГ ЗРАЧЕЊА У
МЕДИЦИНИ ЗА ТЕРАПИЈУ И ДИЈАГНОЗУ – ПРОЦЕСИ,
ЧИЊЕНИЦЕ И СТАТИСТИЧКА АНАЛИЗА**

Савремена медицина (биомедицина) не може да се замисли без дијагностике и терапеутских метода базираних на нуклеарној, ласерској, акустичкој техници и процесима заснованим на њима. Примена ових метода је везана са рачунарском подршком, обрадом сигнала, мерним-контролним техникама, високим степеном аутоматизације и анализом слике. У раду се анализирају савремени проблеми техничке природе који се односе на неонатологију и офталмологију, а заснивају се на дејству нуклеарног зрачења и ласерских снопова. Овде су представљене статистичке обраде резултата из Института за гинекологију и акушерство Клиничког центра Србије, Београд, у вези побољшања вида новорођенчади пренаталног типа са различитим степенима патолошког стања ретинопатије. Упркос добрим резултатима, закључује се да је мултидисциплинарни приступ потребан за боље разумевање улоге ласера и ласерских техника у медицини, као и могућности спрезања. Размотрене су и нове потенцијалне примене ласера од интереса за неонатологију и офталмологију.

Кључне речи: ретинопатија код новорођенчади, неонатологија, ласер, нуклеарно зрачење, оптичење, дозиметрија
